

Transcript of Horst Koller

Date: December 16, 2021

Case: Regeneron -v- Novartis (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

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	Conducte	ed on December 16, 2021
	EVITATE INDEX	⁵ Q. Have you submitted any declarations in
2	EXHIBIT INDEX: NUMBER DESCRIPTION PAGE:	
2		2 any matters other than the declaration you
3		3 submitted in the IPR we are here to talk about
5	for Industry Container Closure Systems for Packaging Human	4 today?
5	Drugs and Biologics"	5 A. No.
7	Exhibit 008 Boulange application 29	6 Q. Are you billing Regeneron as one of
8	W02009/030976 A	7 your consulting clients at HK Consulting?
9	Exhibit 036 Document entitled "Guidance 77	8 A. No.
0		9 Q. So you are billing Regeneron as an
	Produced by Aseptic	10 expert outside of your normal consulting business,
2	Processing, Current Good	11 is that right?
3	Manufacturing Practice"	12 A. I am billing Weil.
4	Exhibit 009 Printout from Drugs.com 85	Q. Sorry. I'll change my question then.
5	on Macugen	14 Are you billing Weil as part of
6	Exhibit 08 Macugen label 99	15 HK Consulting?
7	Exhibit 0 9 20 version of USP 34 N 29 203	16 A. Yes.
8	B Exhibit 0 2 Article "Drug Delivery of 224	17 Q. How many hours have you billed them
9	Sensitive Biopharmaceuticals	18 for since your deposition in February?
20	with Prefilled Syringes"	19 Approximately?
2		20 A. Sixty, 70 hours.
22		
		21 Q. Sixty to 70 hours? 22 A. Yeah.
_		6 8
1	EXAMINATION BY	1 Q. Since you strike that.
2	MR. JAMES:	2 I think you told me that you had
3	Q. Good morning. Could you please sta	
4	1 11 0 1	4 right?
5		5 A. Right.
_	HODOTIOLIED	
6	-	
/	Q. And could you provide us with your	7 you've worked on this matter since 2017?
8	address please?	
	_	8 A. Including deposition?
9	A. Yes, my address is Weinbergweg, l	Route 9 Q. Yes.
9	A. Yes, my address is Weinbergweg, l 0 1 do you want me to spell it?	Route 9 Q. Yes. 10 A. 200. Approximately.
9 1(A. Yes, my address is Weinbergweg, l 0 1 do you want me to spell it? 1 Q. I think so.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money
9 1(11	A. Yes, my address is Weinbergweg, l 0 1 do you want me to spell it? Q. I think so.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you
9 10 11 12	A. Yes, my address is Weinbergweg, lo 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.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately?
9 10 11 12 13	A. Yes, my address is Weinbergweg, lo 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	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately?
9 10 11 12 13	A. Yes, my address is Weinbergweg, lo 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.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately?
9 10 11 12 13	 A. Yes, my address is Weinbergweg, 1 01 do you want me to spell it? 1 Q. I think so. 2 A. W-E-I-N-B-E-R-G-W-E-G 1 in 730 3 U-Z-N-A-C-H, Switzerland. 4 Q. And you understand that you are under this morning, correct? 	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately? er 14 A. I stated, it's times 450 per hour. So
9 10 11 12 13 14 15	A. Yes, my address is Weinbergweg, lo 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 to oath this morning, correct? A. Correct.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately? er 14 A. I stated, it's times 450 per hour. So 15 it's like – I don't recall the amount – it's
9 10 11 12 13 14 15 16	A. Yes, my address is Weinbergweg, lo 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 soath this morning, correct? A. Correct.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately? er 14 A. I stated, it's times 450 per hour. So 15 it's like — I don't recall the amount — it's 16 like if you say 100 hours is 45,000, 200 hours
9 10 11 12 13 14 15 16 17	A. Yes, my address is Weinbergweg, lo 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 soath this morning, correct? A. Correct. Q. I took your deposition this past 8 February. Do you recall that?	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately? er 14 A. I stated, it's times 450 per hour. So 15 it's like — I don't recall the amount — it's 16 like if you say 100 hours is 45,000, 200 hours 17 would be 90,000. Is that right?
9 10 11 12 13 14 15 16 17	A. Yes, my address is Weinbergweg, 101 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 3 U-Z-N-A-C-H, Switzerland. Q. And you understand that you are under soath this morning, correct? A. Correct. Q. I took your deposition this past 8 February. Do you recall that? A. I recall it.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately? er 14 A. I stated, it's times 450 per hour. So 15 it's like — I don't recall the amount — it's 16 like if you say 100 hours is 45,000, 200 hours 17 would be 90,000. Is that right? 18 Q. So 100,000 dollars, something like 19 that?
9 10 11 12 13 14 15 16 17 18 19 20	A. Yes, my address is Weinbergweg, 101 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 soath this morning, correct? A. Correct. Q. I took your deposition this past 8 February. Do you recall that? A. I recall it.	Route 9 Q. Yes. 10 A. 200. Approximately. 11 Q. And what is the total amount of money 12 you've billed Weil for this matter since you 13 began, approximately? er 14 A. I stated, it's times 450 per hour. So 15 it's like — I don't recall the amount — it's 16 like if you say 100 hours is 45,000, 200 hours 17 would be 90,000. Is that right? 18 Q. So 100,000 dollars, something like 19 that?

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Conducted on De	ecember 16, 2021
1 You said 200 hours total?	1 aliants have you consulted with them an I recention
l	1 clients, have you consulted with them on Lucentis?
I	2 MR. PEPE: Objection, same caution. 3 A. No.
Q. So 90,000 dollars or something like	
4 that, right? 5 A. Yeah.	`
1	
6 Q. Now, I think you told me last time we 7 talked that HK has clients other than Regeneron,	
	7 A. Yes, I had one project involving Ilea.
8 right?	8 Q. Is that completed?9 A. Completed.
9 A. I don't have Regeneron as a client. 10 Q. I'm sorry, in addition to Weil, you	•
11 have other clients, right?	10 Q. I'm going to mark a couple of 11 exhibits. I think we will use the exhibit numbers
_	12 from the IPR if that's OK with everybody. This is
	13 Regeneron Exhibit 1001 and it's a copy of the '631
Q. For any of those other clients, have 14 you offered opinions on the '631 patent?	14 patent.
15 A. No.	15 (Exhibit 1001, U.S. Patent
16 Q. What about any foreign counterparts of	16 9,220,631 marked previously for
17 the '631 patent, have you consulted with any of	17 identification.)
18 your other clients on those?	18 Q. And the second exhibit will be the
19 A. What do you mean by foreign	19 declaration of Horst Koller in this IPR Regeneron
20 counterparts of the '631?	20 Exhibit 1003.
21 Q. So the Novartis patent family that	21 (Exhibit 1003, Declaration of
22 resulted in the '631 patent has members that are	22 Horst Koller marked previously for
0	2
1 issued in other countries and I was wondering if	1 identification.)
2 you have offered opinions on any of those other	2 Q. Just take a moment and look through
3 patents to your other consulting clients.	3 Exhibit 1003 and confirm that that is, in fact,
4 MR. PEPE: So Horst, I'm just going	4 your declaration.
5 to object and caution you not to disclose	5 A. Yes, it is my declaration.
6 any confidential information along with your	6 Q. Who drafted that?
7 clients in answering your question. You can	7 A. I drafted that.
8 answer if you can do so without doing that.	8 Q. All of it?
9 A. No, I did not consult any other patent	9 A. I got support from the legal
10 issues besides the IPR here.	10 department on like commercial – I was giving a
11 Q. I think the last time we talked, you	11 layout and then my counsel had me to put it in the
12 mentioned that you had been consulting with a	12 right form because I'm not a native speaker. They
13 client who was making a biosimilar of a VEGF	13 are –
14 antagonist. Right?	14 Q. When you say the legal department,
15 A. Right.	15 what do you mean by that?
16 Q. Is it just one client?	16 A. I mean by Weil.
17 A. No, multiple clients.	17 Q. Weil?
18 Q. For any of those clients, have you	18 A. Yeah.
19 discussed the '631 patent or its foreign	19 Q. So they provided the legal parts of
20 counterparts with them?	20 the declaration, is that right?
21 A. No.	21 A. Yes, that's right.
22 Q. For any of your other HK Consulting	22 Q. Did they provide you with prior art?

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		Conducted on Do	ecem	ber 1	6, 2021
l .		3			5
1		Yes.	1	A.	Right.
2	Q.	And you searched for some of the prior	2	Q.	You're not a physician?
3 ar	-	self as well, right?	3	A.	I'm not a physician.
4		Right.	4	Q.	You you've never given an intravitreal
5		A couple of the references that you	5 in	-	n, right?
		ed on are the Sigg and Lam applications.	6	A.	Right.
7 D	•	recall what those are?	7	Q.	You have no experience administering
8		Yes, I recall what those are.	8 in	travitr	eal injections, right?
9		Did Weil provide those to you?	9	A.	Right.
10		I I don't remember. I mean, I	10	Q.	You have no personal experiences with
		in 2017. I'm not — I cannot recollect			es that are associated with an
	-	which one was given and which one I found	12 in		eal injection, right?
	•	y having to look into prior art	13		No, not right. I mean, forces should
14 re	eferenc			_	eneral level. So — and I have designed
15	Q.	And what about the Boulange reference?	1 -	_	es with typically low break loose, glide
16	A.	Same.	16 fc	rces	for general purposes.
17	Q.	Were you aware of the Boulange	17		So I was designing prefilled
18 re	ference	e before 2017?	1 -	_	es with, you know, break loose and glide
19		I was not aware of the Boulange			for the intended use for application of
20 re	eferenc	ce prior to 2017.	20 si	mple	biotech products and they require for
21		You were working in the industry but			aneous or, you know, low — suitable low
22 yc	ou were	en't aware of the Boulange reference,	22 g	liding	forces and break forces.
	1.40	4			6
_	ght?	D. I.		Q.	But you have no personal experience
2		Right.	1		e actual forces that a doctor feels when
3	Q.	So how much time did you spend	١.		re an intravitreal injection, right?
		that declaration?	4		Right, I never gave an intravitreal
5	A.	This declaration, the new one here?	1	•	on myself.
6 -	Q.	Yes.	6	Q.	And you have no personal hands-on
7	A.	Thirty, 40 hours.		-	nce with how differing forces can impact an
8	Q.	And that was on top of the time that	1	ıravıır	eal injection, right?
		nt on your earlier declarations that built	9		MR. PEPE: Object to form.
		correct?	10		I cannot judge that one on
11		Yes. On top. Yeah.			treal injection. But I have enough
12		Are there any things in that		_	ence to judge differences in break loose
		on you would like to correct?	"	_	force performance independent of the
14		No.			ed use.
15		Now, you have the equivalent of a	15	-	But you have no experience, personal
		in engineering from a university in		-	nce with how the change in forces of an
		y, right?		•	inge can impact an intravitreal injection,
18		Right.	18 ri	ght?	
19	Q.	You're not a chemist?	19		MR. PEPE: Object to form.
20	Α.	I'm not a chemist.	20	A.	As I said, I don't have intravitreal

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Q. And you don't hold yourself out as an

22 expert in chemistry, right?

21 injection experience. But the systematic behind 22 low forces and avoiding shattering or stick slip

20

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.

- 11 Q. But the impact of a slip stick effect, 12 when giving an intravitreal injection, can have a 13 much more deleterious effect on the patient than 14 the same effect in a subcutaneous injection, 15 right?
- 16 A. It depends on the outcome of that one, 17 because if you are using like low volume syringes 18 also for injection of hyaluronic acid around the 19 eye or around sensitive, you know, areas in your 20 body, let's say in your face, then this, of 21 course, the stick slip effect has the same also, 22 very, you know, let's say effect regarding pain.

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.

5 Q. And it can have a very deleterious 6 effect on a patient's eye, correct?

A. Correct.

8 Q. That's why extreme care is needed when 9 giving an intravitreal injection, right?

10 A. Right.

11 Q. Have you ever discussed with a 12 physician the forces that are required for an 13 intravitreal injection?

14 A. No.

15 Q. Now, at one point in your career, you 16 worked at Abbott, right?

17 A. Right.

18 Q. And at Abbott, you worked on HIV and 19 hepatitis test kits and pregnancy kits, right?

20 A. Right.

21 Q. You didn't do any work during your 22 time at Abbott on the preparation of prefilled

1 syringes, right?

2 A. Right.

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

6 A. Right.

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

A. Right.

10 Q. And what years were you at Schott?

11 A. I joined Schott in the year 2000 and 12 left Schott in the year 2015.

13 Q. While you were at Schott, you used 14 ethylene oxide sterilization, right?

15 A. Right. Not only.

16 Q. But you do have experience at Schott 17 using ethylene oxide sterilization?

18 A. Right.

19 Q. And that was on at least syringes that 20 were filled with water, right?

21 A. Yes. In addition to that, ethylene 22 oxide is used to sterilize the prefilled syringes

1 prior to filling.

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

5 A. The syringe's barrel, right. It might

6 be different sterilization for the rubber

7 components involved in the aseptic filling

8 process.

9 Q. And why might it be a different 10 process for the rubber components?

11 A. That depended on intended use because 12 of convenience. If you do gamma irradiation, you 13 can sterilize a full pallet load and it is sort of 14 like continuous process.

15 If you do, as an example, steam 16 sterilization or ETO, it's always a batch process.

17 And you need have to have different packaging

18 available like Tyvek for gas permeation and double

19 PE bag for gamma irradiation or E-beam.

20 Q. Now, during your time at Schott, you 21 didn't use ethylene oxide to sterilize a syringe 22 filled with a sensitive biologic, right?

