Transcript of Horst Koller

Date: December 16, 2021
Case: Regeneron -v- Novartis (PTAB)

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UNITED STATES PATENT AND TRADEMARK O ICE

BE ORE THE PATENT TRIAL AND APPEAL BOARD

REGENERON PHARMACEUTICALS, INC.
Petitioner,
v.
NOVARTIS PHARMA AG,
NOVARTIS TECHNOLOGY LLC,
NOVARTIS PHARMACEUTICALS CORPORATION,
Patent Owners.

Patent Number:
9,220,63

DEPOSITION O HORST KOLLER
Thursday, December 6, 202

Reported by:
MARY . BOWMAN, RPR, CRR
JOB NO. 4 5628

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December 6, 202
9:00 a.m.

Deposition of HORST KOLLER, held at 767 ifth Avenue, New York, New York, 0 53, before Mary . Bowman, a Registered Professional Reporter, Certified Realtime Reporter, and Notary Public of the State of New Jersey.

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EXAMINATION BY
MR. JAMES:

Q. Good morning. Could you please state and spell your name for the record.

A. Yeah, my name is Horst Koller, H-O-R-S-T, K-O-L-L-E-R.

Q. And could you provide us with your address please?

A. Yes, my address is Weinbergweg, Route 1 -- do you want me to spell it?

Q. I think so.

A. W-E-I-N-B-E-R-G-W-E-G 1 in 730 U-Z-N-A-C-H, Switzerland.

Q. And you understand that you are under oath this morning, correct?

A. Correct.

Q. I took your deposition this past February. Do you recall that?

A. I recall it.

Q. And have you given any other testimony since I took your deposition in February?

A. No.

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Q. Have you submitted any declarations in any matters other than the declaration you submitted in the IPR we are here to talk about today?

A. No.

Q. Are you billing Regeneron as one of your consulting clients at HK Consulting?

A. No.

Q. So you are billing Regeneron as an expert outside of your normal consulting business, is that right?

A. I am billing Weil.

Q. Sorry. I'll change my question then. Are you billing Weil as part of HK Consulting?

A. Yes.

Q. How many hours have you billed them for since your deposition in February? Approximately?

A. Sixty, 70 hours.

Q. Sixty to 70 hours?

A. Yeah.

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Q. Since you -- strike that. I think you told me that you had been working on the '631 patent matter since 2017, right?

A. Right.

Q. And how many total hours would you say you've worked on this matter since 2017?

A. Including deposition?

Q. Yes.

A. 200. Approximately.

Q. And what is the total amount of money you've billed Weil for this matter since you began, approximately?

A. I stated, it's times 450 per hour. So it's like -- I don't recall the amount -- it's like if you say 100 hours is 45,000, 200 hours would be 90,000. Is that right?

Q. So 100,000 dollars, something like that?

A. Something like that.

Q. It's been a long time since I've done math.

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You said 200 hours total?
A. Um-hm.
Q. So 90,000 dollars or something like that, right?
A. Yeah.
Q. Now, I think you told me last time we talked that HK has clients other than Regeneron, right?
A. I don't have Regeneron as a client.
Q. I'm sorry, in addition to Weil, you have other clients, right?
A. I have other clients, yes.
Q. For any of those other clients, have you offered opinions on the '631 patent?
A. No.
Q. What about any foreign counterparts of the '631 patent, have you consulted with any of your other clients on those?
A. What do you mean by foreign counterparts of the '631?
Q. So the Novartis patent family that resulted in the '631 patent has members that are

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issued in other countries and I was wondering if you have offered opinions on any of those other patents to your other consulting clients.
MR. PEPE: So Horst, I'm just going to object and caution you not to disclose any confidential information along with your clients in answering your question. You can answer if you can do so without doing that.
A. No, I did not consult any other patent issues besides the IPR here.
Q. I think the last time we talked, you mentioned that you had been consulting with a client who was making a biosimilar of a VEGF antagonist. Right?
A. Right.
Q. Is it just one client?
A. No, multiple clients.
Q. For any of those clients, have you discussed the '631 patent or its foreign counterparts with them?
A. No.
Q. For any of your other HK Consulting clients, have you consulted with them on Lucentis?
MR. PEPE: Objection, same caution.
A. No.
Q. What about Ilea?
MR. PEPE: I will object and give you the same caution.
A. Yes, I had one project involving Ilea.
Q. Is that completed?
A. Completed.
Q. I'm going to mark a couple of exhibits. I think we will use the exhibit numbers from the IPR if that's OK with everybody. This is Regeneron Exhibit 1001 and it's a copy of the '631 patent.
(Exhibit 1001, U.S. Patent 9,220,631 marked previously for identification.)
Q. And the second exhibit will be the declaration of Horst Koller in this IPR Regeneron Exhibit 1003.
(Exhibit 1003, Declaration of Horst Koller marked previously for

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identification.)
Q. Just take a moment and look through Exhibit 1003 and confirm that that is, in fact, your declaration.
A. Yes, it is my declaration.
Q. Who drafted that?
A. I drafted that.
Q. All of it?
A. I got support from the legal department on like commercial -- I was giving a layout and then my counsel had me to put it in the right form because I'm not a native speaker. They are --
Q. When you say the legal department, what do you mean by that?
A. I mean by Weil.
Q. Weil?
A. Yeah.
Q. So they provided the legal parts of the declaration, is that right?
A. Yes, that's right.
Q. Did they provide you with prior art?

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A. Yes.
Q. And you searched for some of the prior art yourself as well, right?
A. Right.
Q. A couple of the references that you have relied on are the Sigg and Lam applications. Do you recall what those are?
A. Yes, I recall what those are.
Q. Did Weil provide those to you?
A. I -- I don't remember. I mean, I started in 2017. I'm not -- I cannot recollect exactly which one was given and which one I found myself by having to look into prior art references.
Q. And what about the Boulange reference?
A. Same.
Q. Were you aware of the Boulange reference before 2017?
A. I was not aware of the Boulange reference prior to 2017.
Q. You were working in the industry but you weren't aware of the Boulange reference, right?
A. Right.
Q. So how much time did you spend drafting that declaration?
A. This declaration, the new one here?
Q. Yes.
A. Thirty, 40 hours.
Q. And that was on top of the time that you spent on your earlier declarations that built into that, correct?
A. Yes. On top. Yeah.
Q. Are there any things in that declaration you would like to correct?
A. No.
Q. Now, you have the equivalent of a master's in engineering from a university in Germany, right?
A. Right.
Q. You're not a chemist?
A. I'm not a chemist.
Q. And you don't hold yourself out as an expert in chemistry, right?

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A. Right.
Q. You're not a physician?
A. I'm not a physician.
Q. You you've never given an intravitreal injection, right?
A. Right.
Q. You have no experience administering intravitreal injections, right?
A. Right.
Q. You have no personal experiences with the forces that are associated with an intravitreal injection, right?
A. No, not right. I mean, forces should be in general level. So -- and I have designed syringes with typically low break loose, glide forces for general purposes.
So I was designing prefilled syringes with, you know, break loose and glide forces for the intended use for application of simple biotech products and they require for subcutaneous or, you know, low -- suitable low gliding forces and break forces.

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Q. But you have no personal experience with the actual forces that a doctor feels when they give an intravitreal injection, right?
A. Right, I never gave an intravitreal injection myself.
Q. And you have no personal hands-on experience with how differing forces can impact an intravitreal injection, right?
MR. PEPE: Object to form.
A. I cannot judge that one on intravitreal injection. But I have enough experience to judge differences in break loose gliding force performance independent of the intended use.
Q. But you have no experience, personal experience with how the change in forces of an -- in a syringe can impact an intravitreal injection, right?
MR. PEPE: Object to form.
A. As I said, I don't have intravitreal injection experience. But the systematic behind low forces and avoiding shattering or stick slip

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effect and having decent glide force is the same for other syringe application as well. Not for only intravitreal.

You need to take extra care, as it is written in the prior art, to find the right spot in doing intravitreal injection. But the handling of a systematic approach for break loose and glide forces and, therefore, injection is a general design feature for development of prefilled syringes.

Q. But the impact of a slip stick effect, when giving an intravitreal injection, can have a much more deleterious effect on the patient than the same effect in a subcutaneous injection, right?

A. It depends on the outcome of that one, because if you are using like low volume syringes also for injection of hyaluronic acid around the eye or around sensitive, you know, areas in your body, let's say in your face, then this, of course, the stick slip effect has the same also, very, you know, let's say effect regarding pain.

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Q. Right. I think we can agree that the stick slip effect can have a negative impact on injection anywhere in the body, right?

A. Right.

Q. And it can have a very deleterious effect on a patient's eye, correct?

A. Correct.

Q. That's why extreme care is needed when giving an intravitreal injection, right?

A. Right.

Q. Have you ever discussed with a physician the forces that are required for an intravitreal injection?

A. No.

Q. Now, at one point in your career, you worked at Abbott, right?

A. Right.

Q. And at Abbott, you worked on HIV and hepatitis test kits and pregnancy kits, right?

A. Right.

Q. You didn't do any work during your time at Abbott on the preparation of prefilled syringes, right?

A. Right.

Q. You didn't do any work related to intravitreal injections while you were at Abbott, right?

A. Right.

Q. And after Abbott, you moved on to a company called Schott, right?

A. Right.

Q. And what years were you at Schott?

A. I joined Schott in the year 2000 and left Schott in the year 2015.

Q. While you were at Schott, you used ethylene oxide sterilization, right?

A. Right. Not only.

Q. But you do have experience at Schott using ethylene oxide sterilization?

A. Right.

Q. And that was on at least syringes that were filled with water, right?

A. Yes. In addition to that, ethylene oxide is used to sterilize the prefilled syringes prior to filling.

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Q. So ethylene oxide is used to sterilize the components of a prefilled syringes before they are filled, is that right?

A. The syringe's barrel, right. It might be different sterilization for the rubber components involved in the aseptic filling process.

Q. And why might it be a different process for the rubber components?

A. That depended on intended use because of convenience. If you do gamma irradiation, you can sterilize a full pallet load and it is sort of like continuous process.

If you do, as an example, steam sterilization or ETO, it's always a batch process. And you need have to have different packaging available like Tyvek for gas permeation and double PE bag for gamma irradiation or E-beam.

Q. Now, during your time at Schott, you didn't use ethylene oxide to sterilize a syringe filled with a sensitive biologic, right?

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A. Right.
Q. I think you also told me that while you were at Schott, you used vaporized hydrogen peroxide to sterilize something you called a biosafety cabinet, right?
A. That was during my time at Abbott.
Q. At Abbott?
A. Yes.
Q. OK. What's a biosafety cabinet?
A. Biosafety cabinet is a device which can work sterile, in a sterile environment. But it has the features that the worker is safe because it sucks in from the outside to the inside to have a user safety in combination with sterile environment. That's why it is called biosafety cabinet.
Q. While you were at Schott, you did not use vaporized hydrogen peroxide to sterilize a prefilled syringe, right?
A. Right.
Q. Now, none of your other work at Schott was directly related to work on syringes that were

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used for intravitreal injection, right?
A. I was working on a development of a prefilled syringe where the intended use was the idea of using that one as an intravitreal injection.
Q. And was that the Ingentle syringes?
A. That was the Ingentle syringe.
Q. That was never commercialized for intravitreal injection while you were at Schott, right?
A. Right.
Q. Now, I think you told me last time that you couldn't provide me with any documents on your R&D work at Schott because it was confidential, right?
A. Right.
Q. Do you want to look in your declaration there, paragraph 72, please.
In 72, you have a quote that refers to the shelf life of the plunger, right?
A. In 72?
Q. Yes.

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A. Yes, from the near mark.
Q. And do you have experience -- let me strike that.
Do you have experience determining the shelf life of devices?
A. Yes.
Q. Would you agree devices must exhibit some degree of shelf life stability to obtain approval, right?
A. No.
Q. So devices don't need any shelf life stability, is that your testimony?
A. No, this is how we need to define device. If I am a device manufacturer and I have a certain functional shelf life, then the pharma company needs to prove the shelf life of the drug product. This is not the responsibility of a device manufacturer.
And shelf life sometimes mean, for PFS manufacturer, I can guarantee a certain sterility claim up to a certain point, and then the responsibility goes to the pharma company to fill

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the drug substance, do some stability testing and then perform some shelf life testing.
PFS manufacturer usually have shelf life testing regarding functional properties like the removal of a tip cap, break loose, glide force over typically shelf life storage time under certain let's say real temperature or accelerated aging conditions.
Q. There was a lot there so I'm going to ask you a couple of questions to follow up.
I think that you mentioned that the shelf life issue could be sort of divided up between the syringe manufacturer and the pharmaceutical company that puts the drug into the syringe, is that right?
A. That's right.
Q. And the total container closure system with the drug in it, you would agree that has to have some sort of shelf life in order to be approved by a regulatory agency, right?
A. The shelf life which the pharma company will claim is then not what the company

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will approve.
So if you claim two years but only can show data on one year, you don't get approved for two years from like the FDA.
If you have shelf life data for three year, but you still want to do two years, then you get approval for two years. It's always what you claim you need to show facts and data for shelf life.
Q. So you have to show some sort of shelf life in order to get approval, but the length of the shelf life can vary depending on what the company can prove in terms of stability over time, right?
A. Right.
Q. And I think you mentioned two different kinds of stability. One was sterility and the other was functional, right?
A. Sterility is not a -- a claim of shelf life. Sterility is sterility. This is defined, as you say if I have a sterile system, it needs to keep sterility over shelf life. Independent of if

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it's like one month or three years shelf life. So sterility is a fixed claim.
Shelf life, unless if I say it's like I have a functional shelf life where the device manufacturer knows that my system is capable of surviving three-year functional shelf life because I know I can remove my tip cap, I know my rubber is tight. I have decent break-away and glide forces. This is designed and this is what I write and this is usually what I will tell as a device manufacturer listed also like in the FDA in the so-called drug master file. This is where I put all my information about the technical stuff into the system.
Then if a pharma company is interested in that system, sterility is a lot of work, of course, in order to verify that their specific drug product can be used within the container closure system.
This is a different issue. They might have something in it which does not allow me that I can basically remove my tip cap or I might have different forces because they do a different

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treatment to what I have done to my system.
So the shelf life is not only one claim. It's a combination of functional quality and then the drug stability quality and then the sterility behind it.
Q. OK.
The sterility part of it, if you have a shelf life claim for your device of, for example, two years, I think what you are saying is your device has to be sterile for two years, right?
A. Right, this is the claim. As a syringe manufacturer, my claim is two-year sterility. Within two years, the pharma company should use it and fill it.
Q. Right, OK. And I think you mentioned that for functional stability, break loose and glide force would be something that you would have to show over time, right?
A. Yeah, under certain combination which is either used in-house as my standard rubber component or if you want to offer different

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possibilities that you say, OK, I want to check on different rubber formulation or component, then this is a typical usage of a system that you check on break loose, glide force, particle content.
Also you try -- you make sterility testing that you know that your system is tight. This is part of the testing for functionality of syringes.
Q. And it's part of the testing of functionality of syringes over time because the regulatory agency is interested in the fact that your device can perform the same way over time for the entire shelf life, right?
A. Yes. The pharma company filling the drug product needs to be able to show the functionality to the end their claimed shelf life. That whatever the PFS manufacturer is doing before, this needs to be sort of, of course, verified.
I can give certain input and I can say what our typical performance is.
Q. OK, in the real world, let's call it,

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after the syringe manufacturer provides the syringe to the pharma company who then fills it or has it filled and now you have a product that has a shelf life claim on it, how does that stability over time get assessed?

A. So it depends on the specification of your specific drug product. So if you would use as an example WFI, which is not officially a drug product, but very difficult product to fill and keep safe, you say the quality which I put into my syringe that's available for all the drug products should be the same or maybe only maybe have a minimized effect after two or three years at the end of shelf life.

So it's if a water injection, I will check on conductivity, on pH, whatever -- in this water quality which goes into the -- we say water quality and end of shelf life.

For typical drug products, potency effect, if they have a certain potency or if they have a certain cleanliness, then this is what you know when you put it in, basically

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cleanliness -- or I mean potency would be and then at the end of the one, two, three-year shelf life, you need to show that the potency is still the same. This is standard sort of stability claim over shelf life.

Q. With respect to functional stability, you would have to demonstrate the same thing, right; that over time, your syringe had the appropriate function, I think you mentioned that the tip cap would come off in a certain way, and also that your break loose and glide forces didn't change over time, right?

A. This is complete. One is the functional issue and one the drug stability issue.

Q. Do you know what the shelf lives are for the commercially available VEGF antagonist prefilled syringes?

A. I don't know.

Q. One last question on that. We talked about functionality stability over time, but with respect to maintaining sterility over time, to demonstrate that your product is living up to its

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shelf life, let's say, how is that assessed?

A. So you know that you have a sterile product in the first place which are filled into the syringes, and then at certain time points, what you usually do like every three months or every six months depending on your test scheme, you take out samples. And one claim for it standard USP 71 sterility test where you check, if I see bioburden inside, because that would mean that I had a container closure integrity breach.

Q. When you test that bioburden, do you compare it to a sterility assurance level?

A. No. A sterility assurance level is given by the sterilization of the system, by a so-called media verified that your aseptic filling process is done, performed in such a way, and then you check and the sterility testing is that you don't have any bioburden ingress or that you don't show any bioburden, living organism in your drug product.

Q. So the sterility assurance level is a validated level that you've demonstrated your

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process can achieve, is that right?

A. This is -- a sterility assurance level is used during the validation of my sterilization process to show minimum of 10 minus 6 log reduction. This is a validated process.

Q. So if you do a single test on a device and you get a certain result, you can't say whether or not the process met a certain sterility assurance level, right?

MR. PEPE: Object to form.

A. Sterility is only checking on bioburden, independent on what the validation was doing for your process.

Q. OK. The sterility assurance level is a validation of your process, is that right? Do I have that right?

A. It's a validation of the sterilization process, yeah.

Q. And whereas an individual test is simply a measure of the bioburden of that particular device, whether it has decreased and how much, is that right?

