UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

ALLERGAN, INC.,

Patent Owner.

_____/

Case IPR2016-01127
Patent 8,685,930
Case IPR2016-01128
Patent 8,629,111
Case IPR2016-01129
Patent 8,642,556
Case IPR2016-01130
Patent 8,633,162
Case IPR2016-01131
Patent 8,648,048
Case IPR2016-01132
Patent 9,248,191

DEPOSITION OF ANDREW F. CALMAN, M.D., PH.D.

WEDNESDAY, JULY 12, 2017

REPORTED BY: MEGAN F. ALVAREZ, RPR, CSR 12470
JOB LA-133836

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BE IT REMEMBERED that, pursuant to Notice, and on Wednesday, JULY 12, 2017, commencing at WILSON SONSINI GOODRICH & ROSATI, One Market Street, Spear Tower, Suite 3300, San Francisco, California, before me, Megan F. Alvarez, a Certified Shorthand Reporter, Registered Professional Reporter, personally appeared for their deposition

ANDREW F. CALMAN, M.D., PH.D.

called as a witness by Patent Owner, who, having been first duly sworn, was examined and testified as follows:

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I N D E X

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EXHIBITS MARKED FOR IDENTIFICATION

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EXHIBITS PREVIOUSLY MARKED FOR IDENTIFICATION

REFERRED TO IN THIS DEPOSITION

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1007	49	25
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A P P E A R A N C E S

APPEARANCES:

FOR THE PATENT OWNER:
MICHAEL J. KANE, ESQ.
TASHA M. FRANCIS, PH.D., ESQ.
FISH & RICHARDSON P.C.
3200 RBC PLAZA
60 SOUTH SIXTH STREET
MINNEAPOLIS, MINNESOTA 55402
612.335.5070
KANE@FR.COM
TFRANCIS@FR.COM

FOR THE REMAINING PETITIONERS:
(APPEARING TELEPHONICALLY)
GARY SPEIER, ESQ.
CARLSON, CASPERS, VANDENBURGH, LINDQUIST & SCHUMAN, P.A.
225 SOUTH SIXTH STREET, SUITE 4200
MINNEAPOLIS, MN 55402
GSPEIER@CARLSONCASPERS.COM

FOR THE RESPONDENT:
JAD A. MILLS, ESQ.
ANNA PHILLIPS, ESQ.
WILSON SONSINI GOODRICH & ROSATI
701 FIFTH AVENUE, SUITE 5100
SEATTLE, WASHINGTON 98104
206.883.2554
JMILLS@WSGR.COM

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WEDNESDAY, JULY 12, 2017, 9:08 A.M.

ANDREW F. CALMAN, M.D., PH.D.,
having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. KANE:

Q. Good morning. Could you state your name for the record?

A. Andrew Frederick Calman.

Q. And what's your current business address, Dr. Calman?

A. 2480 Mission Street, San Francisco, California 94110.

Q. And I believe you've been deposed before, right?

A. Yes.

Q. How many times?

A. About 18.

Q. Okay. So you know the general ground rules, then. But before we get started, I'm going to ask you a series of questions, you're going to provide the answers. It will be important to let me finish my question before you start your answer so that she can get our both of our comments down. I'm a fast talker as well, so we'll both have to try to watch that a little bit and not try to step on each other. Okay?

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A. Yes.

Q. If I ask you a question that you don't understand, please let me know and I'll to do a better job on that. Okay?

A. Okay.

Q. It's also important that since we are trying to create a transcript here that you need to answer verbally. Yeses, nos, not nods of the head or shaking of the head or the uh-huhs or huh-uhs, that kind of thing. All right?

A. Yes.

Q. We'll try to take a break approximately on an hourly basis or so. But if you need a break somewhere in the middle, let us know. We can do that. We just won't -- we'll just ask if there's an outstanding question, that you answer the question before we take a break. All right?

A. Yes.

Q. Of the 18 times you've been deposed, how many of those related to patent issues?

A. Two, to the best of my recollection.

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Q. And can you describe generally what those depositions were?

A. Well, there was one in the Markman case, and I believe there's just one -- in the Markman phase of Allergan v. Teva Mylan, et al., for this product. And there was one or two, but I believe it's just one, on the invalidity and noninfringement phase of that same case.

Q. So both of your depositions that related to patents were in connection with the district court litigation over Restasis currently pending in Texas?

A. Correct.

Q. Okay.

A. There was another matter, but it was an antitrust matter that had grown out of a patent matter. But I was not involved in the patent phase at all.

Q. Okay. And then, in general, in the other 16 or so depositions that you've given, what did they generally relate to?

A. Injuries and medical malpractice.

Q. Okay.

A. With a smattering of other things. There was an employment discrimination case.

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I think that's it.
Q. Okay.
A. Off the top of my head.
Q. The other --
A. Oh, there was a wrongful death case.
Q. Okay. The other matter that related -- the antitrust matter that you mentioned, did that relate to a drug?
A. Yes.
Q. What kind of drug was that?
A. An antibiotic eye drop.
Q. Who were the parties?
A. Apotex and Allergan.
Q. And who did you represent in that case?
A. Well, I was engaged by Allergan -- excuse me -- by Apotex.
Q. Where was that case located, if you recall?
A. I think Delaware. But it never went to trial, so I don't know for sure.
Q. What was the name of the product?
A. Zymaxid.
Q. Do you recall the time frame when that occurred?
A. It settled earlier this year.

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Q. Okay. And generally --
A. You know what? I don't think I was deposed for that case, though. I didn't actually testify.
Q. Did you provide a report?
A. Yeah.
Q. And, again, just at a high level, what did the report relate to?
A. Well, it's subject to a protective order which I believe is still in effect. So what I think I can probably safely share is what I've seen in public press releases, that it was -- not my term but press term -- was a product switching case related to this drug.
Q. Okay. You understand that this deposition relates to several -- what are called IPRs pending in the patent office?
A. That's my understanding.
Q. And what do you understand an IPR to be?
A. Well, my understanding of inter partes review is it's a pathway where parties can challenge the validity of patents through -- rather than going through the court system, going through what's called the PTAB, which I believe stands for Patent and Trademark Appeals Board, which is a part of

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the -- to my knowledge, is part of the U.S. Patent and Trademark Office.
Q. Okay. And you understand you're testifying under oath today?
A. Of course.
Q. So the testimony today is just as though you were in a courtroom giving it in front of a judge or jury.
A. Of course.
Q. Okay. Any reason you can't give accurate or truthful, complete testimony today?
A. No.
Q. What did you do to prepare for the deposition today?
A. I reviewed various documents. I met with counsel, reviewed -- you know, obviously reviewed my declaration and others and prior art.
Q. When did you meet with counsel?
A. Yesterday and the day before.
Q. How long?
A. About eight hours each day.
Q. Okay. And who -- who was present at those meetings?
A. Jad Mills. Anna Phillips. I think Wendy Devine may have poked her head in for a brief

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period.
Q. Anyone else?
A. Not that I recall.
Q. Anybody on the phone?
A. Not that I'm aware of.
Q. Okay. Do you recall what documents you reviewed?
A. Well, I'm sure I can't remember every single thing. But, in general, I reviewed the various declarations in the case, the various -- not court, but the various PTAB documents such as institution, petition, response, order, and then the various prior art references.
Q. Okay. Okay. Did you talk to anyone other than counsel in preparation for your deposition?
A. No.
Q. Did you talk to anyone at Mylan in preparation for the deposition?
A. No.
Q. Have you ever spoken to anyone at Mylan about this case?
A. Not to the best of my recollection.
Q. Okay. All right. We have -- handing you what's been marked previously as Exhibit 1039. And do you recognize this document,

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Dr. Calman?
A. Yes.
Q. What is this?
A. This is my declaration for the six IPR cases.
Q. Okay. And if you turn to page 55, that's your electronic signature?
A. Yes.
Q. And it's dated June 30th, 2017?
A. Yes.
Q. And you understand this same declaration was filed in all six of the IPR proceedings?
A. That is my understanding.
Q. Okay. When did you begin working on the declaration for the IPRs?
A. It would have been late May or early June, to the best of my recollection.
Q. Okay. Do you recall approximately how much time you spent drafting the declaration?
A. I don't have a precise idea of that. I can give you an estimate. It's probably somewhere between 20 and 30 hours.
Q. Okay. Did you draft the declaration yourself?
A. Well, it was a -- it was a collaboration

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with counsel.
Q. And which counsel collaborated?
A. WSGR.
Q. Anyone else?
A. No, not unless -- not that I'm aware of.
Q. And which counsel at Wilson?
A. I'm sorry?
Q. Which counsel at Wilson Sonsini?
A. Let's see. Jad Mills. Grace Winschel, W-I-N-S-C-H-E-L. Anna Phillips. Wendy Devine. I think Jacqueline Altman may have been involved.
And there may have been others involved, but those are the ones that I'm aware of.
Q. And can you describe the drafting process generally?
MR. MILLS: And I'm -- at this point, I'm just going to issue an instruction that, on the basis of work product and privilege, you should disclose in answering the questions posed to you today your opinions as well as the bases for your opinions, but you should not disclose the contents of any confidential communications you may have had with counsel.
THE WITNESS: So let me look at the question again.

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The drafting process generally included sending drafts back and forth and changing them.
BY MR. KANE:
Q. And did you -- did you originate the first draft that was exchanged back and forth, or did counsel do the drafting?
A. I think there were parts of both. Parts of it were initially written by me, and parts were initially written by counsel, if I recall correctly. I don't -- there were a lot of drafts. I don't have a precise recollection.
Q. Okay. Let's take a quick look and hand you another exhibit here, Dr. Calman.
Handing you what's been marked previously as Exhibit 42.
Do you recognize this?
A. I do.
Q. What is this?
A. This is my CV.
Q. And is this dated June 29, 2017?
A. Yes.
Q. Was it accurate as of that date?
A. Yes.
Q. Have there been any changes?
A. Let me look.

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Not to the best of my knowledge.
Q. And --
A. Actually, there's one change. Let me look at this. And I have changed this on my subsequent versions.
There are two hospitals here where I no longer practice in the list of admitting privileges, and those are San Francisco General Hospital and St. Mary's Hospital.
Q. Okay. Thank you for that update.
And when you say "practice," you are a practicing ophthalmologist, right?
A. Correct.
Q. And in preparing your analysis, you relied on lawyers for the legal principles that you were to incorporate?
A. In part.
Q. And where else did you obtain information about the legal principles you were to use?
A. I have done some background reading over the last couple of years.
Q. In what -- can you explain what kind of background reading you've done?
A. I actually enrolled in a course called OmniPrep Patent Course, which I didn't complete, but

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I did enroll in it and went through some of their materials.

I went to two continuing legal education courses over the last two years on Hatch-Waxman.

And I read a book called -- it's called "The Generic Challenge."

And I've read various articles online about various patents' issues.

Q. Okay. In forming your opinions, you relied on that additional outside reading?

A. Well, I would say that that was background information.

Q. Okay. In forming your opinions, did you follow any guidance that the lawyers provided in terms of the legal principles that you were to apply?

A. I would say that's a fair statement.

Q. I understand that you're not a lawyer; is that correct?

A. That is correct.

Q. What caused you to be interested in the subject of patents over the last couple of years?

A. I saw -- I thought it was very interesting. I had some exposure to patents. My brother holds 55 patents in the technology field and

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has been an expert witness in high-tech patent cases.

I had an invention a few years ago which I thought about patenting and elected not to.

So that was my exposure, and my brother encouraged me to explore this. And I started reading about Hatch-Waxman. Some people may think it's dry; I actually found it kind of interesting. So I saw it as a natural outgrowth of my expert witness work on smaller cases.

Q. When you say "smaller cases," what are you referring to?

A. Mostly ocular injuries and medical malpractice.

Q. I see.

You don't consider yourself an expert in patent law?

A. I don't consider myself an expert in any form of law.

Q. You don't consider yourself an expert in statistics, do you?

A. Well, what I would say is that there are degrees of expertise. And through my knowledge, skills, experience, training, and education as a scientist and as a clinician over many years, I do

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have the ability to read and understand and apply, to some degree, statistical principles. That does not mean that I hold myself out to be an expert in statistics per se.

Q. Okay. Are you offering opinions in these matters as a expert in statistics?

A. Well, again, I think that there's some semantics here. I think my prior answer is applicable to your question. I do have an ability to read and understand statistical data. I did not perform my own statistical analysis.

Q. And we'll come to that.

You talked to Dr. Bloch, I understand?

MR. MILLS: Objection. Foundation.

THE WITNESS: Not in connection with this case.

BY MR. KANE:

Q. Okay. You reviewed Dr. Bloch's declaration in connection with this case?

A. I did.

Q. Okay. Do you consider yourself an expert in pharmacokinetics?

A. Again, through my knowledge, skills, training, education in 27-plus years -- more if you count my lab career working in labs on various

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projects, reviewing scientific and clinical publications, working on clinical trials, and serving as an expert on various cases, and, you know, taking various courses, including, you know, courses on evidence-based medicine and epidemiology, I have acquired some expertise in understanding and interpreting pharmacokinetic studies.

That said, I do not hold myself out an expert in pharmacokinetics per se.

Q. Do you still work at Premier Eyecare in San Francisco?

A. I do.

Q. And you're also an associate clinical professor?

A. Yes.

Q. Have you taken any additional roles besides those that are not listed in your CV?

A. Not to my knowledge.

Q. Okay.

A. "Roles" is a pretty broad category, but I think I've listed the relevant professional roles that I've had.

Q. Okay. If we look at the list of publications that starts on page 8 of Exhibit 1042...

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A. Yeah.
Q. To the best of your knowledge, is that a complete list of your publications?
A. Yes.
Q. Do any of these publications relate to dry eye?
A. No. Well, not directly anyway.
Q. Okay. Have you published in any papers on KCS?
A. No.
Q. Have you published any papers on making ophthalmic formulations?
A. Not to the best of my recollection, no.
Q. And I guess on that front, do you consider yourself to be an expert in making ophthalmic formulations?
A. Again, I've had 27 years in labs -- well, 27 years in clinical work plus 12 years in labs doing basic research. And through that knowledge, education, skills, training, and experience, I have acquired certain knowledge about pharmaceutical formulations, including ophthalmic formulations and their application in clinical practice, in clinical trials, et cetera.
So although I do have -- I have acquired

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some expertise in that area, I don't hold myself out to be an expert in formulation per se.
Q. Okay. You mentioned you thought about filing a patent application a couple years ago.
Have you ever filed a patent application?
A. No.
Q. In connection with that potential invention a couple years ago, did you talk to a patent lawyer?
A. I don't remember if I actually talked to a patent lawyer. And it was more than a couple; it was about 12 years ago.
Q. Okay. I assume that means there was never an application drafted?
A. That's correct.
Q. And, again, just generally, what was the nature of the potential invention?
A. It was a surgical instrument.
Q. For ophthalmic surgery?
A. Yes.
Q. So that -- do I understand correctly, then, you've never applied for a patent?
A. That is correct.
Q. Have you ever been involved in developing a cyclosporin ophthalmic product?

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A. No, with the caveat that I did -- I was working with professors as a resident in ophthalmology, and we certainly used ophthalmic cyclosporin formulations at that time. Whether any of them published anything on any of the patients that I collaborated with them on, I don't know. So not to the best of my knowledge.
Q. What were the nature of those formulations that you were working on?
A. To the best of my recollection -- again, this was a long time ago -- we were using 2 percent cyclosporin in olive oil.
Q. And was it a commercial product?
A. It was a compounded product.
Q. What do you mean when you say "compounded product"?
A. So you go through what's called a compounding pharmacy -- in this case, it was the UCSF pharmacy -- and the pharmacist makes up the drug custom for you.
Q. Okay. And this is during the time you were a resident?
A. Yes.
Q. And --
A. And possibly part of the time I was a

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medical student as well.
Q. Okay. And what were you using that compounded product on patients for?
A. Well, we used it for sure on some patients who had had corneal transplants, and we used it on a rare condition called ligneous, L-I-G-N-E-O-U-S, conjunctivitis.
You know, It's been a long time. I don't remember whether we used it on other conditions as well. I just don't remember.
Q. Okay. And did you have any involvement in deciding what the formulation would be made by the compounding pharmacy?
A. Well, there may have been some discussions, but I don't remember specifically.
Q. Have you ever been involved in any other development of a cyclosporine ophthalmic formulation?
A. Not to the best of my recollection.
Q. Have you been involved in the development of any ophthalmic formulation?
A. I guess it depends what you mean by "development." I've been involved certainly in clinical trials.
Q. Do you recall which clinical trials?

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A. Well, I believe they're listed in my CV. Page 11 --

Q. Okay.

A. -- and 12.

Q. All right. And that's a complete list?

A. Well, to the best of my recollection and knowledge, yes.

Q. And in these clinical trials, did you have any input into the formulations that would be used in the trials?

A. Not to the best of my recollection. But I should add that there were some additional discussions with personnel in the research department at Alcon over some clinical trials of glaucoma drugs where I would have had input into which formulations were used. However, we never got past the initial discussion.