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23 A. Right. Yes, from the near mark. 2 Q. I think you also told me that while 2 And do you have experience -- let me 3 you were at Schott, you used vaporized hydrogen strike that. peroxide to sterilize something you called a Do you have experience determining the biosafety cabinet, right? shelf life of devices? A. That was during my time at Abbott. 6 A. Yes. O. At Abbott? Q. Would you agree devices must exhibit 8 some degree of shelf life stability to obtain A. Yes. Q. OK. What's a biosafety cabinet? approval, right? A. Biosafety cabinet is a device which 10 A. No. 11 can work sterile, in a sterile environment. But 11 So devices don't need any shelf life 12 it has the features that the worker is safe 12 stability, is that your testimony? A. No, this is how we need to define 13 because it sucks in from the outside to the inside 14 to have a user safety in combination with sterile 14 device. If I am a device manufacturer and I have 15 environment. That's why it is called biosafety 15 a certain functional shelf life, then the pharma 16 cabinet. 16 company needs to prove the shelf life of the drug Q. While you were at Schott, you did not 17 product. This is not the responsibility of a 17 18 use vaporized hydrogen peroxide to sterilize a 18 device manufacturer. 19 prefilled syringe, right? And shelf life sometimes mean, 20 A. Right. 20 for PFS manufacturer, I can guarantee a certain 21 Q. Now, none of your other work at Schott 21 sterility claim up to a certain point, and then the 22 was directly related to work on syringes that were 22 responsibility goes to the pharma company to fill 22 1 used for intravitreal injection, right? the drug substance, do some stability testing and A. I was working on a development of a then perform some shelf life testing. 3 prefilled syringe where the intended use was the PFS manufacturer usually have 4 idea of using that one as an intravitreal 4 shelf life testing regarding functional properties 5 injection. 5 like the removal of a tip cap, break loose, glide force over typically shelf life storage time under Q. And was that the Ingentle syringes? That was the Ingentle syringe. 7 certain let's say real temperature or accelerated That was never commercialized for aging conditions. 9 intravitreal injection while you were at Schott, Q. There was a lot there so I'm going to 10 right? 10 ask you a couple of questions to follow up. 11 11 I think that you mentioned that A. Right. 12 Q. Now, I think you told me last time 12 the shelf life issue could be sort of divided up 13 that you couldn't provide me with any documents on 13 between the syringe manufacturer and the 14 your R&D work at Schott because it was 14 pharmaceutical company that puts the drug into the 15 confidential, right? 15 syringe, is that right? 16 A. Right. 16 A. That's right. 17 Q. Do you want to look in your 17 Q. And the total container closure system

18 declaration there, paragraph 72, please. 18 with the drug in it, you would agree that has to

In 72, you have a quote that

19 have some sort of shelf life in order to be

In /2, you have a quote that 19 have some sort of shelf life in order to be

20 refers to the shelf life of the plunger, right? 20 approved by a regulatory agency, right?

21 A. In 72?
22 Q. Yes.
21 A. The shelf life which the pharma
22 company will claim is then not what the company

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27

25

1 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.

5 If you have shelf life data for 6 three year, but you still want to do two years, 7 then you get approval for two years. It's always 8 what you claim you need to show facts and data for 9 shelf life.

Q. So you have to show some sort of shelf

11 life in order to get approval, but the length of 12 the shelf life can vary depending on what the 13 company can prove in terms of stability over time, 14 right?

15 A. Right.

10

16 Q. And I think you mentioned two 17 different kinds of stability. One was sterility 18 and the other was functional, right?

19 A. Sterility is not a -- a claim of shelf
20 life. Sterility is sterility. This is defined,
21 as you say if I have a sterile system, it needs to
22 keep sterility over shelf life. Independent of if

treatment to what I have done to my system.

2 So the shelf life is not only one 3 claim. It's a combination of functional quality

4 and then the drug stability quality and then the 5 sterility behind it.

Q. OK.

7 The sterility part of it, if you have 8 a shelf life claim for your device of, for 9 example, two years, I think what you are saying is 10 your device has to be sterile for two years, 11 right?

12 A. Right, this is the claim. As a 13 syringe manufacturer, my claim is two-year 14 sterility. Within two years, the pharma company 15 should use it and fill it.

16 Q. Right, OK. And I think you mentioned 17 that for functional stability, break loose and 18 glide force would be something that you would have 19 to show over time, right?

20 A. Yeah, under certain combination which 21 is either used in-house as my standard rubber 22 component or if you want to offer different

26

1 it's like one month or three years shelf life. So2 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

10 is usually what I will tell as a device manufacturer
11 listed also like in the FDA in the so-called drug

12 master file. This is where I put all my information

13 about the technical stuff into the system.

Then if a pharma company is interested 15 in that system, sterility is a lot of work, of 16 course, in order to verify that their specific drug 17 product can be used within the container closure 18 system.

19 This is a different issue. They
20 might have something in it which does not allow me
21 that I can basically remove my tip cap or I might
22 have different forces because they do a different

1 possibilities that you say, OK, I want to check on 2 different rubber formulation or component, then

3 this is a typical usage of a system that you check

4 on break loose, glide force, particle content.

5 Also you try – you make

6 sterility testing that you know that your system is

7 tight. This is part of the testing for

8 functionality of syringes.

Q. And it's part of the testing of 10 functionality of syringes over time because the 11 regulatory agency is interested in the fact that 12 your device can perform the same way over time for 13 the entire shelf life, right?

14 A. Yes. The pharma company filling the 15 drug product needs to be able to show the 16 functionality to the end their claimed shelf life. 17 That whatever the PFS manufacturer is doing 18 before, this needs to be sort of, of course, 19 verified.

20 I can give certain input and I21 can say what our typical performance is.

Q. OK, in the real world, let's call it,

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29

1 after the syringe manufacturer provides the
2 syringe to the pharma company who then fills it or
3 has it filled and now you have a product that has
4 a shelf life claim on it, how does that stability
5 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 10 keep safe, you say the quality which I put into my 11 syringe that's available for all the drug products 12 should be the same or maybe only maybe have a 13 minimized effect after two or three years at the 14 end of shelf life.

So it's if a water injection, I will 16 check on conductivity, on pH, whatever — in this 17 water quality which goes into the — we say water 18 quality and end of shelf life.

19 For typical drug products, 20 potency effect, if they have a certain potency or 21 if they have a certain cleanliness, then this is 22 what you know when you put it in, basically 1 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.

11 Q. When you test that bioburden, do you 12 compare it to a sterility assurance level?

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

Q. So the sterility assurance level is a 22 validated level that you've demonstrated your

30

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

5 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?

13 A. This is complete. One is the 14 functional issue and one the drug stability issue.

15 Q. Do you know what the shelf lives are 16 for the commercially available VEGF antagonist 17 prefilled syringes?

18 A. I don't know.

19 Q. One last question on that. We talked 20 about functionality stability over time, but with 21 respect to maintaining sterility over time, to 22 demonstrate that your product is living up to its

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?

10 MR. PEPE: Object to form.

11 A. Sterility is only checking on 12 bioburden, independent on what the validation was 13 doing for your process.

14 Q. OK. The sterility assurance level is 15 a validation of your process, is that right? Do I 16 have that right?

17 A. It's a validation of the sterilization 18 process, yeah.

19 Q. And whereas an individual test is 20 simply a measure of the bioburden of that 21 particular device, whether it has decreased and 22 how much, is that right?

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A. Right.

So just staying with the sterility 2 3 assurance level for a moment, you mentioned that 4 it's a validated level or value. Can you tell me how it's -- how the validation is achieved? 6

A. Yeah.

So sterility is claimed by the 8 sterility assurance level, SAL, and sterility is 9 defined as having a bioburden reduction of like a 6 10 log, reduction so 10 minus 6.

11 How it's done is I have certain 12 so-called bio indicators which have a certain load, 13 known and specific for the sterilization specific 14 bioburden, and then I need to show that my 15 sterilization kills enough microorganism to 16 guarantee the 6 log reduction. Like survival of 17 one out of one million, that would be a typical 18 value for 6 log reduction.

Q. So the sterility assurance level is a 20 probabilistic value in that you can assert that 21 your process will result in a product that would 22 only have say one in a million chance of a

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1 nonsterile product, is that right?

A. That is right that you say from 1 million to 1.

What you usually is that you have 5 a higher bioburden load so you can, you know, at least get to the 10 minus 6 log reduction and that 7 then guarantees you that you have a sterile 8 product.

What you then need to show in your 10 existing current process like for the finishing, you 11 keep the environment in such a place that you never 12 get above this amount sterilized that you know my 13 sterility assurance level from 10 minus 6. So I 14 don't have a process which introduce a high amount 15 of bioburden, and even if I would have a 10 minus 6 16 log reduction, yeah, I would have nonsterile 17 product. So this is how you verified the overall 18 system.

19 So the SAL is a probabilistic value, Q. 20 right?

21 A. Right.

22 If you have an SAL of 10 to the minus 1 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 6 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, 9 outside contamination.

So sterility would always be claimed, 11 based on my knowledge, what I have seen on their 12 validations I did was always 10 to the minus 6.

Q. So if you had 10 to the minus 3, you 14 could call it, as you said, something like surface 15 decontamination or outside decontamination, is 16 that right?

17 A. You can prove a certain log reduction 18 which helps to minimize apparent ingress into the 19 product. But it would not usually show a 20 sterility claim because the industry expectation 21 is, notice from the agencies that is a 10 to minus 226 log reduction.

36 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

4 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 11 claim a sterile product. So people are putting in 12 place features that they do even a 10 to the minus 13 12 log reduction to have a safety system effect. 14 So sterile is a certain claim for me that's 10 to 15 the minus 6 log reduction. This is a validated 16 process.

So from your perspective, a claim of 18 10 to the minus 3 SAL would not be sterile, is 19 that right?

20 A. Based on my knowledge, right.

Q. Did you know whether the FDA has ever 22 approved a product as sterile with a 10 to the

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39 minus 3rd SAL? considered to be a problem for the patient, right? A. I don't know. 2 A. Right. Could cause floaters or Q. Now, it's your opinion that prior to increasing of ocular pressure. 4 January of 2012, a person of skill in the art Q. Now, you also mentioned in 68 that would have been motivated to use low amounts of lowering the amount of silicone oil by using a 6 silicone oil for an intravitreal syringe, right? baked-on siliconization process can reduce the incidence of the break loose effect, right? A. Right. Q. And if you want to look in your 8 A. Right. 9 declaration there at paragraphs 66 to 68, you list 9 Q. With respect to the amount of oil 10 some of the reasons for that, right? 10 that's injected into patients' eyes and what its 11 impact might be, you cite this Kocabura reference, 11 A. Right. So for example, in paragraph 66, you 12 Exhibit 1080, in paragraph 66, right? 13 list one reason would be to avoid protein 13 A. Right. 14 aggregation? 14 Q. So Exhibit 1080, Regeneron Exhibit A. Right. 15 1080 from the IPR is a letter to the editor in a 15 Q. And also you list that another reason 16 journal called Acta Opthalmologica entitled, 16 17 would be to avoid the interaction of silicone with 17 "Intravitreal silicone Oil Droplets Following a 18 the drug formulation, right? 18 Cap Knife Injection." A. Yeah, where protein aggregation would 19 (Exhibit 1080, article entitled 20 20 be an interaction between the silicone oil and the "Intravitreal siliconee Oil Droplets 21 drug product. 21 Following a Cap Knife Injection" marked 22 Q. Lower silicone oil would be less previously for identification.) 38 40 1 likely to interact with the drug, right? Q. Is this the paper you cited in paragraph 66? 2 A. Right. Q. And then you also reference that A. This is the paper I cited. 4 decreasing silicone oil would result in less oil And this is from someone named M. being injected into the eye of patients, right? Selim Kocabura, is that right, and her coworkers? A. Right. A. Right. Q. And you mentioned that the injection And this is from an ophthalmology 8 of silicone oil into the eye can result in clinic in Istanbul, Turkey, right? floaters in the patient's eyes, right? A. Right. A. I just need to read through. Is it 10 Q. In this paper, Kocabura reports on 11 three cases of silicone oil in the eye after 11 paragraph 66 you are pointing me? 12 administration of pegaptanib? Q. Yeah, in paragraph 66, 67, 68, you 13 list several of the reasons for your opinion. 13 A. Could you please repeat your question. A. Yeah. As I explained, reducing the Q. Yes, the author in this letter or 15 amount of silicone oil in syringe was known to be 15 paper reports on three cases of silicone oil in 16 the eye of the patients after administration of 16 desirable in terms of complications, right. Q. And one of the reasons was to decrease 17 pegaptanib? 18 the silicone oil droplets that were injected into A. In the first paragraph, in the first 19 patients' eyes, right? 19 column, it states, "We report three cases..."

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21

22

Q.

Α.

Q.

Right.

20

21

A. Right.

Q. And those silicone oil droplets that

22 were injected into patients' eyes, they were

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And pegaptanib is Macugen, right?