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A. Right.
Q. So just staying with the sterility assurance level for a moment, you mentioned that it's a validated level or value. Can you tell me how it's -- how the validation is achieved?
A. Yeah.
So sterility is claimed by the sterility assurance level, SAL, and sterility is defined as having a bioburden reduction of like a 6 log, reduction so 10 minus 6.
How it's done is I have certain so-called bio indicators which have a certain load, known and specific for the sterilization specific bioburden, and then I need to show that my sterilization kills enough microorganism to guarantee the 6 log reduction. Like survival of one out of one million, that would be a typical value for 6 log reduction.
Q. So the sterility assurance level is a probabilistic value in that you can assert that your process will result in a product that would only have say one in a million chance of a

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nonsterile product, is that right?
A. That is right that you say from 1 million to 1.
What you usually is that you have a higher bioburden load so you can, you know, at least get to the 10 minus 6 log reduction and that then guarantees you that you have a sterile product.
What you then need to show in your existing current process like for the finishing, you keep the environment in such a place that you never get above this amount sterilized that you know my sterility assurance level from 10 minus 6. So I don't have a process which introduce a high amount of bioburden, and even if I would have a 10 minus 6 log reduction, yeah, I would have nonsterile product. So this is how you verified the overall system.
Q. So the SAL is a probabilistic value, right?
A. Right.
Q. If you have an SAL of 10 to the minus

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3rd, let's say, can you make a sterility claim?
A. Sterility is usually claimed to 10 to the minus 3 -- 10 to the minus 6, excuse me. But if you can show 10 to the minus 3 and you still show sterility in the end and you can show that your overall load of bioburden is not going above this, you know, 3 log, then, you know, this is usually called also like surface decontamination, outside contamination.
So sterility would always be claimed, based on my knowledge, what I have seen on their validations I did was always 10 to the minus 6.
Q. So if you had 10 to the minus 3, you could call it, as you said, something like surface decontamination or outside decontamination, is that right?
A. You can prove a certain log reduction which helps to minimize apparent ingress into the product. But it would not usually show a sterility claim because the industry expectation is, notice from the agencies that is a 10 to minus 6 log reduction.

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Q. Have you seen examples where companies have made a claim that their product is sterile where the SAL is something less than 10 to the minus 6?
A. No, I don't have seen information. If they claim sterile, for me, that's usually 10 to the minus 6.
Q. You keep saying usually. Just why do you use the word "usually"?
A. FDA requires 10 to the minus 6 to claim a sterile product. So people are putting in place features that they do even a 10 to the minus 12 log reduction to have a safety system effect. So sterile is a certain claim for me that's 10 to the minus 6 log reduction. This is a validated process.
Q. So from your perspective, a claim of 10 to the minus 3 SAL would not be sterile, is that right?
A. Based on my knowledge, right.
Q. Did you know whether the FDA has ever approved a product as sterile with a 10 to the

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minus 3rd SAL?
A. I don't know.
Q. Now, it's your opinion that prior to January of 2012, a person of skill in the art would have been motivated to use low amounts of silicone oil for an intravitreal syringe, right?
A. Right.
Q. And if you want to look in your declaration there at paragraphs 66 to 68, you list some of the reasons for that, right?
A. Right.
Q. So for example, in paragraph 66, you list one reason would be to avoid protein aggregation?
A. Right.
Q. And also you list that another reason would be to avoid the interaction of silicone with the drug formulation, right?
A. Yeah, where protein aggregation would be an interaction between the silicone oil and the drug product.
Q. Lower silicone oil would be less

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likely to interact with the drug, right?
A. Right.
Q. And then you also reference that decreasing silicone oil would result in less oil being injected into the eye of patients, right?
A. Right.
Q. And you mentioned that the injection of silicone oil into the eye can result in floaters in the patient's eyes, right?
A. I just need to read through. Is it paragraph 66 you are pointing me?
Q. Yeah, in paragraph 66, 67, 68, you list several of the reasons for your opinion.
A. Yeah. As I explained, reducing the amount of silicone oil in syringe was known to be desirable in terms of complications, right.
Q. And one of the reasons was to decrease the silicone oil droplets that were injected into patients' eyes, right?
A. Right.
Q. And those silicone oil droplets that were injected into patients' eyes, they were

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considered to be a problem for the patient, right?
A. Right. Could cause floaters or increasing of ocular pressure.
Q. Now, you also mentioned in 68 that lowering the amount of silicone oil by using a baked-on siliconization process can reduce the incidence of the break loose effect, right?
A. Right.
Q. With respect to the amount of oil that's injected into patients' eyes and what its impact might be, you cite this Kocabura reference, Exhibit 1080, in paragraph 66, right?
A. Right.
Q. So Exhibit 1080, Regeneron Exhibit 1080 from the IPR is a letter to the editor in a journal called Acta Opthalmologica entitled, "Intravitreal silicone Oil Droplets Following a Cap Knife Injection."
(Exhibit 1080, article entitled "Intravitreal siliconee Oil Droplets Following a Cap Knife Injection" marked previously for identification.)

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Q. Is this the paper you cited in paragraph 66?
A. This is the paper I cited.
Q. And this is from someone named M. Selim Kocabura, is that right, and her coworkers?
A. Right.
Q. And this is from an ophthalmology clinic in Istanbul, Turkey, right?
A. Right.
Q. In this paper, Kocabura reports on three cases of silicone oil in the eye after administration of pegaptanib?
A. Could you please repeat your question.
Q. Yes, the author in this letter or paper reports on three cases of silicone oil in the eye of the patients after administration of pegaptanib?
A. In the first paragraph, in the first column, it states, "We report three cases..."
Q. And pegaptanib is Macugen, right?
A. Right.
Q. And then at the end of the paper, in

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the last paragraph, it says, "The functional and clinical consequences of intravitreal silicone oil droplets are unknown, but their occurrence could be avoided by using new generation prefilled syringes that do not have an internal silicone coating."

Do you see that?

A. I see that.

Q. You would agree in that paragraph, they are suggesting changing the Macugen product to decrease the amount of silicone oil in it, right?

A. Let me look through one second. I say silicone oil properties most likely associated with use of prefilled syringes, yeah, but their occurrence could be used by using new generation prefilled syringes that do not have internal silicone coating.

Q. So they're suggesting there to change Macugen by decreasing the amount of silicone oil in the Macugen product, right?

A. Right.

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Q. And you would agree that clinicians would want a prefilled syringe that had lower amounts of silicone oil, right?

A. Right.

Q. But at the priority date of the '631 patent, doctors did not have access to an intravitreal syringe containing a VEGF antagonist that had less than 100 micrograms of silicone oil, correct?

A. Not correct. The Boulange reference, references functional syringe with a low amount of silicone oil used for sensitive application which is gas tight, as well as break loose and glide forces.

Q. The Boulange application doesn't disclose a syringe for intravitreal administration, right?

A. Right, but the POSITA would know on certain functional performances that this can be used for intravitreal --

Q. I understand that's your position, but my question was different.

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At the priority date, clinicians did not have access to a VEGF antagonist for intravitreal administration that had less than 100 micrograms of silicone oil, right?

A. In a syringe.

Q. Yes. In the syringe.

A. No, there was nothing on the market that had access to syringes for filling certain needs for intravitreal injection with a low amount of silicone oil besides the Macugen.

Q. Maybe we are talking past each other.

MR. PEPE: Objection.

Horst, were you done answering?

THE WITNESS: Yes.

Q. At the critical date in July of 2012, doctors didn't have access to a commercially available product, a VEGF antagonist for intravitreal administration in a syringe that had less than 100 micrograms of silicone oil, right?

MR. PEPE: Objection, asked and answered.

A. I don't understand your question. If you say access, what do you mean by that.

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Q. Could a doctor pull a syringe having less than 100 micrograms of silicone oil off the shelf and use it to treat patients in July of 2012?

A. As a prefilled syringe?

Q. Yes.

A. I'm not aware of it or know that.

Q. I'm sorry, I don't understand you?

A. I don't know.

Q. You don't know if there were any commercial products on the market for intravitreal administration of a VEGF antagonist that had less than 100 micrograms? You don't know, that's your answer?

MR. PEPE: Objection, asked and answered.

A. I don't know.

Q. Well, Macugen didn't have less than 100 micrograms of silicone oil, correct?

A. Correct.

Q. And in July of 2012, Macugen was the

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only intravitreal VEGF antagonist in a prefilled syringe, right?

A. Right.

Q. The next exhibit will be Regeneron Exhibit 1007.

A. Counsel, can I come back to the last question again?

Q. Sure.

A. So I know that I cite it in my report that in 2012, Ilea was introduced in Australia. I'm not aware -- and I don't have top of my head, I don't have the date of the Ilea submission in Australia compared to the priority date of the '631 patent.

Q. The Ilea prefilled syringe that you reference in your report in Australia, was it launched in 2012?

A. It was submitted in 2012.

Q. Right, but was it available as a product for doctors in 2012?

A. No, it needs to be approved.

Q. Right, so it was not available? The

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Ilea prefilled syringe that you referred to in the Australian document was not available to doctors in 2012, right?

A. Right.

Q. So the next exhibit, Regeneron Exhibit 1007, is a copy of the Sigg application, it's WO2001/006877 A1.

(Exhibit 1007, Sigg application, WO2001/006877 A1 marked previously for identification.)

Q. If you could just take a moment and look at that and confirm that's the Sigg application that you referenced in your report or your declaration.

A. Yes.

Q. If you could turn to page 2. In the second paragraph, the reference talks about cold sterilizations, right?

A. Right.

Q. And there, the reference is referring to gases like ethylene oxide and hydrogen peroxide that can be used to sterilize materials, right?

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A. Right.

Q. And at the end, it says, "Infusion of gas into the product container affects the stability of the drug product through chemical modification by gas vapors such as alkylation and oxidation."

Do you see that?

A. Yes.

Q. You would agree that is a concern that a person of skill would have to take into account in sterilizing a drug product, right?

A. Right.

Q. If you look down at line 20, it says there that some sensitive drug products such as proteins can't be sterilized using things like steam, irradiation -- or irradiation, right?

A. Right.

Q. And at the end of that paragraph, it discusses why that is and that's because these -- some of these -- let me strike that.

At the end of the paragraph, it again refers to the fact that the oxidizing gases can

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harm biological molecules and sensitive therapeutic solutions, right?

A. Right.

Q. And on paragraph -- let me strike that.

Page 3 in the summary, the reference talks about the use of VHP for terminal sterilization, right? and VHP is vaporized hydrogen peroxide, is that correct?

A. Right.

Q. And then at the end of that page or the bottom of the page, around line 27, it says that, "It further has been found that among the commercially available primary packaging components, there are only very few packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gases into the pharmaceutical liquid enclosed by the prefilled container."

Do you see that?

A. I see that.

Q. Just so we are on the same page, the

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primary packaging components here, do you have an understanding of what that would refer to?

A. The packaging components will refer to the syringe barrel, the front end closure and the piston.

Q. So in a prefilled syringe, it's basically the things that come into contact with the drug product, right?

A. Right.

Q. And the reference says there are only very few packaging material combinations that provide the required tightness, but the reference doesn't provide any details of any particular combinations, right?

A. Right, it doesn't talk about specifics.

Q. Now, when you applied vaporized hydrogen peroxide treatment, that involves putting the product into a sterilization chamber and applying a vacuum, right?

A. Right.

Q. And the vacuum causes a pressure

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change in the chamber that can cause the stopper to move, right?

A. Right.

Q. And is it also the case that prefilled syringes, the drug product will at some times have an air bubble inside them that can expand under negative pressure?

A. Right.

Q. And you would agree that vaporized hydrogen peroxide could not be used with every possible combination of barrel and stopper and protect the drug product inside the syringe, right?

A. I would distinguish that a plastic barrel might have significant issues with VHP. Glass, which is typically the preferred option here would be, you know, VHP tight, and then a POSA would know what kind of front end component or back end component needs to be chosen in order to make a gas tight system. And that has been shown also in prior art.

Q. Right, but I think implicit in your

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answer is that you would have to select the right components in order for the system to be gas tight and protect the drug product solution, right?

A. Right, but this is not only for sterilization. So gas tightness is something which needs to take place during shelf life of a standard PFS. So you always need to avoid ingress from gases from the outside to the inside into the drug product environment. Not only during terminal sterilization or sterilization.

Q. Now, Sigg suggests -- let me strike that.

So this Exhibit 1007, this reference suggests that one post treatment measure that can be used is the application of a vacuum at the end of the antimicrobial treatment in order to remove the VHP, right?

A. Right.

Q. And that process would also impart a decreased pressure on the product, right?

A. It depends on the level of vacuum.

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Q. If you apply a high enough vacuum, the pressure can decrease inside the chamber and cause a stopper to move, right?

MR. PEPE: Object to form.

A. Again, it depends on the level and then it needs to overcome the break force in order to be able to move at all.

Q. And there is no disclosure in the Sigg reference, 1007, of any structure to prevent the movement of the stopper either during VHP sterilization or the removing of the VHP, right?

A. There is no specific feature to avoid piston moving in the Sigg document.

Q. You would agree that a syringe where the stopper has a low break loose force, that would have a higher chance of moving during the application of negative pressure, right?

A. Depending on the level of vacuum, yes.

Q. All things being equal, lower break loose force would allow easier movement of the stopper, right?

A. Right.

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Q. If you look at page 20 of the reference, 1007, there is an example of the sterilization of some syringes using vaporized hydrogen peroxide, right?
A. Right.
Q. And the example refers to the syringes as prefilled syringes, correct? In the first sentence?
A. Correct.
Q. But there are no specifics given about the make-up of the syringes, right?
A. Right.
Q. There is no disclosure of the syringe materials, right?
A. There is no disclosure of the syringe material, right.
Q. There is no disclosure of the specific stopper design or the materials the stopper is made from, right?
A. Right.
Q. There is no disclosure of whether the barrel was lubricated with silicone oil or not,

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right?
A. It would be, you know, a syringe -- it should be lubricated independent of the material to get to a, you know, decent break loose glide force. So I would say that syringes, the state of the art, will be lubricated.
Q. Glass syringe barrels would be lubricated, right?
A. Always the polymer barrels should be lubricated.
Q. But the example doesn't mention lubrication of the barrel, right?
A. It doesn't mention explicitly lubrication of a barrel.
Q. It doesn't disclose how much, if any, silicone oil was used in the barrel, right?
A. Right.
Q. There is no disclosure of the break loose or glide force for those syringes, right?
A. No. If it's filled with, let's say, MTHF, a POSA would know typically break forces should be low enough in order to do intravitreal

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injection.
Q. I understand that's your interpretation. My question is just that the example itself doesn't disclose the break loose and glide force for these syringes, right?
A. Right.
Q. There is no disclosure of whether the break loose and glide forces change after the application of vaporized hydrogen peroxide, right?
A. Right.
Q. There is no mention of parylene C, right?
A. Right.
Q. There is no discussion of the shelf life of these syringes, right?
A. Right.
Q. So if you look at --
A. Excuse me, sir.
There is a general statement in that -- in such treatment, on page 21, "The results seen were within the requirement. There were no differences between results of the untreated

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syringes and with hydrogen peroxide-treated syringes. Analysis can also be carried out at different time points following treatment," and over shelf life.
So it gives an indication that you need to check this one over shelf life.
Q. Right. It indicates that the syringes should be tested to determine their shelf life, but it doesn't provide any indication that such testing was done or the results of such testing, right?
A. Right.
Q. And the table just above the paragraph you were just pointing me to reports on protein stability following treatment with vaporized hydrogen peroxide, right?
A. Right.
Q. It doesn't report on force measurements over time, right?
A. Right.
Q. Now, in that example, example 1, is there any evidence that sterility of the syringes

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was achieved?
A. It says approximately 10 ml of solution was filtered to a .22 micrometer syringe filter. This is how you prepare your drug product because that's a sterile filter. And then filling .5 ml syringes was performed in a sterile lab for hydrogen peroxide treatment with the syringes here.
Q. The syringes were aseptically filled?
A. Right.
Q. And does that mean that they were sterile?
A. I mean, a POSA would ask himself why do all the effort if the syringe was not sterile in the first place.
Q. You can claim sterility for a claim that is aseptically filled, right?
A. Right.
Q. And then they applied the vaporized hydrogen peroxide terminal sterilization process to these syringes, right?
A. Right.

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Q. Is there any indication that the outside of the syringes was rendered sterile by the vaporized hydrogen peroxide application?
A. There is a general description on page 15, like line 30, that references made to treatment times that are sufficient to terminally sterilize the prefilled container.
Q. OK. There is a general reference on page 15 to times that could achieve sterility, is that your testimony?
A. Yes.
Q. And on page --
A. Excuse me, sir. And on page 7, he describes the claimed sterility.
Q. I'm sorry, what page?
A. Page 7, under line 5. Sterility is Sterility as used herein is meant to refer to complete absence of microbial life and required -- sterility is used herein is meant to refer to complete absence of microbial life as defined by a probability of nonsterility or a sterility assurance level, SAL.

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And he references, for example, a required SAL for ASCA products are defined to be at least 10 minus 6.
Q. He refers to an SAL. But he doesn't provide any data in example 1 demonstrating that any particular SAL was achieved, right?
A. No mentioning an example that he was testing on the 10 to the minus 6. But if he claims that, in the prefix, that he says sterility claim in his document is at least a 10 minus 6, then he achieved the sterile product, then this is in reference back to the 10 minus 6.
Q. But he doesn't actually say that the syringes in example 1 were sterile, correct?
A. He says he sterilized them.
Q. He said he sterilized them, but were they sterile? It doesn't say, right?
A. Right.
MR. PEPE: Objection, asked and answered.
Q. Let's take a quick break.
(Recess; 10:20 to 10:34 a.m.)

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Q. So Mr. Koller, I think when we took our break, we were looking at Exhibit 1007. That's the Sigg application?
A. Right.
Q. And if you look at that definition of sterility that you pointed me to on page 7, if you could let me know when you're there.
A. Yes, I'm there.
Q. And in the first sentence, it says, "Sterility as used herein is meant to refer to complete absence of microbial life as defined by a probability of nonsterility or a sterility assurance level, SAL."
Do you see that?
A. I see that.
Q. And then it says the required SAL for a given product is based on regulatory requirements. Right?
A. Right.
Q. The next sentence that you pointed me to, it starts with the words, "For example," and then it says "SALs for healthcare products are

defined to be at least 10 to the minus 6," right?
A. Right.
Q. So you would agree that the paragraph suggests that there are other SALs and that an SAL of 10 to the minus 6 is just one example, right?
A. Right.
Q. And the particular SAL that you're able to achieve or that you're required to achieve will be determined based on the regulatory requirements for your product, right?
A. Right.
Q. And I think you mentioned earlier that, for example, an SAL of 10 to the minus 3rd might be referred to as surface decontamination, right?
A. As an example, depending on the, you know, intended use of the device.
Q. Right. And here, an SAL of 10 to the minus 3rd could be referred to as sterile under this paragraph that you pointed me to, depending on the product?
MR. PEPE: Object to form.