Q. In that sort of a discussion, though, are you talking about the specific, say, excipients and other ingredients, or are you just talking about choosing between formulations that have been developed already?

A. Definitely the second part. Potentially the first part. We didn't get to that stage --

Q. Okay.

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A. -- in the discussions.

Q. Were there any other projects you were involved in where you were having detailed discussions about excipients and other components in ophthalmic formulations in development stages?

A. Well, again, it depends what stages you're talking about. The Travatan, or travoprost, studies were in part an effort to minimize toxicity to the ocular surface. And so the excipients were an important issue in those clinical trials. I was definitely involved in Phase 3 and Phase 4. I don't think I was involved in Phase 1 or Phase 2 or preclinical.

Q. And in those trials, what was the excipient of concern?

A. Well, the goal was to eliminate BAK. And so they were using a novel -- a novel preservative which the name is escaping me at this point. But that was the goal.

Q. Okay. All right.

A. And there were similar considerations. I don't know if they applied to the ones that I was directly involved with, but some of the Brimonidine formulations were also formulated -- reformulated in such a way as to eliminate BAK. And that was a

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focus of their research.

Q. Okay. In the Brimonidine formulations, did you have any input into what could be used in place of the BAK?

A. No. I believe that was -- that was at an earlier stage than my involvement.

Q. Okay. All right. And likewise in the Travatan, did you have any input into which preservative would be used in place of the BAK?

A. Well, I know I was certainly involved in discussions. I don't remember if they were at -- you know, certainly at the stage where they were disclosing the treatment protocols and rationale and basic science to the clinical investigators. Whether I was involved in discussions earlier than that, I don't have a recollection.

Q. All right. Have you ever performed bioavailability analysis for the delivery of ocular drugs in animals?

A. Not that I can recall.

Q. Okay. Do you use Restasis in your practice?

A. I do.

Q. And how do you use Restasis in your practice?

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A. Well, as I discussed in my declaration, I individualize treatment. Some individuals with some types of dry eye and some clinical pictures, I employ it as one treatment modality.

Q. Can you explain what you mean by that?

A. Well, it's a -- it would be a rather lengthy discussion. But I think to summarize, I typically use it in patients with moderate to severe aqueous-deficient dry eye where I believe there is an inflammatory component as one component of their treatment plan.

Q. Okay. And you understand that Restasis has been indicated to increase tear production in certain patients?

A. Well, it's a very specific labeled indication. To paraphrase without having the label in front of me, it's indicated to increase tear production in patients whose tear production is presumed to be suppressed by inflammation associated with KCS.

Q. And are you using it consistent with that labeling?

A. To some extent, yes, but I do individualize treatment, and I don't necessarily perform before and after measurement of

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tear production.
Q. Okay. If we look back at the clinical trials you've been involved in, you mentioned Brimonidine as an example. And isn't it -- is it true that many of these studies involve glaucoma-related drugs?
A. That is true.
Q. Did any of them involve cyclosporin?
A. I don't believe so.
Q. Did any of them involve treatments for dry eye patients?
A. In a sense because the -- again, the thrust of eliminating the BAK was to facilitate treatment of patients with ocular surface conditions, including that broad constellation of entities collectively known as dry eye, to be able to treat those patients for their glaucoma without comprising their ocular surface.
And so that was a major focus of the Brimonidine and travoprost development. And probably was -- I mean, this was a long time ago; I don't remember the exact study protocols. But it probably was reflected in the -- in the patients -- in the target patient population and the monitoring modalities.

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Q. If I understand correctly, the active ingredient in the treatment was being offered for glaucoma, but the concern or the issue with BAK was not to aggravate patients that were also suffering with some sort of a dry eye condition?
A. That's close. I wouldn't say it exactly that way. But, yes, many of the patients who have glaucoma are also elderly. And there is a strong overlap in the target population between dry eye and glaucoma, and so that was underlying this effort.
Q. But the focus was the treating the glaucoma?
A. Well, these are glaucoma drugs, obviously. But at least in some cases -- and I -- I would have to go read these study protocols from 15, 20 years ago -- was towards protecting the ocular surface while treating the glaucoma.
Q. Turn back to your declaration, Dr. Calman. And if we turn to appendix at page 56, please. This is entitled "List of Exhibits." Do you see that?
A. I do.
Q. And is this the documents that you relied upon in forming your opinions in these matters?
A. Well, it's not meant to be an exhaustive

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list. These are some of the documents that I relied upon, yes.
Q. Okay. What other documents did you rely upon?
A. Well, just off the top of my head, I'm not seeing, for example, the petition, response, institution decision. I'm looking for the various declarations.
So I did review petitions, responses, preliminary responses, institution decisions. I think there were a couple of orders. And then the declarations of Dr. Sheppard; Loftsson, L-O-F-T-S-S-O-N; Amiji, A-M-I-J-I; and Bloch, B-L-O-C-H.
Again, off the top of my head, that's -- that's what I remember reviewing. And I believe that everything that is referenced in here is listed the appendix. If not, then the reference would be in the text.
Q. Okay. And so was this listing an attempt to call out the specific documents referenced in your opinion?
A. I think that would be the overall thrust of it, yes.
Q. Were there any documents that you

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recall -- well, let me strike that.
If you start, other than Dr. Amiji -- as you 1001 of the patents at issue, so those are six patents that are subject to the IPRs, I assume?
A. Yes.
Q. And 1002 is the declaration of Dr. Amiji as filed in the IPRs?
A. There were six different ones, and I read one in detail and skimmed the others looking for, you know, areas that were different.
Q. All right. 1004 is the file history for the '930 patent in this list.
Is that a file history that you reviewed?
A. Well, I reviewed all of the six file histories about a year and a half ago. And I reviewed a few relevant sections of the '930 file history for the -- in preparation for this.
So, yes, I have reviewed the entire file history.
Q. Okay. You have an syllabus, a file history for a U.S. patent application.
Do you see that?
A. That's right.
Q. That's also something that you reviewed?
A. Well, again, I skimmed it and I read some

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relevant portions, some in more detail.

Q. Okay. Starting at 1006 -- strike that.

Again, are there other technical documents that you relied upon in forming your opinions that are not listed in the appendix?

A. Well, I'm looking. Again, you know, there are a lot of documents here, and I've reviewed a lot of documents.

What I would say is that there are certainly other documents that I may have glanced at but that I did not incorporate explicitly into the declaration but that I reviewed over the years or been exposed to during my training and practice and/or during the earlier parts of the district court case.

But that anything that substantively, you know, I'm quoting and relying upon directly should be referenced and/or listed in this -- in this list. But, again, as I said at the outset, this is not meant to be exhaustive.

Q. How did you come into possession of the documents that are on this list?

A. Most of them I encountered through the district court proceeding. Some of them I found during my literature searches.

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Some of them, I believe, came to my attention through the various other declarations in the case. That's -- you know, that's what I recall.

Q. Did you request or look for any documents that you weren't able to obtain?

A. Yes.

Q. What documents were those?

A. The Restasis NDA.

Q. Okay. Anything else?

A. Not that I recall off the top of my head.

Q. Okay. Did you look at any of the FDA documents or filings related to the Restasis?

MR. MILLS: Objection. Form.

THE WITNESS: Not in conjunction with this case.

BY MR. KANE:

Q. Okay.

A. Which is to say the IPR case.

Q. Understood. Thank you.

Did you look at any public FDA filings with respect to Restasis?

MR. MILLS: Objection. Form.

THE WITNESS: Well, that's what I thought you were talking about. Not in conjunction with the IPR case.

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BY MR. KANE:

Q. Okay. You didn't feel that those were necessary to form your opinions in this case?

A. It was more that I was not sure whether they would have been available to a POSA as a priority date.

Q. Did you talk to Dr. Amiji in forming your opinions in this case?

A. No.

Q. Did you talk to Dr. Bloch in forming any opinions in connection with this case?

A. No.

Q. Did you talk to --

A. Well, I should say Dr. Bloch and I had a conversation a few months ago in conjunction with the district court case. There may have been some overlap in materials, but they were different cases.

Q. Okay.

A. I have not had any discussions with Dr. Bloch with regard to the IPR case.

Q. Okay. Have you ever had a discussion with Dr. Amiji?

A. Not to the best of my recollection.

Q. Have you had any discussions with Mr. Hoffman?

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A. I think I may have had a discussion with him during the district court case, but I'm not sure.

Q. Before you -- before filing the declarations that you filed in the IPR, did you review the declaration of Dr. Amiji filed in the IPR?

MR. MILLS: Objection. Form.

THE WITNESS: Yes. Well, the declarations, yes, plural.

BY MR. KANE:

Q. Okay. And before filing your declarations in the IPR, did you review the declarations of Dr. Bloch?

MR. MILLS: Objection. Form.

THE WITNESS: Yes. Or a version thereof, yes.

BY MR. KANE:

Q. Okay. Before filing your declarations in the IPRs, did you review the declarations of Mr. Hoffman?

A. I don't believe so.

Q. In reviewing the matters related to the IPR petitions, did you review the petitions filed by Apotex?

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A. I don't think I've seen those documents.
Q. Did you review any petitions filed by Akorn?
A. You know, I'm trying to remember whether the petitions had other applicants besides -- or other petitioners besides Mylan on that front sheet. I don't remember.
So if I did, it would have been only because they were on the same -- you know, they were cosignatories to the same petition as Mylan.
Q. You don't recall reviewing any petitions other than petitions where Mylan was a party?
A. That's correct.
Q. Okay. You don't recall filing a -- reviewing a petition by Famy Care?
A. That's correct.
Q. And you don't recall reviewing a petition by Teva?
A. We're talking about the IPR here. That is correct.
Q. You don't recall reviewing a petition by Argentum?
A. No, I don't.
Q. And you obviously mentioned you're aware that there are district court cases ongoing and you

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filed declarations in connection with that, correct?
A. I think they were reports, but yes.
Q. But you've stated a couple times that those are separate cases and you view the opinions here as being separate from the opinions that you may be offering in the district court case?
A. Well, I guess it depends what you mean by "separate." There are obviously different rules and different legal standards and different bodies of knowledge that can be considered in those two venues. So I have done my best to consider each one as a separate matter.
Q. Okay. And you've done -- you've tried to segregate the information that might be involved in one matter versus the other and use the information for the appropriate matter?
A. I probably used it in a -- say it in a slightly different way. But my intent was to basically follow the rules for each of the two matters in terms of what information could be used and what could not.
Q. Okay. If we turn to paragraph 10 of Exhibit 1039, please.
A. I'm sorry. Which exhibit is that one now?
Q. Your report, 1039 -- or your declaration.

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I'm sorry.
You see that a section with the heading "Claim Construction"?
A. I do.
Q. And in paragraph 10 there, you describe that you've been advised that the PTAB has construed the claims of the patents in suit in a particular way.
Do you see that?
A. I do.
Q. And you say that that -- that PTAB's construction encompasses both palliative and curative treatments of the various dry eye conditions?
A. To give you a precise answer, I'd prefer to have the actual institution decisions in front of me.
But off the top of my head, to the best of my recollection, this is what they said.
Q. Okay. And -- and this is what you used in forming your opinions?
A. Correct.
Q. Okay. In forming your opinions, you have relied upon the PTAB's construction as the term -- in terms of the patent is encompassing treatments

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that are both palliative and curative in nature?
A. I have used the PTAB's construction in that manner.
Q. And you say at the bottom of the paragraph 11: "Any remedy that provides relief to the patient's dry eye/KCS symptoms would be considered by the patient as well as by the prescribing physician to demonstrate therapeutic efficacy."
Do you see that?
A. I do see that.
Q. And how does that relate, then, to the PTAB's construction regarding palliative and curative treatments?
A. That's a broad question. And I think there's been a lot of confusion in this between the various parties as to what these terms mean.
But applying -- in my mind, "curative" means that you give a treatment and that the condition is cured, i.e., it's gone, it's done, it's finished. It doesn't come back, which obviously does not apply to, frankly, any of these topical treatments. It may apply to some surgical treatments, for example, or in some of the other examples that I've given in the declaration.
What I was trying to say in the last

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sentence of 11 is that patient's concept of what's therapeutically effective and a doctor -- practicing clinician's concept of what's therapeutically effective is something that makes the patient feel better, patient's symptoms improve.

Q. Okay. And so that would include remedies that do not increase tear production, right?

A. Yes.

Q. Now, Dr. Calman, you mentioned in your declaration that there are, I guess, at least two types of tears that patients form: Basal tears and reflexive tears.

Do you recall that?

A. I think it's an oversimplification, but it's one that we use.

Q. Basal tears are produced by the lacrimal gland?

A. No, that's not right.

Q. Where are basal tears produced?

A. They're produced in the various lacrimal glands, plural.

Q. Okay.

A. Which includes the main lacrimal gland and the accessory lacrimal glands.

Q. And reflexive tears are also produced in

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the lacrimal glands?

A. Reflexive tears are produced in the lacrimal glands. And the extent to which they're produced by different types of lacrimal glands is an area that is not fully known.

Q. Okay. And reflexive tears are produced in response to an irritant to the eye?

A. Typically, yes.

Q. And basal tears are not typically produced in response to an irritant?

A. That's a pretty good -- yeah, that's a pretty close approximation, yes.

Q. Okay.

A. I -- to be very precise, I think -- you know, to be more precise, basal tears are still produced in the presence of an irritant as well. They're produced both in the presence and absence of an irritant.

Q. Okay.

A. And they may -- you know, basal, it's just -- it may vary by time of day and many other factors, so it's not like it's some concrete thing.

Q. But reflexive tears are produced only in response to an irritant?

A. Well, generally in response to noxious

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stimuli. And there are also emotional tears which some people consider a form of reflex tears and others consider to be a separate category.

Q. All right.

MR. KANE: It's been about an hour. Take a short break?

THE WITNESS: Sure.

(Off the record at 9:57 a.m. and back on the record at 10:10 a.m.)

BY MR. KANE:

Q. Now, Dr. Calman, in your practice, have you used the Schirmer tear test?

A. Yes.

Q. And you've used that to quantify tear production?

A. It's a rough clinical test that is proxy for tear production.

Q. And it provides a quantitative measurement of tear production?

A. Well, it's quantitative in the sense that it gives a number and has some limitations, some of which were discussed in my declaration.

Q. Okay. And that -- that test can be done with or without anesthesia?

A. Yes. There's actually at least three ways

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to do it, yes.

Q. What are the three ways to do it?

A. Without anesthesia, with a topical anesthesia drop in the eye, or with nasal stimulation.

Q. Okay. And is it true that Schirmer -- a Schirmer test without anesthesia measures both basal and reflexive tears?

A. Well, you know, all of these are somewhat oversimplifications. But to a first approximation, I think most clinicians would agree with that statement.

Q. If you perform that Schirmer test without anesthesia, is there any way to distinguish between the amount of basal tears being produced as opposed to the amount of reflexive tears being produced?

A. Generally by subtracting the Schirmer without anesthesia with all the caveats and limitations of that test.

Q. Okay. But running the Schirmer test without anesthesia alone, you can't distinguish between the amount of the basal tears produced and reflexive tears produced?

A. Pretty much what you're getting is the total of those two.

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Q. So as you said, then, to determine the -- or strike that.

In order to distinguish between the amount of basal tears and reflexive tears, you would run a Schirmer with anesthesia?

A. Well, to a first approximation and within the limitations and problems within all these -- problems with and limitations of all these tests, yes.

It says "limitation," but it's limitations.

Q. And, in fact, at paragraph -- if you want to look at paragraph 37 of your declaration, Dr. Calman.

A. Yes.

Q. The second sentence says: "However, the STT" -- and that stands for Schirmer tear test?

A. Correct.

Q. -- "with anesthesia, which is thought to measure the basal aqueous tear secretion."

You see that?

A. Yes.

Q. So that's consistent with what you discussed, that the Schirmer tear with anesthesia is thought to measure the basal aqueous

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tear production?

A. Well, with the caveats I've expressed. I mean, if I put every caveat in every sentence, the thing would be a hundred pages long.

Q. Okay.

A. But, yeah, I think we all understand these tests are imperfect, but they're common clinically performed tests that are reasonable proxies for these -- these entities -- these quantities.

Q. And if we turn to paragraph 34 of your declaration, the last sentence is what I want to focus on here.

A. I'm sorry. Which one?

Q. The last one.

A. Okay.

Q. All right. And you say there that "The basal tear production as measured by the STT with anesthesia is highly relevant to patient symptoms"?

A. Correct.

Q. Okay. And then you continue on to say: "Total aqueous tear production capacity as measured by Schirmer tear without anesthesia also provides important information regarding the severity of the patient's dry eye condition," right?