And then at the end of the paper, in

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4	43
1 the last paragraph, it says, "The functional and	1 At the priority date, clinicians
2 clinical consequences of intravitreal silicone oil	2 did not have access to a VEGF antagonist for
3 droplets are unknown, but their occurrence could	3 intravitreal administration that had less than 100
4 be avoided by using new generation prefilled	4 micrograms of silicone oil, right?
5 syringes that do not have an internal silicone	5 A. In a syringe.
6 coating."	6 Q. Yes. In the syringe.
7 Do you see that?	7 A. No, there was nothing on the market
8 A. I see that.	8 that had access to syringes for filling certain
9 Q. You would agree in that paragraph,	9 needs for intravitreal injection with a low amount
10 they are suggesting changing the Macugen product	10 of silicone oil besides the Macugen.
11 to decrease the amount of silicone oil in it,	11 Q. Maybe we are talking past each other.
12 right?	MR. PEPE: Objection.
13 A. Let me look through one second.	Horst, were you done answering?
14 I say silicone oil properties	14 THE WITNESS: Yes.
15 most likely associated with use of prefilled	15 Q. At the critical date in July of 2012,
16 syringes, yeah, but their occurrence could be used	16 doctors didn't have access to a commercially
17 by using new generation prefilled syringes that do	17 available product, a VEGF antagonist for
18 not have internal silicone coating.	18 intravitreal administration in a syringe that had
19 Q. So they're suggesting there to change	19 less than 100 micrograms of silicone oil, right?
20 Macugen by decreasing the amount of silicone oil	20 MR. PEPE: Objection, asked and
21 in the Macugen product, right?	21 answered.
22 A. Right.	22 A. I don't understand your question. If
42	44
Q. And you would agree that clinicians	1 you say access, what do you mean by that.
2 would want a prefilled syringe that had lower	Q. Could a doctor pull a syringe having
amounts of silicone oil, right?	3 less than 100 micrograms of silicone oil off the
4 A. Right.	4 shelf and use it to treat patients in July of
Q. But at the priority date of the '631	5 2012?
6 patent, doctors did not have access to an	6 A. As a prefilled syringe?
7 intravitreal syringe containing a VEGF antagonist	7 Q. Yes.
8 that had less than 100 micrograms of silicone oil,	8 A. I'm not aware of it or know that.
9 correct?	9 Q. I'm sorry, I don't understand you?
10 A. Not correct. The Boulange reference,	10 A. I don't know.
11 references functional syringe with a low amount of	
12 silicone oil used for sensitive application which	12 commercial products on the market for intravitreal
13 is gas tight, as well as break loose and glide	13 administration of a VEGF antagonist that had less
14 forces.	14 than 100 micrograms? You don't know, that's your
15 Q. The Boulange application doesn't	15 answer?
16 disclose a syringe for intravitreal	MR. PEPE: Objection, asked and
17 administration, right?	answered.
18 A. Right, but the POSITA would know on	18 A. I don't know.
19 certain functional performances that this can be	19 Q. Well, Macugen didn't have less than
20 used for intravitreal —	20 100 micrograms of silicone oil, correct?
21 Q. I understand that's your position, but	21 A. Correct.
22 my question was different.	22 Q. And in July of 2012, Macugen was the

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47 1 only intravitreal VEGF antagonist in a prefilled A. Right. 2 syringe, right? 2 And at the end, it says, "Infusion of A. Right. gas into the product container affects the Q. The next exhibit will be Regeneron stability of the drug product through chemical Exhibit 1007. modification by gas vapors such as alkylation and A. Counsel, can I come back to the last oxidation." question again? Do you see that? Q. Sure. 8 Yes. A. So I know that I cite it in my report Q. You would agree that is a concern that 10 that in 2012, Ilea was introduced in Australia. 10 a person of skill would have to take into account 11 in sterilizing a drug product, right? 11 I'm not aware - and I don't have top of my head, 12 I don't have the date of the Ilea submission in A. Right. 12 13 Australia compared to the priority date of the 13 Q. If you look down at line 20, it says 14'631 patent. 14 there that some sensitive drug products such as 15 proteins can't be sterilized using things like Q. The Ilea prefilled syringe that you 16 reference in your report in Australia, was it 16 steam, irradiation -- or irradiation, right? 17 launched in 2012? 17 A. Right. 18 A. It was submitted in 2012. Q. And at the end of that paragraph, it 19 Q. Right, but was it available as a 19 discusses why that is and that's because these --20 product for doctors in 2012? 20 some of these -- let me strike that. At the end of the paragraph, it again 21 A. No, it needs to be approved. 22 Right, so it was not available? The 22 refers to the fact that the oxidizing gases can 46 48 1 Ilea prefilled syringe that you referred to in the harm biological molecules and sensitive 2 Australian document was not available to doctors therapeutic solutions, right? 3 in 2012, right? 3 A. Right. A. Right. 4 Q. And on paragraph -- let me strike that. Q. So the next exhibit, Regeneron Exhibit 6 1007, is a copy of the Sigg application, it's Page 3 in the summary, WO2001/006877 A1. the reference talks about the use of VHP for 8 (Exhibit 1007, Sigg application, terminal sterilization, right? and VHP is WO2001/006877 A1 marked previously for vaporized hydrogen peroxide, is that correct? 10 identification.) 10 A. Right. 11 Q. If you could just take a moment and 11 Q. And then at the end of that page or 12 look at that and confirm that's the Sigg 12 the bottom of the page, around line 27, it says 13 application that you referenced in your report or 13 that, "It further has been found that among the 14 your declaration. 14 commercially available primary packaging 15 15 components, there are only very few packaging A. Yes. 16 material combinations that provide the required 16 Q. If you could turn to page 2. In the 17 second paragraph, the reference talks about cold 17 tightness of the system such as to avoid ingress 18 sterilizations, right? 18 of sterilizing gases into the pharmaceutical 19 A. Right. 19 liquid enclosed by the prefilled container." 20 Do you see that? Q. And there, the reference is referring 21 to gases like ethylene oxide and hydrogen peroxide 21 A. I see that. 22 that can be used to sterilize materials, right? 22 Just so we are on the same page, the

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1 primary packaging components here, do you have an 2 understanding of what that would refer to?

- 3 A. The packaging components will refer to 4 the syringe barrel, the front end closure and the 5 piston.
- Q. So in a prefilled syringe, it's basically the things that come into contact with the drug product, right?
- 9 A. Right.
- 10 Q. And the reference says there are only 11 very few packaging material combinations that 12 provide the required tightness, but the reference 13 doesn't provide any details of any particular 14 combinations, right?

15 A. Right, it doesn't talk about 16 specifics.

- 17 Q. Now, when you applied vaporized 18 hydrogen peroxide treatment, that involves putting 19 the product into a sterilization chamber and 20 applying a vacuum, right?
- 21 A. Right.
- Q. And the vacuum causes a pressure
- 1 change in the chamber that can cause the stopper2 to move, right?
- 3 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?
- 8 A. Right.
- 9 Q. And you would agree that vaporized 10 hydrogen peroxide could not be used with every 11 possible combination of barrel and stopper and 12 protect the drug product inside the syringe, 13 right?
- 14 A. I would distinguish that a plastic15 barrel might have significant issues with VHP.
- 16 Glass, which is typically the
- 17 preferred option here would be, you know, VHP
- 18 tight, and then a POSA would know what kind of
- 19 front end component or back end component needs to
- 20 be chosen in order to make a gas tight system. And 21 that has been shown also in prior art.
- Q. Right, but I think implicit in your

- answer is that you would have to select the right
- 2 components in order for the system to be gas tight
- 3 and protect the drug product solution, right?
- 4 A. Right, but this is not only for sterilization.
- 6 So gas tightness is something
- which needs to take place during shelf life of a
- 8 standard PFS. So you always need to avoid ingress
- 9 from gases from the outside to the inside into the
- 10 drug product environment. Not only during terminal 11 sterilization or sterilization.
- 12 Q. Now, Sigg suggests -- let me strike 13 that.
- So this Exhibit 1007, this reference 15 suggests that one post treatment measure that can 16 be used is the application of a vacuum at the end 17 of the antimicrobial treatment in order to remove 18 the VHP, right?
- 19 A. Right.

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- Q. And that process would also impart a
- 21 decreased pressure on the product, right?
 - A. It depends on the level of vacuum.
- 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.
- 5 A. Again, it depends on the level and 6 then it needs to overcome the break force in order 7 to be able to move at all.
- 8 Q. And there is no disclosure in the Sigg 9 reference, 1007, of any structure to prevent the 10 movement of the stopper either during VHP 11 sterilization or the removing of the VHP, right?
- 12 A. There is no specific feature to avoid 13 piston moving in the Sigg document.
- 14 Q. You would agree that a syringe where 15 the stopper has a low break loose force, that 16 would have a higher chance of moving during the 17 application of negative pressure, right?
- 18 A. Depending on the level of vacuum, yes.
- 19 Q. All things being equal, lower break
- 20 loose force would allow easier movement of the 21 stopper, right?
- 22 A. Right.

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53	55
1 Q. If you look at page 20 of the	1 injection.
2 reference, 1007, there is an example of the	2 Q. I understand that's your
3 sterilization of some syringes using vaporized	3 interpretation. My question is just that the
4 hydrogen peroxide, right?	4 example itself doesn't disclose the break loose
5 A. Right.	5 and glide force for these syringes, right?
6 Q. And the example refers to the syringes	6 A. Right.
7 as prefilled syringes, correct? In the first	7 Q. There is no disclosure of whether the
8 sentence?	8 break loose and glide forces change after the
9 A. Correct.	9 application of vaporized hydrogen peroxide, right?
10 Q. But there are no specifics given about	10 A. Right.
11 the make-up of the syringes, right?	11 Q. There is no mention of parylene C,
12 A. Right.	12 right?
13 Q. There is no disclosure of the syringe	13 A. Right.
14 materials, right?	14 Q. There is no discussion of the shelf
15 A. There is no disclosure of the syringe	15 life of these syringes, right?
16 material, right.	16 A. Right.
17 Q. There is no disclosure of the specific	17 Q. So if you look at
18 stopper design or the materials the stopper is	18 A. Excuse me, sir.
19 made from, right?	19 There is a general statement in
20 A. Right.	20 that — in such treatment, on page 21, "The results
21 Q. There is no disclosure of whether the	21 seen were within the requirement. There were no
22 barrel was lubricated with silicone oil or not,	22 differences between results of the untreated
54	56
1 right?	1 syringes and with hydrogen peroxide-treated
2 A. It would be, you know, a syringe it	2 syringes. Analysis can also be carried out at
3 should be lubricated independent of the material	3 different time points following treatment," and
4 to get to a, you know, decent break loose glide	4 over shelf life.
5 force. So I would say that syringes, the state of	5 So it gives an indication that
6 the art, will be lubricated.	6 you need to check this one over shelf life.
7 Q. Glass syringe barrels would be	7 Q. Right. It indicates that the syringes
7 Q. Glass syringe barrels would be	 Q. Right. It indicates that the syringes should be tested to determine their shelf life, but it doesn't provide any indication that such
7 Q. Glass syringe barrels would be8 lubricated, right?	7 Q. Right. It indicates that the syringes 8 should be tested to determine their shelf life,
 Q. Glass syringe barrels would be lubricated, right? A. Always the polymer barrels should be 	 Q. Right. It indicates that the syringes should be tested to determine their shelf life, but it doesn't provide any indication that such
 Q. Glass syringe barrels would be lubricated, right? A. Always the polymer barrels should be lubricated. 	7 Q. Right. It indicates that the syringes 8 should be tested to determine their shelf life, 9 but it doesn't provide any indication that such 10 testing was done or the results of such testing,
 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 	7 Q. Right. It indicates that the syringes 8 should be tested to determine their shelf life, 9 but it doesn't provide any indication that such 10 testing was done or the results of such testing, 11 right? 12 A. Right. 13 Q. And the table just above the paragraph
 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? 	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 description.
 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 	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
 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. 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 description.
 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, 	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
 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? 	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?
7 Q. Glass syringe barrels would be 8 lubricated, right? 9 A. Always the polymer barrels should be 10 lubricated. 11 Q. But the example doesn't mention 12 lubrication of the barrel, right? 13 A. It doesn't mention explicitly 14 lubrication of a barrel. 15 Q. It doesn't disclose how much, if any, 16 silicone oil was used in the barrel, right? 17 A. Right.	Q. Right. It indicates that the syringes 8 should be tested to determine their shelf life, 9 but it doesn't provide any indication that such 10 testing was done or the results of such testing, 11 right? 12 A. Right. 13 Q. And the table just above the paragraph 14 you were just pointing me to reports on protein 15 stability following treatment with vaporized 16 hydrogen peroxide, right? 17 A. Right.
7 Q. Glass syringe barrels would be 8 lubricated, right? 9 A. Always the polymer barrels should be 10 lubricated. 11 Q. But the example doesn't mention 12 lubrication of the barrel, right? 13 A. It doesn't mention explicitly 14 lubrication of a barrel. 15 Q. It doesn't disclose how much, if any, 16 silicone oil was used in the barrel, right? 17 A. Right. 18 Q. There is no disclosure of the break	Q. Right. It indicates that the syringes 8 should be tested to determine their shelf life, 9 but it doesn't provide any indication that such 10 testing was done or the results of such testing, 11 right? 12 A. Right. 13 Q. And the table just above the paragraph 14 you were just pointing me to reports on protein 15 stability following treatment with vaporized 16 hydrogen peroxide, right? 17 A. Right. 18 Q. It doesn't report on force

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22 should be low enough in order to do intravitreal

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22 there any evidence that sterility of the syringes

59 1 was achieved? And he references, for example, a A. It says approximately 10 ml of required SAL for ASCA products are defined to be at 3 solution was filtered to a .22 micrometer syringe least 10 minus 6. 4 filter. This is how you prepare your drug product Q. He refers to an SAL. But he doesn't 5 because that's a sterile filter. And then filling provide any data in example 1 demonstrating that 6 .5 ml syringes was performed in a sterile lab for any particular SAL was achieved, right? 7 hydrogen peroxide treatment with the syringes A. No mentioning an example that he was 8 here. testing on the 10 to the minus 6. But if he Q. The syringes were aseptically filled? claims that, in the prefix, that he says sterility 10 Α. Right. 10 claim in his document is at least a 10 minus 6, And does that mean that they were 11 O. 11 then he achieved the sterile product, then this is 12 sterile? 12 in reference back to the 10 minus 6. 13 A. I mean, a POSA would ask himself why Q. But he doesn't actually say that the 14 do all the effort if the syringe was not sterile 14 syringes in example 1 were sterile, correct? 15 in the first place. 15 A. He says he sterilized them. Q. You can claim sterility for a claim Q. He said he sterilized them, but were 16 17 that is aseptically filled, right? 17 they sterile? It doesn't say, right? 18 A. Right. 18 A. Right. 19 Q. And then they applied the vaporized 19 MR. PEPE: Objection, asked and 20 hydrogen peroxide terminal sterilization process 20 answered. 21 to these syringes, right? 21 Q. Let's take a quick break. 22 A. Right. 22 (Recess; 10:20 to 10:34 a.m.) 58 60 Q. Is there any indication that the Q. So Mr. Koller, I think when we took 2 outside of the syringes was rendered sterile by our break, we were looking at Exhibit 1007. the vaporized hydrogen peroxide application? That's the Sigg application? A. There is a general description on page A. Right. 5 15, like line 30, that references made to And if you look at that definition of sterility that you pointed me to on page 7, if you 6 treatment times that are sufficient to terminally could let me know when you're there. 7 sterilize the prefilled container. Q. OK. There is a general reference on 8 A. Yes, I'm there. 9 page 15 to times that could achieve sterility, is Q. And in the first sentence, it says, 10 that your testimony? 10 "Sterility as used herein is meant to refer to 11 11 complete absence of microbial life as defined by a A. Yes. 12 12 probability of nonsterility or a sterility Q. And on page --13 A. Excuse me, sir. And on page 7, he 13 assurance level, SAL." 14 describes the claimed sterility. 14 Do you see that? 15 Q. I'm sorry, what page? 15 A. I see that. 16 A. Page 7, under line 5. Sterility is 16 Q. And then it says the required SAL for 17 Sterility as used herein is meant to refer to 17 a given product is based on regulatory 18 requirements. Right? 18 complete absence of microbial life and required -19 sterility is used herein is meant to refer to 19 A. Right. 20 20 complete absence of microbial life as defined by a The next sentence that you pointed me 21 to, it starts with the words, "For example," and

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21 probability of nonsterility or a sterility

22 assurance level, SAL.