A. If I consider a PFS as a healthcare product, which I do, then it says required SAL minimum 10 to the minus 6.
Q. But it does leave open the fact that sterility here could also refer to other SALs, right?
MR. PEPE: Object to form.
A. Yes.
Q. Now, if you look at the claims of the application -- I guess, before we go there, if you look for a moment at example 2 of the application, it starts on page 21. And in that example, they report on an experiment that was carried out to determine the effectiveness of surface decontamination using beta radiation, right?
A. Right.
Q. And then if we look at the claims now, if you look at claim 8, you will see that it's directed to a method for surface decontamination of a prefilled container in secondary packaging.
Do you see that?
A. Yes, I see that.

Q. So that could include a prefilled syringe in a blister pack for example, right?
A. Right.
Q. And then you would agree that surface decontamination could include SALs that were less than an SAL of 10 to the minus 6, right?
A. Right.
Q. If you look at claim 15, which it says that it's the method of any one of claims 8 to 14, and it says, "Wherein sufficient energy to decontaminate a surface of a prefilled container is that which provides a dose of beta radiation yielding a 10 to the minus 6 sterility assurance level of the outside of the container surface," right?
A. Right.
Q. And so that indicates that using beta radiation in this claim, you can achieve a 10 to the minus 6 assurance SAL which, as you pointed out, is an SAL for healthcare products, right?
A. Right.
Q. But there is no reference to achieving a 10 to the minus 6 SAL for the vaporized hydrogen peroxide treatment, right?
MR. PEPE: Object to form.
A. I mean, as he described healthcare products, 10 to the minus 6 would be the legal requirement. So I would do the testing to show that I can sterilize to the 10 to the minus 6 which then would be accepted by the healthcare agency for -- to be a healthcare product out in the field, where they have a 10 to the minus 6.
Q. Yes, I understand you could do the testing and demonstrate an SAL of 10 to the minus 6.
My question is a little different. My question is in the claims, they don't claim a 10 to the minus 6 sterility assurance level for the application of vaporized hydrogen peroxide, right?
A. Right.
Q. So the only 10 to the minus 6 SAL that is actually claimed in this application is directed to the use of beta radiation, right?

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A. Right.
Q. You would agree with me that there are instances where you can't get a product to a 10 to the minus 6 SAL without causing the degradation of the product using vaporized hydrogen peroxide, right?
A. Just repeat your question again please.
Q. Yes, you would agree that there are -- strike that.
You would agree that it is possible that you could have a situation where you wouldn't be able to get to a 10 to the minus 6 SAL without causing degradation of the product, right?
MR. PEPE: Object to form.
A. No, because I could check that no ingress would take place into my drug product by routine testing.
Q. I understand that you are saying -- let me strike that.
Isn't it the case that there could be situations in which you would not be able to

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achieve the SAL 10 to the minus 6 without destroying your product with your vaporized hydrogen peroxide?
MR. PEPE: Same objection.
A. I would, as a POSA, I would say what is the issue here. One is to do outside decontamination in a blister packaging or outside sterilization of blister packaging. The other one that I immediately always need to keep my product safe inside.
So if I could achieve a 10 minus 3 on the outside, but still 10 minus 3 will damage my product, then this would not be a suitable option.
So I clearly would distinguish between a safe product on the inside of ingress of gases and the possibility of claiming -- and let's say I can have a gas tight system on the inside, but still have some features or some mechanical issues there in order that I cannot get the 10 to the minus 6 maybe to the outside or 10 to the minus 3 would be possible within a blister.
Q. Right. So I think -- if I can unpack

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that, you're saying that there are instances where you might not be able to get to an SAL other than 10 to the minus 3 without damaging the product inside the syringe, but that wouldn't be acceptable to you. Is that -- that was what you said, right?
MR. PEPE: Object to form.
A. I said that the drug product comes first and if there are some other legal requirement and you could not achieve a 10 to the minus 6, then a 10 to the minus 3 on the outside might be possible depending on the feedback from the agencies. But the drug product needs to be safe. It needs to be a gas tight system.
Q. Right, OK.
So that would be an instance where the particular product, you could not get to an SAL of 10 to the minus 6 without damaging the product, and so you would potentially propose 10 to the minus 3rd to the FDA or EMA in order to protect your product?
A. Right. The claims here, some post

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treatment possibilities to avoid ingress of systems or of gas, of VHP into the drug product.
So as soon as the -- let's say the microbial fluid has done its job on the outside of the syringe and the inside of the blister, it says that by removal per vacuum or other plasma treatment can withdraw or basically convert the flow that gas doesn't go in, but that I can pull it away from my drug product in order to keep the drug product safe.
So he is implementing here, he is saying in case the system, you know, would have a problem, that post treatment could help you in that way.
Q. Mr. Koller, is it true that in some instances, you need to ask the FDA or the EMA for a 10 to the minus 3rd claim rather than a 10 to the minus 6 claim because the product is being damaged by the sterilization process?
MR. PEPE: Object to form.
A. I personally didn't talk to the FDA in such a way. But based on my POSA, if you cannot achieve a 10 to the minus 6 in the first place,

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then you might need to go and look for other component system which can survive a 10 to the minus 6 without damaging the product.

But this is a routine optimization of some of the systems in order to get to the 10 to the minus 6 which is the FDA requirement for sterile product in the first place.

Q. Right. You could redesign your product in order to try to achieve 10 to the minus 6. But if product redesign wasn't a possibility, aren't there circumstances where a company needs to request a 10 to the minus 3rd approval for their product?

MR. PEPE: Same objection.

A. I can't answer that because I never talked to the FDA to reduce a 10 to the minus 6 to a 10 to the minus 3 and what would be a circumstance for that one.

Q. Can you envision such a circumstance existing though?

MR. PEPE: Same objection.

A. As a POSA, by knowing what is -- let

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me -- if you can't approve the terminal sterilization to the 10 to the minus 6 to the end, then you already made the mistake in the first place by choosing the right component.

So if a product was not designed for terminal sterilization, then you might have an issue in the first place.

If I know that the system needs to survive terminal sterilization, I don't see the point why you then should ask me to go for a 10 to the minus 6 to 10 to the minus 3 because you design your product in such a way that it can survive the requirements. Yeah.

Q. Right, but if -- absent redesigning your product, under those circumstances, you're only recourse would be to ask the FDA for a 10 to the minus 3rd approval, right?

A. For the outside surface.

Q. Yes.

A. I could imagine that you could go to the FDA and ask if in what kind of circumstances they would accept it and how you control the

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system.

Q. The next exhibit will be the IPR Exhibit Regeneron Exhibit 1029. This is a copy of the Lam application, WO2008/077155A1.

(Exhibit 1029, Lam application, WO2008/077155A1 marked previously for identification.)

Q. Mr. Koller, if you could take a moment and look at that application and confirm that that's the Lam application that you have opined about in your declaration?

A. Yes.

Q. This is an application by Genentech, correct?

A. Correct.

Q. And Genentech developed Lucentis, right?

A. Right.

Q. And the application is directed to methods for terminal sterilization of syringes including Lucentis, right?

A. Right.

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Q. The file date of this application is the 21st of December 2007.

Do you see that?

A. Yes, I see that.

Q. And then there is an earlier priority date of the 21st of December, 2006, right?

A. Right.

Q. Do you know if a patent ever issued from this application?

A. What I see is a patent application.

Q. Have you seen a patent that issued from this application to the best of your recollection?

A. No.

Q. So you're not aware of a patent?

A. I'm not aware of a patent.

Q. Now, the patent application discusses the use of ethylene oxide as an oxidizing -- sorry. Strike that.

It discusses the use of ethylene oxide as a sterilizing agent, right?

A. Right.

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Q. And ethylene oxide is an oxidizing agent?
A. Ethylene oxide is an alkylating agent.
Q. Ethylene oxide alkylates?
A. Yes.
Q. Contact between ethylene oxide and a sensitive drug would damage the drug, is that right?
A. It could damage the drug, right.
Q. So you would agree that it would be important for the container to be ethylene oxide impermeable when performing terminal sterilization on these syringes, right?
A. Right.
Q. And you would agree that not every combination of syringe and barrel would achieve ethylene oxide impermeability, right?
A. Again, if I would use a polymer barrel, then the likelihood that it would survive ETO treatment would be limited.
Q. That's because the ethylene oxide could seep into the drug product and damage it?

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A. It could migrate through the polymer itself because it has, you know, less barrier properties then of course glass, just from the material point of view, not from the front end closure or back end closure.
If your syringe barrel and stopper combination were not sufficiently tight, you could also get gas ingress into the drug product in that instance, right?
A. Right.
Q. So a person of skill would have to select suitable components in order to apply the ethylene oxide sterilization method to the syringe, right?
A. Right.
Q. If you turn to page 14 of this exhibit -- sorry, before you do that, could you turn to page 4, please.
A. Yes.
Q. At the top of the page, at about line 3, there is a paragraph that discusses the meaning of the term "sterilized."

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Do you see that?
A. Yes.
Q. And then here it says that, as used herein, the surface of an object is "sterilized when the amount of at least one biological contaminant present on the surface of the object being treated, according to the present invention, is reduced following the treatment."
Do you see that?
A. I see that.
Q. So in that sentence, they're indicating that the meaning of sterilized could embrace simply reducing a biological contaminant, right?
A. Right.
Q. And then in the next sentence, it says "Typically, the amount is reduced by at least one log, i.e. by at least tenfold. In some embodiments of the invention, the amount is reduced by 2 logs, 3 logs, 4 logs, 5 logs or 6 logs."
Do you see that?

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A. I see that.
Q. And the thing we have been talking about, 10 to the minus 6, that would be the same as what they are referring to as six logs in that last sentence, right?
A. Right.
Q. And so at 10 to the minus 6 SAL -- let me strike that.
A 10 to the minus 6 reduction would only be one of the examples in this paragraph, right?
A. Right.
Q. If you turn now to the example that begins on page 13 and then runs through page 16. Do you see that?
A. The example?
Q. Yes.
A. Yes.
Q. And on page, at the bottom of page 13 and spanning on to page 14, there is a table that provides some test runs for ethylene oxide sterilization, right?

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A. Right.
Q. And on the top of page 14, there is a row with sterility log reduction results, right?
A. Right.
Q. And some of the log reductions were greater than six logs, right?
A. Right.
Q. And others were less, correct?
A. Right.
Q. And in terms of the definition of "sterility" or "sterilized" that we looked at earlier, all of these results would fit within the definition of sterilized in that earlier paragraph, right?
A. Right.
Q. If you look in your declaration at paragraph 288, please.
Do you see that in paragraph 288, you are discussing the claim 21 of the '631 patent? Do you see that?
A. Yes.
Q. And claim 21, as you recite there,

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claims that the syringe has been sterilized using ethylene oxide or hydrogen peroxide with a sterility assurance level of at least 10 to the minus 6.
Do you see that?
A. I see that, yes.
Q. And then you have a few paragraphs discussing the results in Lam. And then at the end of paragraph 290, if we could look at that sentence --
A. Yes.
Q. It says, "A POSITA," a person of skill in the art, "would understand that Lam's disclosure of reducing the biological contaminants by at least, quote, 6 logs means that the sterilization cycle has achieved a sterility assurance level of at least 10 to the minus 6."
Do you see that?
A. On 290?
Q. 290. The last sentence.
A. OK, yes, I see it now. Sorry.
Q. In the beginning of the paragraph, you

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are discussing that paragraph in Lam that you and I just looked at where it talked about the embodiments.
A. Yeah.
Q. And in that last sentence, do I understand correctly that you are simply saying that if you have a -- that -- strike that.
That a 6 log reduction -- let me strike that.
Does it necessarily follow that if you have 6 log reduction, you have achieved a sterility assurance level of 10 to the minus 6?
A. So if you say you have a 6 log reduction, meaning you have an SAL of 10 to the minus 6.
Q. If you have one result where you get a bioburden reduction of 10 to the minus 6, does that mean that you have a sterility assurance level of 10 to the minus 6?
A. Yes, it's a reduction.
Q. I thought you told me earlier that a sterility assurance level is a validated process

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where you can, on the basis of probability, say that you have no more than one nonsterile component in a million?
A. Yeah, this is a 6 log reduction from one million to 1.
Q. Right. But the fact that you have a result with a 6 log reduction is not the same thing as having a process that you can say has an SAL of 10 to the minus 6, right?
A. No, for me it's the same.
So 6 log reduction is used like a 10 to the minus 6. The starting level could be different. I could start from 1 million down to 1. I could start from 10 million and then a 6 log reduction. I could start at 100 million. So it depends on the starting level.
But a 6 log is 6 log reduction. That's -- you can verify that your sterility process has a 6 log reduction which is then considered as they state in the art as sterility claim.
Q. Looking at the results of the example,

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in Lam on page 14 at the top --
A. Yes.
Q. Some of the results were greater than 6 logs, some were less.
A. Right.
Q. So is that achieving a sterility assurance level of 10 to the minus 6?
A. Run 4 and 5 will do so because the log reduction is log 6 -- in run 5, it's 6.3.
Q. Some of the runs had log reductions of less than 10 to the minus 6, right?
A. Right.
Q. So is this a process that has an SAL of 10 to the minus 6?
A. No.
Q. Can you tell from this example whether this process has been validated to achieve an SAL of 10 to the minus 6?
A. He doesn't talk about validation, but if he knows that he has a 6 log reduction, he was using bio indicators.
So there is no way that you can

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just count the numbers. So you need to have a certain level of bioburden and then you checking, after your sterilization process, to what level you come down.
Q. Do these data indicate to a person of skill in the art that this process is validated to an SAL of 10 to the minus 6?
MR. PEPE: Object to form.
A. I mean, he doesn't talk about validation. He talks about the 6 log reduction.
And then what I would do is that I use either run number 4 or run number 5 where it says I have a 6 log reduction or larger 6, and then I do a validation which are certain ISO requirements for ETO sterilization which clearly describes what you need to do to get to a validated process.
This is a test where he shows that on ETO process, he still has a safe product, but he still could achieve a 6 log reduction with a process.
Q. In some instances?

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A. In some instances. This is what you do as a routine optimization. You never know what your process parameter should be.
So if I would go back to run number 1, that does not mean that I have a completely different process -- different syringe in place. I might have used different performances, like vacuum, temperature, humidity, and also Sigg describes that it's a routine optimization of certain controlled parameters in order to achieve the desired 6 log reduction.
It does not talk about validation. But he talks that he had -- he found a cycle for 6 log reduction.
And then if I go to table number 2, then he was checking the content, if there is any influence regarding the protein. And he shows that, you know, the protein was stable. Even at the 6 log reduction, a POSITA would read out that this is a tight system which can survive ETO sterilization.
Q. Well, the process that's disclosed in

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the example has results that are both above and below 10 to the minus 6, right?
A. Right.
Q. Mr. Koller, so these results that are provided here in example 1 are results of the testing of the process at time zero, right?
A. Right.
Q. There are no data provided for these results either sterility or protein content over time, right?
MR. PEPE: Object to form.
A. Right. But you need to understand how you do that.
I mean, this process here has an evacuation cycle. So what it's describing -- Sigg describing as well that a post treatment measure is that, you know, you evacuate the chamber or you get the residual ETO out. There are some legal requirements that, you know, no residual ETO above a certain limit should be there. You need to show that. This is a regulatory requirement. So you pull out all the vacuum.

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That means, you pull out the residual ETO by example by vacuum and you have a low level of residual ETO on the system. Likelihood that something might migrate later into the system is nonexistent because you will see the ingress right away if you check on the inside.

Based on my POSITA knowledge, this is not a long term effect. This is like if it happened, if there is an ingress, there is an ingress. It happens right away because the ETO cannot migrate into the system if it's not there anymore.

Q. And there is no indication here of a shelf life for this product in example 1, right?

MR. PEPE: Object to form.

A. I can't see any shelf life claims there. Right.

Q. And there is no demonstration of sterility over any particular shelf life in the example, right?

A. Right. He was checking that he can terminally sterilize the outside surface and the

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piston. But, it's not -- again, it's not sterility shelf life claim on the inside. Going back --

Q. Well, there is no shelf life claim either of the product inside or the outside of the product or the function of the product or any shelf life claim, right?

MR. PEPE: Objection.

Horst, first, were you done with your previous answer?

THE WITNESS: I'm done.

MR. PEPE: Are you sure? OK.

Q. Did you understand my question?

A. Can you repeat your question, please.

Q. Yes, there is no assertion of any shelf life in the example one whether it's sterility or function or protein content over time, right?

A. Right.

Q. Now, if you did see protein degradation in the product after sterilization over time, that would indicate that there was a

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problem with the system in terms of preventing ingress of the gas into the drug product, right?

A. If the control would be OK, yes. I mean, if you control it, it would not have an issue. Then it might come from not only the VHP or ETO, it might come from other issues which could happen if you choose the wrong components, yes.

Q. And that's the reason that a person of skill would test the protein over time is to ensure that you didn't see an impact later on from the initial exposure to ethylene oxide, right?

A. Again, to -- there are two points here. One is what we discussed before. So it's a question about product shelf life, stability, sterility over shelf life and finding a process where I can terminally sterilize the outside or maybe on the inside of a blister.

So I understand, yes, that if you do shelf life testing on your final drug product as an example, a pharma company for a specific product I want to bring to the market, I need to show

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stability testing, sterility and functional performance.

This is a complete package then, you know, pharma company needs to show. It's independent if you validate the sterilization process where the goal is really to show 10 to the minus 6 log reduction, then you can basically then show and have the sterile claim which is the industry expectation.

Q. But just focusing -- just focusing on the protein degradation, you measure protein degradation over time in order to assess whether or not there was exposure of your product to the ethylene oxide, for example, when the sterilization process occurred, right?

A. You check on the product stability because of extractables, leachables. So you would not check VHP or ETO residuals at the end of shelf life.

Q. Setting -- sorry.

A. This does not make sense because you're checking on the stability of the drug

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product, now independent where it comes from. And if you usually have vapor or oxidizing ingress or VHP or ETO ingress into the drug product, you see that right away within like time point zero testing after sterilization or at least within three months. So you see.