A. Correct.

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Q. And you understand that Restasis was the first drug approved by the FDA to increase tear production?

MR. MILLS: Objection. Form.

THE WITNESS: Well, I think that depends, again, semantically on what you mean by that. It's the first prescription drug that says on the label that it increases tear production, to the best of my knowledge.

BY MR. KANE:

Q. Okay.

A. That doesn't mean it's the first drug that increases tear production. And it doesn't mean it's the first eye drop that, including nonprescription eye drops, that increase tear production.

Q. Okay. But, again, my question was this: Restasis was the first drug that the FDA included a reference on the label as increasing tear production?

A. Well, not to be argumentative, that was not your question; this is a new question phrased differently.

And it was the first -- so what I'm alluding to is that there was at least one nonprescription drug that includes an ingredient

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that has been shown to increase tear production. But as far as prescription drugs that I'm aware that on the label it says "increases tear production," I'm not aware of any other than Restasis.

Q. Okay. Hand you, Dr. Calman, what's been previously marked as Exhibit 2008.

Have you seen this before?

A. Yes.

Q. And what is your understanding of what this document is?

A. This is at least a version of the FDA label for Restasis.

Q. Okay. Do you know when Restasis was approved first by the FDA?

A. Not exactly off the top of my head, but I think 2002.

Q. Okay. And were you using Schirmer tear tests in your practice in 2002?

A. Yes.

Q. Okay. And were you using it to measure tear production in 2002?

A. Tear production? Loosely speaking, yes.

Q. All right. Hand you what's been marked as Exhibit 1007, Dr. Calman.

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Are you familiar with this document?
A. Yes.
Q. And do you understand this is the Sall paper that's been referred to in the proceedings?
A. Yes.
Q. And what do you understand this paper to be describing?
A. This paper describes two Phase 3 pivotal trials of two different cyclosporin emulsions for treatment of moderate to severe KCS.
Q. Okay. If we look at the second page, page 632, you see the section called "Materials and Methods"?
A. Yes.
Q. And there's a section in the middle of the right-hand column called "Study Medications"?
A. Yes.
Q. And you would agree that this paper describes that there was a 0.5 percent and a 0.1 percent ophthalmic emulsion and vehicle that included cyclosporin A?
MR. MILLS: Objection. Form.
THE WITNESS: Well, the vehicle didn't include cyclosporin A. I would disagree with that part.

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BY MR. KANE:
Q. Okay. So there was a 0.5 percent CsA ophthalmic formulation?
A. Yes.
Q. And there was a 0.1 percent CsA ophthalmic emulsion formulation?
A. Yes.
Q. And then there was a vehicle?
A. That's what's described.
Q. Okay. And you'd agree that Sall does not describe what the vehicle used in the studies?
A. Not --
MR. MILLS: Objection. Form.
THE WITNESS: Not explicitly.
BY MR. KANE:
Q. Okay. It doesn't -- it doesn't tell you how much castor oil is used in the vehicle?
A. Not explicitly.
Q. Does it tell how much surfactant is used in the vehicle?
A. Not explicitly.
Q. Does it describe the number of surfactants used in the vehicle?
A. The what?
Q. The number of surfactants used in the vehicle?

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A. Let me look a second.
I don't see that explicitly stated.
Q. In fact, it says that the castor oil in water emulsions were a proprietary formulation?
MR. MILLS: Objection. Form.
THE WITNESS: It says the precise formulation is proprietary.
BY MR. KANE:
Q. Okay. So there's nothing in Sall that tells you what the components in that proprietary formulation consist of?
MR. MILLS: Objection. Form.
THE WITNESS: Well, not explicitly in black and white words on paper, no.
BY MR. KANE:
Q. Okay.
A. And, again, I think what we're talking about, if I'm assuming correctly when you say, "There's nothing that would tell you," I think you mean nothing to tell a person of ordinary skill in the art as of the priority date.
Q. Yes. That's what --
A. As of the priority date. I didn't hear what you said.

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Q. I was going to say, and so you've answered the questions with that understanding of my question?
A. Well, the questions that you've asked me about Sall, yes.
Q. Okay. So let's look at Figure 1 of Sall which is on page 635.
A. Yes.
Q. And this shows the results of the study formulations with respect to corneal staining.
Do you see that?
A. Yes.
Q. And what does corneal staining indicate to a physician?
A. Well, typically with corneal staining, most of the time you're using fluorescein, F-L-U-O-R-E-S-C-E-I-N. And basically you're instilling a fluorescein solution or using a fluorescein impregnated test strip to instill a small amount of dye in the eye. This dye has different colors depending on its concentration and depending on the underlying tissue, but typically it's orange.
But if it adheres to devitalized spots or spots that are what we call epithelial defects on

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the cornea, you will see a green glow or a green spot when you illuminate it with cobalt blue light. So it's a way of staining or identifying devitalized or denuded, D-E-N-U-D-E-D, areas of the cornea.

Q. What is the clinical significance of identifying those areas?

A. It's a proxy for basically an unhealthy corneal or stressed epithelium, which is the outer layer of the cornea, which is seen in various dry eye conditions and other types of -- many other types of eye conditions.

Q. Okay. But it provide a measure --

A. I'm sorry. I'm just looking at the transcript here.

It's a proxy for basically an unhealthy corneal epithelium, E-P-I-T-H-E-L-I-U-M.

A proxy for -- maybe I shouldn't look at this.

Q. Does it provide a measure of tear production in the patient?

A. Not directly.

Q. Okay. And at six months, the 0.5 formulation was found to have been statistically significantly better than vehicle?

A. I think you meant to say .05. And at six

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months, both the .05 and -- well, first of all, to state the data more completely for that time point, all of the solutions, including vehicle, showed a statistically significant improvement from baseline at all follow-up visits including Month 6.

And the -- I believe that's correct. Let me just double-check that.

Yes. "The improvement" -- and I'm reading from the text here. "The improvement in corneal staining was significantly greater in both CsA groups than the vehicle group (P less than 0.044) at Month 4, and in the CsA 0.05 percent group at Month 6 (P equals 0.008)."

And then it also says -- let's see. "There was also a trend (P equals 0.062) toward a significantly greater improvement in the CsA 0.1 percent group than the vehicle group at Month 6 (Figure 1)."

That's a quotation from Sall, page 635.

And just to put this in context -- well, I'll just stop there.

Q. Okay. And so what Sall, the portion you just read, states is that the P value at Month 6 for the 0.05 percent was less than .05, whereas the P value for the 0.1 percent formulation was greater

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than 0.5. -- .05 -- excuse me.

A. That is factually correct. I think the way that most clinicians would interpret that and that scientists would interpret that is that if you set the level of significance at P equals .05, which is a fairly standard level, with caveats that we could perhaps discuss later, then this achieved statistical significance for the .05 approached but did not quite reach statistical significance for the .1.

Q. Okay.

A. And if you look at the bar graph, that's illustrated graphically.

And, you know, if you -- if you look at the Month 4, you see a numerically better result with the .1, although the difference between the groups was not significant. And -- the difference between significant -- between the .05 and the .1 was not reported as being significant at any time point.

Q. But it's -- and at six months, the 0.05 percent was numerically superior to either -- to both the 0.1 percent and the vehicle?

MR. MILLS: Objection. Form.

THE WITNESS: Numerically superior, yes.

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Just as at Month 1, the .1 was numerically superior to the other two.

BY MR. KANE:

Q. Okay.

A. And I'm not asserting that there's a statistically significant difference between the .1 and .05 at Month 4, just that there is none at any of the other time points, including Month 6.

Q. Okay. And then if we look at Sall Figure 2, at three months the 0.05 percent formulation has a P value of less than 0.5 compared to vehicle, correct?

MR. MILLS: Objection. Form.

THE WITNESS: Well, I think you meant to say .05. And to put that in context, this is categorized Schirmer values with pitfalls that I discussed at length, as did Dr. Bloch, in our declarations, measured with anesthesia at the -- at a time point that -- and which was measured only at two time points in contrast to most of the other measures.

And at the time point that was not the key time point of six months as identified by Allergan, none of these emulsions achieve any significant change or seen -- none of these emulsions achieve a

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significant change compared to baseline at Month 3.

But there was a statistically significant difference between the .05 and vehicle but not between .05 and .1.

So I think it's -- it's a big issue and can't be capsulized in one sentence.

BY MR. KANE:

Q. And, in fact, at Month 3, as reported in Sall, there was a significant worsening in patients treated with vehicle, correct?

MR. MILLS: Objection. Form.

THE WITNESS: Well, again, I think you're taking that out of context because if you look -- it was a result that's very odd. Because if you look at the Schirmer's without, which measures both basal and reflex to a first approximation, all of the groups, including the vehicle group, showed a statistically significant improvement at all time points. And they measured four time points: 1, 3, 4, and 6.

So how do you explain that the Schirmer's without anesthesia was statistically significantly increased at the same time point as the Schirmer's with anesthesia categorized would significantly decrease.

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So as a person of ordinary skill, when I look at that, I'm thinking this is very strange. And I would like to see the underlying raw Schirmer data, which we asked for which the patent owner did not want to disclose. But I would be surprised if the -- if the raw data would bear this out, and I would be surprised if Allergan had bothered to test this at other time points whether this decrease would -- would bear out.

So I see that time point, that particular one data point out of this entire study where they studied 15 or 20 different efficacy variables, as an outlier. And -- and that is difficult to understand.

BY MR. KANE:

Q. Okay. But you agree that Schirmer states at Month 3 -- excuse me -- Sall states: "At Month 3, there was a significant worsening with the vehicle group (P equals 0.014) and a significant difference among the treatment groups"?

A. I'm looking for that in the text. Can you point me to where that is?

Q. Yes. It's above Sall Figure 2 there, middle of the first paragraph. Starts off "At Month 3."

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A. Yes. So, as I said, I can read -- of course, I can read that text there. And as a person of ordinary skill accustomed to reading scientific papers, I'm very troubled by this use of categorized Schirmer value, especially with these very broad categories and especially when changes -- small clinically insignificant changes up or down from baseline may have unpredictable effects on the score.

For example, if you had a Schirmer of 3 and you're in that Category 2, if you have a .1 millimeter decrease in Schirmer, that's going to show up as one unit decrease. If you have a 2.9 or even a 3-millimeter increase, it's not going to show up as a change at all.

So it's a very strange way to obscure -- well, to put an additional layer from the original data to what's being reported graphically here, that I don't understand why they did it. At least I don't agree with why they did it. And I think creates data points that just don't make sense in the overall context, particularly the Schirmer's without anesthesia, which showed an increase at all time points, four different time points with the vehicle.

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So how do you explain that? And the authors couldn't and didn't. They didn't make any attempt to explain that.

Q. Okay. But, again, my question is: Sall reports what it -- that there was a -- let me just read it.

"At Month 3, there was a significant worsening with the vehicle group (P equals 0.014) and a significant difference among the treatment groups, with CsA 0.05 percent group significantly greater than the vehicle group (P equals 0.009)."

Do you see that?

A. I do see that, and I think I agree that I read that there. I just don't think that's the end of the analysis as a person of ordinary skill.

Q. Okay.

A. I agree that that sentence appears in the text there.

Q. Okay. But you are choosing to reject that sentence?

A. Well, it's not a matter of the choosing. It's a matter of applying the -- you know, applying the rest of the data set and other relevant data sets and my knowledge in reading and understanding clinical and scientific trials. I think it's an

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outlier.

You know, I -- we -- we do use .05 P value. We use it a lot. It's a convenient P value. It's appropriate for a wide variety of tests, but it's not perfect.

And, you know, there is a concept -- there's a -- there's a concept called the Bonferroni correction, B-O-N-F-E-R-R-O-N-I, and other similar corrections which basically say when you're looking at 50 or 100 or 200 data points, some of them are going to come up as apparently statistically significant changes just by random chance.

And, you know, if I have 20 types of jelly beans -- 20 different colors of jelly beans, and I distribute them to people with cancer, one of those 20 is probably going to show statistically significant effect in curing cancer. Does that mean that grape jelly beans cure cancer? Probably not. If you repeated the test, you would probably not get that result.

So, as scientists, we see this come up all the time. And so you look at and say that doesn't make sense physiologically, it doesn't make sense in the context of the rest of the data set, doesn't make sense in the context of other studies, and it

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can be explained as the fact that you're measuring a bunch of variables.

It's as if your doctor ordered a panel of 100 blood tests. Probably five of them are going to come back abnormal. If you retest them, they may not be abnormal but just on the basis of random chance.

Q. Okay. You would agree -- and in this case, the P value compared between the 0.05 group and the vehicle at three months is .009.

Do you see that?

A. I see that. I'm not -- I'm not -- I haven't done my own calculation, but I'm not questioning their calculation.

Q. Right.

A. I'm just applying -- I'm putting it in context, and I won't repeat that whole last paragraph that I said.

Q. Okay. So that's far below the P value of .05, true?

A. Well, it's -- yeah, it's .014, which is less than .05.

Q. I was actually pointing to the second P value, .009.

A. .009 is also less than .05.

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Q. At six months, the vehicle results shown in Schirmer tear -- excuse me -- in Figure 2 also show that the vehicle group was below baseline?

A. Not to a statistically significant value.

And, again, at the six-month time point as well as, just as at the one-, three-, and four-month time points, vehicle showed a statistically significant increase in baseline on Schirmer's without anesthesia, which measures total tear secretion ability. And not only that, there were no differences, no statistically significant differences between any of the formulations at any time point for Schirmer's without anesthesia.

So, number one, I'd like to see the raw Schirmer data with anesthesia, both with and without, but especially with.

And, number two, nobody has explained to me, either Sall and their co-authors, nor any of Allergan's experts, exactly how it is physiologically that supposedly this vehicle increases total tear production at the same time as it decreases basal tear production. That makes no sense. You know, it just doesn't make any sense based on anything that we have that we know.

Q. Okay. But you agree with what's reported

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in Sall Figure 2?

MR. MILLS: Objection.

THE WITNESS: Well, I think I've answered that. I've tried to. I've explained that I can read the numbers on the page and I can put them in context, and that's what I've attempted to do.

BY MR. KANE:

Q. Okay.

A. Well, you know, the other thing is -- well, I'll just leave it at that.

Q. And you agree that the data in Sall Figure 2 shows that the 0.5 is numerically superior to both the 0.1 percent formulation and the vehicle at six months?

A. Well, I -- "numerically superior" is a little bit of a loaded term. It is not statistically significantly different.

The number, the average number, the mean is higher. All of these are very small changes. But the number -- the change is slightly higher for the .05 on this particular time point.

Q. You mentioned earlier that these are the categorized Schirmer scores, correct?

A. Yes.

Q. Do you know if the FDA relied upon

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categorized Schirmer scores in approving Restasis?

A. So, again, using the available data for the IPR, I have not seen -- the only thing I have seen that is responsive to that question is -- actually, let me just double-check one other thing here because I don't think there was a reference to the FDA in here.

So I don't think there's anything in Sall that refers to the FDA.

The label actually uses a different -- different set of data or a different analysis of the data. It's not clear from, again, just using the documents available for the IPR.

But what they are looking at -- let me find the correct part of this label -- is they're looking at a 10-millimeter increase in -- here it is. Page 5 of the FDA label.

"Restasis demonstrated statistically significant increases in Schirmer wetting" -- W-E-T-T-I-N-G -- "of 10 millimeters versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation."

Now, that's a little different from -- that's a lot different, actually, from Sall because

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it's not categorized, it's millimeters, which is how we as clinicians measure and interpret and read studies about Schirmer's. So it's not clear from...

And then the vehicle -- sorry. "This effect was seen" -- I'm quoting: "This effect was seen in approximately 15 percent of Restasis ophthalmic emulsion-treated patients versus approximately 5 percent of the vehicle-treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal" -- P-U-N-C-T-A-L -- "plugs."

So it doesn't mention categorized, and it does mention Schirmer. And whether this patient population is the same as the patient population in Sall is not specified in the available documents.

And I think that's the only reference to Schirmer, but let me just double-check that.

So that is the only reference to Schirmer that I'm seeing just in rapidly skimming this FDA label.

Q. Okay.

A. If there are others, please point them out.

Q. So, as you sit here today, you don't know whether the FDA relied on any of the Phase 3 data

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that related to categorized Schirmer tests -- categorized Schirmer values in approving Restasis?

MR. MILLS: Objection. Form.

THE WITNESS: I want to be careful here because I have been shown information in the district court case which is subject to protective order. And I've also seen some materials in the district -- some FDA documents in the district court case which may not be subjected -- subject to the protective order but which I have not considered for the IPR because I'm not sure that they were available to a POSA, P-O-S-A, as of the priority date. So I want to be careful in answering that question.

Using the data set that -- that we've identified here -- and particularly the only FDA communication that I've identified is the FDA label -- there's nothing that suggests that they considered categorized Schirmer value.