22 then it says "SALs for healthcare products are

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1 defined to be at least 10 to the minus 6," right?

2 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?

6 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 10 requirements for your product, right?

11 A. Right.

12 Q. And I think you mentioned earlier 13 that, for example, an SAL of 10 to the minus 3rd 14 might be referred to as surface decontamination, 15 right?

16 A. As an example, depending on the, you 17 know, intended use of the device.

18 Q. Right. And here, an SAL of 10 to the 19 minus 3rd could be referred to as sterile under 20 this paragraph that you pointed me to, depending 21 on the product?

22 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.

8 A. Yes.

Q. Now, if you look at the claims of the 10 application -- I guess, before we go there, if you 11 look for a moment at example 2 of the application, 12 it starts on page 21. And in that example, they 13 report on an experiment that was carried out to 14 determine the effectiveness of surface 15 decontamination using beta radiation, right?

16 A. Right.

17 Q. And then if we look at the claims now, 18 if you look at claim 8, you will see that it's 19 directed to a method for surface decontamination 20 of a prefilled container in secondary packaging.

21 Do you see that?

22 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.

8 Q. If you look at claim 15, which it says
9 that it's the method of any one of claims 8 to 14,
10 and it says, "Wherein sufficient energy to
11 decontaminate a surface of a prefilled container
12 is that which provides a dose of beta radiation
13 yielding a 10 to the minus 6 sterility assurance
14 level of the outside of the container surface,"
15 right?

16 A. Right.

17 Q. And so that indicates that using beta 18 radiation in this claim, you can achieve a 10 to 19 the minus 6 assurance SAL which, as you pointed 20 out, is an SAL for healthcare products, right?

21 A. Right.

62

22 Q. But there is no reference to achieving

64

2 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

1 a 10 to the minus 6 SAL for the vaporized hydrogen

6 requirement. So I would do the testing to show

7 that I can sterilize to the 10 to the minus 6

8 which then would be accepted by the healthcare

9 agency for — to be a healthcare product out in 10 the field, where they have a 10 to the minus 6.

11 Q. Yes, I understand you could do the 12 testing and demonstrate an SAL of 10 to the minus 13 6.

My question is a little

15 different. My question is in the claims, they 16 don't claim a 10 to the minus 6 sterility assurance

17 level for the application of vaporized hydrogen 18 peroxide, right?

19 A. Right.

Q. So the only 10 to the minus 6 SAL that 21 is actually claimed in this application is 22 directed to the use of beta radiation, right?

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67 A. Right. 1 that, you're saying that there are instances where Q. You would agree with me that there are 2 you might not be able to get to an SAL other than 3 instances where you can't get a product to a 10 to 10 to the minus 3 without damaging the product 4 the minus 6 SAL without causing the degradation of inside the syringe, but that wouldn't be acceptable to you. Is that -- that was what you the product using vaporized hydrogen peroxide, 6 right? said, right? A. Just repeat your question again MR. PEPE: Object to form. please. A. I said that the drug product comes Q. Yes, you would agree that there are --9 first and if there are some other legal 10 strike that. 10 requirement and you could not achieve a 10 to the You would agree that it is possible 11 minus 6, then a 10 to the minus 3 on the outside 12 that you could have a situation where you wouldn't 12 might be possible depending on the feedback from 13 be able to get to a 10 to the minus 6 SAL without 13 the agencies. But the drug product needs to be 14 causing degradation of the product, right? 14 safe. It needs to be a gas tight system. MR. PEPE: Object to form. Q. Right, OK. 15 15 A. No, because I could check that no 16 So that would be an instance 16 17 ingress would take place into my drug product by 17 where the particular product, you could not get to 18 an SAL of 10 to the minus 6 without damaging the 18 routine testing. Q. I understand that you are saying --19 product, and so you would potentially propose 10 to 20 let me strike that. 20 the minus 3rd to the FDA or EMA in order to protect 21 Isn't it the case that there could be 21 your product? 22 situations in which you would not be able to A. Right. The claims here, some post 68 66 1 achieve the SAL 10 to the minus 6 without treatment possibilities to avoid ingress of destroying your product with your vaporized systems or of gas, of VHP into the drug product. So as soon as the -- let's say 3 hydrogen peroxide? MR. PEPE: Same objection. the microbial fluid has done its job on the outside A. I would, as a POSA, I would say what of the syringe and the inside of the blister, it 6 is the issue here. One is to do outside says that by removal per vacuum or other plasma 7 decontamination in a blister packaging or outside treatment can withdraw or basically convert the 8 sterilization of blister packaging. The other one flow that gas doesn't go in, but that I can pull it 9 that I immediately always need to keep my product away from my drug product in order to keep the drug 10 safe inside. 10 product safe. 11 11 So if I could achieve a 10 minus 3 on So he is implementing here, he is saying 12 the outside, but still 10 minus 3 will damage my 12 in case the system, you know, would have a problem, 13 product, then this would not be a suitable option. 13 that post treatment could help you in that way. 14 So I clearly would distinguish between a 14 Q. Mr. Koller, is it true that in some 15 safe product on the inside of ingress of gases and 15 instances, you need to ask the FDA or the EMA for 16 the possibility of claiming -- and let's say I can 16 a 10 to the minus 3rd claim rather than a 10 to

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19

20

17 have a gas tight system on the inside, but still

19 in order that I cannot get the 10 to the minus 6

21 possible within a blister.

18 have some features or some mechanical issues there

20 maybe to the outside or 10 to the minus 3 would be

Right. So I think -- if I can unpack

A. I personally didn't talk to the FDA in 21 such a way. But based on my POSA, if you cannot

17 the minus 6 claim because the product is being

MR. PEPE: Object to form.

22 achieve a 10 to the minus 6 in the first place,

18 damaged by the sterilization process?

7 1 then you might need to go and look for other 1 system. 2 component system which can survive a 10 to the 2 The next exhibit will be the IPR Q. 3 minus 6 without damaging the product. Exhibit Regeneron Exhibit 1029. This is a copy of But this is a routine the Lam application, WO2008/077155A1. 5 optimization of some of the systems in order to get (Exhibit 1029, Lam application, 6 to the 10 to the minus 6 which is the FDA WO2008/077155A1 marked previously for requirement for sterile product in the first place. identification.) Q. Right. You could redesign your Q. Mr. Koller, if you could take a moment 9 product in order to try to achieve 10 to the minus 9 and look at that application and confirm that 10 6. But if product redesign wasn't a possibility, 10 that's the Lam application that you have opined 11 aren't there circumstances where a company needs 11 about in your declaration? 12 to request a 10 to the minus 3rd approval for 12 A. Yes. 13 their product? 13 Q. This is an application by Genentech, 14 MR. PEPE: Same objection. 14 correct? 15 A. I can't answer that because I never 15 Correct. 16 talked to the FDA to reduce a 10 to the minus 6 to 16 Q. And Genentech developed Lucentis, 17 a 10 to the minus 3 and what would be a 17 right? 18 circumstance for that one. 18 A. Right. Q. Can you envision such a circumstance And the application is directed to 19 20 existing though? 20 methods for terminal sterilization of syringes 21 MR. PEPE: Same objection. 21 including Lucentis, right? 22 As a POSA, by knowing what is -- let 22 Right. 70 72 1 me -- if you can't approve the terminal Q. The file date of this application is the 21st of December 2007. 2 sterilization to the 10 to the minus 6 to the end, 3 then you already made the mistake in the first 3 Do you see that? 4 A. Yes, I see that. 4 place by choosing the right component. So if a product was not designed for And then there is an earlier priority date of the 21st of December, 2006, right? 6 terminal sterilization, then you might have an issue Right. 7 in the first place. 8 Q. Do you know if a patent ever issued If I know that the system needs to 9 survive terminal sterilization, I don't see the 9 from this application? 10 point why you then should ask me to go for a 10 to A. What I see is a patent application. 10 Have you seen a patent that issued 11 the minus 6 to 10 to the minus 3 because you design 11 12 from this application to the best of your 12 your product in such a way that it can survive the 13 recollection? 13 requirements. Yeah. Q. Right, but if -- absent redesigning 14 A. No. 14 15 15 your product, under those circumstances, you're So you're not aware of a patent? 16 only recourse would be to ask the FDA for a 10 to 16 A. I'm not aware of a patent. 17 Now, the patent application discusses 17 the minus 3rd approval, right? 18 the use of ethylene oxide as an oxidizing --18 A. For the outside surface. 19 19 sorry. Strike that. Q. Yes. 20 It discusses the use of ethylene oxide 20 A. I could imagine that you could go to 21 as a sterilizing agent, right? 21 the FDA and ask if in what kind of circumstances 22 they would accept it and how you control the A. Right.

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22

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73	75
1 Q. And ethylene oxide is an oxidizing	Do you see that?
2 agent?	2 A. Yes.
3 A. Ethylene oxide is an alkylating agent.	Q. And then here it says that, as used
4 Q. Ethylene oxide alkylates?	4 herein, the surface of an object is "sterilized
5 A. Yes.	5 when the amount of at least one biological
6 Q. Contact between ethylene oxide and a	6 contaminant present on the surface of the object
7 sensitive drug would damage the drug, is that	7 being treated, according to the present invention,
8 right?	8 is reduced following the treatment."
9 A. It could damage the drug, right.	9 Do you see that?
10 Q. So you would agree that it would be	10 A. I see that.
11 important for the container to be ethylene oxide	11 Q. So in that sentence, they're
12 impermeable when performing terminal sterilization	12 indicating that the meaning of sterilized could
13 on these syringes, right?	13 embrace simply reducing a biological contaminant,
14 A. Right.	14 right?
15 Q. And you would agree that not every	15 A. Right.
16 combination of syringe and barrel would achieve	Q. And then in the next sentence, it says
17 ethylene oxide impermeability, right?	17 "Typically, the amount is reduced by at least one
18 A. Again, if I would use a polymer	18 log, i.e. by at least tenfold. In some
19 barrel, then the likelihood that it would survive	19 embodiments of the invention, the amount is
20 ETO treatment would be limited.	20 reduced by 2 logs, 3 logs, 4 logs, 5 logs or 6
21 Q. That's because the ethylene oxide	21 logs."
22 could seep into the drug product and damage it?	Do you see that?
74	76
1 A. It could migrate through the polymer	1 A. I see that. 76
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier	1 A. I see that. 2 Q. And the thing we have been talking
1 A. It could migrate through the polymer	1 A. I see that.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier	1 A. I see that. 2 Q. And the thing we have been talking
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure.	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right?
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight,	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right?	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right.	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right?
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the 14 syringe, right?	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that 14 begins on page 13 and then runs through page 16.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the 14 syringe, right? 15 A. Right.	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that 14 begins on page 13 and then runs through page 16. 15 Do you see that?
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the 14 syringe, right? 15 A. Right. 16 Q. If you turn to page 14 of this	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that 14 begins on page 13 and then runs through page 16. 15 Do you see that? 16 A. The example?
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the 14 syringe, right? 15 A. Right. 16 Q. If you turn to page 14 of this 17 exhibit sorry, before you do that, could you	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that 14 begins on page 13 and then runs through page 16. 15 Do you see that? 16 A. The example? 17 Q. Yes.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the 14 syringe, right? 15 A. Right. 16 Q. If you turn to page 14 of this 17 exhibit — sorry, before you do that, could you 18 turn to page 4, please.	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that 14 begins on page 13 and then runs through page 16. 15 Do you see that? 16 A. The example? 17 Q. Yes. 18 A. Yes.
1 A. It could migrate through the polymer 2 itself because it has, you know, less barrier 3 properties then of course glass, just from the 4 material point of view, not from the front end 5 closure or back end closure. 6 If your syringe barrel and 7 stopper combination were not sufficiently tight, 8 you could also get gas ingress into the drug 9 product in that instance, right? 10 A. Right. 11 Q. So a person of skill would have to 12 select suitable components in order to apply the 13 ethylene oxide sterilization method to the 14 syringe, right? 15 A. Right. 16 Q. If you turn to page 14 of this 17 exhibit sorry, before you do that, could you 18 turn to page 4, please. 19 A. Yes.	1 A. I see that. 2 Q. And the thing we have been talking 3 about, 10 to the minus 6, that would be the same 4 as what they are referring to as six logs in that 5 last sentence, right? 6 A. Right. 7 Q. And so at 10 to the minus 6 SAL let 8 me strike that. 9 A 10 to the minus 6 reduction 10 would only be one of the examples in this 11 paragraph, right? 12 A. Right. 13 Q. If you turn now to the example that 14 begins on page 13 and then runs through page 16. 15 Do you see that? 16 A. The example? 17 Q. Yes. 18 A. Yes. 19 Q. And on page, at the bottom of page 13