But you need to check then what kind of degradation of my protein because if it is alkylated, then my guess would be that it comes from the ETO. Is it -- it has a different degradation, yeah, like application. It could come from the silicone oil.

So, then of course, you do a sort of root cause analysis to see what is causing my degradation of the product.

Q. Let's focus on alkylation.

Setting aside whether you look at that at the end of the shelf life, you would measure the amount of protein alkylated over time to assess whether or not there had been an ingress of alkylating agent during sterilization, right?

A. Right, this is part of the

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specification that you say I have less than certain percentage of alkylation that's allowed in my product spec. You will check on that one, right.

Q. It is possible that you cannot see a problem with alkylation at time zero and see the problem develop over the months that follow, right?

A. As I explained before, in theory, yes. But I don't know where the alkylation took place, if it's based on the sterilization gas or agent, then there is no sterilization gas or agent anymore because you need to make sure that you are below a certain safety level for exposure to like the people using it.

Q. So it is theoretically possible, I think you said?

A. It is theoretically possible, yes.

Q. Is it possible for your components of your system to absorb, for example, ethylene oxide and then release it slowly over time into your drug product and cause degradation?

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A. I need to split it up in two answers.

One, it is theoretically possible.

Secondly, this is what you avoid by having this post treatment measures in place. This is exactly what Sigg describes that I will help by pulling a vacuum to get to reverse the flow from the outside to the inside. So I pull it out. It's pulled out. There is nothing there which can later migrate into the system.

And also, you know, as a POSITA, exactly for that reason I need to avoid any gas ingress, I know which kind of rubber formulation I need to choose to the tip cap, also for the piston side. So this is usually chloro or bromobutyl which has a very high permeation barrier because they are designed for keeping the product safe.

Q. Looking at example 1 of Lam again, Mr. Koller, in the example on page 15, does the author provide some information about the stopper and the FluroTec barrier film on the stopper, right?

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A. Between line 10 and 15?

Q. Yes. Between line 12 and 17.

A. OK, yes.

Q. Other than that, does the Lam application provide any details about the syringe design?

MR. PEPE: Object to form.

A. It does not specifically mention any syringe design. Again, at the POSA, by knowing what is the drug product, I can do for sure some read-outs which would be for benefit for optimizing the system.

Q. But the Lam application itself doesn't specify, for example, the design of the syringe barrel or the stopper, right?

A. Right.

Q. There is no specification of the design of the plunger rod, right?

A. Right.

Q. There is no indication of the brand of syringe barrel that Genentech was using here, right?

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A. Right.
Q. There is no indication that the product was in a glass or plastic syringe barrel, right?
A. Right.
Q. There is no indication of whether the syringe barrel contains silicone oil, right?
A. Right.
Q. There is no disclosure of the break loose or glide force, right?
A. Right.
Q. There is no indication or data showing that the break loose and glide force can be maintained after ethylene oxide sterilization, right?
A. It does not state that, but I still disagree with that option because prefilled syringes are routinely ETO sterilized. So I know that ETO sterilization of prefilled syringes will not negatively influence the break loose glide force.
Q. But there is no data in Lam indicating

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that that was, in fact, the case, right?
A. Right.
Q. Let me ask you a follow-up question about the stoppers, Mr. Koller, if you could stay on page 15 of Lam for a moment.
A. Yes.
Q. So those stoppers, they indicate that they have a FluroTec barrier film, right?
A. Right.
Q. And that would be in most instances a tip cap that would prevent the rubber from coming into contact with the drug product, right?
MR. PEPE: Object to form.
A. I mean, it states here where the stopper only plunger comprised the 777-7 laminated micrometer coating of FluroTec barrier film and where the tip cap have comprised either 777 or D21 laminated. So it stops that -- it is not only the tip cap which is coated.
Q. So from your perspective, would a person of skill in the art be motivated to coat a FluroTec-coated stopper with parylene C?

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A. Yes, because according to Boulange, it gives them an additional benefit.
Q. So you believe a POSA would put two coatings on the stopper; both FluroTec and parylene C. Is that your testimony?
A. My testimony is you need to know the design of the stopper because there are FluroTec stoppers out where only the front end, the product contact side, is -- which is the so-called West FluroTec stopper, where it is only laminated to the product contact side.
If I do parylene C on this system, which is a plasma coating, I will coat the ribs which has a benefit on break loose glide force according to Boulange. So yes.
And I would put parylene C on top of the system because it doesn't do any harm to the system. So it depends on the type of system you are using.
Q. Regardless of whether the FluroTec is just on the tip or it's on the sides, when you do the plasma deposition of the parylene C, you're

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going to cover the whole thing up, right?
A. Right.
Q. So the FluroTec won't have any effect on the stop -- the function of that stopper, right?
A. Right.
Q. The next exhibit is IPR Exhibit 2022. This is a copy of a journal article, first author, Chan called "Syringe Siliconization Process Investigation and Optimization" from the PDA Journal of Pharmaceutical Science and Technology.
(Exhibit 2022, article entitled "Syringe Siliconization Process Investigation and Optimization" marked previously for identification.)
Q. Mr. Koller, if you could take a moment and look at that and tell me if you recall seeing it previously.
A. Right, this is the --
Q. I'm sorry, I didn't --
A. This is the reference, yes.
Q. You examined this --

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A. Yes.
Q. -- Chan reference before?
And the paper indicates on page 2022.002 that Chan and his coauthors are from Genentech, right?
A. Right.
Q. And Genentech is a company that makes protein pharmaceutical products, right?
A. Right.
Q. In fact, they were the developers of Lucentis, right?
A. Right.
Q. And would you agree that they had a motivation to decrease silicone oil interaction between -- let me strike that.
You would agree that Genentech had a motivation to decrease the interaction between silicone oil and its protein products, right?
A. Right. If -- if syringes -- I mean if functionality is guaranteed in the first place.
Q. Right. If you can't guarantee

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function, then you have to add more silicone oil in order to achieve the function that you need, right?
A. I disagree with that.
Q. OK, then I didn't understand your answer. I was trying to understand your answer.
A. The article here shows that they used a diving nozzle and static nozzle.
And it was known in the industry that static nozzle has certain technical limitations. It doesn't spray up all the way. So we have some undercoated system.
If you use a diving nozzle or if you say the only way that you can increase that by spray up is by significantly increasing, you know, the amount of silicone oil spray in the system.
So yes, the read-out is that I need to increase my system, my amount of silicone oil in order to, you know, coat the complete entire syringe.
If I am using a diving nozzle, there is also prior art out there which I have

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stated in my declaration that a certain diving nozzle has a feature where I can reduce the amount of silicone oil from point A to .5 or even down to .2.
Q. Just so I understand the numbers that you used there.
A. Yes.
Q. You're saying that you could decrease them down to 200 micrograms, right?
A. Spray technique --
Q. Is that your answer?
A. Spray technology allows a decrease down to approximately 200 micrograms.
Q. If you look at page 145 of the article, it is Exhibit page 2022.0011.
A. Yes.
Q. You see that there is a paragraph entitled, "Coated Silicone Amount"?
A. Yes.
Q. And the first sentence says, "There is a clear trend is that regardless of the spraying condition the higher the amount of coated

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silicone, the easier the syringe passes the glide force test."
Do you see that?
A. I see that.
Q. And you don't disagree that increasing the amount of silicone oil will decrease the glide force, right?
A. I disagree with that statement and I disagree with the statement in my first declaration.
Q. You disagree with the statement in this article, right?
A. Right.
Q. At the bottom of that paragraph, the authors say that the preferred amount -- let me strike that.
"The preferred silicone amount for the 1 ml long syringe is in the range of .2 to .5 milligrams per syringe."
Do you see that?
A. I see that.
Q. So these authors had concluded that

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the preferred amount was 200 micrograms to 500 micrograms per syringe, right?
A. Right.
Q. Right below that, under the title, "Optimization Considerations," it says, "The parameter investigation above was used to support the selection of optimum siliconization conditions. In the optimum -- in the optimization test we targeted a 0.3 milligram silicone coating dose which is near the low range of the preferred silicone amount."
Do you see that?
A. Right.
Q. So these authors, after having performed this optimization test, they landed on an amount of silicone oil of 300 micrograms, right?
A. Right.
Q. Regardless of whether or not you agree with the statement that the higher amount of coated silicone, the easier the syringe passes the glide force test, you would agree that this

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statement was available for a person of skill in the art to act on and analyze, right?
A. Right.
Q. This Chan article also reports on -- let me strike that.
The Chan article is also disclosing what has been referred to as oily siliconization as opposed to baked-on siliconization, right?
A. Can you point me to that one please.
Q. I thought that that was what you told me in your first deposition was that this reports on oily siliconization. Is that wrong?
A. No, I know it's an oily -- it tells you about the spray technique on oily deposition.
Q. There is nothing in here about baked-on siliconization, right?
A. Again, I would need to read through the article. I can't remember from the top of my head. I know it's talking about oily. But I don't know if it was also talking about baked siliconization.

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Q. The amount of silicone oil that's being referred to in that optimization paragraph, the 300 micrograms, that's an oily silicone application process?
A. It's an oily application process.
Q. So is it fair to conclude from this article that in 2012, Genentech was still using an oily silicone application in its syringes?
MR. PEPE: Object to form.
A. I mean, the article shows that they did some investigation on optimizing silicone performance. It doesn't say that they have been using only oily application in their syringes.
Q. So whether or not they were only using oily siliconization, they were still working with oily siliconization in 2012, right?
A. Right.
MR. PEPE: We have been going about an hour. Is there a good time for a break soon?
MR. JAMES: Yeah, good time.
(Recess; 11:34 to 11:48 p.m.)

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Q. Mr. Koller, I think you had in your declaration that you have a deep understanding of the worldwide syringe market.
Is that true?
A. I don't know if I have written that one in my declaration. But I have an understanding of the PFS market, yes.
Q. OK. How long after a prefilled syringe is manufactured does it take for the product to reach a doctor?
MR. PEPE: Object to form.
A. Can you -- what do you mean by manufactured?
Q. So how long does it take from the time that the product is filled and packaged and terminally sterilized for it then to be available to a doctor in order to use it in a patient?
MR. PEPE: Same objection.
A. You are not talking about the development. It's about fill finishing?
Q. Yes. From -- the final product is filled, sterilized, and it's in a box, in a carton

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on a pallet, whatever, how long does it take to get to a doctor?
I'm assuming it doesn't happen like in a day. That's what I am trying to get at. How long does it take based on your experience?
MR. PEPE: Same objection.
A. I can't talk to that one. Because that depends on the supply chain and logistics the companies have.
Q. Would it be fair to say that it would be at least a week?
A. It is fair to say at least a week, depending on the tests you need to do prior to release. This is only to ship it out. And then certainly where the product needs to be. So --
Q. So as a person of skill in your field, you don't have an estimation of like roughly how long it would take to get to a doctor? A month maybe?
MR. PEPE: Same objection.
A. As I said, there is some requirements around testing. So if you check on sterility, it

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takes a certain time in order to incorporate the system and you need to do some paperwork, and I can't speak to companies to say, OK, between like the last syringe fill and getting out to the first doctor. I can't talk to that one.
Q. Would it be fair to say that for some physicians, it would be perhaps quite a long time, several weeks because of supply chain and shipping and all of those kind of things? Would that be a fair assumption to make?
A. Could be the case, yes.
Q. However long it is, you would agree that it takes some time from the time that the product is finished until it's available on the shelf for a doctor to pull off and use on the patient's eye?
MR. PEPE: Object to form.
A. It takes some time.
Q. Now, I think we talked earlier about the fact that a prefilled syringe is a primary container closure, right?
A. Right.

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Q. It comes in contact with the drug solution, right?
A. Right.
Q. Would you agree that the components of a primary container closure need to be compatible with the human body, right?
MR. PEPE: Objection to form.
A. No.
Q. Would you agree that the components of the primary container closure need to be compatible with one another when they're filled with the drug?
A. This would come out of the -- during your development and testing. If they -- if they, you know, rubber works with the syringe and if the tip caps works with the syringe.
Q. OK. Just going back to my other -- my earlier question, maybe my question relates more to leachables. I believe you consult with companies on regulatory issues relating to leachables, right?
A. Extractables and leachables, yes, I

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do.
Q. What's the difference in an extractable?
A. So extractable is a compound you force to come out. So you are using a strong solvent under worst case conditions. So you force the compound out.
This gives you an idea about the system itself and you would do a toxicologic assessment on the identified compounds to verify if this would cause some potential toxicity if a component might come out as a leachable. And this is more material testing. So in extraction testing, you are the material and the likelihood what might come out.
On the leachable study, you do that under similar use under standard conditions, how you usually would store your syringe. That means it needs to be done with the actual drug product. So the final leachable study is usually done by pharma company with the final drug product under standard storage conditions. And then they

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check what leachable is coming out which is then completely different to the extractables just because of you don't exert a certain force to it. So understand the conditions.

Q. So an extractable test is where you expose the material to some sort of condition like a solvent to try to force out any potential compound that might come out over time, is that right?

A. Right.

Q. And then you test the compounds that come out for toxicological effects, is that right?

A. No, that's not right. You don't test the compounds coming out for toxicological effects.

If you know what kind of -- you know if it's a semi-volatile, volatile, nonvolatile component, then you have so-called toxicologists in-house which have access to certain databases where they can check regarding on the chemistry of the system if this has a toxicological impact.

Q. So the toxicological impact of the compounds that come out in an extractability test have to be checked, right?

A. Yes.

Q. And that can be that you look at a toxicology database and you see that this particular compound has been reported in the past and it does or does not have some sort of toxicological impact. So testing isn't required, right?

A. There are some circumstances where testing would be required. If you cannot identify the compound, which could happen because it could be a degradation product which, you know, develops itself. So then you need to do certain analysis. There is a certain procedure in place.

But people very often mix up the toxicity in comparison to biocompatibility testing for use in container closure systems.

This is then described in the ISO 10993, biocompatability evaluation of medical devices which gives you then, you know -- there is a table in there which classifies your device, could be in case of prefilled syringe and then asks you to perform certain biocompatability testing. This is part of the evaluation.

So as a POSA in general for a container closure system, I usually use or get data from the manufacturer regarding biocompatability. Some data -- some might have extraction data that refers to a toxicity assessment. But usually you ask for biocompatability data regarding -- according either to USP 6 or ISO 10993.

Q. And then a leachability test is where you test for the presence of compounds that might come out into your drug product solution in simulated use conditions, right?

A. Right.

Q. So three different things, extractability testing, leachability, and then this biocompatability assessment, is that right?

A. Right.

Q. And then do each of the three tests have to be done on every component of a primary container closure system?

A. So usually -- like the syringe manufacturer, he would have a syringe paddle, silicone, tip cap from company A and rubber component maybe from the same company A or maybe could be from company B.

All these components usually require, would ask for some sort of regulatory information. So that this raw material is using, in my PFS, are compliant to either ISO -- certain ISO requirements, material requirements in Pharmacopoeia that includes also some biocompatibility testing.

And then if I mix that together, I would do a sort of additional extract to verify the combination of this one and depending on the need, there could be -- there is no need to do so, but it could help your customer if you give them a list of possible extractables which might come out of container closure system.

Q. For every primary container closure system, whether it comes from your customer or from you, the person of skill needs to assess the

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extract, leachability, biocompatibility of all of the components of the system, right?
MR. PEPE: Object to form.
A. So it can be done on paperwork if customer can supply me that this system was USP classics tested.
If he shows me some reports that he did some additional testing about, let's say, function or performance.
So I don't need always to repeat that one if I know that the system is there. I could, I could do, but there is no request. So the pharma company which has the drug product inside, they are legally required to show stability and that involves also leachability study.
Q. OK, I wasn't intending to suggest that you would have to test for all those things, but I think what my -- I think what I was trying to ask was that for every primary container closure system, for all the components that come into contact with the drug, that you have to assess whether on paper or by testing biocompatibility,

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extractability, leachability, is that correct?
MR. PEPE: Object to form.
A. The biocompatibility, extractables, leachables, it's -- as a component manufacturer, leachables is not usually what we test because you don't have an extraction behavior. Extraction gives you idea. So if you design a system, you would do sort of extraction to see how the system, you know, performs, behaves.
Q. OK, and then the pharmaceutical company would be required to demonstrate stability of the product in the primary container closure system over time which would be -- which would include leachability, right?
A. Right.
Q. Again, a leachable is a compound that could come out of the materials that come into contact with the drug product, right?
MR. PEPE: Objection, asked and answered.
A. Right.
Q. In your experience, would the FDA or

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EMA approve a product if a leachable compound could not be identified?
MR. PEPE: Object to form.
A. You ask me if I have experience.
Q. From your experience, would the FDA or EMA approve a product if there was a leachable compound that could not be identified?
A. I mean, it would be a requirement to identify them. They are all pathways to do so.
But because one lab could not be able to identify and if this is an issue with some labs, that you need to have a really sophisticated labs in order to do so, it could be that they say OK, I have a leachable, I would not go in front of the EMA to represent a known -- unknown leachables.
So despite the safety concerns, threshold level is below a certain -- so there is a systematic in place that is regarding related to toxicity on so-called safety concern threshold.
So toxicologist find out for certain toxicology classes 1 to 3, there are certain limits which allows you a daily intake and

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they have certain classifications 1, 2 and 3. So class 3 is the more stringent one.
And if I know what to do and what to look for, then I need to find methods, analytical methods which show me a certain analytical evaluation thresholds, which clearly shows me that I can identify this low amount of leachable.
So everything which is below that threshold, even if it's like ten peaks which are unknown, are not of interest regarding toxicity because that classification for certain compounds is below that threshold, it's not toxic.
If it is above that toxic, then yes, it asks me to do some additional toxicology studies.
Q. So the FDA or EMA would require toxicity evaluation for any leachable that's above some threshold value that is set by the agency, right?
A. Yeah, set on the classification of toxicity. For example, it says, it is a nontoxic system, then the evaluation threshold can low and

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the compound which might come out could have a very high concentration toxicology-wise, this would not be an issue.

Q. And there are several different types of toxicity tests that could be performed on a leachable like that, right?

A. There are so-called biocompatibility evaluation which ask you like about systematic or systemic toxicity, yes. It's addressed in the ISO 10993.