If you want me to go into information that I may be aware of from the district case, I would be very -- I think I would be very cautious about doing so.

BY MR. KANE:

Q. Okay.

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A. I'm looking at the transcript. It says "to oppose a POSA." It supposed to say "to a POSA," P-O-S-A.

Q. Is it your understanding that unexpected results can only be shown by data that was available to a POSA as of the priority date?

MR. MILLS: Objection. Form. Foundation.

THE WITNESS: I think that's a legal question, not a -- not a medical or scientific question. And so I'm reluctant to give a definitive answer other than to say that what I have considered in my declaration is the information that has either been -- that was either clearly available to a POSA at the time of the priority date or that has been introduced and permitted by the PTAB.

BY MR. KANE:

Q. You don't have an opinion as to what information can be used from a legal perspective to show unexpected results?

A. I don't have a definite enough understanding of that topic to express an opinion other than what may be in my -- let me just look at my...

You know, Dr. Amiji may have addressed that as well because he had some information about

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the legal framework in his -- let me look at mine first.

I see in Dr. Amiji's declaration, paragraph 29, it says: "The conclusion of obviousness must be firmly based on the knowledge and skill of a person of ordinary skill in the art at the time the invention was made."

And there's a discussion of secondary considerations in paragraphs 32 and 33 which do not specifically address or answer that -- your question.

The paragraph 34 also addresses the time frame.

And let's see. One more place.

I need a minute to think.

I -- I'm thinking that in reading the Schiffman and Attar declarations -- and, again, although I'm somewhat reluctant to offer an opinion that might verge on being a legal opinion -- my understanding is that they offered their declarations, which I do not have in front of me, stating that there was new data to indicate that the -- the claim formulation exhibited unexpected results.

Now, as it happened, the new information

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that they offered was actually old information from before the priority date. But the fact that they offered supposedly new information would suggest to me that at least Allergan's counsel was of the opinion that information after the priority date could be admissible for the purpose of unexpected results.

But I say that just as a piece -- as a data point, not that I'm expressing a conclusive legal opinion on that because I'm not.

Q. Okay. So the record's clear, you've been looking at the declaration of Dr. Amiji?

A. Yes, Amiji.

Q. Is that marked as Exhibit 1002?

A. It is, yes. This is actually -- yes, it is.

Q. I see you've brought some other documents. What other documents do you have with you?

A. I also have my declaration and Dr. Bloch's declaration. And then you handed me my CV, the FDA label, and Sall.

Q. Okay. What's --

A. And another copy of my declaration.

Q. What's the exhibit number of Dr. Bloch's declaration?

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A. That is Exhibit 1040.

Q. If you'd turn to paragraph 77 of Dr. Amiji's declaration for me.

A. Yes.

Q. And you see there's -- the second sentence of that paragraph says: "At six months of treatment, Figure 2 in Sall depicts a negative change in Schirmer value (indicating worse dry eye disease/KCS) and positive changes (indicating improvement) for both CsA treatments, with the CsA 0.05 percent treatment having an average change in Schirmer score more than one standard deviation higher (better) than the CsA 0.1 percent treatment."

Do you see that?

A. I do see that.

Q. And do you agree with Dr. Amiji's interpretation of Sall Figure 2?

A. Well, it's a literal -- it's a literal statement that is not factually wrong.

The context that I would add in addition to what I stated a few minutes ago is that -- because, you know, there is no statistically significant difference between the .01 -- the .1 and the .05, and that the actual changes in Schirmer score, which is about .3 to .4 units, those are very

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small and potentially, you know, either very mildly clinically meaningful or not clinically meaningful.

So literally speaking, I agree with his statement.

Q. Okay.

A. You know, I think, looking at it -- I'm sorry. Looking at it more closely, I'm not sure that he's demonstrated that it's more than one standard deviation higher. I don't know that you can do that just by looking at the graph.

Q. So you disagree with Dr. Amiji's statement?

A. Well, I don't -- I don't -- I haven't done a statistical analysis, and I don't know where he got that conclusion. So I'm not agreeing or disagreeing; I'm just saying I don't know for sure if that is correct.

Q. Okay. If we look at Sall on page 637, please.

And there's a paragraph in the middle of the page. It begins "This study."

A. Uh-huh.

Q. Do you see that?

This paragraph is talking about improvements in categorized Schirmer value obtained

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with anesthesia?
A. Yes.
Q. And it says -- the concluding sentence says: "Consequently, the results presented here suggests that the CsA treatment is affecting baseline tearing, not reflexive tearing."
Do you see that?
A. I see that.
Q. Okay. And do you agree with that interpretation of Sall?
A. It's -- it doesn't explain all of the data. I -- I don't understand how, for example, if -- you know, again, I think there's some -- there's some issues with the data set, particularly the three-month figures for the .1 percent. Why would it go down at three months and go up -- why would the, quote/unquote, basal the category Schirmer with anesthesia go down at three months when the categorized Schirmer without anesthesia goes up at the same time point? That would suggest basal tearing went down and reflex tearing went up. And how do you explain that?
And similarly -- and then how do you explain that that's not -- you know, that that's also the effect with the castor oil at three months?

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So, you know, I think they're making this conclusion, and they probably had some access to the raw Schirmer data which we do not have in this article. So I -- I think the data set raises some questions in addition to the sort of pat answer.
And the other thing that I would say is that they have not given us any actual numbers for Schirmer's without anesthesia. So it may be that cyclosporin is affecting both baseline and reflexive tearing, but they have not shown their work so we don't know. We just have this sentence.
And -- you know, again, I think if we could get our hands on the NDA actual data in millimeters, which is the way the data were collected and the way that the clinicians used the test, it might clarify some of these apparent disparities.
Q. Okay. But you do agree that the authors of the paper reached the conclusion that the CsA treatment is affecting the baseline tearing and not reflexive tearing?
MR. MILLS: Objection. Form.
THE WITNESS: That's one of the things that they say. They say a lot of things. But that sentence does appear in there.

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BY MR. KANE:
Q. Okay. All right. Let's look at Figure 3. And this is measuring change from baseline in blurred vision.
Do you see that?
A. Yes.
Q. And how do you measure blurred vision in patients with dry eye disease?
A. So -- well, how do I measure it or how did they measure it?
Q. How did they measure it?
A. Well, they measured it, at least on this particular one that they're reporting, it appears to be a subjective patient-reported zero to 4 scale. It was one of many, many subjective symptoms that they measured, including -- and I reviewed them at length in my declaration.
So this is only one of a lot, including OSDI, subjective facial expression rating scale, stinging and burning, itching, sandiness and grittiness, blurred vision, dryness, light sensitivity, pain, soreness, investigator's global evaluation, patient use of artificial tears, number of artificial tears per day. Number of days per week that they did not use the tears.

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So there's a lot of these subjective measures. They chose to emphasize this one in the graph, but there were a whole bunch of them and...
So that's, you know -- and as far as I can tell from what's provided in the "Materials and Methods" section, this was the patient self-reported zero to 4 for scale, "Doc, my eyes aren't blurry at all. Doc, my eyes are really blurry." That's a 4 presumably.
I mean, how do we measure it in the clinic? We determine a best corrected visual acuity.
Q. Have you ever been involved in the design of a Phase 3 study?
A. You know, I was certainly involved in discussions with investigators who were doing Phase 3 studies, and I don't remember exactly at what stage.
Q. Have you ever been involved in discussions with the FDA in design of a Phase 3 study?
A. Directly with the FDA, no.
Q. Okay. You would agree that, in Figure 3, the 0.05 percent formulation is numerically superior at all time frames?
MR. MILLS: Objection. Form.

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THE WITNESS: Well, if you put it in context, this one of more than a dozen subjective measures shows numeric superiority showing small changes of .3 to .5 units on a zero to 4 scale at all time points.

BY MR. KANE:

Q. Okay. Is change baseline -- excuse me.
Is change in blurred vision a measure of increased tear production?

A. Well, you know, blurred vision can be caused by a lot of things. However, certainly one of many factors that can affect blurred vision is tear production. But it is, at best, an indirect measure.

Q. Does it provide any sort of quantification of increased tear production?

A. I think that would be a stretch.

Q. Does that mean no?

A. I think that would be a stretch.

Q. What do you mean when you say it would be a stretch?

A. Well, I think that it would be a stretch to say decreased blurred vision implies increased tear production, although in many cases, many patients -- increased tear production across -- as a

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blanket statement, although that may be true for some of these patients.

Q. And let's look at Figure 4 in Sall.

A. Yes.

Q. This is change in baseline in average daily use of artificial tears.
Do you see that?

MR. MILLS: Objection. Form.

THE WITNESS: Well, there are some issues with this graph that maybe we can talk about. It does say that, yes.

BY MR. KANE:

Q. Okay. And is a change in baseline in average daily use of artificial tears a direct measure of increased tear production?

A. Not a direct measure, no.

Q. Okay. Okay. Is it a -- well, is it a stretch again?

A. Well, it's a less of a stretch because there are a lot more things that cause blurred vision than there are that cause people to use their tears more often.

Again, it's not a direct measure but, generally speaking, if -- if you have a group of people who have lower tear production, they will

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typically use their artificial tears more frequently.

Now, that said, this graph, I believe, was disavowed because it appears to be a copy of Figure 3, which was probably just a -- an error in production of this paper.

Q. Yeah. Okay. But --

A. But I think I've answered your question too.

Q. Yes. Exactly.
I think in paragraph 58 of your declaration, Dr. Calman --

A. I'm going to ask that we take a break very soon.

Q. Why don't we just take it right now.

(Off the record at 11:07 a.m. and back on the record at 11:21 a.m.)

BY MR. KANE:

Q. All right. I think we were going to paragraph 58 of your declaration, Exhibit 1039.

A. Yes.

Q. Okay. And we -- you go through a list of the parameters that were considered in the Allergan Phase 3 study disclosed in Sall.
Do you see that?

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A. I go through a variety of the efficacy outcome measures, yes.

Q. I think we've already talked about the corneal staining in connection with the Figure 1, so I'll move past that.
The next one is conjunctival staining. Would you agree that that does not directly measure increased basal tear production?

A. Well, it's a very important outcome for dry eyes because it's a measure of devitalized conjunctiva at the ocular surface.

And so, although there may be a correlation with basal tear production, it is not a -- it is not a direct measure of basal tear production.

Q. Okay. And then we've already talked at length about Schirmer tear with anesthesia and Schirmer tear without anesthesia. So we can move past that.
Blurred vision, we've talked about.
Dryness. Would you agrees dryness is not a measure of increased basal tear production?

A. Well, first of all, dryness here, as I understand it reading "Materials and Methods" section is a patient's subjective self-assessment of

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how dry their eyes feel. And, again, I think there is a correlation between that and basal tear production in this type of patient, but it is not a direct measure of basal tear production.

Q. Next listed here is a sandy, gritty feeling.

Do you see that?

A. Yes.

Q. And would you agree that a sandy, gritty feeling is not a direct measure of increased basal tear production?

A. It would be my same answer. This is, again, a subjective self-assessment of sandy and gritty feeling in the patient's eye. And although it's an important symptom and it tends to correlate with basal tear secretion in this type of patient, it is not a direct measurement of basal tear secretion.

Q. Next is itching.

Do you see that?

A. I do.

Q. And would you agree that itching is not a direct measurement of increased basal tear secretion?

A. So similar answer. I think this is a

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common symptom in patients with dry eye and other ocular surface conditions, including blepharitis, B-L-E-P-H-A-R-I-T-I-S.

And in this type of patient, it does tend to correlate with basal tear secretion, but it is not a direct measurement of basal tear secretion.

Q. Next is photophobia.

Do you see that?

A. Yes.

Q. And would you agree that photophobia is not a direct measurement of increased basal tear production?

A. I would say that photophobia is a less common symptom seen in some dry eye patients and also seen in many, many other types of conditions. And that although this in type of patient there may be some correlation between photophobia and basal tear secretion, it is not a direct measurement of basal tear secretion.

Q. Next is burning and stinging.

Do you see that?

A. I do.

Q. Would you agree that burning and stinging is not a direct measurement of basal tear secretion?

A. I would say that these are important and

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common symptoms in patients with various dry eye conditions as well as some other ocular conditions. And that although they do tend to correlate with basal tear secretion in this type of patient, they are not a direct measurement of basal tear secretion.

Q. Next is pain.

Do you see that?

A. I do.

Q. And do you agree that pain is not a direct measurement of increased basal tear secretion?

A. So pain, I would say, is also an important symptom in this type of patient, although it can be seen with many other types of ocular conditions. In my experience, this is -- this does correlation well with basal tear secretion but it is not a direct measurement.

And this is one of the parameters where the .1 percent performed numerically better than the .05 percent.

Q. Okay. Next is the physician's subjective assessment of global response to treatment.

Do you see that?

A. I do.

Q. And would you agree that that measure is

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not a direct measure of increased basal tear secretion?

A. So this -- now we're shifting to the physician's assessment. And although it says "subjective," it is the physician's overall impression as defined in more detail in the "Materials and Methods" of the patient's response overall to treatment.

And in my experience this would correlate fairly well with basal tear secretion in this patient population with this type of problem, but it is not a direct measurement of basal tear secretion.

I would point out again this is another area of where the .1 percent had some numerical superiority.

Q. And we've talked already about artificial tear use. We can skip that.

The next then in the listing is Ocular Surface Disease Index.

Do you see that?

A. I do.

Q. And would you agree that Ocular Surface Disease Index is not a direct measurement of basal tear secretion?

A. The Ocular Surface Disease Index, as I

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understand it, is a patient questionnaire with a variety of questions relevant to patients with dry eye symptoms. And although in my experience it does correlate well with basal tear secretion in this patient population, it is not a direct measurement of -- of basal tear secretion.

Q. And then finally, subjective facial expression rating scale.

Do you see that?

A. I do.

Q. Do you agree that the subjective facial rating scale is not a direct measurement of increased basal tear secretion?

A. So the subjective facial rating schedule is basically a patient self-rating of whether they're happy or sad according to their symptoms related to dry eye. And although there is some correlation, in my experience, between this type of self-evaluation and basal tear secretion, I would not say that it is a direct measurement of basal tear secretion.

Q. If we look at -- take a quick look at Exhibit 2008.

A. I'm not sure what that is.

Q. It's the FDA label for Restasis.

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A. Okay.

Q. If we look at what we had seen previously on page 5.

Do you see that?

A. Okay. I'm on page 5.

Q. Okay. Isn't it true that the FDA relied only on the Schirmer wetting of greater than 10 millimeters in describing the studies that they base their approval upon?

MR. MILLS: Objection. Form.

THE WITNESS: You're asking me to get inside the mind of the FDA which I can't -- cannot do with this one paragraph. This is a piece of information that they cite. And, again, I want to be careful not to get into information that is not within the scope of a POSA at the priority date.

However, there are some exhibits, other exhibits in evidence, where they talked about the failure of Restasis to be approved in 1999 and the relative success of the vehicle. And, you know, ultimately they got approved in 2002, presumably -- again, as a POSA in 2003 looking at this, I would say well presumably, the FDA was impressed by this 10-millimeter increase even though only a small minority of Restasis-treated patients got it and an

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even smaller minority of vehicle patients -- treated patients got it.

But, you know, what I do know is that the FDA looks at a large body of information when they make a decision on approval, and it's generally not just one thing. They look at a variety of parameters to determine whether a drug is safe and effective.

And although I cannot get inside of the mind of the FDA and I'm not relying on any materials that would not have been available through a POSA at that time, I would be surprised if that were the only piece of information that they considered. Although they cite it, so I presume it was a material aspect that they considered.

BY MR. KANE:

Q. Okay. We've just gone through this sort of laundry list in paragraph 58 of other efficacy measures.

Does the FDA mention any of those efficacy measures on page 5 of 2008?

MR. MILLS: Objection. Form.

THE WITNESS: Well, you're asking me is it on the label, and this is a very brief document.

So in this particular document -- I can

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read as well as you can -- it doesn't state anything about those, at least on this page 5. If you'd like me to go through the rest of it, I will.

BY MR. KANE:

Q. No, that's fine. Thank you.

A. Again, I don't think that's the sum total of what the FDA reviewed.

Q. If we go to paragraph 67 of your declaration, Dr. Calman.

A. Uh-huh.

Q. In this section sort of 67 through 71 --

A. Yes.

Q. -- you attempt to infer from values from Sall Figure 2.

Do you see that?

A. Well, that's not quite right.

Q. Well, that -- for instance, paragraph 68, above the graph there, you say: "These putative conversions are meant to be used in inferring differences from baseline"?

A. Rather than -- yes. "These putative conversions are meant to be used in inferring differences from baseline, rather than interpreted as literal conversions (which would ultimately require that Allergan provide the raw data)."