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77	79
1 A. Right.	1 are discussing that paragraph in Lam that you and
2 Q. And on the top of page 14, there is a	2 I just looked at where it talked about the
3 row with sterility log reduction results, right?	3 embodiments.
4 A. Right.	4 A. Yeah.
5 Q. And some of the log reductions were	5 Q. And in that last sentence, do I
6 greater than six logs, right?	6 understand correctly that you are simply saying
7 A. Right.	7 that if you have a that strike that.
8 Q. And others were less, correct?	8 That a 6 log reduction let me
9 A. Right.	9 strike that.
10 Q. And in terms of the definition of	Does it necessarily follow that if you
11 "sterility" or "sterilized" that we looked at	11 have 6 log reduction, you have achieved a
12 earlier, all of these results would fit within the	12 sterility assurance level of 10 to the minus 6?
13 definition of sterilized in that earlier	13 A. So if you say you have a 6 log
14 paragraph, right?	14 reduction, meaning you have an SAL of 10 to the
15 A. Right.	15 minus 6.
16 Q. If you look in your declaration at	16 Q. If you have one result where you get a
17 paragraph 288, please.	17 bioburden reduction of 10 to the minus 6, does
Do you see that in paragraph 288, you	18 that mean that you have a sterility assurance
19 are discussing the claim 21 of the '631 patent?	19 level of 10 to the minus 6?
20 Do you see that?	20 A. Yes, it's a reduction.
21 A. Yes.	21 Q. I thought you told me earlier that a
Q. And claim 21, as you recite there,	22 sterility assurance level is a validated process
78	80
1 claims that the syringe has been sterilized using	1 where you can, on the basis of probability, say
2 ethylene oxide or hydrogen peroxide with a	2 that you have no more than one nonsterile
3 sterility assurance level of at least 10 to the	3 component in a million?
4 minus 6.	4 A. Yeah, this is a 6 log reduction from
5 Do you see that?	5 one million to 1.
6 A. I see that, yes.	6 Q. Right. But the fact that you have a
7 Q. And then you have a few paragraphs	7 result with a 6 log reduction is not the same
8 discussing the results in Lam. And then at the	8 thing as having a process that you can say has an
9 end of paragraph 290, if we could look at that	9 SAL of 10 to the minus 6, right?
10 sentence	10 A. No, for me it's the same.
11 A. Yes.	So 6 log reduction is used like a
12 Q. It says, "A POSITA," a person of skill	12 10 to the minus 6. The starting level could be
13 in the art, "would understand that Lam's	13 different. I could start from 1 million down to 1.
14 disclosure of reducing the biological contaminants	14 I could start from 10 million and then a 6 log
15 by at least, quote, 6 logs means that the	15 reduction. I could start at 100 million. So it
16 sterilization cycle has achieved a sterility	16 depends on the starting level.
17 assurance level of at least 10 to the minus 6."	17 But a 6 log is 6 log reduction.
18 Do you see that?	18 That's — you can verify that your sterility
19 A. On 290?	19 process has a 6 log reduction which is then
20 Q. 290. The last sentence.	20 considered as they state in the art as sterility
21 A. OK, yes, I see it now. Sorry.	21 claim.
22 Q. In the beginning of the paragraph, you	22 Q. Looking at the results of the example,
22 V. In the organisms of the paragraph, you	2. Looking at the results of the example,

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83 1 in Lam on page 14 at the top --A. In some instances. This is what you A. Yes. do as a routine optimization. You never know what Q. Some of the results were greater than your process parameter should be. 6 logs, some were less. So if I would go back to run A. Right. number 1, that does not mean that I have a Q. So is that achieving a sterility 6 completely different process -- different syringe assurance level of 10 to the minus 6? in place. I might have used different A. Run 4 and 5 will do so because the log performances, like vacuum, temperature, humidity, 9 reduction is log 6 — in run 5, it's 6.3. 9 and also Sigg describes that it's a routine Q. Some of the runs had log reductions of 10 10 optimization of certain controlled parameters in 11 less than 10 to the minus 6, right? 11 order to achieve the desired 6 log reduction. 12 A. Right. 12 It does not talk about Q. So is this a process that has an SAL 13 13 validation. But he talks that he had -- he found a 14 of 10 to the minus 6? 14 cycle for 6 log reduction. 15 And then if I go to table number Q. Can you tell from this example whether 16 2, then he was checking the content, if there is 17 this process has been validated to achieve an SAL 17 any influence regarding the protein. And he shows 18 of 10 to the minus 6? 18 that, you know, the protein was stable. Even at A. He doesn't talk about validation, but 19 the 6 log reduction, a POSITA would read out that 20 if he knows that he has a 6 log reduction, he was 20 this is a tight system which can survive ETO 21 using bio indicators. 21 sterilization. So there is no way that you can Q. Well, the process that's disclosed in 82 84 1 just count the numbers. So you need to have a 1 the example has results that are both above and 2 certain level of bioburden and then you checking, below 10 to the minus 6, right? 3 after your sterilization process, to what level you 3 A. Right. 4 come down. Q. Mr. Koller, so these results that are Q. Do these data indicate to a person of provided here in example 1 are results of the 6 skill in the art that this process is validated to testing of the process at time zero, right? 7 an SAL of 10 to the minus 6? A. Right. MR. PEPE: Object to form. There are no data provided for these A. I mean, he doesn't talk about results either sterility or protein content over 10 validation. He talks about the 6 log reduction. 10 time, right? 11 And then what I would do is that 11 MR. PEPE: Object to form. 12 I use either run number 4 or run number 5 where it 12 A. Right. But you need to understand how 13 says I have a 6 log reduction or larger 6, and then 13 you do that. 14 I do a validation which are certain ISO 14 I mean, this process here has an 15 requirements for ETO sterilization which clearly 15 evacuation cycle. So what it's describing -- Sigg 16 describes what you need to do to get to a validated 16 describing as well that a post treatment measure is 17 process. 17 that, you know, you evacuate the chamber or you get

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This is a test where he shows that on

19 ETO process, he still has a safe product, but he

20 still could achieve a 6 log reduction with a

Q. In some instances?

21 process.

22

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18 the residual ETO out. There are some legal

19 requirements that, you know, no residual ETO above

20 a certain limit should be there. You need to show

21 that. This is a regulatory requirement. So you

22 pull out all the vacuum.

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Transcript of Horst Koller

Conducted on December 16, 2021 That means, you pull out the 2 residual ETO by example by vacuum and you have a 3 low level of residual ETO on the system. 4 Likelihood that something might migrate later into 5 the system is nonexistent because you will see the 6 ingress right away if you check on the inside. Based on my POSITA knowledge, 8 this is not a long term effect. This is like if it 9 happened, if there is an ingress, there is an 10 ingress. It happens right away because the ETO 11 cannot migrate into the system if it's not there 12 anymore. 13 Q. And there is no indication here of a 14 shelf life for this product in example 1, right? 15 MR. PEPE: Object to form. A. I can't see any shelf life claims 16 17 there. Right. Q. And there is no demonstration of 19 sterility over any particular shelf life in the 20 example, right? A. Right. He was checking that he can 22 terminally sterilize the outside surface and the 86 1 piston. But, it's not - again, it's not 2 sterility shelf life claim on the inside. Going performance. 3 back --Q. Well, there is no shelf life claim either of the product inside or the outside of the

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, Q. And that's the reason that a person of 10 skill would test the protein over time is to 11 ensure that you didn't see an impact later on from 12 the initial exposure to ethylene oxide, right? A. Again, to -- there are two points 14 here. One is what we discussed before. So it's a 15 question about product shelf life, stability, 16 sterility over shelf life and finding a process 17 where I can terminally sterilize the outside or 18 maybe on the inside of a blister. So I understand, yes, that if you do 20 shelf life testing on your final drug product as an 21 example, a pharma company for a specific product I 22 want to bring to the market, I need to show

product or the function of the product or any shelf life claim, right?

MR. PEPE: Objection.

Horst, first, were you done with

10 your previous answer?

11 THE WITNESS: I'm done.

12 MR. PEPE: Are you sure? OK.

13 Q. Did you understand my question?

A. Can you repeat your question, please. 14

15 Q. Yes, there is no assertion of any

16 shelf life in the example one whether it's 17 sterility or function or protein content over 18 time, right?

19 A. Right.

Q. Now, if you did see protein

21 degradation in the product after sterilization

22 over time, that would indicate that there was a

stability testing, sterility and functional

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

11 the protein degradation, you measure protein

12 degradation over time in order to assess whether

13 or not there was exposure of your product to the

14 ethylene oxide, for example, when the

15 sterilization process occurred, right?

A. You check on the product stability 17 because of extractables, leachables. So you would 18 not check VHP or ETO residuals at the end of shelf 19 life.

20 Setting -- sorry.

21 This does not make sense because 22 you're checking on the stability of the drug

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- 1 product, now independent where it comes from. And 1
- 2 if you usually have vapor or oxidizing ingress or
- 3 VHP or ETO ingress into the drug product, you see
- 4 that right away within like time point zero
- 5 testing after sterilization or at least within
- 6 three months. So you see.
- But you need to check then what
- kind of degradation of my protein because if it is
- 9 alkylated, then my guess would be that it comes
- 10 from the ETO. Is it -- it has a different
- 11 degradation, yeah, like application. It could come 12 from the silicone oil.
- So, then of course, you do a sort of 14 root cause analysis to see what is causing my
- 15 degradation of the product.
- 16 Q. Let's focus on alkylation.
- 17 Setting aside whether you look at
- 18 that at the end of the shelf life, you would
- 19 measure the amount of protein alkylated over time
- 20 to assess whether or not there had been an ingress
- 21 of alkylating agent during sterilization, right?
- 22 A. Right, this is part of the

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- 1 specification that you say I have less than
- 2 certain percentage of alkylation that's allowed in
- 3 my product spec. You will check on that one,
- 4 right.
- 5 Q. It is possible that you cannot see a
- 6 problem with alkylation at time zero and see the
- 7 problem develop over the months that follow,
- 8 right?
- 9 A. As I explained before, in theory, yes.
- 10 But I don't know where the alkylation took place,
- 11 if it's based on the sterilization gas or agent,
- 12 then there is no sterilization gas or agent
- 13 anymore because you need to make sure that you are
- 14 below a certain safety level for exposure to like 15 the people using it.
- 16 Q. So it is theoretically possible, I
- 17 think you said?
- 18 A. It is theoretically possible, yes.
- 19 Q. Is it possible for your components of
- 20 your system to absorb, for example, ethylene oxide
- 21 and then release it slowly over time into your
- 22 drug product and cause degradation?

- A. I need to split it up in two answers.
 - One, it is theoretically
- 3 possible.
- Secondly, this is what you avoid
- 5 by having this post treatment measures in place.
- 6 This is exactly what Sigg describes that I will
- 7 help by pulling a vacuum to get to reverse the flow
- 8 from the outside to the inside. So I pull it out.
- 9 It's pulled out. There is nothing there which can 10 later migrate into the system.
- 11 And also, you know, as a POSITA, exactly
- 12 for that reason I need to avoid any gas ingress, I
- 13 know which kind of rubber formulation I need to
- 14 choose to the tip cap, also for the piston side. So 15 this is usually chloro or bromobutyl which has a
- 16 very high permeation barrier because they are
- 17 designed for keeping the product safe.
- 18 Q. Looking at example 1 of Lam again,
- 19 Mr. Koller, in the example on page 15, does the
- 20 author provide some information about the stopper
- 21 and the FluroTec barrier film on the stopper,
- 22 right?

1 A. Between line 10 and 15?

- Q. Yes. Between line 12 and 17.
- 3 A. OK, yes.
- Q. Other than that, does the Lam
- 5 application provide any details about the syringe
- 6 design?
 - MR. PEPE: Object to form.
- 8 A. It does not specifically mention any
- 9 syringe design. Again, at the POSA, by knowing 10 what is the drug product, I can do for sure some
- 11 read-outs which would be for benefit for
- 12 optimizing the system.
- Q. But the Lam application itself doesn't
- 14 specify, for example, the design of the syringe 15 barrel or the stopper, right?
- 16 A. Right.
- 17 Q. There is no specification of the
- 18 design of the plunger rod, right?
- 19 A. Right.
- 20 Q. There is no indication of the brand of
- 21 syringe barrel that Genentech was using here,
- 22 right?

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1 A. Right.	1 A. Yes, because according to Boulange, it
2 Q. There is no indication that the	2 gives them an additional benefit.
3 product was in a glass or plastic syringe barrel,	Q. So you believe a POSA would put two
4 right?	4 coatings on the stopper; both FluroTec and
5 A. Right.	5 parylene C. Is that your testimony?
6 Q. There is no indication of whether the	6 A. My testimony is you need to know the
7 syringe barrel contains silicone oil, right?	7 design of the stopper because there are FluroTec
8 A. Right.	8 stoppers out where only the front end, the product
9 Q. There is no disclosure of the break	9 contact side, is - which is the so-called West
10 loose or glide force, right?	10 FluroTec stopper, where it is only laminated to
11 A. Right.	11 the product contact side.
12 Q. There is no indication or data showing	12 If I do parylene C on this
13 that the break loose and glide force can be	13 system, which is a plasma coating, I will coat the
14 maintained after ethylene oxide sterilization,	14 ribs which has a benefit on break loose glide force
15 right?	15 according to Boulange. So yes.
16 A. It does not state that, but I still	16 And I would put parylene C on top
17 disagree with that option because prefilled	17 of the system because it doesn't do any harm to the
18 syringes are routinely ETO sterilized. So I know	18 system. So it depends on the type of system you
19 that ETO sterilization of prefilled syringes will	19 are using.
20 not negatively influence the break loose glide	20 Q. Regardless of whether the FluroTec is
21 force.	21 just on the tip or it's on the sides, when you do
22 Q. But there is no data in Lam indicating	22 the plasma deposition of the parylene C, you're
94	96
1 that that was, in fact, the case, right?	1 going to cover the whole thing up, right?
2 A. Right.	2 A. Right.
Q. Let me ask you a follow-up question	Q. So the FluroTec won't have any effect
4 about the stoppers, Mr. Koller, if you could stay	4 on the stop the function of that stopper,
5 on page 15 of Lam for a moment.	5 right?
6 A. Yes.	6 A. Right.
7 Q. So those stoppers, they indicate that	7 Q. The next exhibit is IPR Exhibit 2022.
8 they have a FluroTec barrier film, right?	8 This is a copy of a journal article, first author,
9 A. Right.	9 Chan called "Syringe Siliconization Process
10 Q. And that would be in most instances a	10 Investigation and Optimization" from the PDA
11 tip cap that would prevent the rubber from coming	11 Journal of Pharmaceutical Science and Technology.
12 into contact with the drug product, right?	12 (Exhibit 2022, article entitled
13 MR. PEPE: Object to form.	13 "Syringe Siliconization Process
14 A. I mean, it states here where the	14 Investigation and Optimization" marked
15 stopper only plunger comprised the 777-7 laminated	previously for identification.)
16 micrometer coating of FluroTec barrier film and	16 Q. Mr. Koller, if you could take a moment
17 where the tip cap have comprised either 777 or D21	17 and look at that and tell me if you recall seeing
18 laminated. So it stops that — it is not only the	18 it previously.
19 tip cap which is coated.	19 A. Right, this is the –
20 Q. So from your perspective, would a	20 Q. I'm sorry, I didn't
21 person of skill in the art be motivated to coat a	21 A. This is the reference, yes.
<u> </u>	
22 FluroTec-coated stopper with parylene C?	22 Q. You examined this