Q. One of the types of biocompatibility tests is an in vitro cytotoxicity test, right?

A. That's one of them.

Q. And that's a test that's done in the lab to see if a compound causes toxicity in cells, right?

A. This is 10993-5.

Q. I don't know the number, but that is what a cytotoxicity test is, right; a test done in the lab to assess toxicity to cells?

A. There are different cytotoxicity tests. So if you talk about 10933-5, then I know

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that's a cell test.

Q. And the reason that a cytotoxicity test would be done would be to assess the potential for that compound to cause toxicity in patient cells if the compound was introduced into the patient, right?

A. So ISO test, as I said in the 10933-1, there is a certain table which guides you along to say what is the intended use for your medical device, and according to that medical device, it gives you a list of toxic studies or biocompatibility tests you need to prove.

Q. The next exhibit is IPR Exhibit 1041. The title is "Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics."

(Exhibit 1041, article entitled "Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics" marked previously for identification.)

Q. Mr. Koller, if you could take a look

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at that and tell me if you have seen it before.

A. Yes, I've seen that before.

Q. Can you explain what Exhibit 1041 is?

A. It's a guidance for industry to check on container closure systems for packaging human drugs and biologics.

So it gives you a guidance what would you need to do in order to check that my container closure system is sound and safe.

Q. Is this a document that you work with in your practice?

A. Yes.

Q. If you look at page 2, which is Exhibit 1041.005.

A. Yes.

Q. Toward the bottom it says, "A container closure system refers to the sum of packaging components that together contain and protect the dosage form."

Do you see that?

A. I see that.

Q. The next sentence says, "This includes

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primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product," right?

A. Right.

Q. And in that sentence, primary packaging components would refer to those components that come in contact with the drug solution?

A. Primary packaging system is designed above.

Q. OK. And there it says a primary packaging component means a packaging component that is or may be in direct contact with the dosage form, right?

A. Right.

Q. If you could turn to page 6, do you see a table there, examples of packaging concerns for common classes of drug products?

A. Table 1, yes, I see.

Q. OK, now, injectables have the highest degree of concern associated with the route of

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administration, right?
A. In this table, yes, but this table changed in the latest USP version for extractables and leachables, 1663. And the injectables moved to medium instead of high.
Q. This table doesn't have a medium. So the new table has additional rows in that left-hand column?
A. No. I mean, I see the highest, high, low on the left-hand side. You see high, medium, low for the likelihood of packaging component form interaction.
Q. Is this FDA guidance that we are looking at, is this still in effect for companies that are trying to get PFS approved?
A. Yes. So it's still in use and it's still used widely. But some references where there have been changes in the United States Pharmacopoeia and it is worthwhile to look if there would be any additional features to look and check for.
Q. And then the USP injectables have been

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moved down one notch, is that right?
A. They moved down to the right. They moved from high high to highest medium.
Q. OK. Focusing on this particular table, the fact that you have an injectable in the highest category here, does that indicate that it's especially important to evaluate potential impact of packaging materials on the drug product?
MR. PEPE: Object to form.
A. I mean, it says that, you know, it has the highest rating on the degree of concern with the root of administration, like inhalation or injectables, and it says there is a likelihood of packaging component dosage form interaction which is also high, or the new one would be medium.
Q. If you could turn to the next page, please, page 7.
Under general considerations part 1, suitability for intended use. There it says, "Every proposed packaging system should be shown to be suitable for its intended use and should adequately protect the dosage form. It should be

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compatible with the dosage form and it should be composed of materials that are considered safe for use with the dosage form and the route of administration."
Do you see that?
A. I see that.
Q. Do you agree those are the considerations that go into the design of a prefilled syringe?
A. One of the considerations, yes.
Q. When it says the materials are considered safe for use with the dosage form and route of administration, what do you understand that to mean?
A. Just let me read through.
So to check the below basically defines, you know, what -- there is a general understanding of say and this is also my, let's says, expertise that you say you have container closure system which guarantees a certain protection and then you follow certain guidelines on protection, it has certain issues on, B, on

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compatibility and then, C, on safety and, D, performance.
So it's not only that you say, OK, I can explain what safe means in general terms for prefilled syringe, but as the system describes, it needs to protect the drug over shelf live and then needs to be still usable at the end of shelf life and it gives you a guidance here and, again, this is an FDA guidance which is, yeah, not mandatory to follow, but a good advice to follow.
Q. Just so I understand, protection which starts on page 7, that refers to simply keeping the drug product from being negatively impacted, right?
A. It says, you know, the dosage form of a shelf life, common causes of such degradation are exposure to light, loss of solvent, so if it is not gas tight, and exposure to reactive gases, e.g. oxygen.
So you need to take care in general terms that no oxygen might come in for oxidation of the product, absorption of water

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vapor, that you don't lose any water inside the syringe or water might migrate into the system, if you have a lyophilized product.

So, and it is defined what light protection mean in USP, you need to do certain testing, and of course, there is a difference with that one because this is not specific only on glass or polymer. It describes different materials.

Q. And the next one was compatibility and that refers to the interaction between the primary container system components and the drug product?

A. Yeah, and here, they mention is the packaging components that are compatible with the dosage form, will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component.

So it is known that there could be some minor changes in the system. But if it doesn't lead to any toxicity concern or to unacceptable changes in the system because like a purity below a certain level, then this slightly

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changes to the control part is still acceptable if I can prove all the other system, like extractables, leachables, safety and so forth.

Q. One of the examples of compatibility that's listed there is loss of potency due to absorption or adsorption of the active drug substance, right?

A. Are you in the second paragraph of compatibility?

Q. Yes.

A. Yes, absorption or adsorption of the active drug substance.

Q. Then the next section is safety and there it says, "Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product."

Do you see that?

A. I see that.

Q. From your perspective, a person of skill designing a prefilled syringe would follow

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these guidelines, right?

A. I would follow certain guidelines, but there is no requirement that a PFS manufacturer needs to do all the -- because some is related to the extra drug product which is then, again, pharma company.

Q. Would you agree that all these factors that we have been talking about are important for a prefilled syringe that is filled with a biologic for intravitreal administration?

MR. PEPE: Object to form.

A. There is a general statement what primary packaging means to protect the product -- or the shelf life. And even a syringe manufacturer can act up to a certain point and then he does not know -- sometimes he does not know what the syringe is used for, what is the drug product, what is the route of administration.

So he can give some data up to a certain point and then the responsibility, you know, is then within the pharma company in order to fill the gap which is needed for the submission.

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Q. Regardless of whether it's the syringe manufacturer or the pharmaceutical company, you would agree that each of these factors, protection, compatibility, safety are important aspects of the design of an intravitreal prefilled syringe, right?

MR. PEPE: Object to form.

A. Including performance, they are designed for all PFS applications.

Q. We didn't talk about performance yet, but performance is a requirement that the container closure system maintains its ability to function in the manner it was designed, right?

A. Right.

Q. And that's over the shelf life of the product?

A. Right.

Q. In the context of a prefilled syringe, performance would include measurement of break loose and glide force, right?

A. Right.

Q. The next exhibit will be IPR Exhibit

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1008. It's a copy of the Boulange application WO2009/030976 A1.

(Exhibit 1008, Boulange application WO2009/030976 A1 marked previously for identification.)

Q. Mr. Koller, if you could take a look at that and confirm that that is the Boulange application that you offered your opinions about in this IPR?

A. Yes.

Q. This is an application that's assigned to Becton Dickinson, right?

A. Right.

Q. And it was filed in 2007?

A. Right.

Q. And if you could turn to page 14. There is a table there entitled, "Configurations of pistons A, B1 and C."

Do you see that?

A. I see that.

Q. In that table, the piston referenced as B1 is indicated to be the invention, right?

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A. Right.

Q. And -- let me strike that.

Let's turn to page -- B1, the invention, just so we are on the same page is a bromobutyl rubber stopper coated with parylene C, right?

A. Right.

Q. And by comparison, stopper A is bromobutyl rubber with no parylene C coating, right?

A. It says no coating.

Q. And stopper C is a chlorobutyl rubber stopper with no coating, right?

A. So by coating definition here, it does have para -- not parylene C coating. The rubber component itself, as we discussed, could be coated by a FluroTec film.

Q. Does it say that in here?

A. No. It says, Coating, yes. Parylene C and coating, no.

Q. So from the perspective of this particular table, stopper C doesn't have a

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coating, right?

A. It doesn't have parylene C coating.

Q. And there is no indication it has any other coating, right?

A. I would need to -- you would need to give me time if I can go through if I can see if they have a reference if they use as an example FluroTec-coated piston.

Q. If you could turn to page 21, please. Look at table 7.

A. Yes.

Q. So in table 7, there are two scenarios that are compared, correct?

A. Correct.

Q. Scenario 1, the syringe barrels are siliconized with 4 micrograms per centimeter squared silicone oil. Right?

A. Right.

Q. And scenario 2, the syringe barrels are coated with 50 micrograms per centimeter squared of silicone oil, right?

A. Right.

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Q. Then the various pistons that we just talked about, A, B1 and C, are tested for their break loose and glide forces under both of those scenarios, right?

A. Right.

Q. The results for the break loose and glide forces are recorded at -- for A, and B and C time zero and then time 1. A also has two other time points. But just focusing on time zero, do you see that each of them was tested at time zero?

A. I see that. Yes.

Q. And what does time zero mean?

A. Time zero usually means that if you put in the rubber component into the syringe and perform a testing within a certain time frame and that is then your day 1, your time point zero before you start, like your four weeks at 40 degrees centigrade storage.

Q. So in general, how long after you put the stopper into the syringe do you test and call it time zero?

A. There is no rule for that. Companies

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do have different rules in place for -- between the alignment of the stopper. POSITA knows that you should usually do it in a certain, let's say, short time frame in order to get the actual results there.

Q. And from the point of view of a person of skill in the art, what is that short time frame generally?

A. Coming back to having experience as a syringe manufacturer, the system we have been using there was to qualify the siliconization of the syringe.

So I wanted to check if the glide force of my syringe was there because then I could say I have an even distribution of the silicone oil in my syringe.

So this test was limited then like it needs to be tested less than 24 hours.

Q. Would you agree that a doctor could not have gotten this syringe filled with the antiVEGF drug solution and administer it to a patient at time zero?

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MR. PEPE: Object to form.

A. Are you talking -- are you asking if the 6.6 is not suitable?

Q. No, I'm just asking in terms of timing, it says that these were tested at time zero, and I'm asking if time zero corresponds to a time when a doctor could actually have gotten this product and administered it to a patient?

A. If the internal design was time point zero was measurement in 24 hours, then they would not have access to that.

Q. And then the tests are -- let me strike that.

After that, they did testing at one month for each of these stopper configurations, right?

A. A test at one months at 40 degrees centigrade, 75 percent humidity, according to accelerated aging, this relates to three months at real-time temperature.

This is routine testing for break loose and glide force, that you accelerate the aging in order to find out what could possibly happen at real-time aging. And there are some calculations in place which span 28 days for the 40 degree relates to three month three times storage.

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Q. OK, let me make sure I understand.

You are saying that the accelerated aging that is reported here is a routine test on these kinds of syringes, right?

A. Right.

Q. And you're further saying that in your opinion, the aging test at time one month actually approximates what would happen at three months?

A. Based on the accelerated aging calculation, this is a good estimate. But you still need to verify what your actual performance.

Q. What is the three-month factor that you are talking about there? What is that based on? Is there a document that I can look at for that?

A. A POSA knows that there is an ASTM method out which qualifies accelerated aging.

Q. Can you tell me what ISTM stands for?

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A. I think it is American Society for Testing of Materials.

Q. So ASTM?

A. ASTM.

Q. OK. So there is an ASTM guideline on accelerated aging?

A. Right.

Q. And does that have the three-month factor in it?

A. They give you certain guidance how you calculate based on storage time at 40 degree with a certain factor, what this relates to at three time room temperature.

Q. OK. OK, so then looking at the data for the break loose force for the first scenario, for A, the break loose force from time zero to one month more than doubled, right, from 6.6 to 15.7 newtons, right?

A. Right.

Q. And for stopper B, the force stayed lower, it was 2.1 at time zero and went up to 3.0 at time one month, right?

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A. Right.
Q. And then for stopper C, at time zero was 3.9 and then it went up again more than twice to 14.4. Right?
A. Right.
Q. And then just below the table, it says, "With pistons A and C the friction force BS and F were relatively high, something which does not appear to be acceptable for a medical device."
Do you see that?
A. I see that.
Q. And you would agree that that statement is something that a person of skill in the art could factor in when deciding to -- whether or not to use the technology disclosed in Boulange, right?
MR. PEPE: Object to form.
A. I don't dis-- I disagree with that statement here due to following reason that the silicone on the piston is zero.
So there is no silicone oil on the rubber, which is usually state of the art that

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you siliconize the system. This is given in prior art by Nema and others. So I usually would expect that my piston has some kind of silicone oil in the system.
The other side says it does not appear to be acceptable for medical devices. So A shows an increase to 16 or 15.7, but even 15.7 is still within, let's say, you know, the explanation on the '631 patent that, you know, PFS used with NTGBF applications had prior art usually break force lower than 20 newton.
So there is an increase, but this increase would be minimized if you would have silicone oil on the piston and still the forces could be used for certain application even in medical devices.
And you know the statement only relates to table 7 which is specific that there is no silicone on the piston. It doesn't disqualify piston A and C for other experiments Boulange is showing.
Q. Well, whether or not you disagree with

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the statement, the statement is still there for a person of skill in the art to take into account in deciding whether or not to adopt the technology in Boulange, right?
MR. PEPE: Object to form.
A. The person of ordinary skill in the art would read, look at the data, look at the table and would come up with an explanation that this is still good to go.
I don't see the point why a POSITA should discard piston A and C. I would go ahead with piston B1 because it shows me that there is hardly any increase in the break loose glide force even after T1 months.
Q. Is it your position that a person of skill in the art would simply ignore that sentence where it says it does not appear to be acceptable for a medical device?
A. It says "does not appear." Does not mean it is excluded.
Q. My question was, is it your position that a person of skill in the art would ignore

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that statement?
MR. PEPE: Objection, asked and answered.
A. First of all, a person of ordinary skill in the art would look why the statement is there.
Q. So they would not ignore the statement, right?
A. I would not ignore the statement. Usually I find the root cause for that it says not to be acceptable.
Because it is clear Boulange is promoting, of course, the parylene C coating. So if I take off -- the silicone coating off the piston, of course, I would expect then different forces than if I would have siliconized piston which you showed in table 5. If you use scenario 1 with siliconized pistons that you have by far a less increase and that then, of course, these forces become even lower and will fall within the claim range.
Q. Now, the explanation that you are

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providing for why you had a certain understanding of that sentence, that it's really about the A and C stoppers not being siliconized. That doesn't appear anywhere in that paragraph, right?

MR. PEPE: Object to form.

A. I mean, it says with pistons A and C, relatively high, which does not appear to be acceptable to medical devices is a side statement. But the explanation is below table 7 and table 7 clearly shows there is no silicone on the piston. So I would not see how somebody could ignore that or just make sure that he is able to see what he's talking about if it's not about table 7.

Q. So I think what you are saying is that you would look at the statement and come up with an explanation for why it doesn't mean that A and C are not -- are not acceptable, is that right?

A. I would not look for excuses. I would say what is the fact, and the fact is there is no silicone on the piston, the numbers go up, yes. This is what I would expect as a POSA. But the other numbers would still be acceptable for some of the applications for a medical device. This is my POSITA read-out.

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Q. But these authors wrote that A and C did not appear to be acceptable, right? That's what it says?

A. That is what it says, yes.

Q. It contrasts that with B1 which says that the forces of B1 were entirely compatible with the way in which a medical device is used, right?

A. Right.

Q. And an intravitreal syringe is a medical device, right?

A. You can call it that, yes.

Q. And the next paragraph, it talks about the one month of aging and it says that the one month of aging, the friction forces had increased appreciably.

Do you see that?

A. I see that.

Q. That was for A and C, correct?

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A. Yes.

Q. And so would you understand the first paragraph to relate to the time zero measurements and the second paragraph to relate to the time one-month aging data?

MR. PEPE: Object to form.

A. Second paragraph clearly references the aging data.

Q. Now, you reference table 5. Let's look at that. That's on page 19. And here again, you have data for the pistons A and B1 and C, right?

A. Right.

Q. Then if you just compare the time zero break loose force for A and C in table 7 with the time zero break loose force for A and C in table 5.

Do you see that?

MR. PEPE: Object to form. Which A and C?

Q. The time zero break loose force in table 7 compared to the time zero break loose force in table 5 or A and C?

Do you have that?

A. Table 7, A time point zero, 66 break force?

Q. Yes.

A. Compared to the A time point zero B66 in table 5?

Q. Right.

A. Right.

Q. And how does C compare?

A. C time point zero is 3.9.

Q. In table 7?

A. In table 7, and is 4.7 in table 5.

Q. And so the break loose force for both of those stoppers was higher at time zero as recorded in table 5 than in table 7, right?

MR. PEPE: Object to form, mischaracterizes the document.

A. If it's -- if it's the same time point zero, I don't know. But it's higher.

Q. Just so the record is clear, it's the same for piston A and it's higher for piston C, at

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time zero, right?
A. Right.
Q. And then just below table 5, in the second sentence, it says, "The results obtained with a piston having no coating, piston C, are markedly inferior."
Do you see that?
A. I see that.
Q. And again, this is a statement that a person of skill could take into account in determining whether or not to employ the technology disclosed in Boulange, right?
A. Right. But again, the results obtained with a piston having no coating, piston C are marketedly inferior, does not mean I can't use it.
If I look at the data and if I know what is useful certain application, a break force of 547, or even after one month of a break force of 84, is -- even in table 5, far within the claimed ranges of the '631 patent and far below the 20 newton, which has shown that these forces have

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been used for typical application of syringes with VGF or with VGF.
I don't see the point, as a POSA, that this one teaches away that you could not use piston C. It is his statement because it's inferior compared to his invention, yeah, but it's not that I cannot use it for application.
Q. So you would agree with me that the statement under table 5 and statement under table 7 makes clear that piston B1 is superior to piston A and piston C, right?
A. Right. So if I know parylene C and if I know the systematic or -- the date of prevalency, so I, as a POSITA, I could go ahead and say I would use the B1 invention and my back-up would be like a plan C out of table 5.
Q. You would agree describing something as markedly inferior and unacceptable are not terms that would motivate a person to use a particular technology, right?
MR. PEPE: Object to form.
A. I don't disagree with that -- I mean,

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I disagree with your fact.
So markedly inferior in table 5 is a clear expression. But I need to put it in relation on what the results on piston C is. And if I see the results, yeah, it's not as good as B1, but suitable for my intended use if I want to use it.
Q. But you would agree that markedly inferior and unacceptable are not motivating statements, right?
MR. PEPE: Object to form. Asked and answered.
Q. It's just -- that's just English, right? Those are not motivating statements, are they?
MR. PEPE: Objection, argumentative.
MR. DESAI: And rude.
Q. Do you understand my question?
A. I understand your question.
MR. PEPE: You had about three questions. Can you ask a proper question. You have three pending.