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That's what it says.
Q. Okay. And have you ever done this sort of inferring differences in analyzing scientific data before?
A. Sure.
Q. Have you published any papers where you've done such a thing?
A. No, not that I can recall. I may have. Many of my papers were published many years ago. Scientists interpret data all the time.
Q. I'm talking about specifically this sort of interpretation where you're taking a bar chart and concluding and changing it into these conversions to infer differences from baseline.
A. Doctors and scientists convert things all the time, even as simple things as converting different units and different scales. You know, for example, the Stevenson paper used a zero to 3 scale for corneal staining, and the Sall paper used a zero to 5 scale.
People are constantly coming up with new classification schemes and scales and gradings and cutoffs for all kinds of parameters throughout medicine and science. So this is a common issue that we run into.

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And the attempt -- again, I wanted -- I qualified it in the text. I'm not saying this is a literal conversion. This is an attempt to understand what these arbitrary units mean, especially since it's sort of a strange way and uncommon way to, you know, to treat Schirmer data.
So they're reporting certain changes. Their -- I think most of the reporting was done in the form of change analysis. I'm trying to understand what do these changes mean, how big are they, and are they clinically material.
Of course, if I had the raw data which we asked for repeatedly, it would have been much easier to use the raw data but we couldn't get it.
Q. Have you ever seen any papers where there's been a conversion -- putative conversion published like this?
A. I'm sure I have. I can't give you chapter and verse. I haven't seen -- I haven't for Schirmer's because I don't believe -- I can't recall any papers that I've seen other than Sall and Stevenson where categorized Schirmer's were reported.
Q. Okay.
A. But in other areas of science, sure.

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Q. Can you identify any of those papers today?
A. I haven't thought about it. I haven't been asked to opine on it. It's not something I've given any thought to. You know, there's so many -- I'll probably think of 10 examples when I leave but...
Q. If you look at -- if we go back to paragraph 67, please.
A. Okay.
Q. There's a description there. It says: "Sall Figure 2 demonstrates the average change in Schirmer score experienced at Month 3 was actually very small for both CsA groups with patients in the 0.05 percent CsA group experiencing a plus 0.09 change in Schirmer score" -- "categorized score" -- excuse me -- "versus minus 0.10 for patients in the 0.1 percent CsA group."
Do you see that?
A. I see where it says that.
Q. Okay. And did you determine those numbers?
A. Well, I cite to Bloch actually. I can eyeball it, but that's not a -- I wouldn't up come up with a precise number like that for my modeling.

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I was relying on Bloch, who has a methodology to determine that more precisely.
Q. And what do you understand Dr. Bloch did to determine those numbers?
A. I would be hesitant to put words in his mouth. But my understanding is it involved magnifying the graph and measuring the height of the bars and standard deviation or standard error bars.
Q. And is that something that you have done in your analysis of peer-reviewed papers that you've reviewed previously?
A. I don't know if I've actually magnified them. I probably have from time to time just informally for myself to get a better idea of the numeric data when the data were not directly cited.
Q. Okay. And you think that you could measure to two decimal points using a magnifying glass and a ruler, I guess, of some type?
A. Well, that's a very broad statement. I think that would depend on a lot of factors.
Q. Okay. Well, let's look at Sall --
A. Incomplete.
Q. Can we look at Sall Figure 2?
Do you think you could measure those values to two decimal points?

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A. It's not a question I was asked to opine on; it's a question I've thought about. And so the best answer I can give you is maybe. If I were really to analyze that, I would probably, you know, need to do some additional research and -- you know, so I can't give you an answer other than maybe.

Q. Okay. Do you know how accurate graphs in the publications are?

A. Well, that's a very broad and very nonspecific question, so I can't give you a specific answer to such a vague question.

Q. Would you base a conclusion based strictly on measuring a graph in a publication?

A. Again, it's a very vague and broad question. It's an incomplete hypothetical.

And so in some situations, you might. Of course, all of this could be avoided if Allergan would produce the actual data.

Q. Okay. You relied on Dr. Bloch's measurements in this case, correct?

A. For that particular thing, yes.

Q. Yeah. So -- and that underlies your opinion, correct?

A. Well, to the extent that I relied on it in that particular part of my -- my declaration, yes.

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Q. So, in this case, you believe that Dr. Bloch's two decimal places is sufficiently accurate that you can rely upon it?

A. Well, hang on. First of all, I'm not sure where you're getting two significant digits, so I'm not sure I can accept the premise of your question.

Q. Well --

A. Which paragraph are we on?

Q. Paragraph 67.

A. So when you say -- okay. So the .09 has only one significant digit. .10 has two significant digits.

These are questions that I think you should be asking Dr. Bloch. Dr. Bloch is one of the most eminent biostatisticians in the world, is my understanding.

And so you're asking me to question his methodology. I think I'm the wrong person to ask those questions. I rely on him because of his expertise and stature, and if he says that he can determine these to that degree of precision and accuracy, I do not have reason to question him.

Q. And because of that, you felt comfortable relying on that in your analysis?

A. You know, I'm not -- again, to the extent

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that -- that we're even talking about those particular numbers in this particular part of my declaration, and, you know, frankly, I don't know why we're quibbling over this because even if there were a small error because of either the journal making an error or the -- or Dr. Bloch not being able to estimate with a certain degree of precision, my point in this is these differences are small. If you told me he was off by 50 percent, it wouldn't change my conclusion that these differences are small.

I don't care if it's one, two, or three significant digits. It wouldn't materially affect my conclusions.

Q. Okay.

A. And what I can provide that Dr. Bloch doesn't provide is the clinical context. And I can say that a difference of 1 or 2 or even 3 millimeters is not a big difference in Schirmer scores clinically. A difference of 10 is.

Q. Uh-huh.

A. And that's what I say in my declaration.

Q. Okay. And if we -- let's compare your table on paragraph 68 to Sall Figure 2.

And we see in Sall Figure 2 there's going

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to be a value of 3 assigned to all scores between 7 and 10 millimeters.

Do you see that?

A. I do.

Q. Okay. And then we compare your table. You have a score of 3 assigned to 7. You have a score of 3.25 assigned to 8. You have a score of 3.5 assigned to 9. And you have a score of 3.75 assigned to 10.

Do you see that?

A. Yeah. But the context, again -- I have to remind you -- is what I said at the outset of this analysis, is it's -- we read it into the record already -- that these putative conversions -- "These putative conversions are meant to be used in inferring differences" -- underlined "differences," I'm underlining it in my -- what I'm saying now -- "from baseline, rather that are interpreted as literal conversions (which would ultimately require that Allergan provide the raw data)."

Q. Uh-huh.

A. And Figure 2 is a different plot. I'm not saying that a Schirmer score of 2 is literally 3 millimeters.

I'm saying that if you're in that range of

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around 2 and you have a plus .1 putative difference, what does that equate to in terms of millimeters of change from baseline? And that's what I'm focused on.

And so I don't care if you arbitrarily adjust these and quibble a little bit over whether it's -- whether a score of 2 is 3 millimeters or 4 millimeters or 5 millimeters. It doesn't really materially affect my analysis because what I'm looking for is the difference between the baseline and post-treatment.

Q. But you agree that the values you've assigned are different than the values in Sall Figure 2?

MR. MILLS: Objection. Foundation. Mischaracterization.

THE WITNESS: Totally mischaracterizes what I said. I'm just going to defer to my previous answer.

These are -- the ranges were set up by this group of doctors, this group of investigators. What I'm trying to do is say how do these differences in arbitrary categorized units as a mean of a population translate to changes in actual Schirmer data in millimeters, which is how we do the

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test, on average as a means of these -- of data in these population groups.

So, in other words, we can quibble over whether they're going from 3 millimeters to, you know, 3.5 millimeters. I don't care if it's 4 millimeters to 4.5 or 5 millimeters to 5.5. We're still talking about small changes. That's the whole point of this investigation. I wouldn't have done this in the first place if Allergan had supplied the primary data, but they didn't.

BY MR. KANE:

Q. And, Doctor, you've said that multiple times. You understand that Mylan asked for that data from the patent office, don't you?

MR. MILLS: Objection. Foundation. Argumentative.

THE WITNESS: I understand that I requested it from WSGR counsel. And I'm not privy to the conversations between them and opposing counsel or the -- or the PTAB.

BY MR. KANE:

Q. Okay.

A. So I don't know exactly who did what or who said what. What I know is that I asked for the data and we didn't get it.

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Q. Okay. And I'll just tell you that the PTAB denied Mylan's request for the data. They didn't feel that you needed it.

MR. MILLS: Objection. Foundation. Mischaracterization.

THE WITNESS: Well, I'm not going to respond to that. It wasn't a question.

BY MR. KANE:

Q. I thought it might be interesting for you to know.

So let's try to kind of bear this out a little bit. Let's look at your chart again on 68.

So if you had a patient that went from a Schirmer score of 7 to 8, let's say. All right?

A. Yes.

MR. MILLS: Objection. Form.

BY MR. KANE:

Q. Okay. They, in Sall Figure 2, would be a 3, Category 3 patient, correct?

A. Yes.

Q. And they would be a Category 3 patient at 7?

A. Yes.

Q. And they would be a Category 3 patient at 8?

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A. Yes.

Q. And they would be a Category 3 patient at 9?

A. Yes.

Q. And a Category 3 patient at 10?

A. Yes.

Q. So they could actually have a 2- or 3-millimeter increase in their Schirmer wetting score, and they would still be the same categorized -- have the same categorized Schirmer score, right?

A. Unfortunately, that is correct. That is the way they, unfortunately, decided to set this up.

Q. Okay.

A. I think it's important to make a distinction between individual patients and large groups of patients.

Obviously in a large group of patients, the mean is going to be more -- if you do this categorization on a single patient, you're going to have a large disconnect between the actual values in millimeters and the categories. If you're looking at means of large numbers of patients, that will tend to decrease the lack of correlation between the categorized and the raw Schirmer's, although it's

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still an issue.
Q. Did you attempt to quantify the impact on individual patients -- on the fact that this was done on a means of patients in this case?
A. I'm not sure I understand the question.
Q. Well, I understood what you were trying to say, that if you look at means of large numbers of patients, you tend to decrease the lack of correlation, right?
A. In general, yes.
Q. Okay. What impact did the number of patients in this study have on that lack of correlation?
MR. MILLS: Objection. Form.
THE WITNESS: Yeah, I don't know of a way -- the method that I would be aware of to determine that would be to compare the actual raw data for individual patients with the actual means. And to do that data analysis, it could be done if you had each individual patient's data, both raw and categorized.
BY MR. KANE:
Q. Okay. So you can't do it based on the data in Sall Figure 2?
A. Unfortunately, no.

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Q. Okay. And so you can't do it with respect to your putative conversions that you've attempted to infer differences here?
MR. MILLS: Objection. Form.
THE WITNESS: Well, you -- I'm not trying to oversell this. I'm saying that this is an attempt to determine if the changes are small or large. And so I'm not trying to make any, you know, much more precise statement than that. But I think that this is useful in determining whether these are small or large differences on these mean populations. And in the absence of more fundamental data, it's hard to get more specific than that.
But I would say that the largest increase you can have and still remain within a category, the boundary condition, in this range is 3 millimeters.
So, you know, you can't have a 4-millimeter change that doesn't result in a change in category. And 3 millimeters or less, in my mind as a clinician, is a small difference.
Especially -- you know, Dr. Sheppard actually admitted this to -- the variability of Schirmer testing. And this was also brought out in the 1994 text, Smolin text, S-M-O-L-I-N, that I cited talking about the known variability of

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Schirmer testing. And in my experience, the variability is even worse with the Schirmer's with anesthesia because, if you think about it, when you put that eye drop in, it's hard to get all of that anesthetic eye drop out. The anesthetic eye drop itself sometimes causes some reflex tearing because it stings.
And so that's why I've been careful all along to say to a first approximation, Schirmer's with anesthesia reflects basal tearing because it's an imperfect test. And in my experience, it's more variable than the Schirmer's without. Because if you've got that eye drop left over in the eye, that's going to give you a few millimeters right there. You know, if you've got reflexive tearing because the patient's getting stinging from the aesthetic, that's going to potentially give you more millimeters there. Those can vary from day to day, you know.
It's -- it's -- so, you know, it's an imperfect test as it is, and you then put categories in and it makes it even more difficult to understand.
BY MR. KANE:
Q. You stated paragraph -- at the bottom of

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68, for instance, you say a change in categorized score of approximately .25 would equate to 1 millimeter.
Do you see that?
A. Correct.
Q. And how --
A. Well, no, it says 1.6 actually. Sorry.
The whole sentence says: "A change in categorized score of approximately 0.40 would be 8/5ths of the 0.25 required to increase 1 millimeter, or 1.6 millimeter." That's what it says.
Q. I was asking about the next section.
A. I'm sorry. The next sentence says: "And a change in categorized score of approximately 0.25 would equate to 1 millimeter."
Again, I'm not being literal here. I'm just trying to get an idea of the magnitude of the change in the population.
Q. But so we're clear on this. An individual patient can't get a change in categorized score of .25, right?
A. Strictly speaking, no.
Q. And you didn't do any analysis to determine what a change in average score on this

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patient population of .025 would mean, correct?
MR. MILLS: Objection. Form.
THE WITNESS: I disagree. I did the best -- you seem to be criticizing or quibbling with me for doing the best I can with the limited data set to try to put these into clinical context, and I resent that. I don't think it's appropriate.
If I had more data, I would have done a more complex analysis, but those data were not provided by whomever.
So, in my experience, the -- the best that we can infer from this data set is that, on average, a change of .25 in categorized Schirmer score in a population, on average, would equate to 1 millimeter on average approximately.
You know what? If we got the raw data and we did the analysis on the individual patients, maybe it's not 1 millimeter. Maybe it's a half a millimeter. Maybe it's 2 millimeters. It's not 8 millimeters. It's not 5 millimeters. It's hard to see how it would even be 3 millimeters.
BY MR. KANE:
Q. But you didn't do that analysis because you can't do the analysis?
A. Well, you're blaming me for the lack of

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available data to do a more full analysis, and I don't think that's fair.
Q. Okay. Would you feel comfortable standing up and presenting this analysis at a medical conference?
A. If I had to present this data at a medical conference, I would be deeply apologetic at the fact that whoever was providing the data to me had given me an incomplete data set.
And if for some reason I were presenting this -- let's say I was presenting some publication from a foreign country where I couldn't get any underlying data from the study participants. And I said, "This is the best I can do to translate this into raw Schirmer scores which you and I use in clinical practice. Please understand the limitations of this. This is not meant to be a literal conversion, and it has its limitations because we don't have the raw data set." But, yeah, I'm comfortable saying that what study shows is small changes in Schirmer scores.
Q. If we look at the paragraph 69, there's -- again, there's a lot of values in here. For instance, Schirmer score under the "Baseline" column on the top section, 1.94 to 2.11.

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Do you see that?
A. I do.
Q. And where did you get those numbers?
A. That was from Sall, I believe. Look at the -- let's see. Table -- let's see. That's actually in page 635 under "Schirmer tear test reporting baseline."
Q. Okay. And then what about the 2. -- if you go to Month 3, baseline plus .09? So that is just an addition?
A. Yes.
Q. Based on Dr. Bloch's measurements?
A. Yes.
Q. And then Month 6, baseline plus 0.39, was an addition based on Dr. Bloch's measurements?
A. Correct. I mean, obviously, I looked at the figure to verify that there was not a gross error, but yes.
Q. If you want to go back, Dr. Calman, and look at paragraph 77 of Dr. Amiji's report.
A. 77?
Q. Yes. Dr. Amiji.
THE WITNESS: And I note that the time now is 12:02.
MR. KANE: Do you want to take a lunch

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break?
THE WITNESS: I don't know if lunch has been brought in. I just note the time.
MR. MILLS: I expect that it has.
BY MR. KANE:
Q. You recall earlier we looked at a sentence in here where Dr. Amiji concluded that 0.05 percent treatment has an average change in Schirmer score of more than one standard deviation higher (better) than the CsA 0.1 percent treatment.
Do you recall that?
A. I also recall that I wasn't sure exactly where he got that number.
Q. Okay.
A. And I would also point out, I think that probably everybody knows that one standard deviation does not imply statistical significance.
Q. And --
A. He did write that.
Q. He did write that. And despite his statement to that effect, you look at the Sall Figure 2 and conclude, based on your analysis, that it is not a clinically significant change, correct?
A. Well, hang on a second. You're conflating a bunch of things here.

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Where's the statement that you're talking about with the one standard deviation?

Q. Bottom of page 33 in paragraph 77.

A. All right. Let me just read your question here.

Well, so, first of all, I think you're taking that one sentence out of context.

Allergan itself did the analysis and did not report a statistically significant difference between .05 and .1 at any time point with regard to any of the types of Schirmer testing.