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1 A. Yes.	1 stated in my declaration that a certain diving
Q Chan reference before?	2 nozzle has a feature where I can reduce the amount
And the paper indicates on page	3 of silicone oil from point A to .5 or even down to
4 2022.002 that Chan and his coauthors are from	4 .2.
5 Genentech, right?	Q. Just so I understand the numbers that
6 A. Right. 7 Q. And Genentech is a company that makes	6 you used there.
1	7 A. Yes.
8 protein pharmaceutical products, right?	8 Q. You're saying that you could decrease
9 A. Right.	9 them down to 200 micrograms, right?
10 Q. In fact, they were the developers of 11 Lucentis, right?	10 A. Spray technique
1	11 Q. Is that your answer?
	12 A. Spray technology allows a decrease
Q. And would you agree that they had a 14 motivation to decrease silicone oil interaction	13 down to approximately 200 micrograms. 14 Q. If you look at page 145 of the
15 between let me strike that.	14 Q. If you look at page 145 of the 15 article, it is Exhibit page 2022.0011.
16 You would agree that Genentech	
17 had a motivation to decrease the interaction	1
18 between silicone oil and its protein products,	17 Q. You see that there is a paragraph 18 entitled, "Coated Silicone Amount"?
19 right?	19 A. Yes.
20 A. Right. If – if syringes – I mean if	20 Q. And the first sentence says, "There is
21 functionality is guaranteed in the first place.	21 a clear trend is that regardless of the spraying
22 Q. Right. If you can't guarantee	22 condition the higher the amount of coated
98	22 condition the higher the amount of coated
1 function, then you have to add more silicone oil	1 silicone, the easier the syringe passes the glide
2 in order to achieve the function that you need,	2 force test."
3 right?	3 Do you see that?
4 A. I disagree with that.	4 A. I see that.
5 Q. OK, then I didn't understand your	5 Q. And you don't disagree that increasing
6 answer. I was trying to understand your answer.	6 the amount of silicone oil will decrease the glide
7 A. The article here shows that they used	7 force, right?
8 a diving nozzle and static nozzle.	8 A. I disagree with that statement and I
9 And it was known in the industry	9 disagree with the statement in my first
10 that static nozzle has certain technical	10 declaration.
11 limitations. It doesn't spray up all the way. So	11 Q. You disagree with the statement in
12 we have some undercoated system.	12 this article, right?
13 If you use a diving nozzle or if	13 A. Right.
14 you say the only way that you can increase that by	14 Q. At the bottom of that paragraph, the
15 spray up is by significantly increasing, you know,	15 authors say that the preferred amount let me
16 the amount of silicone oil spray in the system.	16 strike that.
17 So yes, the read-out is that I	17 "The preferred silicone amount for the
18 need to increase my system, my amount of silicone	18 1 ml long syringe is in the range of .2 to .5
19 oil in order to, you know, coat the complete entire	19 milligrams per syringe."
20 syringe.	Do you see that?
21 If I am using a diving nozzle,	21 A. I see that.
22 there is also prior art out there which I have	22 Q. So these authors had concluded that
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1 the preferred amount was 200 micrograms to 500	1 Q. The amount of silicone oil that's
2 micrograms per syringe, right?	2 being referred to in that optimization paragraph,
3 A. Right.	3 the 300 micrograms, that's an oily silicone
4 Q. Right below that, under the title,	4 application process?
The state of the s	
6 parameter investigation above was used to support	Q. So is it fair to conclude from this
7 the selection of optimum siliconization	7 article that in 2012, Genentech was still using an
8 conditions. In the optimum in the optimization	8 oily silicone application in its syringes?
9 test we targeted a 0.3 milligram silicone coating	9 MR. PEPE: Object to form.
10 dose which is near the low range of the preferred	10 A. I mean, the article shows that they
11 silicone amount."	11 did some investigation on optimizing silicone
Do you see that?	12 performance. It doesn't say that they have been
13 A. Right.	13 using only oily application in their syringes.
14 Q. So these authors, after having	14 Q. So whether or not they were only using
15 performed this optimization test, they landed on	15 oily siliconization, they were still working with
16 an amount of silicone oil of 300 micrograms,	16 oily siliconization in 2012, right?
17 right?	17 A. Right.
18 A. Right.	MR. PEPE: We have been going about
19 Q. Regardless of whether or not you agree	an hour. Is there a good time for a break
20 with the statement that the higher amount of	20 soon?
21 coated silicone, the easier the syringe passes the	21 MR. JAMES: Yeah, good time.
22 glide force test, you would agree that this	22 (Recess; 11:34 to 11:48 p.m.)
02	04
1 statement was available for a person of skill in	Q. Mr. Koller, I think you had in your
2 the art to act on and analyze, right?	2 declaration that you have a deep understanding of
3 A. Right.	3 the worldwide syringe market.
4 Q. This Chan article also reports on	4 Is that true?
5 let me strike that.	5 A. I don't know if I have written that
6 The Chan article is also	6 one in my declaration. But I have an
7 disclosing what has been referred to as oily	7 understanding of the PFS market, yes.
8 siliconization as opposed to baked-on	8 Q. OK. How long after a prefilled
9 siliconization, right?	9 syringe is manufactured does it take for the
10 A. Can you point me to that one please.	10 product to reach a doctor?
11 Q. I thought that that was what you told	MR. PEPE: Object to form.
12 me in your first deposition was that this reports	12 A. Can you – what do you mean by
13 on oily siliconization. Is that wrong?	13 manufactured?
14 A. No, I know it's an oily – it tells	14 Q. So how long does it take from the time
15 you about the spray technique on oily deposition.	15 that the product is filled and packaged and
16 Q. There is nothing in here about	16 terminally sterilized for it then to be available
17 baked-on siliconization, right?	17 to a doctor in order to use it in a patient?
18 A. Again, I would need to read through	18 MR. PEPE: Same objection.
19 the article. I can't remember from the top of my	19 A. You are not talking about the
20 head. I know it's talking about oily. But I	20 development. It's about fill finishing?
21 don't know if it was also talking about baked	21 Q. Yes. From – the final product is
22 siliconization.	22 filled, sterilized, and it's in a box, in a carton

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05 07 1 on a pallet, whatever, how long does it take to Q. It comes in contact with the drug get to a doctor? 2 solution, right? I'm assuming it doesn't happen A. Right. 4 like in a day. That's what I am trying to get at. Would you agree that the components of How long does it take based on your experience? a primary container closure need to be compatible MR. PEPE: Same objection. with the human body, right? 7 A. I can't talk to that one. Because MR. PEPE: Objection to form. 8 that depends on the supply chain and logistics the 8 companies have. Would you agree that the components of Q. Would it be fair to say that it would 10 the primary container closure need to be 10 11 be at least a week? 11 compatible with one another when they're filled 12 12 with the drug? A. It is fair to say at least a week, 13 depending on the tests you need to do prior to A. This would come out of the – during 14 release. This is only to ship it out. And then 14 your development and testing. If they - if they, 15 certainly where the product needs to be. So -15 you know, rubber works with the syringe and if the Q. So as a person of skill in your field, 16 tip caps works with the syringe. 17 you don't have an estimation of like roughly how Q. OK. Just going back to my other -- my 18 long it would take to get to a doctor? A month 18 earlier question, maybe my question relates more 19 to leachables. I believe you consult with 19 maybe? 20 MR. PEPE: Same objection. 20 companies on regulatory issues relating to 21 A. As I said, there is some requirements 21 leachables, right? 22 around testing. So if you check on sterility, it 22 A. Extractables and leachables, yes, I 06 08 1 takes a certain time in order to incorporate the 1 do. Q. What's the difference in an 2 system and you need to do some paperwork, and I 2 3 can't speak to companies to say, OK, between like extractable? 4 the last syringe fill and getting out to the first A. So extractable is a compound you force doctor. I can't talk to that one. to come out. So you are using a strong solvent Q. Would it be fair to say that for some under worst case conditions. So you force the physicians, it would be perhaps quite a long time, compound out. 8 several weeks because of supply chain and shipping This gives you an idea about the 9 and all of those kind of things? Would that be a 9 system itself and you would do a toxicologic 10 fair assumption to make? 10 assessment on the identified compounds to verify if 11 Could be the case, yes. 11 this would cause some potential toxicity if a 12 However long it is, you would agree 12 component might come out as a leachable. And this 13 that it takes some time from the time that the 13 is more material testing. So in extraction 14 product is finished until it's available on the 14 testing, you are the material and the likelihood 15 shelf for a doctor to pull off and use on the 15 what might come out. 16 patient's eye? On the leachable study, you do 16 17 MR. PEPE: Object to form. 17 that under similar use under standard conditions, A. It takes some time. 18 18 how you usually would store your syringe. That Q. Now, I think we talked earlier about 19 means it needs to be done with the actual drug 20 the fact that a prefilled syringe is a primary 20 product. So the final leachable study is usually 21 container closure, right? 21 done by pharma company with the final drug product A. Right. 22 under standard storage conditions. And then they

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Conducted on December 16, 2021 check what leachable is coming out which is then 1 could be in case of prefilled syringe and then asks 2 completely different to the extractables just you to perform certain biocompatability testing. because of you don't exert a certain force to it. This is part of the evaluation. So understand the conditions. So as a POSA in general for a container closure system, I usually use or get data Q. So an extractable test is where you from the manufacturer regarding biocompatability. 6 expose the material to some sort of condition like Some data - some might have extraction data that a solvent to try to force out any potential compound that might come out over time, is that 8 refers to a toxicity assessment. But usually you right? ask for biocompatability data regarding -10 according either to USP 6 or ISO 10993. A. Right. 10 Q. And then you test the compounds that Q. And then a leachability test is where 11 12 you test for the presence of compounds that might 12 come out for toxicological effects, is that right? No, that's not right. You don't test 13 come out into your drug product solution in 14 simulated use conditions, right? 14 the compounds coming out for toxicological 15 effects. 15 A. Right. 16 Q. So three different things, 16 If you know what kind of -- you 17 know if it's a semi-volatile, volatile, nonvolatile 17 extractability testing, leachability, and then 18 this biocompatability assessment, is that right? 18 component, then you have so-called toxicologists 19 in-house which have access to certain databases 19 A. Right. 20 And then do each of the three tests 20 where they can check regarding on the chemistry of Q. 21 have to be done on every component of a primary 21 the system if this has a toxicological impact. 22 container closure system? So the toxicological impact of the 0 2 A. So usually -- like the syringe 1 compounds that come out in an extractability test have to be checked, right? manufacturer, he would have a syringe paddle, silicone, tip cap from company A and rubber A. Yes. Q. And that can be that you look at a component maybe from the same company A or maybe 5 toxicology database and you see that this could be from company B. particular compound has been reported in the past All these components usually and it does or does not have some sort of require, would ask for some sort of regulatory toxicological impact. So testing isn't required, information. So that this raw material is using, 9 right? 9 in my PFS, are compliant to either ISO -- certain 10 10 ISO requirements, material requirements in A. There are some circumstances where 11 testing would be required. If you cannot identify 11 Pharmacopoeia that includes also some 12 the compound, which could happen because it could 12 biocompatibility testing. 13 be a degradation product which, you know, develops 13 And then if I mix that together, 14 I would do a sort of additional extract to verify 14 itself. So then you need to do certain analysis. 15 There is a certain procedure in place. 15 the combination of this one and depending on the 16 need, there could be -- there is no need to do so, 16 But people very often mix up the 17 toxicity in comparison to biocompatibility testing 17 but it could help your customer if you give them a 18 for use in container closure systems. 18 list of possible extractables which might come out

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19 of container closure system.