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MR. JAMES: I think he understandings my question.
A. Not very motivated, but it's not that I would not have a Plan B in place.
Q. OK. If you could look in your declaration at paragraph 143. Actually, I want to look at table 17 -- I'm sorry, strike that.
I want to look at footnote 17 on that page. Page 84.
Do you see that?
A. Yes.
Q. OK, there you write about table 7 of Boulange and you say, "The aged syringes were stored in a chamber for a period of time before testing at extreme conditions, i.e. 40 degrees, to assess the worst case performance of the syringe over its shelf life."
Do you see that?
A. Um-hm.
Q. Now, Boulange doesn't call the aging tests worst case, correct?
A. Correct. He says -- let me check it,

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one minute please.
So he says, "In order to study the evolution of the interface, namely, the contact region between the piston and the container, samples undergo an accelerated aging in climactic room. The conditions of the Heraeus climactic room were temperature 40 degrees and humidity rate of 75 percent. The systems assessment were placed in the climatic room during 1, 3 and 6 months."
Q. And just for the record, you were reading from page 15, lines 17 to 21?
A. Page 15, line 17 to 21.
Q. Boulange doesn't describe the accelerated aging testing as worst case in that paragraph, right?
MR. PEPE: Objection. Asked and answered.
A. Boulange is working for BD. So BD is the provider for prefilled syringes. So BD has knowledge and experience that 40 degrees centigrade for four weeks is reaching a certain plateau on the break force.

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So this is why it is industry standard to use 40 degrees for a month to see what the possible outcome can be.
Q. But you don't know what Boulange was thinking other than what they wrote in this application, right?
A. I mean, I guess that he has also some knowledge like me for a POSITA, so I can immediately translate 40 degrees centigrade one month to a certain worst case scenario.
Q. I understand you're guessing about it. But I am -- all I'm asking you to confirm this application does not describe the aging as worst case, correct?
A. It's not describing the aging as worst case.
MR. PEPE: We have been going about an hour. If you can find a place for a break soon.
MR. JAMES: This is fine for a break.
(Luncheon recess; 12:49 to 1:20 p.m.)

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AFTERNOON SESSION
1:34 p.m.
BY MR. JAMES:
Q. Welcome back. If you -- let me ask you this, can you just explain what the break loose effect is?
A. The break lose effect?
Q. Yes.
A. If you store a rubber -- like siliconized rubber in a silicone oily glass syringes, usually it pushes away. Due to compression, it pushes away a little bit the silicone oil on the surface.
Then the rubber comes direct contact with the container surface, and due to stickiness of rubber and by pushing the stopper away, it results in typically a break force.
So usually you have a sort of baked system, then, you know, you should have a layer between the rubber and the container surface because it's like a sort of, you know, siliconized layer and that would avoid that the rubber comes in

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contact with the surface of the container and it should show less break loose effect. That means that over the shelf life, there is a certain increase in the break force.
Q. So with the oily, as compared to the baked-on siliconization, you would expect the oily break loose force to go up over time compared to baked-on, is that right?
A. If the prior art is confirming what I know based on my own experience but depending on the type of pistons, that break loose effect might be limited. So it's always a combination between the type of rubber and the surface.
Q. OK. So the break loose effect is not necessarily limited to the impact of whether the silicone is sprayed on or baked on, it also includes a contribution by the stopper?
A. Right.
Q. If you could look back at table 6 of Boulange, please.
And if you compare 9, scenario 1 and scenario 2 results for the A stopper, am I correct

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that the break loose force increases more with the baked-on syringe barrel than it does with the oily siliconization barrel?

A. Correct.

Q. So in this instance, the oily siliconization exhibits less break loose effect than baked-on siliconization?

A. Right.

Q. Which is contrary to the way the break loose effect -- the way you described the break loose effect a few minutes ago, right?

MR. PEPE: Object to form, mischaracterizes testimony.

A. What I said is that it can show break loose effect. There is no need to show break loose effect.

Q. You would agree if there is a break loose effect shown as between these two, it's with baked-on siliconization, right?

A. Yes.

Q. And the same thing is true for the C stopper comparing scenario 1 and scenario 2, the

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break loose effect, right?

A. Right.

Q. If we look at table 5, how does the break loose -- how does the break loose effect compare between -- the baked-on and the oily siliconization?

MR. PEPE: Object to form.

A. Table 5 doesn't have the scenario 2. Table 5 only shows the scenario 1 or the baked siliconization.

But what is missing, what they have is that the silicone on the rubber.

Q. So it's a different stopper? It has a coating on it?

A. It has silicone coating on it.

Q. You pointed out that you can't really compare with table 5. I guess I was confused about that. Thank you.

So if we compare table 5 and table 4, table 5 is baked-on siliconization, table 4 is sprayed-on siliconization, right?

A. Let me read through that because this

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table did not cite table 4 in my declaration.

So table 4 is on -- OK.

Q. Yeah, it's on page 18.

A. OK.

Q. Again, the break loose force goes up more with the baked-on siliconization than it does with the oily siliconization comparing these two tables, right?

A. Right.

Q. So at least these two examples that we just looked at, tables 4, 5 and 7 in the Boulange application, they are inconsistent with the conclusion that sprayed-on siliconization will result in a higher break loose effect than baked-on siliconization, right?

A. If I leave the spray on to a certain amount? Then yes.

Q. Let me make sure I understand your answer.

With the amounts of silicone oil that are described in these tables, then the answer is yes, is that right?

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A. Does not support the break loose effect.

Q. You would agree that Boulange does not disclose testing the syringes with ethylene oxide or vaporized hydrogen peroxide, correct?

A. It says develop the system which can withstand sterilization but is -- what was your question again, please?

Q. There is no reference to sterilization with ethylene oxide or vaporized hydrogen peroxide in Boulange?

A. There is no reference to a specific sterilization method.

Q. Do you know whether Boulange ever issued as a patent?

A. This is a patent application I have here.

Q. That's correct.

A. In front of me. So I'm not aware if there is an actual filed patent.

Q. You just don't know either way?

A. I don't know.

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Q. Do you know whether Becton Dickinson ever came out with a syringe using parylene C coating on the stopper?
A. I don't know.
Q. You are not aware of one, right?
A. I don't have access to that data to prove that because this is usually not disclosed, depending on how you do your type of submission. I don't even know if Becton Dickinson has a drug master file assigned which would describe a parylene C coated syringe.
Q. So you don't know whether Becton Dickinson filed a DMF on a parylene C coated stopper or ever had a commercial production with parylene C coated stopper, right?
A. Right.
Q. Are you familiar with the BD Hypak or Biotech SCF syringe?
A. Yes, I am.
Q. What do you know about that syringe?
A. BD developed the Hypak. That was a trade name for Becton Dickinson. And they have

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different rates or different grades and one they call Biotech and it's -- so, this was usually if you talk about Biotech in general terms, they have low tungsten, they have controlled siliconization process, and they have more, let's say, controlled dimensions for certain application in the biotech industry.
Q. Do you know whether the BD Hypak for Biotech SCF was available prior to July of 2012?
A. I know that the Hypak SCF was available prior to 2012.
Q. Do you know how much silicone oil it had in it?
A. I don't --
MR. PEPE: I'm going to object to form. Try to segregate what you know that's confidential information versus what's public. But obviously Bausch or anyone else associated with Macugen isn't here and wouldn't want their information disclosed.
A. Right.
Q. Setting aside any confidential

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information you might have, based on publicly available information and your work in the industry, do you know how much silicone oil was in the BD Hypak Biotech SCF syringe?
A. I don't know. I would have to look in their product specifications.
Q. Do you know whether the silicone oil was baked on or sprayed on?
A. If it's a stake needle syringe, it needs to be sprayed on.
Q. Is it a stake needle syringe?
A. If it's a stake needle syringe, it's a stake needling syringe. But Hypak is available also with luer-lock or luercone.
Q. Maybe you could spell that for her?
A. L-U-E-R and then lock, or L-U-E-R-C-O-N-E.
Q. So you are saying that the -- that BD Hypak for Biotech syringe was available with staked-on needle, a luer-lock or a luer cone, is that right?
A. I said that it -- BD Hypak was

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available.
I would need to go back -- I don't have it top of my head if the BD Hypak Biotech was there because they have different grades and I can't just recall when the Biotech syringe came out on the market.
But I know if it is a stake needle syringe, it is for sure sprayed siliconization and usually Biotech syringes are stake needle syringes for certain applications.
Q. Does a stake needle syringe need to have spray siliconization?
A. Because the needle bonding takes place prior to siliconization, and if you do a baking it would not survive the 330 degree for half an hour.
Q. Do you know if Becton Dickinson promoted the Hypak for Biotech syringe as its best syringe for biotechnology products?
MR. PEPE: Object to form.
A. Are you referring to a special date for promoting or is it in general terms?
Q. Well, do you know at any date?

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A. BD is the main supplier. So BD is the forerunner of all PFS development out in the field. So whatever, you know, is out, BD was first.

Q. OK.

A. So I have different, as I explained, they have different grades in place.

Q. Right.

A. So Hypak is Hypak SCF is a certain trade name for a certain sterile clean fill. This is a ready-to-use syringe. And based on that, they do offer different type of syringes intended for different use in application.

Q. OK, so sorry if this seems like the same question, but prior to July of 2012, do you know if Becton Dickinson was promoting the BD Hypak for Biotech SCF as its best syringe for biotechnology products?

MR. PEPE: Object to form.

A. It's -- Biotech is a sort of trade name. There might be a syringe out which might do the job for a biotech application which is not

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called a Biotech syringe.

So it -- this is a trade name which says, according to my customer, I get the syringe with certain specification, and even if this -- if it says it is a Biotech syringe does not necessarily mean that my drug product which is a biotech product is compatible with the type of syringe.

So you always need to check on that one. It could be that my biotech product is on a standard syringe available because it might not be silicone sensitive, tungsten sensitive, or might not require special cosmetic issues or dimension or specifications.

Q. Do you know if the BD Hypak Biotech was available with luer-lock prior to July 2012?

A. I don't know the exact date. I know that BD luer-lock -- I mean, BD luer-lock syringes and luer cone syringes with OBS or with a certain luer-lock adapter have been available in the market. But I cannot refer to a certain date without having proof or evidence.

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Q. Was Hypak the trade name for the Becton Dickinson prefillable syringes?

A. BD developed the prefillable syringes as a ready-to-use system and their -- one of the first name was BD Hypak.

Q. What does the Hypak indicate to a person of skill?

MR. PEPE: Object to form.

A. It has to do something with packaging and maybe high expectation. I don't know what the --

Q. You don't actually know what the -- if Hypak was a trade name that was associated with any particular kind of syringe for any particular use, is that right?

MR. PEPE: Same objection.

A. Right.

Q. You don't know if Hypak was limited to prefillable syringes or if it could also be used as a trade name for syringes that could be used to extract from a vial and inject, is that right?

A. Hypak SCF is a ready-to-use system.

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Q. So Hypak SCF, sterile clean fill is a prefillable syringe?

A. Right.

Q. Now, going back to talk a little bit more about Boulange, and parylene C, did you investigate whether parylene C would actually stay bonded to rubber stoppers over time?

A. During my time at Schott, we had a product development, which is called Ingentle, where we coated one of the rubber components and we needed to verify that the rubber, if the parylene C stays on the system and if it's doing the job as designed for this specific need.

Q. And in that Ingentle system, the parylene C was not used on the stopper of the syringe, right?

A. Right. It was used in the place which is in direct drug product contact.

Q. And as far as you know, that syringe has not been commercialized for use with any product, right?

A. In 2015, until I left Schott, right.

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Q. If you look at the figure in Boulange -- before I ask you questions about this the figure, if the -- excuse me -- if the Boulange application was abandoned by Becton, would you assume that the product had not been commercialized?

MR. PEPE: Object to form. Calls for speculation.

A. I don't know if it was abandoned and I don't know if the invention still has been used. Sometimes people using invention without claiming a patent out of that one.

Q. Would you say that it's more likely than not that if a company has a commercial product that's covered by a patent, that they will continue to prosecute the patent? Isn't that your experience?

MR. PEPE: Same objection.

A. I can't answer that. I would need to speculate. I don't know what the patent structure of the company would mean -- what they do.

Q. But have you -- do you have experience

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with a company giving up its patent protection where it had a commercial product covered by the patent application?

A. Not knowingly. I might have. Might cross my desk that I work with something like that.

Q. Would you agree that a person of skill in the art would think that if the patent application was abandoned, that the company did not have a commercial product covered by the patent?

MR. PEPE: Object to form. Calls for speculation.

A. Not necessarily.

Q. That would be a logical conclusion for the POSA to come to though, right?

MR. PEPE: Same objection.

A. It could be product development still taking place without following up the patent. So a product development type of stuff is not limited to having a patent in place. I can develop, you know, a functional syringes -- I

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what I did in my time at Schott without having patents in place which made it to the market.

Q. You don't have to have a patent in order to work on a product?

A. Yes.

Q. But if you have a patent application that covers a product that you're commercializing, wouldn't it be fair for a person of skill in the art to assume you wouldn't abandon that patent if you had a commercial product?

MR. PEPE: Same objection.

A. The question, what you want to do with the patent. So as a POSITA, if I look through and I say, as a POSITA, I would, you know, the technical information out of that patent.

Based on the technical information, I could use that for development to my own purposes. If the patent is there, I might, you know, take the risk of infringing or look to see if it's not there, I might be able to take that one and still develop my syringe. If the patent is abandoned, it doesn't mean it is actually a

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nonfunctional system that I could not use for my purposes.

Q. But if a company has a commercial product, they wouldn't abandon the patent protection for that product, right?

MR. PEPE: Objection, calls for speculation.

A. Again, there is the patent -- did she have a patent where I say -- I don't know, if it's not really helping me to have that patent.

Q. But from a -- as a company, having a patent protect your product would help you, right?

A. It could help you, yes.

Q. It wouldn't make economic sense to abandon it if you have a commercial product, correct?

A. As I said, it depends. It could make economic sense not to proceed with the system if this was too much. I mean, this is -- I cannot speculate what other people might do on their patent strategy.

Q. Just talking about parylene C for a

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moment, is there any information in Boulange demonstrating compatibility of parylene C with a VEGF antagonist?

A. There is no specific mentioning in the examples on the MTVGF product.

Q. Is there any information in the Boulange application demonstrating the safety of parylene C for intravitreal use?

MR. PEPE: Object to form.

A. It's generally –

MR. PEPE: Sorry, Horst. Go ahead. I'm done.

A. General information of a suitable, safe development here, independent if this can be used for intravitreal application.

So what Boulange is claiming that he has a low silicone oil, gas tight PFS, glass PFS with low enough break loose glide forces in order to use that in combination with the sterilization method as described in Sigg or Lam as a syringe for intravitreal injection. This would be my motivation to combine as a POSITA.

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Q. Is there any information in Boulange demonstrating the -- let me strike that.

Is there any information in Boulange relating to extractables that could be -- that could result from parylene C?

A. Boulange says that you need to have certain container closure system like also viscoelastic material for the wrapper components which allows you to store the product and storing means keeping it safe over shelf life as well as still have a functional system.

So -- and of course, if I would use parylene C, what we have discussed before, for sure Boulange has enough data on hand to show and prove that parylene C is biocompatibility was P class 6 and parylene C and that's prior art in the SCS documentation that parylene C was used for syringes and medical devices prior to 2012.

Q. None of that information relates to it's use for intravitreal administration, correct?

MR. PEPE: Object to form. Sorry.

A. That's not specifically mention

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intravitreal, but based on the function and performance, as a POSITA, I would know that I could use the syringe based on this functional explanation for intravitreal injection.

Q. But there is no information in the documents you are alluding to demonstrating the safe use of parylene C as a primary container closure for an intravitreal injection, right?

MR. PEPE: Object to form.

A. It doesn't say the same for the silicone, so.

Q. Whether it says the same for silicone or not, my question is relating to parylene C.

MR. PEPE: You need to stop interrupting the witness when he is answering a question. OK. It's got to stop.

Q. Do you understand my question?

A. Can you please repeat your question.

Q. Yes. There is nothing in the documents that you are referring to demonstrating that the safety of parylene C as a primary

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container closure for intravitreal injection, correct?

MR. PEPE: Object to form.

A. Again, what I explained again, and I do it again, if I look at the data, as a POSITA, I have a read-out that based on functional performance, I can use it for intravitreal injection, given the intravitreal injection might not be explicitly mentioned in the Boulange document.

So this is the know-how of a POSITA to combine prior art and use prior art to get to a certain, get to a certain result.

Q. Whether or not you can make certain inferences, my question is, there are no data demonstrating the safety of parylene C for an intravitreal syringe prior to July of 2012, correct?

MR. PEPE: Objection, asked and answered.

A. I don't understand your question. What is the information you are looking for?

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Q. We talked about -- are you finished?
A. Yes.
Q. We talked about the fact that a person of skill in the art would do safety studies and that they would do extractable testing and that they would do leachable testing to demonstrate that there was nothing in the product or in the compounds that come into contact with the product that could cause toxicity, you recall that?
A. I recall that.
Q. There are no such data in the prior art that you are referring to demonstrating the safety or compatibility of parylene C for intravitreal use? That's my question. Is that correct?
A. Boulange is from Becton Dickinson. They are one of the main leader for PFS, and they for sure followed the container system closure guidelines from 1999.
So if I set up a system like that, for sure, they need to follow certain guidelines. Otherwise, I would not be able to do a

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good job.
Q. You can't point me to any safety data or compatibility data for parylene C in an intravitreal syringe prior to July of 2012, correct?
A. Correct.
Q. So I just want to go back to the question of whether or not this patent application issued as a patent.
You mentioned a moment ago you're offering opinions that the person of skill in the art. Would a person of skill in the art assume that Becton Dickinson did not commercialize parylene C if this patent was -- this patent application was abandoned?
MR. PEPE: Objection, asked and answered.
A. I don't know.
Q. If it was abandoned, would the person of skill in the art assume that the product was not commercially available?
MR. PEPE: Same objection.