And Dr. Bloch, in his own analysis, did not find such a statistically difference either. So one standard deviation is sort of, you know, neither here nor there. And even if you just take the raw values with all the caveats that I have stated repeatedly I attempted to do in the absence of the raw data, you come up with a difference, on average, of a 1-millimeter increase for the .1 percent and 1.6-millimeter for the .05 percent at Month 6. These are very small increases.

And as a cross-check on this, I note that although we don't have the complete raw data set, Dr. -- the FDA did indicate only 15 percent of the .05 percent CsA group achieved a 10-millimeter

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increase.

So obviously there are some patients who have more of an increase than others. There may be even some who had a decrease. But, on average, these are small increases with a small difference in the means between them. 1 millimeter or 1.6 millimeter. I can't even get a reproducible Schirmer test from day to day that's within 1 millimeter, and Dr. Sheppard admitted as much in his deposition.

Q. And so -- and the 1 millimeter and the 1.6 millimeter are based on your analysis of these inferred values, correct?

A. Correct. And if you think about it, again, as I said, if it were more than 3-millimeter difference on average, then on average you'd have at least one full category change.

So, you know, we can quibble over whether it's really 1, or maybe it's 1 1/2, or maybe it's 2, but it sure isn't 7 or 10.

MR. MILLS: Are we ready for lunch?

MR. KANE: Let's see.

Yeah. We can take lunch now.

(Whereupon the luncheon recess was taken at 12:05 p.m.)

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JULY 12, 2017 AFTERNOON SESSION 12:49 P.M.

--o0o--

BY MR. KANE:

Q. Okay. Let's turn to paragraph 73 of your declaration, Dr. Calman.

And the first sentence there refers to the Restasis label that we've discussed earlier, Exhibit 2008. And as we've seen, it mentions an increase in Schirmer wetting of 10 millimeters or greater.

Do you recall that?

A. I want to look and see if -- did you say 2008?

Q. Exhibit 2008, yes.

A. Oh, okay.

I do recall that.

Q. And then the second sentence of paragraph 73, you're stating that, in your view, a Schirmer tear test with anesthesia, increase of greater than 10 millimeters, is clinically meaningful and material, right?

A. Well, I didn't say without anesthesia or with anesthesia. But I would agree that, in general, an increase in Schirmer test of 10 millimeters is clinically meaningful and material

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in an individual patient, yes.
Q. Okay. I mean, with respect to the FDA label where it says "STT," do you understand that to be with or without anesthesia?
A. Let me go back. I believe that was on page 5.
Q. Correct.
A. It does not state.
Q. Would it make a difference if it was with or without anesthesia?
A. Well, theoretically, it might. I'm trying to envision a situation where all the -- you know, in theory, if it were all reflex only and you had a patient with very low basal Schirmer score and a theoretical drug increased only the reflexive aspects of tearing with all the caveats we discussed earlier regarding testing methodology and oversimplification, in that situation, the patient still might be symptomatic from dryness. But I think that would be rather unusual.
So, you know, again, to a first approximation, in general, if you had an increase in Schirmer score of that magnitude, whether with or without anesthesia, it would likely correlate with material improvement of the patient's condition.

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Q. Okay. And that's what you say in paragraph 73, is that it's generally clinically meaningful and material?
A. In fewer words with less nuance, but yes.
Q. All right. And then at the end of paragraph 73, you say -- and can read the whole paragraph, if you need to. But you say: "Based upon my review of those declarations, exhibits they rely upon, I have seen no clinical evidence that the 0.5 percent formulation works better or works differently than the 0.1 percent" -- "0.05." I might have said that wrong. I keep saying that wrong. Let me start over.
You say: "I have seen no clinical evidence that the 0.05 percent formulation works better or works differently than the 0.1 percent CsA formulation evaluated in Sall."
Do you see that?
A. I do see that.
Q. And is that -- is it fair to say that that underlies your entire opinion that there are no unexpected results between the 0.05 percent formulation and the 0.1 percent formulation?
MR. MILLS: Objection. Form.
THE WITNESS: Well, first of all, to be

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clear, I mean what I'm saying here is not that there is no individual piece of data that looks like there's a difference in favor of .05, you know, for that matter in favor of .1. But looking at my review of the declaration and the exhibits and thinking about that totality of data, I've seen no clinical evidence that, in general, that .05 works better or works differently.
I think that is an important basis of my conclusions. I'm not sure I would agree that it underlies the totality of my conclusions.
BY MR. KANE:
Q. Okay. And at the end of paragraph 74, you cite: "There is, in fact, no evidence that the 0.05 percent CsA formulation increased tear production, more than the 0.1 percent CsA formulation," correct?
A. That's what I wrote.
Q. And that's your understanding?
A. Well, yeah, you know, again, taking into account all the other arguments in my declaration and the underlying data and other materials.
Q. If there were evidence that the 0.05 percent CsA formulation increased tear production more than 0.1 percent CsA

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formulation, would that change your opinion?
A. Well, it would depend. I mean, if you showed me that it increased tear production a little bit more, you know, I don't think that would change my overall conclusions.
If you showed me that it increased it but it was -- the increase was not statistically significant, that probably would not change my opinion.
If you showed me that it did increase it by a little bit but not an amount that I would consider clinically material, that would probably not change my opinion.
If the increase were by a methodology that was flawed, that would probably not change my opinion.
But if you came to me with a well-controlled study with good data that showed that, say, the mean, hypothetically, you know, the mean increase in Schirmer was 7 or 8 millimeters more than the .05, than the .1, and that that was statistically significant and that that was reproducible and that the study was well designed and well controlled, I would certainly have to give that some weight and rethink my conclusions.

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But to my knowledge, such a hypothetical study does not exist.

Q. Can you look back at 2008 again for me?

A. So this is the label?

Q. Yes. So there again it refers to STT increases of greater than 10 millimeters, correct?

A. Yes.

Q. And we've talked about that, that you view that as clinically meaningful and material, right?

A. In that individual patient who gets the 10-millimeter increase, yes.

Q. And as the FDA describes the Phase 3 studies, it says that 15 percent of the patient population achieve that score using the Restasis formulation, correct?

A. Well, 15 percent of "a patient population," and we don't know what that patient population is and whether it's the same as the one in Sall. I can only go by what it says here.

Q. Okay. But it's referring to -- well, okay.

It's referring, though, to the randomized multicenter studies, correct?

MR. MILLS: Objection. Form.

THE WITNESS: So I have to say that the

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reason I'm trying to -- you know, again, confining to this only what a POSA would have known at the time. But the way the label is worded, it does say: "Patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS."

So I guess my question is: Is this the whole study group or is it some subgroup? And I don't know from this document.

So in some particular group or subgroup of patients, they're asserting that, you know, 15 percent of them had this 10-millimeter response. And there's just not enough detail to go -- to understand it more throughly.

BY MR. KANE:

Q. And they also say that Restasis demonstrated statistically significant increases in Schirmer wetting scores.

Do you see that?

A. Where are we seeing that?

Q. In the first sentence.

A. Versus vehicle at six months.

Q. Versus vehicle, right.

And so if there's a patient population that has a statistically significant increase in

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Schirmer wetting score of 10-millimeter or greater, would that change your opinion?

MR. MILLS: Objection. Form. Incomplete hypothetical.

THE WITNESS: I'm not sure I understand the question. It is incomplete and there are other problems as well.

Part of the problem is that you have to look at the totality of the study. If the study were designed at the outset to look specifically at this 10-millimeter increased parameter and that were not some retrospective relook at the data or reanalysis of the data, then I would give it more weight.

If the increase in Schirmer score was superior and lots of other parameters that I would expect to be correlated with that were also superior, I would give it more weight.

Frankly, if it affected more than 15 percent of the patients, I would give it more weight because 15 percent is a pretty small number.

So it really is very situation-specific.

You know, the problem is that if you take a big data set and you do a reanalysis, you can -- it would be an exaggeration to say that you can

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prove anything you want, but you could prove a lot of things that might turn out not to be true if the study were repeated.

Again, it comes back to this notion of the Bonferroni correction, which I didn't explain in detail, but it's an attempt to say that a P of less than .05 is a useful cutoff, but if you measure a lot of measure -- a lot of parameters, some of them are going to be positive at a P .05 level by random chance alone. In fact, about 1 out of 20.

So what these corrections -- and there are a variety of them. Bonferroni, I think, was the first. What they do is they, at the simplest level, you simply divide the .05 threshold by the number of parameters you're testing.

So if I'm doing 20 blood tests on you, I would consider something to be -- a blood test may be not the best criterion. If I'm doing 20 -- if I'm evaluating a patient for 20 different parameters and comparing two subgroups, two treatments in two different population subgroups, on average, one of them is going to appear to be positive at a .05 level. So what I should do is divide that .05 by some factor.

Well, Bonferroni, if I recall correctly,

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is to just divide it by the 20, which is the number of parameters.

So, in that situation, it would have to be significant P less than .0025, which is 1/20th of .05.

And there are others because that's thought to be somewhat too conservative.

But my point remains that you know, if you're doing these sort of post hoc analyses, you have to either very good collateral evidence of the validity of the conclusion or reproducibility when you say, "Oh, well, it looks like we did a reanalysis of our study and this popped out." Now that is a study where that is the thing we're going to measure. We're going to decide that at the outset, and that's our treatment goal.

Or the stats have to show just an extremely strong correlation or some kind of combination of those.

So I can't just give you a one size fits all answer to that question.

BY MR. KANE:

Q. Okay. Well, Restasis got approved by the FDA, right?

A. Correct.

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Q. And this is how they described the results on the label, correct?

A. Well, I'm sure there's another document that has a much more detailed description because that's the way the FDA operates. But there is this paragraph on the label.

Q. And so -- and you understand that -- you agree the FDA has expertise in approving drugs?

A. Well, that's a pretty broad blanket statement. One would hope so. I don't think they do a perfect job.

Q. Okay. And you understand the FDA has statisticians who analyze clinical results to determine whether or not the trials have shown safety in efficacy of the drugs?

A. I do understand that they employ statisticians.

Q. Have you ever worked with the statisticians at the FDA?

A. Not that I recall.

Q. Okay. And so is it your understanding that the -- that the FDA concluded that Restasis had demonstrated statistically significant increases in Schirmer wetting of greater than 10 millimeters versus vehicle and that that effect had been seen in

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approximately 15 percent of the -- of the patients versus 5 percent of the vehicle-treated patients?

MR. MILLS: Objection. Form.

THE WITNESS: That's not exactly what it says, but it's close. And it's close to my understanding.

BY MR. KANE:

Q. Okay. And you're not taking an issue with what the FDA did, right?

A. Well, I think in order to answer that question, I would have to be provided with more -- more information, including the NDA and the FDA correspondence, because I -- don't think they're infallible.

Q. Okay. I think we talked about this earlier. You didn't look at any of the public FDA files in connection with the IPR declaration that you've submitted here, correct?

A. Not in connection with the IPR declaration, no.

Q. Okay. I want to turn to paragraph 78 of your declaration, Dr. Calman. And this is a discussion of Dr. Attar's presentation of PK data.

Do you see that?

A. Yes.

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Q. And you see there you've got some bold text that says -- well, the sentence says: "However, this presentation is misleading, because each formulation delivered CsA to the corneal conjunctiva well above" -- I think I said that wrong -- "well above the threshold required for therapeutic efficacy."

Do you see that?

A. I see that.

Q. Okay. And then if you turn to -- well, okay. So let's -- in that context, let's look at a document we previously marked as Exhibit 1058.

Do you recall reviewing this document as part of your work in this matter, Dr. Calman?

A. Yes.

Q. Okay. And you'd agree that this document is relating to the use of cyclosporin as an immunosuppressant in organ transplantation?

A. Generally speaking -- generally speaking, that's true.

Q. Okay. And you understand that these organ transplant patients are not generally treated with topical cyclosporin?

A. That is my understanding.

Q. Okay. And the paper here is describing

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therapeutic ranges of CsA in the blood streams of patients?

A. Yes.

Q. And, in fact, if you look -- looks like -- excuse me. Table 2 on page 651.

A. Yes.

Q. You see there that it's titled "Therapeutic ranges for cyclosporin stratified according to transplanted organ, immunosuppressive regime, induction/maintenance therapy and immunoassay technique."

Do you see that?

A. I do.

Q. And you see there they've got then for kidney triple therapy, heart triple therapy, liver triple therapy, and liver double therapy categories, right?

A. Yes.

Q. And for the different therapies, there are actually different therapeutic ranges shown, aren't there?

A. Somewhat.

Q. Okay.

A. They're not dramatically different.

Q. But they are different and they are

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measured in the bloodstream?

A. They are somewhat different, and they are measured in the bloodstream.

Q. Okay. And they're not being measured in any targeted issues, are they?

A. The data that we've talked about so far are not. I'm not sure if there are any -- some of the references stated in here may refer to targeted issue. But this particular one was looking at blood levels.

Q. Okay. Hand you a document previously marked as Exhibit 1011, Dr. Calman.

A. Correct.

Q. Are you familiar with this document?

A. Yes.

Q. This is an article by Dr. Kaswan?

A. Yes.

Q. And if we look at paragraph 79, this is the -- one of the references that you cite --

A. Correct.

Q. -- as being -- well, cite for the proposition that the values shown in the Attar PK study are higher than those that had been identified in the literature prior to September 15, 2003, as therapeutically effective, right?

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A. Correct.

Q. And you cite pages 652 to 653?

A. Well, I believe there may be some other pages that have relevant data too. For example -- well, yeah, 652 and 653, yeah. There may be issues on some other pages, but, yeah, that was what I was primarily looking at.

Q. And I believe it's the section at the top of the left-hand column on page 653 is where you have a quote.

A. Yeah.

Q. Well, actually, it starts at 652.

And you state there that the intraocular concentrations of 50 to 300 nanograms per ML were large enough to control uveitis?

A. That's what it says.

Q. And where do you -- where exactly did you find that in there in the paper, Doctor?

A. Top of page 653.

Q. It says -- the sentence that -- let me just read the sentence. It says: "The therapeutic range for organ transplantation is 200 to 600 nanograms per milliliter serum, but intraocular level speculated to be needed for control of uveitis is 50 to 300 nanograms per ML."

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Is that the sentence that we're looking at?

A. I see that, yes.

Q. And that's what you were referring to where this quote comes from in paragraph 69?

A. Yes.

Q. And it says there that -- well, first of all, it's talking about intraocular level.

What do you understand that to be?

A. Well, uveitis is an inflammation of the -- typically of the iris and ciliary -- sometimes ciliary bodies, C-I-L-I-A-R-Y. Sometimes posterior structures as well but usually the iris.

And so typically the target tissue would be the aqueous humour, which is why that specifies nanograms per ML rather than nanograms per gram because the aqueous humour is liquid.

Q. And what is the aqueous humour? Where is that located?

A. Well, the aqueous humour is located posterior to the cornea. It's the fluid that fills the front part of the eye.

Q. So it's a fluid inside the eye?

A. Yes.

Q. Okay. And it says there that it's

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speculated that the level to control uveitis is 50 to 350 milligrams per ML in the aqueous humour.
Is that how you're interpreting that?
A. I see that.
Q. And that's how you interpret that to mean?
A. It says what it says.
Q. Okay. And then there's a -- and you said, I believe, uveitis is a condition affecting the iris?
A. Well, it's a condition -- so, strictly speaking, uveitis is inflammation of the uvea, U-V-E-A. And the uveal tract, U-V-E-A-L, is comprised of the iris; the ciliary body, C-I-L-I-A-R-Y; and the choroid, C-H-O-R-O-I-D. So, strictly speaking, uveitis can be inflammation of any or all of those layers.
Typically, it's if affecting the posterior portion of the eye, we would not typically actually use the term "uveitis." We would call it choroiditis, C-H-O-R-O-I-D-I-T-I-S, or chorioretinitis, C-H-O-R-I-O-R-E-T-I-N-I-T-I-S.
Or if all of the uveal tract is involved, we would call it panuveitis.
So typically when people use the term "uveitis" colloquially, they mean either iritis or

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iridocyclitis, which is I-R-I-D-O-C-Y-C-L-I-T-I-S, which means inflammation of the iris and ciliary body.
So this is an inflammation inside the eye where -- usually manifested by inflammation, including white blood cells and protein exudation, E-X-U-D-A-T-I-O-N, in the anterior chamber in the aqueous humour.
And so the treatment typically requires relatively heavy doses of anti-inflammatory topical drugs, sometimes supplemented with systemic drugs. It's typically a pretty heavy-duty inflammation. It's a semi-occular emergency or urgency.
Q. And Exhibit 1011, is there any mention --
A. 1011 is which one?
Q. The Kaswan paper.
A. Okay.
Q. The sentence that we were just looking at. So it's talking -- that, as we just discussed, is talking about the levels of cyclosporin -- speculated levels of cyclosporin in the intraocular fluid, correct?
A. In the aqueous humour.
Q. Okay. And it's not talking about the levels of cyclosporin in any of the tissues that

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you've just mentioned, correct?
A. I disagree. The aqueous humour is a tissue.
Q. Is the aqueous humour where the inflammation is?
A. Well, the aqueous humor is where the inflammation is manifest, and it is the tissue that bathes the iris and ciliary body. And, in fact, it's, in part, secreted by the ciliary body.
But in terms -- I think I can anticipate what I think you're asking, is they didn't state a level in the iris or the choroid or the ciliary body.
Q. Right. Thank you. You anticipated my question.
And we -- it cites to -- has a Note 6 there.
Do you see that?
A. I do.
Q. And that is Nussenblatt?
A. Nussenblatt, et al., Archives of Ophthalmology.
Q. Okay. Now we are going to have to mark one. This will be 2077.