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This is then described in the ISO

21 devices which gives you then, you know - there is

20 10993, biocompatability evaluation of medical

22 a table in there which classifies your device,

Q. For every primary container closure

21 system, whether it comes from your customer or

22 from you, the person of skill needs to assess the

extract, leachability, biocompatibility of all of EMA approve a product if a leachable compound the components of the system, right? could not be identified? MR. PEPE: Object to form. MR. PEPE: Object to form. A. So it can be done on paperwork if A. You ask me if I have experience. customer can supply me that this system was USP Q. From your experience, would the FDA or EMA approve a product if there was a leachable classics tested. compound that could not be identified? If he shows me some reports that A. I mean, it would be a requirement to 8 he did some additional testing about, let's say, function or performance. identify them. They are all pathways to do so. 10 So I don't need always to repeat 10 But because one lab could not be 11 that one if I know that the system is there. I 11 able to identify and if this is an issue with some 12 could, I could do, but there is no request. So the 12 labs, that you need to have a really sophisticated 13 pharma company which has the drug product inside, 13 labs in order to do so, it could be that they say 14 they are legally required to show stability and 14 OK, I have a leachable, I would not go in front of 15 that involves also leachability study. 15 the EMA to represent a known -- unknown leachables. Q. OK, I wasn't intending to suggest that 16 So despite the safety concerns, 17 you would have to test for all those things, but I 17 threshold level is below a certain -- so there is a 18 think what my -- I think what I was trying to ask 18 systematic in place that is regarding related to 19 was that for every primary container closure 19 toxicity on so-called safety concern threshold. 20 system, for all the components that come into 20 So toxicologist find out for 21 contact with the drug, that you have to assess 21 certain toxicology classes 1 to 3, there are 22 whether on paper or by testing biocompatibility, 22 certain limits which allows you a daily intake and 6 1 extractability, leachability, is that correct? 1 they have certain classifications 1, 2 and 3. So 2 MR. PEPE: Object to form. class 3 is the more stringent one. A. The biocompatibility, extractables, And if I know what to do and what to 4 leachables, it's - as a component manufacturer, 4 look for, then I need to find methods, analytical leachables is not usually what we test because you methods which show me a certain analytical 6 don't have an extraction behavior. Extraction evaluation thresholds, which clearly shows me that I gives you idea. So if you design a system, you can identify this low amount of leachable. would do sort of extraction to see how the system, So everything which is below that 9 you know, performs, behaves. 9 threshold, even if it's like ten peaks which are Q. OK, and then the pharmaceutical 10 10 unknown, are not of interest regarding toxicity 11 company would be required to demonstrate stability 11 because that classification for certain compounds 12 of the product in the primary container closure 12 is below that threshold, it's not toxic. 13 system over time which would be -- which would 13 If it is above that toxic, then 14 include leachability, right? 14 yes, it asks me to do some additional toxicology 15 A. Right. 15 studies. Again, a leachable is a compound that 16 So the FDA or EMA would require 17 could come out of the materials that come into 17 toxicity evaluation for any leachable that's above 18 contact with the drug product, right? 18 some threshold value that is set by the agency, 19 MR. PEPE: Objection, asked and 19 right? 20 answered. A. Yeah, set on the classification of 21 Right. 21 toxicity. For example, it says, it is a nontoxic A. 22 In your experience, would the FDA or 22 system, then the evaluation threshold can low and

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the compound which might come out could have a 1 at that and tell me if you have seen it before. 2 very high concentration toxicology-wise, this A. Yes, I've seen that before. would not be an issue. 3 Q. Can you explain what Exhibit 1041 is? Q. And there are several different types A. It's a guidance for industry to check of toxicity tests that could be performed on a on container closure systems for packaging human leachable like that, right? drugs and biologics. A. There are so-called biocompatibility So it gives you a guidance what evaluation which ask you like about systematic or 8 would you need to do in order to check that my 9 systemic toxicity, yes. It's addressed in the ISO container closure system is sound and safe. 10 10993. 10 Q. Is this a document that you work with 11 Q. One of the types of biocompatibility 11 in your practice? 12 tests is an in vitro cytotoxicity test, right? 12 A. Yes. 13 That's one of them. 13 Q. If you look at page 2, which is 14 Q. And that's a test that's done in the 14 Exhibit 1041.005. A. Yes. 15 lab to see if a compound causes toxicity in cells, 15 16 right? 16 Q. Toward the bottom it says, "A 17 A. This is 10993-5. 17 container closure system refers to the sum of Q. I don't know the number, but that is 18 packaging components that together contain and 19 what a cytotoxicity test is, right; a test done in 19 protect the dosage form." 20 the lab to assess toxicity to cells? 20 Do you see that? A. There are different cytotoxicity 21 A. I see that. 22 tests. So if you talk about 10933-5, then I know The next sentence says, "This includes 20 1 that's a cell test. 1 primary packaging components and secondary Q. And the reason that a cytotoxicity packaging components if the latter are intended to 3 test would be done would be to assess the provide additional protection to the drug 4 potential for that compound to cause toxicity in product," right? patient cells if the compound was introduced into 5 A. Right. the patient, right? Q. And in that sentence, primary 7 packaging components would refer to those A. So ISO test, as I said in the 10933-1, components that come in contact with the drug 8 there is a certain table which guides you along to 9 say what is the intended use for your medical 9 solution? 10 device, and according to that medical device, it 10 Primary packaging system is designed A. 11 gives you a list of toxic studies or 11 above. 12 biocompatibility tests you need to prove. Q. OK. And there it says a primary 13 Q. The next exhibit is IPR Exhibit 1041. 13 packaging component means a packaging component 14 The title is "Guidance for Industry Container 14 that is or may be in direct contact with the 15 Closure Systems for Packaging Human Drugs and 15 dosage form, right? 16 Biologics." A. Right. 16 17 (Exhibit 1041, article entitled 17 Q. If you could turn to page 6, do you 18 "Guidance for Industry Container Closure 18 see a table there, examples of packaging concerns 19 Systems for Packaging Human Drugs and 19 for common classes of drug products? 20 Biologics" marked previously for A. Table 1, yes, I see. 21 identification.) Q. OK, now, injectables have the highest 22 degree of concern associated with the route of 22 Mr. Koller, if you could take a look

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Conducted on December 16, 2021 administration, right? 1 compatible with the dosage form and it should be composed of materials that are considered safe for A. In this table, yes, but this table 2 changed in the latest USP version for extractables use with the dosage form and the route of administration." and leachables, 1663. And the injectables moved Do you see that? to medium instead of high. 6 A. I see that. Q. This table doesn't have a medium. So the new table has additional rows in that Q. Do you agree those are the 8 considerations that go into the design of a left-hand column? prefilled syringe? A. No. I mean, I see the highest, high, One of the considerations, yes. 10 low on the left-hand side. You see high, medium, 10 11 low for the likelihood of packaging component form 11 When it says the materials are 12 interaction. 12 considered safe for use with the dosage form and Q. Is this FDA guidance that we are 13 route of administration, what do you understand 14 that to mean? 14 looking at, is this still in effect for companies 15 that are trying to get PFS approved? 15 A. Just let me read through. So to check the below basically 16 A. Yes. So it's still in use and it's 16 17 still used widely. But some references where 17 defines, you know, what - there is a general 18 understanding of say and this is also my, let's 18 there have been changes in the United States 19 Pharmacopoeia and it is worthwhile to look if 19 says, expertise that you say you have container 20 there would be any additional features to look and 20 closure system which guarantees a certain 21 check for. 21 protection and then you follow certain guidelines 22 Q. And then the USP injectables have been 22 on protection, it has certain issues on, B, on 22 24 1 moved down one notch, is that right? 1 compatibility and then, C, on safety and, D, A. They moved down to the right. They performance. moved from high high to highest medium. So it's not only that you say, OK, I can Q. OK. Focusing on this particular 4 explain what safe means in general terms for table, the fact that you have an injectable in the prefilled syringe, but as the system describes, it highest category here, does that indicate that 6 needs to protect the drug over shelf live and then it's especially important to evaluate potential needs to be still usable at the end of shelf life impact of packaging materials on the drug product? 8 and it gives you a guidance here and, again, this is MR. PEPE: Object to form. 9 an FDA guidance which is, yeah, not mandatory to 10 10 follow, but a good advice to follow. A. I mean, it says that, you know, it has 11 the highest rating on the degree of concern with Q. Just so I understand, protection which 12 starts on page 7, that refers to simply keeping 12 the root of administration, like inhalation or 13 injectables, and it says there is a likelihood of 13 the drug product from being negatively impacted, 14 right? 14 packaging component dosage form interaction which 15 is also high, or the new one would be medium. 15 A. It says, you know, the dosage form of Q. If you could turn to the next page, 16 a shelf life, common causes of such degradation 16 17 please, page 7. 17 are exposure to light, loss of solvent, so if it 18 Under general considerations part 18 is not gas tight, and exposure to reactive gases,

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19 e.g. oxygen.

19 1, suitability for intended use. There it says,

21 be suitable for its intended use and should

20 "Every proposed packaging system should be shown to

22 adequately protect the dosage form. It should be

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So you need to take care in

22 oxidation of the product, absorption of water

21 general terms that no oxygen might come in for

27 vapor, that you don't lose any water inside the these guidelines, right? 2 syringe or water might migrate into the system, if A. I would follow certain guidelines, but 2 you have a lyophilized product. there is no requirement that a PFS manufacturer So, and it is defined what light needs to do all the -- because some is related to protection mean in USP, you need to do certain the extra drug product which is then, again, testing, and of course, there is a difference with pharma company. that one because this is not specific only on glass Would you agree that all these factors 8 or polymer. It describes different materials. 8 that we have been talking about are important for a prefilled syringe that is filled with a biologic 10 for intravitreal administration? 10 Q. And the next one was compatibility and 11 that refers to the interaction between the primary 11 MR. PEPE: Object to form. 12 container system components and the drug product? 12 There is a general statement what Yeah, and here, they mention is the 13 primary packaging means to protect the product --14 packaging components that are compatible with the 14 or the shelf life. And even a syringe 15 dosage form, will not interact sufficiently to 15 manufacturer can act up to a certain point and 16 cause unacceptable changes in the quality of 16 then he does not know -- sometimes he does not 17 either the dosage form or the packaging component. 17 know what the syringe is used for, what is the 18 So it is known that there could 18 drug product, what is the route of administration. 19 be some minor changes in the system. But if it So he can give some data up to a 20 doesn't lead to any toxicity concern or to 20 certain point and then the responsibility, you 21 unacceptable changes in the system because like a 21 know, is then within the pharma company in order to 22 purity below a certain level, then this slightly 22 fill the gap which is needed for the submission. 26 28 1 changes to the control part is still acceptable if 1 Q. Regardless of whether it's the syringe manufacturer or the pharmaceutical company, you 2 I can prove all the other system, like extractables, leachables, safety and so forth. would agree that each of these factors, Q. One of the examples of compatibility protection, compatibility, safety are important that's listed there is loss of potency due to aspects of the design of an intravitreal prefilled absorption or adsorption of the active drug 6 syringe, right? substance, right? MR. PEPE: Object to form. A. Are you in the second paragraph of A. Including performance, they are 9 compatibility? 9 designed for all PFS applications. 10 Q. We didn't talk about performance yet, Q. Yes. 10 11 A. Yes, absorption or adsorption of the 11 but performance is a requirement that the 12 active drug substance. 12 container closure system maintains its ability to 13 Q. Then the next section is safety and 13 function in the manner it was designed, right? 14 there it says, "Packaging components should be 14 15 constructed of materials that will not leach 15 Q. And that's over the shelf life of the 16 harmful or undesirable amounts of substances to 16 product? 17 which a patient will be exposed when being treated 17 A. Right. 18 with the drug product." 18 In the context of a prefilled syringe, 19 Do you see that? 19 performance would include measurement of break 20 A. I see that. 20 loose and glide force, right? Q. From your perspective, a person of 21 A. Right.

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22

Q.

22 skill designing a prefilled syringe would follow

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The next exhibit will be IPR Exhibit

1 1008. It's a copy of the Boulange application 2 WO2009/030976 A1. 3 (Exhibit 1008, Boulange 4 application WO2009/030976 A1 marked 5 previously for identification.) 6 Q. Mr. Koller, if you could take a look 7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 10 A. Yes. 1 coating, right? 2 A. It doesn't have parylene C coating, right? 5 A. I would need to — you would 6 give me time if I can go through if I can go thro	s any I need to can see if an example
2 MO2009/030976 A1. 3 (Exhibit 1008, Boulange 4 application WO2009/030976 A1 marked 5 previously for identification.) 6 Q. Mr. Koller, if you could take a look 7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 10 A. Yes. 2 A. It doesn't have parylene C comparison of the	s any I need to can see if an example
3 Q. And there is no indication it has application WO2009/030976 A1 marked 5 previously for identification.) 5 A. I would need to — you would 6 Q. Mr. Koller, if you could take a look 7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 9 Q. If you could turn to page 21, pl 10 A. Yes. 10 Look at table 7.	s any I need to can see if an example
4 application WO2009/030976 A1 marked 5 previously for identification.) 6 Q. Mr. Koller, if you could take a look 7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 10 A. Yes. 4 other coating, right? 5 A. I would need to — you would 6 give me time if I can go through if I c 7 they have a reference if they use as an application that you offered your opinions about 9 Q. If you could turn to page 21, pl 10 Look at table 7.	I need to can see if an example
5 previously for identification.) 6 Q. Mr. Koller, if you could take a look 7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 10 A. Yes. 5 A. I would need to — you would 6 give me time if I can go through if I c 7 they have a reference if they use as at 8 FluroTec-coated piston. 9 Q. If you could turn to page 21, pl 10 Look at table 7.	can see if an example
6 Q. Mr. Koller, if you could take a look 7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 10 A. Yes. 6 give me time if I can go through if I c 7 they have a reference if they use as at 8 FluroTec-coated piston. 9 Q. If you could turn to page 21, pl 10 Look at table 7.	can see if an example
7 at that and confirm that that is the Boulange 8 application that you offered your opinions about 9 in this IPR? 10 A. Yes. 7 they have a reference if they use as a second piston. 9 Q. If you could turn to page 21, plant 10 Look at table 7.	in example
8 application that you offered your opinions about 9 in this IPR? 9 Q. If you could turn to page 21, pl 10 A. Yes. 10 Look at table 7.	::::::::::::::::::::::::::::::::::::::
9 in this IPR? 9 Q. If you could turn to page 21, pl 10 A. Yes. 10 Look at table 7.	lease.
10 Look at table 7.	icase.
11 Q. This is an application that's assigned 11 A. Yes.	
12 to Becton Dickinson, right? 12 Q. So in table 7, there are two scen	enarios
13 A. Right. 13 that are compared, correct?	
14 Q. And it was filed in 2007?	
15 A. Right. 15 Q. Scenario 1, the syringe barrels a	
16 Q. And if you could turn to page 14. 16 siliconized with 4 micrograms per centim	neter
17 There is a table there entitled, "Configurations 17 squared silicone oil. Right?	
18 of pistons A, B1 and C." 18 A. Right.	528
19 Do you see that? 19 Q. And scenario 2, the syringe bar	
20 A. I see that. 20 are coated with 50 micrograms per centil	imeter
21 Q. In that table, the piston referenced 21 squared of silicone oil, right?	
22 as B1 is indicated to be the invention, right? 22 A. Right.	
30	32
1 Q. Then the various pistons that w	W-1117-1117-1117-1117-1117-1117-1117-11
2 Q. And let me strike that. 2 talked about, A, B1 and C, are tested for	
3 Let's turn to page B1, the 3 break loose and glide forces under both	of those
4 invention, just so we are on the same page is a 4 scenarios, right?	
5 bromobutyl rubber stopper coated with parylene C, 5 A. Right.	
6 q. The results for the break loose	
7 A. Right. 7 glide forces are recorded at for A, and	
8 Q. And by comparison, stopper A is 8 time zero and then time 1. A also has tw	
9 bromobutyl rubber with no parylene C coating, 9 time points. But just focusing on time ze	
10 right? 10 you see that each of them was tested at t	time zero?
11 A. It says no coating.	
12 Q. And stopper C is a chlorobutyl rubber 12 Q. And what does time zero mean	
13 stopper with no coating, right? 13 A. Time zero usually means tha	874
14 A. So by coating definition here, it does 14 put in the rubber component into the	
15 have para — not parylene C coating. The rubber 15 perform a testing within a certain time	
16 component itself, as we discussed, could be coated 16 that is then your day 1, your time point	
17 by a FluroTec film. 17 before you start, like your four weeks	s at 40
18 Q. Does it say that in here? 18 degrees centigrade storage.	
19 A. No. It says, Coating, yes. Parylene 19 Q. So in general, how long after ye	The second secon
20 C and coating, no. 20 the stopper into the syringe do you test a	and call
21 Q. So from the perspective of this 21 it time zero?	
22 particular table, stopper C doesn't have a 22 A. There is no rule for that. Co	ompanies