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A. Could assume that.
Q. Now, if you look in -- on page 29 of Exhibit 1008, the figures -- and there it shows that the parylene C is in figure 3 shows the close-up and it's -- let me strike that.
In figure 2, there is a little bubble with a close-up of the stopper and it shows parylene C coating the ribs of the stopper. Is that right?
A. That's right.
Q. And I think you testified before that you had some experience where Teflon was used to coat a stopper in that same manner, right?
A. Right.
Q. And in that instance, the stopper didn't form a gas tight seal with the syringe barrel, correct?
A. Wrong.
Q. What's wrong about that?
A. I said there was one stopper out which did not form a tight seal. So that is why they made the reinvention of the so-called top face

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cover for FluroTec.
There was another coated stopper out which has similar type of Teflon coating, but not laminated which was tight.
Q. OK. So for one kind of Teflon coating, it didn't work, and for the other, it did, is that right?
A. That's right.
Q. Why was it that the Teflon coating failed to form seal on -- between the stopper and the barrel?
A. Based on my knowledge, the Teflon coating -- the laminate was not flexible enough and Boulange describes that the coating needs to be flexible enough in order to be squeezed and show functional performance.
Q. Have you done any -- let me strike that.
Do you know how the flexibility of parylene C compares to the flexibility of the Teflon that you are referring to?
A. Parylene C is coated as a plasma, as a

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plasma chemical vapor deposition.
And Teflon is usually used as a laminate. So this is a film and the film, you know, to stretch it around the edges of such a wrapper needs to have a certain, like I said, flexibility.
There are systems out that would show it depends on the thickness of the laminate. There is not one laminate out which would fail. It depends on the thickness and some flex models on this, you know, laminate in order to make it work or fail.
Q. The next exhibit is IPR Exhibit 1036. It's a document entitled "Guidance for Industry, Sterile Products Produced by Aseptic Processing, Good Manufacturing Practice " Actually it says "Current Good Manufacturing Practice."
(Exhibit 1036, document entitled "Guidance for Industry, Sterile Products Produced by Aseptic Processing, Current Good Manufacturing Practice" marked previously for identification.)

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Q. Mr. Koller, is this a document that you relied on in your declaration?
A. It says -- I know the guide, but I don't know the top of my head if I cited this in my IPR.
Q. And you look at your list of materials, I can get it for you, I think, but the exhibit number indicates that it's a Regeneron exhibit and it was cited in your declaration. I only have a couple of questions about it. If you turn to page 1.
A. Yes.
Q. Before we start there, this guidance is about aseptic processing, right?
A. Right.
Q. And the introduction in the first sentence says, "This guidance is intended to help manufacturers meet the requirements in the agency's current good manufacturing practice, cGMP, regulations" -- there is a cite to the CFR -- "when manufacturing sterile drug and biological products using aseptic processing."

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Do you see that?
A. I see that.
Q. And we talked about this earlier, but you agree that products can be designated sterile even when they are handled using aseptic processing, correct?
MR. PEPE: Object to form.
A. Sterile filling is a part of aseptic processing, yes.
Q. A product can be manufactured and designated as sterile even if it's manufacture is done using aseptic processing, correct?
MR. PEPE: Object to form.
A. I would need to go through this document in a bit more detail to define what type of aseptic processing they would mention in the guideline.
Q. OK, if you look at page 2 to 3 -- let me just ask you a general question.
In aseptic processing, the individual components of a product are sterilized and then the device is assembled, and if necessary,

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filled under aseptic conditions, right?
A. So aseptic filling means that you have three sterilized components filled it under ISO class 5 clean room environment.
Q. So for a prefilled syringe, that would mean that you would have sterile drug product going into a barrel and having a stopper and a tip cap, for example, all of which were sterile ahead of time, sterilized ahead of time, right?
A. A tip cap would be already preassembled on the syringe, but it would be presterilized on the syringe.
Q. Sorry, there was one question about Boulange I forgot to ask you.
Can you go back to Exhibit 1008 for just a moment. If you could turn to page 4?
A. Yes.
Q. The first paragraph, it says that the first sentence talks about how the viscoelastic material that the piston is made of is generally an elastomeric material which alters in particular degrades chemically over time.

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Do you see that?
A. I see that.
Q. Then the second sentence says, "This possible degradation is sometimes initiated by the processes used to sterilize the medical devices containing them, for example, bringing into contact with ionizing radiation."
Do you see that?
A. I see that.
Q. The degradation that's referred to in that sentence is the degradation of the stopper material, right?
A. It says sterilized medical devices containing them, so by ionization, radiation. So this could also be a polymer syringe, not necessarily a glass syringe which you would then irradiate by gamma E-beam or x-ray.
Q. Well, just looking back at the first sentence again, it's talking about the viscoelastic material that the piston is made of, it says it is generally an elastomeric material which degrades chemically over time, right?

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A. Um-hm.
Q. Then the next sentence refers to that by saying this possible degradation is sometimes initiated by the process used to sterilize the medical devices.
Do you see that?
A. I see that, yeah.
Q. The degradation in that sentence is referring to the degradation of the piston, correct?
A. Correct.
Q. That's not a reference to degradation of the drug product that would be eventually stored in the syringe, right?
A. Not a reference of the drug product.
Q. Can you look in your declaration at paragraph 164; in particular, you can look at any part of it obviously to answer my question, but in particular, the part of the paragraph on page 98, there is a sentence that begins "for example."
It says, "For example, a POSITA would have been aware that Becton Dickinson

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supplied the syringe and needle for Macugen PFS."
Do you see that?
A. Um-hm. I see that.
Q. And then there is a citation to Exhibit 1017 which is the Sapinski application and you said "describing BD syringes for use with Macugen."
Do you see that?
A. I see that.
Q. Was that your understanding at the time in July of 2012 that Macugen used a Becton Dickinson syringe?
A. Do you have to the Exhibit 1017 available for me so I can verify --
Q. I do, but just --
A. -- the statement.
Q. You say in that sentence that the POSITA would have been aware that Becton Dickinson supplied the syringe and needle for Macugen PFS.
Do you see that?
A. Um-hm, I see that.
Q. Is that an accurate statement?

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A. Accurate statement.
Q. Were you aware that Macugen employed the Becton Dickinson syringe?
A. If I was looking at the PFS -- Macugen PFS?
Could you please rephrase your question.
Q. Yes, in 2012, were you personally aware that Macugen employed the Becton Dickinson -- strike that.
Were you aware in 2012 that Macugen employed a Becton Dickinson syringe?
A. The Macugen was developed in the early 2000s and one of the only -- maybe not the only one, but the main syringe supplier was Becton Dickinson.
Q. For Macugen?
A. For PFS in general.
Q. Do you know how much silicone oil was in the Macugen syringe?
A. According to prior art, .821 milligram. But I would point out to the exhibit.

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Q. Let me show you the Macugen label.
Next exhibit is Regeneron Exhibit 1009. It's a printout from Drugs.com on Macugen.
Mr. Koller, is that a document that you relied on offering your opinions in this matter?
A. This is a document I relied on.
Q. Do you know the date of that document?
A. So on page number 11 of 11, it says that marketing information for this is the NEA on 2017 2004 -- 2004 Macugen label.
Q. So it is your understanding that this label came out in 2004?
A. No, it says the NDA was in 2004. The label is established down there was revised in 8/2008 from the Eyetech Inc., the company producing Macugen.
Q. If you could turn in your declaration then to paragraph 149.
A. Yes.
Q. And sorry, paragraph 150.
Do you have a side-by-side there

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or one above the other comparison of the 2004 Macugen label and the 2008 Macugen label which is Exhibit 1009 that we were just looking at.
Do you see that?
A. I see that.
Q. Now, the 2004 label -- let me strike that. Just look at the 2008 label.
It says that "Macugen, pegaptanib sodium injection, is supplied in a sterile foil pouch."
Correct?
A. Correct.
Q. And it's your opinion that from that a person of skill in the art can derive that Macugen was terminally sterilized, is that right?
A. Right.
MR. PEPE: Object to form.
Q. But you'll agree with me that the label does not say how the Macugen was sterilized in the 2008 label, correct?
A. It does not specifically say sterilized by terminal sterilization.

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Q. There is no express reference to terminal sterilization in the label, right?
A. Right.
Q. Now, in addition to that change where they reference the sterile foil pack, they also made another change to the label where they indicated that the -- there was a sterile package BD single-use 30-gauge needle, correct?
A. Correct.
Q. And although the Macugen 2008 label indicates that the foil pouch is sterile, you would agree that you can achieve sterility using aseptic processing in addition to terminal sterilization, correct?
A. I don't agree with that statement.
Q. You don't agree that you can have a product that's designated sterile that's manufactured using aseptic processing?
MR. PEPE: Object to form.
Mischaracterizes testimony.
A. So I need to go back a step.
Compared to label 4 and 5, the

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sterilized foil pouch, and POSITA would understand that the sterilized foil pouch is done by terminal sterilization in combination with other information available in the Macugen label of 2008 where they introduced the clip which is described in the Macugen label, 2008.
As well, it was known in the art and was stated in the Sigg patent that few syringes are not packed in an aseptic environment, that's why terminal sterilization is the choice of the art to do so.
And if you know what needs to be done in such a way, then it's technically not feasible to sterile package a system and also to verify that the system is then really sterile in the end.
So the safe way to go for sure is a terminal sterilization of the listed syringe in the foil pouch.
Q. OK, you would agree with me that in that 2008 Macugen label, where it says sterile foil pouch, there is no reference to any

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particular SAL, correct?
A. You would not state on the label that you have a sterile coating to 10 to the minus 6. Sterile is claimed in the product specification. So it could be 10 to the minus 6. It could be whatever they claim and verify.
Q. It could be 10 to the minus 3, correct?
A. Again, industry expectations for a terminal sterilization of system on components that are allowed to do that, the expectation is that you would have a 10 minus 6.
Q. I understand that's your opinion that it's an expectation. But you could also have a reference to a sterile product that was sterilized to an SAL of 10 minus 3 correct?
MR. PEPE: Objection, asked and answered.
A. A POSA so would not go for that. He would for sure go 10 to the minus 6. This is the official sterile claim in the pharmaceutical industry. With exemptions. He would need to

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prove that you could not do a 10 to the minus 6 in the first place. And prior art shows that by doing ETO, it could go to a 10 to the minus 6 without damaging the product.
So if the FDA would look into such document, they would for sure let you do the 10 to the minus 6 validation compared to the 10 to the minus 3 if it's feasible and that was proven.
MR. PEPE: We have been going about an hour if you find a good spot for a break.
MR. JAMES: Why don't we break right here.
(Recess; 2:33 to 2:48 p.m.)
Q. Mr. Koller, have you heard of a document referred to as ANSI/AAMI ST67?
A. I don't know about the number for sure. Can you let me know the title of that document? Please.
Q. I will try.
It's from American National Standard and it's called, "Sterilization of Healthcare Products, Requirements and Guidance for

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Selecting a Sterility Assurance Level, SAL, For Products Labeled Sterile."
A. I can't remember if I cited this one in my IPR.
Q. You did not, no. I'm just asking you if you know about that document.
A. No. I might have crossed it because I did some validation for sterilization myself for different original areas. But it doesn't ring a bell.
Q. Do you know if there are provisions available for helping companies or -- let me strike that.
Do you know if there are guidelines for companies who are seeking to get an SAL lower than 10 to the minus 6 where it s required for that particular product?
MR. PEPE: Object to form.
A. I don't know.
Q. Would you agree that in a case where you couldn't achieve 10 to the minus 6 without degrading the product, that a company would either

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need to redesign their product or seek from the FDA a lower SAL of 10 to the minus 3?
A. Option 1 has that you would start to redesign to see option -- or basically option 2, if you say you need to go to the FDA.
They would not say that you, you know, would immediately could go to the 10 to the minus 3. You would need to prove data, and then, you know, let them know what is the risk involved and they might then give you such a suggestion on a certain acceptability after they verified all the submission data that would prove the sterilization technique used for a lower log reduction than 10 minus 6.
Q. Have you heard of situations where a company has presented data to the FDA or the EMA about sterilization where they demonstrated a lower bioburden in conjunction with a lower SAL to receive a sterility designation?
A. I haven't heard ever from the EMA or FDA because these submission documents are always confidential and publicly not accessible.

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Q. You don't have any experience with that sort of thing?
A. I don't have any experience.
Q. Do you actually know, going back to my question about that document, what the ANSI American National Standards -- do you know what that is?
A. I mean, could be the organization which, you know, is involved in ISO, but I would need to verify.
Q. What about the AAMI, do you know what that organization is?
A. American Association -- AAIM?
Q. AAMI.
A. AAMI. For American Association -- no. I mean, I know the abbreviation, but I don't know the spelled name.
Q. What does ISO do?
A. ISO does harmonization of existing standards into ISO document which gives then a guideline for, you know, worldwide guideline. As an example, for ISO 11135 or 11137 for irradiation

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or ETO sterilization guidelines on how to validate and check your validation system.
Q. Does ISO have guidelines on setting an SAL?
A. For sure there is a description in the ISO standard for SAL explanation and how to get there, but I can't -- top of my head, I can't talk about detail about the approach there. The ISO guidelines would be typically used to validate your system.
Q. And a person of skill in the art would have had access to the ISO documents, correct?
A. You have free access to an abstract and then through your notified standard could be the AAMI or something, you could buy them through that notice standard -- the American standardization body in Switzerland, it would be like the Swiss Normen Group or Germany, it would be the DIN. This is where you normally get access for this. But you need to buy them. They are not publicly available, only in abstract.
Q. They are publicly available except

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that you have to purchase them, is that fair?
A. That's fair.
Q. If we can go back to the Macugen document we were talking about a moment ago, I think you still have it in front of you?
A. Yes.
Q. Could a POSA understand that the sterility achieved for the Macugen product as reflected in that 2008 label was achieved using an autoclave or beta radiation?
MR. PEPE: Object to form.
A. So depending on the sensitivity to different sterilization products, and as described was in prior art, beta radiation would be something or -- so they would have -- how do I answer the question.
Beside gas are different known sterilization methods in the market, yes.
Q. I didn't understand -- the side cast are different -- I didn't understand what you said there, sorry.
A. I mean beside gas sterilization.

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Q. Beside gas sterilization, thank you.
A. VHP or ETO or maybe other plasma systems, irradiation or steam, hot steam is -- are typical sterilization methods.
Q. So based on this prior art document that you cited to, a person of skill in the art would not be able to tell how the sterility of this product was achieved, right?
MR. PEPE: Object to form.
A. I mean, maybe through terminal sterilization because it is after filling.
Q. I understand that that's your position that it's terminal sterilization. But assume that's true for a moment, you wouldn't be able to tell whether it was terminally sterilized using ethylene oxide, vaporized hydrogen peroxide, autoclave or beta radiation, correct?
A. There is no additional evidence in the label describing the foil pouch that could give you an indication on what is -- what kind of sterilization is used.
Q. You could -- go ahead.

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A. Tyvek is used -- Tyvek pouches or foils or blisters are used for, you know, sterilization with gas because it needs to have a certain permeability to gas to sterilize and then get the gas out. Whereas if you do irradiation, the Tyvek window could be there, but it's not necessarily required.

Q. In the Sigg application we looked at earlier, the second example was about beta radiation, correct? It's Exhibit 1008, I believe -- I'm sorry, it's 1007.

A. Example 2 is using beta irradiation.

Q. And in the first paragraph of the example, they talk about using, in the last sentence, polyethylene bag with a foil thickness of 50 microns, an aluminum bag with foil thickness of 0.1 millimeter.

Do you see that?

A. I see that.

Q. So you're saying, without further information in that Macugen label, you could not determine what method was used to achieve

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sterility, correct?

A. The Macugen label explicitly claims a clip with two functions that is unique to remove the clip in order to make the syringe function. So I can move the piston. And it also says if you are opening the pouch and the clip is removed, don't use the syringe.

So a POSITA would know that the clip is usually used if you have pressure differentiations which would not occur if you do radiation in the system.

So the likelihood that I use a gas system, VHP or ETO because I cannot use steam because of the heat sensitivity of the system, then a POSA would get to the conclusion that it could be either VHP or ETO, but not say exactly which type of gas could be used.

Q. The label does not indicate what the clip is. It just refers to it as a plastic clip.

MR. PEPE: Object to form.

A. It describes the function to remove the clip prior to use. So it fixes the syringe

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and the plunger rod. If it would not have a certain function or feature, then the clip would not be added.

Q. Let me show you the next exhibit, Exhibit 1081, which is a document you cited in your declaration. It's another version of the Macugen label.

(Exhibit 1081, Macugen label marked previously for identification.)

Q. Is this a document you cited in your declaration?

A. Yes.

Q. If you look at the first page, about halfway down, it says number 1, "Remove the syringe from the plastic clip."

A. Um-hm.

Q. Do you see that?

A. I see that.

Q. It doesn't say where the clip is attached, right?

A. Um-hm.

Q. It doesn't say remove the clip from

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the syringe. It says remove the syringe from the clip, right?

A. Yes, it says that.

Q. It doesn't say the clip is attached to the plunger rod?

A. No.

Q. It doesn't say that the clip has to be removed to achieve functionality?

A. No.

Q. Right?

A. It says remove the syringe from the plastic clip.

Q. Right. That is all it says?

A. That is all it says.

Q. It doesn't say anything about terminal sterilization?

A. No.

Q. Now, if you were using a foil bag or a foil pouch with beta radiation, you mentioned that Tyvek window earlier, you wouldn't need a Tyvek window with a foil pouch that was used with beta radiation, right?

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A. For the pure sense of irradiation with beta, you would not need a foil pouch.
If you have a system which undergoes certain pressure differentiations, like in a sort of air transport or something, then it is strongly recommended to use still a foil pouch with the Tyvek window because otherwise, the differentiation in pressure might cause the pouch to break open and then you would have a container closure integrity breach.