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(Whereupon Exhibit 2077 was marked for identification.)
MR. MILLS: So my objection is that Exhibit 1011 was submitted with Dr. Amiji's declaration with the petitioners in these IPRs and that Allergan's submission of Exhibit 2077 at this point in the proceeding after it already has submitted its patent in response and its responsive declarations is belated.
BY MR. KANE:
Q. Dr. Calman, did -- if you look back to Kaswan 6 there. This refers to an article by Nussenblatt, Dinning, Fujikawa in the A-R-C-H. I'm not sure what that stands for, A-R-C-H.
A. Archives of Ophthalmology.
Q. A-R-C-H-O-P-H-T-H-A-L-M-O-L. 103:1559, 1995.
Do you see that?
A. You're asking me?
Q. I'm asking if you see that on 6, yes.
A. You're asking me if I see the citation, Archives of Ophthalmology, or are you asking if I see it on this -- or on Kaswan?
Q. I'm asking first if you see it on Kaswan.
A. Yes.

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Q. Okay. This is -- does what I marked as Exhibit 2077 appear to be that article?
A. Yes.
Q. Is this an article you reviewed?
A. I am sure I read it when it first -- well, actually, it was 1985, so I probably did not read it when it first came out, and I have not read it recently.
So if we're going to talk about it, I'd like a few minutes to read it.
Q. Okay. Why don't you do that.
(Witness reviewing document.)
THE WITNESS: I've read it. Thank you.
BY MR. KANE:
Q. Having read the paper, does it refresh your recollection as to having previously read this paper?
A. I don't think I read this paper prior to this.
Q. Okay. If we turn to page 1562, the middle column, the first sentence there says: "As we have noted, topical therapy" --
A. Wait. Where are we?
Q. Middle column, about halfway down. "As we have noted" in that paragraph.

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A. Yeah.
Q. "As we have noted, topical therapy seemed predictably effective only if serum cyclosporin levels entered what is considered the therapeutic range of 50 to 300 nanograms per ML."
Do you see that?
A. I do see that.
Q. And when it says "serum" there, you understand that means levels in the blood?
A. Yes.
Q. Okay. And I believe that's the only reference in this paper to 50 to 300 nanograms per ML.
A. Well, let me look and see. But there's more to the paper than that, too, that's relevant here.
Yeah, that is a reference to 50 to 300. But also relevant is the fact that when they injected the -- within the intravitreal injection group, as seen on Table 2 on page 1561, you can see that there -- they looked at the -- the level -- the intraocular concentration of cyclosporin after a single injection or after an injection.
And in Table 1, they looked at the efficacy of the intravitreal injection. And what

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they found in Table 1 was that the 80-microgram injection was not effective and that the 500-milligram, which I think is probably a microgram, injection was effective.
In fact, let's go back to materials and methods. It would almost be impossible for it to be milligrams.
In any case, with the lower dosage as seen in Table 2 -- and, again, it may be a typo -- here it says 800 micrograms. But, in any case, with the higher dosage of intravitreal injection, they were seeing cyclosporin levels -- mean cyclosporin levels between 160 and 580 nanograms per gram, depending on the time after injection. And with lower concentration of cyclosporin intravitreal injection, they were seeing intravitreal -- intraocular levels of 30 to 80 nanograms per gram.
And so, again, the one with the higher level worked with levels in tissue, in vitreous tissue, in the 160 to 580 range, which is roughly comparable to all these others ranges we've been discussing with regard to serum levels. And the lower dose, in the 30 to 80 range, was relatively ineffective for EAU, which stands for experimental autoimmune uveitis, which is a model of severe

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chorioretinitis in rats. Again, another pretty big-time, high-powered anti-inflammatory disease.
So reading this, that's my take on this, that we're -- again, we can quibble is it 50 to 300 or is it 160 to 580 or is it 100 to 400. All of these are in the same ballpark.
Q. Okay. So --
A. You know, one of the conclusions we haven't talked about in this paper was that some of the rats got better because rats being small, the dosage administered topically actually resulted in high blood levels of cyclosporin. That's one of the conclusions of the paper.
Q. Okay. So a couple of things.
If we look at Table 2, the results there are being reported in milligrams per milliliter.
Do you see that?
A. Yeah. I think that's wrong too. There's just no way you can get those kinds of levels.
Q. Okay.
A. It wouldn't dissolve. We know that cyclosporin has very low solubility in aqueous solution, and the vitreous humour is an aqueous solution with some collagen strands. It's not an oily tissue. There's just no way.

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And I'm just seeing lots of typos in this paper. You know, is it 500? So we've got 800 micrograms for the intravitreal injection which is plausible. But then in "Materials and Methods," it says 500 milligrams, which is not plausible. You couldn't get that much to dissolve. There's no way you're going to get 500 milligrams of cyclosporin into a rat eye unless it's a hunk of insoluble, you know, solid.

So I think these are typos.

Q. I think in your answer earlier, though, you had mentioned -- you used the term "showing nanograms per gram" in Table 2?

A. Well, it would be nanograms per ML. Gram is the usual way you measure it in a solid tissue.

And a milliliter, which a milliliter of water weighs exactly 1 gram. A milliliter is how you measure it in blood or aqueous.

Vitreous is typically kind of a gel, so it sort of has properties in between a liquid and a solid. So you could actually plausibly measure in vitreous either in nanograms per ML or nanograms per gram. The difference is essentially immaterial.

The "milligrams per ML" is clearly a typo.

Q. Okay. All right.

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A. There's no way physically possible to have a 580 milligrams per ML concentration of cyclosporin in vitreous. It just cannot physically be done. We know it's a very insoluble compound in aqueous solution.

Q. But -- and based on your previous answer, Table 2, then, is reporting the concentrations in the aqueous rather than a concentration in a solid?

A. Well, no. I think you're conflating aqueous as in aqueous humour and aqueous as in not oily.

So, anatomically, you know, there's the aqueous humour in the front part of the eye. There's the vitreous humour in the back part of the eye. They do communicate. The vitreous has a larger volume, and it is a more gelatinous, like a gel, at least in a young individual or animal because it's got a lot of collagen fibers, it's got a lot of high molecular weight dissolved molecules. But, you know, it can be measured either in milliliters or grams.

The -- you know, because a gram of water weighs -- a milliliter of water weighs a gram, a milliliter of a -- you know, an animal liquid or gelatinous tissue weighs, you know, maybe a little

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more than a gram but not a lot. So it's not a material difference.

My interpretation of this is what they're actually measuring here is nanograms per ML.

Q. Right. But it's not nanograms per gram?

A. I just went through that. It could be nanograms per gram. It's essentially the same. It may be off by a few percent. You're asking me -- essentially the question you're asking me is how much does a milliliter of rat vitreous weigh. Well, it probably weighs a little bit more than a gram.

Q. Well, would you express a concentration of cyclosporin in, say, the iris in nanograms per milliliter?

A. Well, again, as I said previously, typically in a solid tissue, you'd measure in nanograms per gram.

In a liquid tissue, like blood or aqueous humour, you'd measure nanograms per ML.

In a vitreous, it's kind of a half solid, half liquid. It's a gel. So you could measure it either way. You could weigh the tissue or you could measure its volume either way.

The results are not going to be very different because a milliliter of a liquid or

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gelatinous animal tissue is not going to weigh a huge amount more than that a milliliter of water.

Q. Okay.

A. There will be a slight difference, but it's not going to be a material difference.

Q. Okay. Back to my page 1562, please.

A. 1562.

Q. Last page.

There they're reporting that the topical therapy seems predictably effective only if the serum cyclosporin levels entered what is considered to be therapeutic range of 50 to 300 nanograms per ML.

Do you see that?

A. I do see that.

Q. And if we look back to Kaswan, you see at the top of page 653, it says that the intraocular level speculated to be needed for control of uveitis is 350 nanograms per ML. And it cites to the Nussenblatt paper we've been looking at, right?

A. I see that.

Q. Isn't it true that Nussenblatt is talking about serum levels, not levels in intraocular levels?

A. Nussenblatt talks about both. I see your

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point, that the 50 to 300 refers to one of several conclusions of Nussenblatt, which is that when -- that the topical cyclosporin did not produce high intraocular levels on its own due to poor -- presumably poor transcorneal permeability. And, therefore, the anti-inflammatory effect of the topical cyclosporin drops in olive oil, I believe they used, was attributable to systemic absorption through the lacrimal system because rats are small.

And so the effectiveness correlated with serum levels rather than, you know, strictly speaking, intraocular levels because they did not measure levels in the solid tissue of the eye.

But the other arm of the study -- another arm of the study where they looked at these intravitreal injections did show a correlation between clinical effectiveness and intravitreal concentrations in the 160 to 580 nanograms per either ML or gram range. And that is looking at an intraocular tissue.

So, you know, those are two of the data points from this study. So we can quibble over whether it's 50 to 300 or whether it's 160 to 580 or whether it's 100 to 400, but, you know, all of these are in comparable ranges and -- and that's my point.

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Q. But the ranges reported, for instance, in Nussenblatt, 50 to 300, are in serum, not in the solid tissue?

A. Well, I think I really just answered that in my last paragraph. So, again, the range in ocular tissue in a similar assay in the same paper was 160 to 580 --

Q. Is that a solid tissue or --

MR. MILLS: Let's try not to talk over each other and interrupt. I don't think that Dr. Calman was finished with his answer.

THE WITNESS: The vitreous is a semisolid tissue. As I've discussed, it's a gel. It has characteristics of both liquid and solid.

BY MR. KANE:

Q. Okay. And all of these papers that we've just looked at, I believe -- excuse me -- Nussenblatt and Kaswan relate to uveitis?

A. Nussenblatt relates to experimental autoimmune uveitis.

And Kaswan, I don't know that it specifically -- let's see. They speculate that it might be possible to treat intraocular diseases such as immune mediated uveitis with topical application. But this particular study was not looking at a

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disease or disease model; it was really a pharmacokinetic study.

Q. And if you look at Kaswan at 653, it also said -- in the right-hand column, there's a paragraph that starts "Topical CsA"?

A. Yes.

Q. And it says: "In dogs with KCS, topical CsA ameliorated the chronic keratitis and increased the average Schirmer test by 9 millimeters per minute."

Do you see that?

A. I see that.

Q. Is there any indication there of what levels increase Schirmer test scores?

A. What levels of?

Q. CsA.

A. You mean topical -- you mean tissue levels?

Q. Yes.

A. I haven't pulled that particular paper, No. 17, I don't believe. It's another Kaswan paper from 1987.

I don't know how to answer the question other than I don't see anything in that paragraph about specific tissue levels.

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Q. Okay.

A. This paper is about tissue levels, obviously.

Q. And does Nussenblatt say anything about the required concentration of CsA in intraocular tissues needed to treat dry eye syndrome?

A. It's sort of a nonsensical question because dry eye is an ocular surface condition, not an intraocular condition.

Q. Okay. Does Kaswan say anything about the required CsA concentration in ocular tissues for treatment of dry eye syndrome?

A. Well, it does certainly talk about the very high levels of cyclosporin achieved in certain tissues that are relevant for dry eye, including a lacrimal gland and cornea. But it -- and it does mention in the first paragraph of the paper that -- it does talk about recently systemically administered CsA has been found to be beneficial in Sjogren's syndrome, S-J-O-G-R-E-N-'-S, which is a subset of aqueous-deficient dry eye. And so it does talk about that explicitly.

It also in the very next sentence mentions keratoconjunctivitis sicca, which is KCS.

And then in the very next paragraph, it

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talks about the efficacy of topically applied CsA for external ocular disorders.

So I think this paper is actually very much responsive to an inquiry as to tissue levels of cyclosporin in relevant tissues in rabbits, which are typical species that's used for these investigations, with a -- with a view towards ameliorating Sjogren's syndrome and KCS, among other things.

Q. I had a question. My question was about Kaswan, but that's --

A. Well, I'm on Kaswan.

Q. No, you're looking at Nussenblatt.

A. No, I'm looking at Kaswan.

Q. Oh, sorry.

A. I can start up --

Q. No, that's fine. I misrepresented. Okay. My question, though, was whether Kaswan says anything about the required concentration of CsA in ocular tissue for treatment of dry eye syndrome.

MR. MILLS: Objection. Form.

THE WITNESS: Yeah, you're trying to combine a whole bunch of different things. This -- this paper talks about, in its introduction, the

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applicability of cyclosporin to KCS and Sjogren's syndrome. And it talks about tissue levels, and it also talks about minimal therapeutic levels of -- they quote 50 to 300 quoting -- citing Nussenblatt.

So I -- you know, I think parts of the paper are quite relevant, particularly the average level of cyclosporin of 2850 -- 2,850 nanograms per gram, and the very high levels in the cornea, well over a thousand nanograms per gram for the first few days after administration.

So, you know, it doesn't -- it wasn't designed to specifically answer your question because it's not in a disease model of KCS, but it is looking at tissue levels and tissues of interest. And it's explicitly designed for the purpose of understanding how topical CsA would be useful in KCS as well as other disorders.

BY MR. KANE:

Q. But it doesn't answer the question that I asked, right?

MR. MILLS: Objection. Form.

THE WITNESS: So it is not a study of a dry eye disease state. It is a pharmacokinetic study that tells you what kind of levels you get. And the levels you get in the tissues relevant to

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dry eye are extremely high.

BY MR. KANE:

Q. Does Nussenblatt say anything about the required concentration of CsA in ocular tissues for treatment of dry eye syndrome?

A. Nussenblatt was designed to look at experimental autoimmune uveitis. So it's not -- it wasn't designed to look at dry eye and it doesn't talk about dry eye, although some of the conclusions from it may be relevant. But it doesn't explicitly discuss dry eye.

Q. And if we look at Oellerich, same question. Does Oellerich provide any information about the required level of CsA in ocular tissues for treatment of dry eye?

A. Well, Oellerich states that the levels required for effective treatment of rejection in a wide variety of tissues are similar. And it discloses ranges, which I've roughly summarized as roughly 100 to 400 nanograms per ML or, as they express it, micrograms per liter, which is the same thing. They did not look specifically in the eyes or at dry eyes.

But, again, this is not -- it's not a high school student but a POSA, a person that would

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understand that if a wide variety of tissues are achieving adequate levels to control disease with these types of levels in the blood, that these are likely to be applicable to other types of tissue as well. There was not a wide range of difference between these different -- you know, different levels.

So unless you posit there is some -- something unique about a particular tissue that would render these levels irrelevant, I think they can be generalized to some degree.

Q. Is it your testimony that you can take serum levels and apply those to solid tissue levels?

A. Well, I think that you can't directly apply them. But I think that what you can say is, for a variety of different tissues that were looked at, there was no indication that there was a big difference in the required levels for different solid tissue. And what that suggests is that the levels are not either being -- either dramatically higher nor dramatically lower in the tissues than they are in the bloodstream that supplies them.

Q. How do you reach that conclusion?

A. Well, for example, let's say that the liver had an active transport mechanism that tended

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to concentrate cyclosporin in tissue. You would expect to be able to prevent liver transplant rejection with a very high -- I mean, with a very low level of serum cyclosporin because the liver was actively concentrating it in the tissue.

I'm just saying hypothetically; I'm not saying this is the case.

Let's say the kidney has an active transport mechanism that pumps cyclosporin out of the cells. Then you would expect that you would need higher serum concentrations of cyclosporin to see the same effect as far as preventing rejection.

Well, that's just not what they found. And this is a very large data set from all over the world. And the remarkable thing about this data set, in my opinion, is its consistency both from center to center and from tissue to tissue.

So, you know, that, to me, indicates that it's not something particular to any particular type of tissue. Nor have I read anything to suggest that that is -- that there is such a concentration -- concentrating or active transport mechanism in either direction in any particular tissue type.

Furthermore, you know, the Nussenblatt study indicates that the same range of serum

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cyclosporin is -- for an intraocular condition is similar to that for these other solid tissues. Suggesting that the eye doesn't behave any differently than any other organ.

Q. Well, Dr. Calman, I mean, what other solid tissue are you referring to? In Oellerich, they're talking about serum levels, right?