Q. If you can turn to paragraph 109 in your declaration, in particular, the portion of the paragraph that's on page 63, toward the end.
At the end of that paragraph, you mentioned that the 2008 Macugen label described that the user must remove a clip from the syringe prior to use.
Do you see that?

A. Yes.

Q. And then the next sentence, you say, "A POSITA would recognize that the clip would serve to prevent the plunger from moving after it

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is placed in a blister pack, including during a terminal sterilization process and during transportation."

A. Right.

Q. Do you see that?

A. I see that.

Q. So the clip can also be there to protect the syringe during transportation, right?

A. Yes.

Q. Now, in your analysis of this case, you have not examined an actual Macugen syringe that was available between 2008 and 2012, right?

A. Right.

Q. And to your understanding, when the makers of Macugen changed their label in 2008, they did not lower the amount of silicone oil in the syringe, correct?

A. Correct.

Q. And to the best of your knowledge, the makers of Macugen never adopted parylene C, right?

A. To the best of my knowledge, right.

Q. The next exhibit is IPR Exhibit 1019.

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This is a copy of a portion of the 2011 version of USP 34-NF29.
(Exhibit 1019, 2011 version of USP 34-NF29 marked previously for identification.)

Q. Is that a document that you relied on in offering your opinions in this matter?

A. Yes.

Q. What is it?

A. The document is an extract out of the United States Pharmacopeia 34 based on 2011 which describes certain specific tests, how to perform tests for certain type of drug products and the -- let's say monograph or chapter 789 describes particulate matter in ophthalmic solutions. And it gives references to test method as well as to test limits.

Q. I just want to walk through this for a minute.
So USP 789 is a test for particulate matter in ophthalmic solutions, right?

A. Right.

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Q. And there are two tests that are referred to in USP 789, correct?

A. Correct.

Q. And the way that USP 789 works is that -- let me strike that.
The two tests are light obscuration particle count test and a microscopic particle count test, right?

A. Right.

Q. Each of the two tests has its own conditions for passing the test, right?

A. The microscopic particle count has an additional condition a compared to the light obscuration test. So it is asking for taking 50 micrometer particles, and not only larger equal 10 or larger equal 25.

Q. I guess my questions was a little different. The light obscuration test has two conditions for passing. One is the number of particles greater than 10 microns and the other is number of particles greater than 25 microns, right?

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A. Right.
Q. And then the microscopic particle count test has a different set of conditions, the -- it has the same limit on the number of particles greater than 10 microns, same limit on number of particles greater than 25 microns, but then also has a limit on the number of microns -- particles greater than 50 microns, right?
A. Right.
Q. Have you ever done this test?
A. Yes.
Q. As I understand it, the way the test is done is that the product to be tested is tested by the light obscuration test first. Is that right?
A. That is right.
Q. If the material passes the light obscuration test, there is no reason to do the microscopic particle count test, right?
A. Right.
Q. So a material could have less than -- let me strike that.

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If you had a material you were testing and you did the light obscuration particle count test and you had less than 50 particles greater than 10 microns and less than 5 particles greater than 25 microns, the material would pass USP 789, right?
A. I mean, this is not material testing. These are container testing. Because depending on the volume needed for the test, which is described in 788 which has the two channels, large or equal 10 and 25, it gives you a description how to prepare certain standards, and then you need to pool in order to be able to measure a certain amount and then it gives you an average count for the channel.
So if you pass light obscuration like a container pull, if you pull 10 or 15 syringes then there would be no need to do microscopic.
Q. So I want to make sure I'm on the same page with you.
How ever much volume you need to test, if you test your container with your material in

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it by light obscuration, and it has fewer than 50 particles greater than 10 microns and fewer than five particles greater than 25 microns, then the material passes USP 789, right?
MR. PEPE: Object to form.
A. So again, this is based on the certain pooling of container tests. It's usually not -- because the equipment, like light obscuration from HIAC Royco as an example, usually requires a certain amount, pooled volume in order to do the measurement.
So like in 788, it describes to say, OK, depending on the system, you should pool so many, let's say, containers that you get at a least up to 25 mls. And then if you put that on the machine, then it flushes the first time to clean the system because you prepared the system with purified water particle measurement as described in 788. With that, you clean all basically the components coming apart with such a solution.
And then you know, it says, OK, then it

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does doing 3 or 4 measurements depending on the volume, each 5 mls and then it gives you, out of four measurements, gives an average regarding the particle size per ml.
So for 788, this is slightly different because then you need to calculate that one according to the container because 788 also describes volume up to 100 mls.
So 789, you do some pooling, as low as possible, let's say, and then do the repeated testing here. If you pass -- if you have enough -- one milliliter -- if the system could work only on one ml, and you would need to pull 5 and it gives you an average of the five syringes.
Q. OK. But if you do the pooling and you get an average per ml that is less than 50 for 10 micron particles and less than 5 for 25 micron particles, the material passes USP 789, correct?
A. You have a solution that passes 789, yes.
Q. And there is no reason then to look for particles greater than 50 microns in that

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material, right?
A. Right.
Q. The material could have more than two, three, four particles greater than 50 microns and still pass USP 789, correct?
A. Correct.
Q. There is nothing in the prior art that would suggest to a person of skill in the art that you would have to use the microscopic test on a VEGF antagonist, right?
A. Depending on the type of VGF, if it's in such a way that it's cloudy, torpidity, and cannot be handled by light obscuration, then membrane method is the only one you can use then for release. And then you have the 50 micrometers included in the MM method.
Q. I understand that some conditions could exist where you would think, oh, I can't use light obscuration, I have to use microscopic. I think that's what you are saying.
My question is a little different. Is there anything in the prior art that suggests that

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the VEGF antagonist would have to be tested by microscopic particle tests?
A. No. It says it needs to be tested according to 789.
Q. Right. And 789 only requires light obscuration if you pass the light obscuration, right?
A. Yes.
Q. You agree there is nothing in the Sigg or Lam references that suggest that the products would have to be tested by the microscopic particle test, right?
A. I would need to go back to Sigg and Lam to verify -- I can't -- Sigg and Lam talks about sterilization. It doesn't talk about particulate matter.
Q. If you would turn to paragraph 205 of your declaration, please.
A. Yes.
Q. In 205, you are discussing the limitation in the claim of no more than two particles greater than 50 microns in diameter per

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ml, right?
A. Right.
Q. If you look at the bottom of that page, 127, there is a sentence that begins "specifically."
It says, "Specifically, a POSITA would know that a VEGF antagonist solution for intravitreal administration would need to comply with USP 789 for regulatory approval, and thus, it would need to meet the microscopic particle count test as set forth in USP 789 which requires no more than two particles of diameter greater than 50 microns per ml."
Right?
A. Right.
Q. But, in fact, a VEGF antagonist solution would not necessarily have to meet the requirement of no more than two particles greater than 50 microns if it met the light obscuration test, correct?
A. Yes, but this is not what I described here. There is no reference here to only the

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light obscuration testing.
It says 789 and 789 has this second method in it, the interpretation of what I need to do, following step. So if I cannot -- and if I don't know what type of VEGF it would be, then if I can't do light obscuration, then membrane is the -- as I said -- is the only way to do so.
Q. But it is not necessary to do the microscopic particle test in order to meet USP 789, right?
A. It states if I pass USP 789, then there would be no requirement to test on 50 ml -- sorry, for 50 micron pieces.
Q. Do you know when the Lucentis prefilled syringe was first approved by the FDA in the United States?
A. I think I cited it in my document. I'm not sure about the exact date, so I would -- I would need to go back to verify the exact date.
Q. I don't think it's all that important for my questions. I think it was at some time in 2016.

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But in any event, at some point, the Lucentis prefilled syringe was approved for use in the United States, right?

A. Yes.

Q. And before that, it was available in a vial presentation, right?

A. Right.

Q. And the vial is -- the vial presentation is the drug in a vial with a rubber stopper on the top, right?

A. Right.

Q. And the physician has to take a syringe, puncture that rubber stopper, draw out the solution, switch needles and then inject it into the patient, correct?

A. Correct.

Q. And with the prefilled syringe, the drug is already in the syringe, right?

A. Right.

Q. By having it in the prefilled syringe, it reduces the steps and is more convenient for the doctor, correct?

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A. Correct.

Q. But the drug inside the prefilled syringe is the same as the drug that was inside the vial, right?

MR. PEPE: Object to form.

A. The active ingredient could be the same. I'm not sure about the formulation because you have silicone oil in the system and so the formulation might need to be adjusted. So I'm not sure about that one.

Q. Whether there are minor differences in the formulation or not, the active ingredient, the ranibizumab is the same in the vial and the prefilled syringe, right?

A. Right.

Q. Both of them contain the same VEGF antagonist, right?

A. Right.

Q. So the difference between the vial and the prefilled syringe is that the container that the drug is supplied in is in a prefilled syringe which is also a delivery device, right?

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A. Right.

Q. And that difference between the two includes the fact that the prefilled syringe has a barrel and a stopper and a plunger rod, right?

MR. PEPE: Object to form.

A. Like a single use syringe would have as well. You know, if you transfer it from the vial into the injection device, then a single use syringe has a barrel, a flange and a plunger rod.

Q. And the Lucentis syringe has a low amount of silicone oil, right?

MR. PEPE: Object to form.

A. Lucentis claims a certain amount of silicone oil in the syringe.

Q. And it's less than 100 micron silicone oil, right?

A. According to the claim, it's less than 100 microns.

Q. And the prefilled syringe has -- exhibits forces of less than 11 newtons for break loose force, right?

MR. PEPE: Object to form. That is

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what this claim anticipated.

Q. And the Lucentis prefilled syringe also has less than two particles per ml of greater than 50 microns, right?

A. The syringe?

Q. Yes.

A. Might not have.

Q. You don't know?

A. If you don't do the testing, you don't know.

Q. So sitting here today, you don't know whether Lucentis meets that particle size limitation, right?

A. I know it is passes 789. So if it fails, then they do MM, and if it then have less than two particles, they release the final drug product.

So it would not be released to the market if they would fail 789 in total which includes both methods if needed.

Q. Other than the things that we have just outlined about the prefilled syringe, is

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there any other feature of the prefilled syringe that is sold with Lucentis in it?
MR. PEPE: Object to form. Vague.
A. Please repeat the question.
Q. Other than the parts of the syringe that I've just gone through, are there any other features or parts of the Lucentis prefilled syringe?
MR. PEPE: Same objection.
A. You have the prefilled syringe comes with a finger flange and which acts as a backstop device. Or plunger.
Q. OK, all right.
Anything else?
MR. PEPE: Same objection.
A. I would need to see an actual package of the Lucentis in order to verify what's around the glass barrel.
Q. You mean in terms of like labeling or something like that?
A. For sure I know it must have a label because of regulatory requirements. But

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additional components around the glass barrel, a feature --
Q. Such as what? Give me an example of something that might be there.
A. For sure it needs to have a plunger rod. It needs to have finger flange extension. It depends on the intended use of the molecule, if you use the finger flange or not. And it comes with, according to the claim, it comes with a sort of backstop feature in combination with the plunger rod.
Q. To prevent the backward movement of the stopper?
A. Right.
MR. JAMES: Why don't we take a short break. Off the record.
(Recess; 3:39 to 3:43 p.m.)
Q. Mr. Koller, do you have the '631 patent in front of you?
A. Yes.
Q. If you could turn to column 5, please. Line 34.

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Did you see there is a sentence that begins with break loose?
A. Yes.
Q. It says, "Break loose in slide forces for prefilled syringes known in the art are typically in the region of the less than 20 newtons."
A. Yes.
Q. I think you referred to this in your testimony earlier, right?
A. Right.
Q. Now, that sentence refers to prefilled syringes, but it doesn't refer to prefilled syringes for intravitreal injection, right?
A. Right.
Q. Could you turn in your declaration to paragraph 94, please.
A. Can you just give me one second.
Q. Yeah, of course.
A. So I was referring to the 20 newton on column number 1, line 65 -- or 60.
So it says, "In one embodiment

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the syringe is suitable for ophthalmic injections, more particularly intravitreal injections, and as such, has a suitably small volume. The syringe may also be silicone oil free or substantially silicone oil free or may comprise a low level of silicone oil as lubricant. In one embodiment, despite the low silicone oil level, the stopper break loose and slide force is less than 20 newton."
Q. But there is no claim in the patent that is limited to 20 newtons, right?
A. There is no claim on 20 newton.
Q. Can you turn to paragraph 94 in your dec, please.
A. Yes.
Q. And in paragraph 94, you are talking about the '631 patent claiming priority to a European patent application that was filed on July 3, 2012, right?
A. Right.
Q. And you say, in the second sentence, that that European patent application does not contain any examples and does not contain any

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disclosure of specific break loose forces for any syringe disclosed therein, right?
A. Right.
Q. Instead, you note that it discloses only glide force for certain embodiments is less than about 11 newtons or less than 9 newtons, less than 7 Newton, less than 5 newtons or between 3 newtons to 5 newtons, right?
A. Right.
Q. And then you have the material from the prosecution history excerpted there in that paragraph, right?
A. Right.
Q. And then in paragraph 95, say that because the independent claim in the '631 patent requires that the break loose force is less than about 11 newtons and this is required for all the claims of the '631 patent, a POSITA would not be able to reasonably conclude the inventors had possession of an invention consisting of a prefilled syringe with the claimed break loose force based on the disclosure of EP 12174860.

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Right?
A. Right.
Q. So your opinion as stated there is that because all that was stated were slide forces, the POSITA could not conclude anything about possession of a break loose force, right?
A. Right. Or had possession of inventing consisting of prefilled syringe with the claimed break force.
Q. So when you look at that excerpted portion where it talks about these glide forces, you don't read the highest number as the break loose force in that sentence?
MR. PEPE: Object to form.
A. So it says in one embodiment the glide force for the stopper within the prefilled syringe is less than about 11 newton or less than 9 newton, less than 7, less than 5 or between about 3 and 5. And it says, embodiment, the glide force for the stopper. So in this sentence, it does not mention the break force.
Q. So in your opinion, you can't take

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away from that sentence about glide forces anything about break loose forces, is that right?
MR. PEPE: Object to form.
A. Right.
Q. If you could turn to paragraph 313 in your declaration, please.
A. Yes.
Q. In that paragraph, you say that with respect to the claimed break loose and glide forces, syringes commercially available before the critical date of the '631 patent were commonly sold as 10 and 5, syringes meaning they would have a maximum break loose force of 10 newtons and slide force of 5 newtons squarely within the ranges claimed.
Do you see that?
A. I see that.
Q. And you're citing Fries, right?
A. Right.
Q. I'll hand you the next exhibit which is IPR Exhibit 1012. It's a 2009 article from Drug Delivery Technology with the first author

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Arnold Fries called "Drug Delivery of Sensitive Biopharmaceuticals with Prefilled Syringes."
(Exhibit 1012, article "Drug Delivery of Sensitive Biopharmaceuticals with Prefilled Syringes" marked previously for identification.)
Q. Just take a look at that and confirm that that is a Fries article that you were citing in paragraph 313?
A. Yes.
Q. It was?
A. It was.
Q. If you turn to page 1012.006.
A. Yes.
Q. It says, at the bottom, "The amount of extractable silicone oil could be reduced below the detection limit (0.03 milligrams of ICPAES according to EN ISO 11885," and then it says, "with low levels of lubricant quantity, the specified syringe functionality was fulfilled, plunger gliding forces in the range of 5 to 10 newtons."

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Do you see that?
A. I see that.
Q. So in that parenthetical at the end, it's only referencing gliding forces, right?
A. Plunger gliding forces, right.
Q. And they are all greater than 5 newtons, correct?
A. In the Fries article.
Q. I'm sorry, in that parenthetical, when he says, "The gliding forces are in the range of 5 to 10 newtons," that means all the gliding forces were greater than 5 newtons, right?
MR. PEPE: Object to form.
A. 5 to 10 newtons, right.
Q. It means above 5, right?
A. Above 5 and below 10.
MR. PEPE: Object to form.
Mischaracterizes the document.
A. Between 5 and 10.
Q. That parenthetical doesn't say anything about break loose force, right?
A. Right.

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Q. You can't glean anything about break loose force from the recitation of those plunger gliding forces, right?
A. Right.
MR. JAMES: I have no further questions for the witness.
MR. PEPE: Why don't you just give me a couple of minutes and then we can step out for a second.
(Recess; 3:54 to 3:56 p.m.)
EXAMINATION BY
MR. PEPE:
Q. Mr. Koller, can you take out Exhibit 1029 which would be on the top of your stack.
Do you recall that that is the Lam publication?
A. Yes.
Q. I would like you to turn to page 15.
A. 15?
Q. Yes.
Do you recall earlier that Mr. James directed you to lines 12 through 17 on

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page 15?
A. Yes.
Q. And after you -- after directing you to that excerpt of Lam, Mr. James asked you whether Lam disclosed a glass syringe.
Do you recall that?
A. I recall it.
Q. I would like you to now turn to page 2 of Lam. And I'm going to direct you to the paragraph starting at line 29.
Do you see it says in some embodiments, the object is a syringe?
Do you see that?
A. On page 2?
Q. Page 2, line 29.
A. Some embodiments, the object is a syringe.
Q. Can you read that paragraph to yourself.
A. Yes.
Q. What does that paragraph describe with respect to the material used for the syringe

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barrel disclosed in Lam?
A. So it says that a glass syringe has been used in combination with a D777 laminated FluroTec, and the D777 -- as a tip cap and also FluroTec, so -- the used syringe material is glass.
MR. PEPE: I have no further questions.
MR. JAMES: Thank you.
(Time noted: 4:00 p.m.)

HORST KOLLER

Subscribed and sworn to
before me this day
of MO , 2021.

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CERTIFICATE

I, MARY F. BOWMAN, Certified Reporter and Notary Public within and for the State of New Jersey do hereby certify:

That Horst Keller, the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, was represented by counsel at the deposition.

I further certify that the deposition of Horst Keller, occurred at the offices of Weil, Gotshal & Manges LLP at 767 Fifth Avenue, New York, New York 10153 on Thursday, December 16, 2021, commencing at 9:00 a.m. EST to 4:00 p.m. EST

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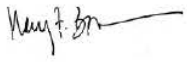
I further certify the inspection, reading and signing of said deposition were not waived by counsel for the respective parties and by the witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties to this action, and that I am in no way interested, financially or otherwise, in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 29th day of December 2021.



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