A. Well, they're talking about -- they're not just talking about -- they're talking about serum levels but -- again, I don't want to have to go through my whole same explanation. But they're looking at kidney liver, heart. Let me see what else.

I think I've explained it. I'm sorry if it wasn't clear. But I went through a whole long explanation of the relationship between tissue levels and serum levels. And so...

Q. But my question is -- let me just try to ask it.

So all the levels that we've looked at, for instance, in Table 2 of Oellerich, are serum levels, right?

A. Yes. But they're serum levels with relationship to preventing transplantation in different types of disease. So if you look at the

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last column, you've got kidney, liver, heart, LU. Let's look at the key here.

So there's a variety of different tissues here: Kidney, heart, liver, lung, pancreas. And then pediatric kidney, you know, pediatric liver.

So -- so that -- I just don't want to have repeat the whole sentence. It's in the transcript. I've explained how similar serum levels are required for efficacy in a variety of solid tissues, which indicates that -- including the eye as based on Nussenblatt, which indicates there is not something magical about the eye or any other tissue that tends to concentrate or reduce the concentration of cyclosporin in tissue with regard -- compared to the blood.

And, furthermore, in the Nussenblatt study, we actually do have a comparison. You know, we do have an actual tissue level of cyclosporin in the vitreous which is very comparable. Instead of, you know, 100 to 400, it's 160 to 580. You know, we're in that same ballpark.

You know, I'm convinced as a scientist reading the totality of this data that those are the kinds of tissue levels that are adequate for efficacy in a variety of tissues.

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MR. MILLS: Is it okay if we take a break?

MR. KANE: Sure.

(Off the record at 2:00 p.m. and back on the record at 2:18 p.m.)

BY MR. KANE:

Q. Okay. So looking at your last answer there, you say: "I'm convinced as a scientist reading the totality of this data that those kinds of issue levels are adequate for efficacy in a variety of issues."

Do you agree with me that Oellerich doesn't provide an indication of the -- let me start over.

Oellerich doesn't say anything about --

A. Oellerich.

Q. Oellerich does not say anything about increasing tear production in dry eye patients?

A. Not explicitly, no.

Q. Okay. Do you agree with me that Nussenblatt doesn't say anything about increasing tear production in dry eye patients?

A. Not explicitly per se, no.

Q. And you would agree with me Kaswan does not say anything about increasing tear production in dry eye patients?

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A. Not explicitly per se, no.
Q. And you would agree with me that Oellerich does not identify the concentration of CSI in ocular tissue necessary to increase tear production in dry eye patients?
A. Well, again, I think I've mentioned -- made it clear how I'm using the information from these various references to establish some conclusions. But there -- you know, not in the black and white of the four corners of this document it doesn't explicitly address that, no.
Q. Okay. And you'd agree with me that Nussenblatt doesn't identify the concentration of CsA -- the concentration of CsA necessary in the ocular tissues to increase tear production in dry eye patients?
A. Only by implication, not in black and white of the four corners of the document.
Q. And you agree with me Kaswan does not identify the concentration of CsA necessary in ocular tissues to increase tear production in dry eye patients?
A. Only by implication, not in black and white in the four corners of this document.
Q. Okay. Okay.

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A. I think the other thing I would say about Kaswan is that there is -- excuse me -- about Nussenblatt is that it does provide at least some indirect evidence that the therapeutic range in local tissue as shown in Table 2 shows good correlation with the level -- the levels needed in serum to achieve or systemically to achieve therapeutic effect for the same disease. Which again suggests that there's not a major difference in tissue levels of cyclosporin compared to serum circulating levels.
Q. Just one second. Sorry.
Dr. Calman, you said earlier that you don't consider yourself an expert in ophthalmic formulations, correct?
MR. MILLS: Objection. Form.
THE WITNESS: That's not what I said. I said what I said. Say it again if you'd like.
BY MR. KANE:
Q. Okay. Go ahead.
A. Well, I -- words to the effect that, you know, in my 12 years in research and basic research and 27 years in clinical ophthalmology, my knowledge, skills, experience, training, and education have given me an understanding of

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important aspects of drug formulation, including topical drug formulations for ophthalmic disease. And I routinely review information about various topical ophthalmic products, including their formulation and excipients.
And so I do have a level of expertise in the area, although it is true that I do not hold myself out as an expert in formulation per se.
Q. Okay.
A. And we discussed earlier today some of the various clinical research studies I was involved in where excipients and formulation were key aspects of the study design.
Q. Okay. Do you recall in Dr. Loftsson's declaration, he offered opinions with respect to what a person of ordinary skill would expect the impact of increasing the amount of castor oil in the emulsion to have on bioavailability based upon thermodynamic principles?
MR. MILLS: Objection. Form.
THE WITNESS: If we're going to talk about the Loftsson declaration, I'd like to see it, please.
BY MR. KANE:
Q. Why don't we look at paragraph 76 of your

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declaration.
Are you there?
A. Yes.
Q. Do you see there in the first sentence Dr. Loftsson asserts that the results of Allergan's confidential internal pharmacokinetic --
A. I'm sorry. Which paragraph are we in?
Q. 76.
Why don't you just read that paragraph to yourself.
A. Yeah.
Q. Okay. And my question is simply: Are you offering any opinions as to what a person of ordinary skill would expect based on thermodynamic principles as described by Dr. Loftsson?
MR. MILLS: Objection. Form.
THE WITNESS: I have a general idea of the issues, and I am certainly deferring to Dr. Amiji as being far more expert in that field. And I know Dr. Loftsson is also very qualified in the area of thermodynamics. But I believe I am qualified to discuss these issues and as well to put them in clinical context which neither of them is a clinician.

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BY MR. KANE:

Q. But are you deferring to Dr. Amiji with respect to the thermodynamic principles associated with the interaction between the CsA and the oil and the water emulsion?

A. Let me just see what I did say in my report.

You know, my -- there are aspects of this that all the experts are in agreement on. And then there are other aspects where I can provide a clinical context that's missing.

And so with regard to any details or any equations regarding thermodynamic activity, I would defer to the formulators, doctors. But with regard to the relationship of the bioavailability to the clinical efficacy, I'm a clinician and they're not.

Q. Okay.

A. And so that was the focus of my -- of my -- my declaration with regard to this issue as well as the issues regarding comparison of disparate studies, which we discussed and I think Dr. Amiji also discussed. And Dr. Bloch as well.

Q. Okay. So just a couple of follow-ups, then.

Did you talk to counsel today on any of the breaks regarding the substance of your testimony today?

A. No.

Q. Okay. And you've brought some documents in we talked about earlier this morning.

Did you have any other notes or handwritten annotations on those documents?

A. Not on these documents, no.

Q. On the documents that you brought?

A. No.

Q. They're just clean copies?

A. Yes.

MR. KANE: No further questions at this time.

MR. MILLS: Let's take a short break.

MR. KANE: Okay.

(Off the record at 2:29 p.m. and back on the record at 2:36 p.m.)

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EXAMINATION

BY MR. MILLS:

Q. Dr. Calman, I have just a couple of questions for you.

Early in your testimony you were asked some questions about cyclosporin A concentrations in -- with relation to transplantations.

Do you recall that?

A. I do.

Q. And I believe at some point you talked about that they were measuring concentrations for preventing transplantation in different tissue?

A. Preventing rejection.

Q. Preventing rejection of transplantation.

Okay. And you were also asked questions regarding whether the Nussenblatt and Kaswan references explicitly disclose CsA concentrations that were therapeutically effective for tear production.

Do you recall those questions?

A. I do.

Q. And I believe that you used the word "by implication"?

A. Yes.

Q. Can you tell us what you mean when you say "by implication"?

A. I lot of this, I think, I went through in my declaration.

Basically, the Nussenblatt paper and the Kaswan paper that references it are discussing what is believed in the field to be adequate concentrations for uveitis, for example, which is an example of a severe ocular inflammatory condition. And, again, the -- the vitreous concentrations that were correlated with clinical efficacy in that Nussenblatt study were comparable to the serum levels of cyclosporin that correlated the efficacy both in that same EUA model and in a variety of different tissues with respect to transplant rejection.

So I'm -- by implication, I'm using my knowledge and skill as a scientist to interpret the data in light of the other available information I would have as a POSA.

Q. Just a moment ago you referred to uveitis as "a severe ocular inflammation"?

A. I did. It's often a vision-threatening inflammation.

Q. Earlier I think you used the phrase "high-powered inflammatory disease" with respect to --

A. Let me give you an example.

When we treat -- there are different types of ocular disease that we treat, for example, with steroids, steroid drops typically. Some of them require very high doses or high-frequency

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administration. Others require very low doses or low-frequency administration.

So examples of clinical entities where you might use a very high concentration would be an autoimmune keratitis or a uveitis where oftentimes we're having patients put in our most potent steroid every one to two hours, sometimes around the clock.

In contrast, there are other conditions where we may use steroids, either short-term or long-term, where much lower concentration or frequency is effective. Examples of that include KCS and certain types of ocular allergy where very low dose, such as a once or twice a day of administration of our lowest potency steroid drop, may be sufficient for clinical effect.

So that was my -- that was my -- just trying -- again, my job here in part is to put all of these things into clinical context.

Q. Earlier you were asked a series of questions by counsel regarding various efficacy measures reported in the Sall reference.

Do you recall that?

A. I do.

Q. You were asked a series of questions about which efficacy measures directly measure an increase in tear production.

Do you recall those questions?

A. Yes.

Q. My question is whether any of the efficacy measures in Sall -- as they were reported in Sall demonstrate a significant or material increase in tear production in the 0.05 percent CsA formulation as compared to the 0.1 percent CsA formulation.

A. Well, what Sall tells us is, with respect to the overall tear secretion capacity of the eye as measured by Schirmer's without anesthesia, that there were no significant differences between the groups and that all of the groups, including vehicle, had a statistically significant increase over baseline at each time point, which included Months 1, 3, 4, and 6.

With regard to Schirmer's with anesthesia, this was only performed at Months 3 and 6.

And, by the way, what I've just talked about, those were categorized.

And with regard to Schirmer's with anesthesia, which was also categorized, the raw value not reported in Sall, there was no statistically significant difference reported between the .05 and the .1.

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And Dr. Bloch did his own statistical analysis to verify that there was no statistically significant difference between the .05 and .1 percent cyclosporin at any time point.

With regard to materiality of differences, I'm unable to assess that for the Schirmer's without anesthesia because no numbers were provided. So I don't know.

I'm just -- to put that -- again, put that in clinical context, you can have a statistically significant increase in some variable without having it be material. And an example of that is where we do have some numbers in the Schirmer's with anesthesia, not to recapitulate that entire discussion, but these changes were small. These changes were the most -- at the most, 0.4 for Schirmer, quote/unquote, units corresponding to a small increase in actual Schirmer score on the order of 2 millimeters. Maybe it's 1, maybe it's 3, maybe it's 2. None of those are, in my experience, material.

Q. Earlier in your testimony I believe you used the word "pivotal" at some point in referencing the Phase 3 studies reported in Sall; is that correct?

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A. Yes.

Q. When you use the word "pivotal," what do you mean by that?

A. Typically the FDA requires two large well-controlled clinical trials in humans before they will approve a new drug as safe and effective. Now, there may be -- and there's a lot more to it than that in terms of what the controls need to be and so forth, but that's the big picture. There may be exceptions, particularly for rare diseases, but that's the general way that drugs get approved by the FDA.

Q. When you used the word "pivotal," were you comparing the Phase 3 trials for Restasis to some other Phase 3 trials and saying that the Restasis trials were more impressive or something of that nature?

A. Well, again now, "pivotal" is a term of art, and I have not researched the term. But as I understand it, pivotal trials are those Phase 3 trials typically sponsored by a drug manufacturer and submitted to the FDA in support of approval of the drug.

Q. Do you recall earlier being asked questions regarding the claim construction that you

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understood to apply in the IPR proceedings?
A. Yes.
Q. And do you recall being asked questions regarding that that claim construction involved that therapeutic efficacy could include palliative treatments?
A. Yes.
Q. If that claim construction in a hypothetical excluded palliative treatments, would that change your opinions in this case? If you know.
A. I think it would depend on your definition of "palliative," and I think there's been a lot of confusion about these terms: Palliative, therapeutic, and curative.
The one thing that I can say I think that we probably would all agree on is that a treatment is only curative if the disease is still cured after you withdraw it.
So I'm not sure I -- I don't have this...
And I think the other thing I've talked about previously is that there are steps in the pathophysiologic change. So if you think about a patient who has rheumatoid arthritis, Sjogren's syndrome, and KCS and complains of dry eye, a

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curative treatment would cure his, or her, rheumatoid arthritis which, unfortunately, we don't have.
You can treat the rheumatoid arthritis or you can treat the Sjogren's syndrome which is downstream. Or you can treat the KCS which is downstream from that. Or you can treat the ocular surface drying which is downstream from that, such as with artificial tears.
So what's palliative and what's therapeutic, I don't see it as quite as much of a bright line as some of the opposing experts do.
Q. As you understand the term "curative," is Restasis a curative treatment?
A. Well, no, because if you stop the treatment, the problems comes back and you have to restart.
Q. Dr. Calman, who was responsible for the opinions expressed in your declaration?
A. I am.
Q. Anyone else?
A. No.
MR. MILLS: Thank you, Dr. Calman.
MR. KANE: I just have a couple of quick follow-up questions.

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EXAMINATION
BY MR. KANE:
Q. Dr. Calman, did you discuss with counsel the questions he was going to ask you during the break?
A. No.
Q. And one question which I should have asked earlier but I didn't. In your list of exhibits, you list the deposition transcript of Dr. Sheppard. I think you cite that in your report Exhibit 57, page 58.
A. I see that.
Q. Okay. And my question is simply: Did you read any of the transcripts from Dr. Loftsson, Dr. Schiffman, or Dr. Attar prior to preparing your opinions?
A. Well, in preparation for the IPR, I read the transcript of Dr. Loftsson. I read the declarations of Dr. Schiffman and Dr. Attar. I did not read any transcripts, deposition transcripts, for Dr. Schiffman or Attar for the purpose of the IPR.
MR. KANE: Okay. No further questions.
MR. MILLS: This will be very brief.

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Sorry.
MR. KANE: Okay.
--o0o--
EXAMINATION
BY MR. MILLS:
Q. Dr. Calman, please take a look at paragraph 58 of your declaration.
A. Okay.
Q. And on page 38 --
A. Okay.
Q. -- the second to the last bullet from the bottom.
A. Okay.
Q. In that paragraph, do you cite the Schiffman deposition transcript?
A. Okay. I do. So I guess I did read it.
I'm sorry. I thought I read it for -- the reason I was careful how I answered your question was I know I've read his depositions, and I thought it was in preparation for the district court case.
And, yeah, I did include a quote -- or not a quote, but I did -- this issue, we actually discussed this issue, the fact that Figure 4 it looks like Figure 3. We actually did discuss that earlier and that is the reference, yes. I apologize

for that confusion on my part.

Q. Let me just ask you this: If you cited to a particular transcript in your declaration, does that indicate that you saw that transcript at some point?

A. Yes.

MR. MILLS: Okay. Thank you.

MR. KANE: No questions.

THE REPORTER: I can have the final to you Friday. And will send you a rough tonight.

MS. FRANCIS: Thanks.

MR. MILLS: Yes.

THE REPORTER: Thank you.

(Whereupon, the deposition was adjourned at 2:49 p.m.)

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I declare under penalty of perjury that the foregoing is true and correct. Subscribed at _____, California, this _____ day of _____, 2017.

_____

ANDREW F. CALMAN, M.D., PH.D.

I, MEGAN F. ALVAREZ, a Certified Shorthand Reporter, License No. 12470, certify:

That, prior to being examined, the witness named in the foregoing proceeding, to wit, ANDREW F. CALMAN, M.D., PH.D., was by me duly sworn to testify to the truth, the whole truth, and nothing but the truth;

That said transcript was taken down in shorthand by me, on Wednesday, July 12, 2017, at 9:08 A.M., before the following adverse parties: MICHAEL J. KANE, ESQ., representing the Patent Owner; and JAD A. MILLS, ESQ., for the Respondent; and GARY SPEIER, ESQ., for all other Petitioners, and was thereafter reduced to computerized transcription under my direction and is a true record of the testimony;

I certify that I have not been disqualified as specified under Rule 28 of the Federal Rules of Civil Procedure.

I further certify that I am not interested in the event of the action.

DATED: July 14, 2017

MEGAN F. ALVAREZ

RPR, CSR 12470

Errata Sheet

NAME OF CASE: MYLAN PHARMACEUTICALS INC. v. ALLERGAN

DATE OF DEPOSITION: 07/12/2017

NAME OF WITNESS: ANDREW F. CALMAN, M.D., PH.D.

Reason Codes:

1. To clarify the record.
2. To conform to the facts.
3. To correct transcription errors.

Page _____ Line _____ Reason _____

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