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Conducted on December 16, 2021 1 do have different rules in place for – between 1 aging in order to find out what could possibly 2 the alignment of the stopper. POSITA knows that happen at real-time aging. And there are some you should usually do it in a certain, let's say, calculations in place which span 28 days for the 40 short time frame in order to get the actual degree relates to three month three times storage. results there. OK, let me make sure I understand. 6 Q. And from the point of view of a person You are saying that the of skill in the art, what is that short time frame 7 accelerated aging that is reported here is a generally? routine test on these kinds of syringes, right? 8 Coming back to having experience as a A. Right. 10 syringe manufacturer, the system we have been 10 Q. And you're further saying that in your 11 using there was to qualify the siliconization of 11 opinion, the aging test at time one month actually 12 approximates what would happen at three months? 12 the syringe. 13 So I wanted to check if the glide Based on the accelerated aging 14 force of my syringe was there because then I could 14 calculation, this is a good estimate. But you 15 say I have an even distribution of the silicone oil 15 still need to verify what your actual performance. 16 in my syringe. Q. What is the three-month factor that 17 So this test was limited then like it 17 you are talking about there? What is that based 18 on? Is there a document that I can look at for 18 needs to be tested less than 24 hours. Q. Would you agree that a doctor could A. A POSA knows that there is an ASTM 20 not have gotten this syringe filled with the 20 21 antiVEGF drug solution and administer it to a 21 method out which qualifies accelerated aging. 22 patient at time zero? Q. Can you tell me what ISTM stands for? 36 MR. PEPE: Object to form. A. I think it is American Society for A. Are you talking - are you asking if **Testing of Materials.** Q. So ASTM? the 6.6 is not suitable? 3 Q. No, I'm just asking in terms of A. ASTM. Q. OK. So there is an ASTM guideline on timing, it says that these were tested at time zero, and I'm asking if time zero corresponds to a 6 accelerated aging? time when a doctor could actually have gotten this 7 A. Right. O. And does that have the three-month product and administered it to a patient? 8 8 A. If the internal design was time point 9 factor in it? 10 zero was measurement in 24 hours, then they would 10 A. They give you certain guidance how you 11 not have access to that. 11 calculate based on storage time at 40 degree with 12 a certain factor, what this relates to at three 12 Q. And then the tests are -- let me 13 strike that. 13 time room temperature. Q. OK. OK, so then looking at the data 14 After that, they did testing at one 15 month for each of these stopper configurations, 15 for the break loose force for the first scenario, 16 for A, the break loose force from time zero to one 16 right? A. A test at one months at 40 degrees 17 month more than doubled, right, from 6.6 to 15.7

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19

18 newtons, right?

22 at time one month, right?

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18 centigrade, 75 percent humidity, according to 19 accelerated aging, this relates to three months at

22 loose and glide force, that you accelerate the

This is routine testing for break

20 real-time temperature.

21

And for stopper B, the force stayed

21 lower, it was 2.1 at time zero and went up to 3.0

Transcript of Horst Koller

Conducted on December 16, 2021 37 A. Right. 1 the statement, the statement is still there for a Q. And then for stopper C, at time zero person of skill in the art to take into account in was 3.9 and then it went up again more than twice deciding whether or not to adopt the technology in to 14.4. Right? Boulange, right? A. Right. 5 MR. PEPE: Object to form. Q. And then just below the table, it 6 A. The person of ordinary skill in the says, "With pistons A and C the friction force BS art would read, look at the data, look at the and F were relatively high, something which does table and would come up with an explanation that not appear to be acceptable for a medical device." this is still good to go. 10 Do you see that? 10 I don't see the point why a 11 A. I see that. 11 POSITA should discard piston A and C. I would go 12 Q. And you would agree that that 12 ahead with piston B1 because it shows me that there 13 statement is something that a person of skill in 13 is hardly any increase in the break loose glide 14 the art could factor in when deciding to --14 force even after T1 months. 15 whether or not to use the technology disclosed in 15 Q. Is it your position that a person of 16 Boulange, right? 16 skill in the art would simply ignore that sentence 17 MR. PEPE: Object to form. 17 where it says it does not appear to be acceptable 18 A. I don't dis- I disagree with that 18 for a medical device? 19 statement here due to following reason that the A. It says "does not appear." Does not 20 silicone on the piston is zero. 20 mean it is excluded. 21 So there is no silicone oil on My question was, is it your position 22 the rubber, which is usually state of the art that 22 that a person of skill in the art would ignore 40 1 you siliconize the system. This is given in prior 1 that statement? 2 2 art by Nema and others. So I usually would expect MR. PEPE: Objection, asked and 3 that my piston has some kind of silicone oil in the answered. 4 system. A. First of all, a person of ordinary The other side says it does not 5 skill in the art would look why the statement is there. 6 appear to be acceptable for medical devices. So A shows an increase to 16 or 15.7, but even 15.7 is Q. So they would not ignore the 8 still within, let's say, you know, the explanation 8 statement, right? 9 on the '631 patent that, you know, PFS used with A. I would not ignore the statement. 10 NTGBF applications had prior art usually break 10 Usually I find the root cause for that it says not 11 force lower than 20 newton. 11 to be acceptable. Because it is clear Boulange is So there is an increase, but this 13 increase would be minimized if you would have 13 promoting, of course, the parylene C coating. So 14 silicone oil on the piston and still the forces 14 if I take off - the silicone coating off the 15 could be used for certain application even in 15 piston, of course, I would expect then different 16 medical devices. 16 forces than if I would have siliconized piston And you know the statement only 17 which you showed in table 5. If you use scenario 1 18 relates to table 7 which is specific that there is 18 with siliconized pistons that you have by far a 19 no silicone on the piston. It doesn't disqualify 19 less increase and that then, of course, these 20 piston A and C for other experiments Boulange is 20 forces become even lower and will fall within the

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21 claim range.

21 showing.

Well, whether or not you disagree with

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Now, the explanation that you are

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4	43
1 providing for why you had a certain understanding	1 A. Yes.
2 of that sentence, that it's really about the A and	2 Q. And so would you understand the first
3 C stoppers not being siliconized. That doesn't	3 paragraph to relate to the time zero measurements
4 appear anywhere in that paragraph, right?	4 and the second paragraph to relate to the time
5 MR. PEPE: Object to form.	5 one-month aging data?
6 A. I mean, it says with pistons A and C,	6 MR. PEPE: Object to form.
7 relatively high, which does not appear to be	7 A. Second paragraph clearly references
8 acceptable to medical devices is a side statement.	8 the aging data.
9 But the explanation is below	9 Q. Now, you reference table 5. Let's
10 table 7 and table 7 clearly shows there is no	10 look at that. That's on page 19. And here again,
11 silicone on the piston. So I would not see how	11 you have data for the pistons A and B1 and C,
12 somebody could ignore that or just make sure that	12 right?
13 he is able to see what he's talking about if it's	13 A. Right.
14 not about table 7.	14 Q. Then if you just compare the time zero
15 Q. So I think what you are saying is that	15 break loose force for A and C in table 7 with the
16 you would look at the statement and come up with	16 time zero break loose force for A and C in table
17 an explanation for why it doesn't mean that A and	17 5.
18 C are not are not acceptable, is that right?	Do you see that?
19 A. I would not look for excuses.	MR. PEPE: Object to form. Which A
20 I would say what is the fact, and	20 and C?
21 the fact is there is no silicone on the piston, the	21 Q. The time zero break loose force in
22 numbers go up, yes. This is what I would expect as	22 table 7 compared to the time zero break loose
42	44
1 a POSA. But the other numbers would still be	1 force in table 5 or A and C?
2 acceptable for some of the applications for a	2 Do you have that?
3 medical device. This is my POSITA read-out.	3 A. Table 7, A time point zero, 66 break
4 Q. But these authors wrote that A and C	4 force?
5 did not appear to be acceptable, right? That's	5 Q. Yes.
6 what it says?	6 A. Compared to the A time point zero B66
7 A. That is what it says, yes.	7 in table 5?
8 Q. It contrasts that with B1 which says	8 Q. Right.
9 that the forces of B1 were entirely compatible	9 A. Right.
10 with the way in which a medical device is used,	10 Q. And how does C compare?
11 right?	11 A. C time point zero is 3.9.
12 A. Right.	12 Q. In table 7?
13 Q. And an intravitreal syringe is a	13 A. In table 7, and is 4.7 in table 5.
14 medical device, right?	14 Q. And so the break loose force for both
15 A. You can call it that, yes.	15 of those stoppers was higher at time zero as
16 Q. And the next paragraph, it talks about	16 recorded in table 5 than in table 7, right?
17 the one month of aging and it says that the one	MR. PEPE: Object to form,
18 month of aging, the friction forces had increased	18 mischaracterizes the document.
19 appreciably.	19 A. If it's – if it's the same time point
20 Do you see that?	20 zero, I don't know. But it's higher.
21 A. I see that.	Q. Just so the record is clear, it's the
22 Q. That was for A and C, correct?	22 same for piston A and it's higher for piston C, at

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45	47
1 time zero, right?	1 I disagree with your fact.
2 A. Right.	2 So markedly inferior in table 5
Q. And then just below table 5, in the	3 is a clear expression. But I need to put it in
4 second sentence, it says, "The results obtained	4 relation on what the results on piston C is. And
5 with a piston having no coating, piston C, are	5 if I see the results, yeah, it's not as good as B1,
6 markedly inferior."	6 but suitable for my intended use if I want to use
7 Do you see that?	7 it.
8 A. I see that.	8 Q. But you would agree that markedly
9 Q. And again, this is a statement that a	9 inferior and unacceptable are not motivating
10 person of skill could take into account in	10 statements, right?
11 determining whether or not to employ the	11 MR. PEPE: Object to form. Asked and
12 technology disclosed in Boulange, right?	12 answered.
13 A. Right. But again, the results	13 Q. It's just that's just English,
14 obtained with a piston having no coating, piston C	14 right? Those are not motivating statements, are
15 are marketedly inferior, does not mean I can't use	15 they?
16 it.	MR. PEPE: Objection, argumentative.
17 If I look at the data and if I	17 MR. DESAI: And rude.
18 know what is useful certain application, a break	18 Q. Do you understand my question?
19 force of 547, or even after one month of a break	19 A. I understand your question.
20 force of 84, is even in table 5, far within the	20 MR. PEPE: You had about three
21 claimed ranges of the '631 patent and far below the	21 questions. Can you ask a proper question.
22 20 newton, which has shown that these forces have	22 You have three pending.
46	48
1 been used for typical application of syringes with	1 MR. JAMES: I think he understandings
2 VGF or with VGF.	2 my question.
I don't see the point, as a POSA,	3 A. Not very motivated, but it's not that
4 that this one teaches away that you could not use	4 I would not have a Plan B in place.
5 piston C. It is his statement because it's	5 Q. OK. If you could look in your
6 inferior compared to his invention, yeah, but it's	6 declaration at paragraph 143. Actually, I want to
7 not that I cannot use it for application.	7 look at table 17 I'm sorry, strike that.
8 Q. So you would agree with me that the	8 I want to look at footnote 17 on that
9 statement under table 5 and statement under table	9 page. Page 84.
10 7 makes clear that piston B1 is superior to piston	Do you see that?
11 A and piston C, right?	11 A. Yes.
12 A. Right. So if I know parylene C and if	12 Q. OK, there you write about table 7 of
13 I know the systematic or – the date of	13 Boulange and you say, "The aged syringes were
14 prevalency, so I, as a POSITA, I could go ahead	14 stored in a chamber for a period of time before
15 and say I would use the B1 invention and my	15 testing at extreme conditions, i.e. 40 degrees, to
16 back-up would be like a plan C out of table 5.	16 assess the worst case performance of the syringe
17 Q. You would agree describing something	17 over its shelf life."
18 as markedly inferior and unacceptable are not	18 Do you see that?
19 terms that would motivate a person to use a	19 A. Um-hm.
20 particular technology, right?	Q. Now, Boulange doesn't call the aging
MR. PEPE: Object to form.	21 tests worst case, correct?
22 A. I don't disagree with that – I mean,	22 A. Correct. He says – let me check it,

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1 one minute please.	1 AFTERNOON SESSION
2 So he says, "In order to study	2 1:34 p.m.
3 the evolution of the interface, namely, the contact	3 BY MR. JAMES:
4 region between the piston and the container,	4 Q. Welcome back. If you let me ask
5 samples undergo an accelerated aging in climactic	5 you this, can you just explain what the break
6 room. The conditions of the Heraeus climactic room	6 loose effect is?
7 were temperature 40 degrees and humidity rate of 75	7 A. The break lose effect?
8 percent. The systems assessment were placed in the	8 Q. Yes.
9 climatic room during 1, 3 and 6 months."	9 A. If you store a rubber like
10 Q. And just for the record, you were	10 siliconized rubber in a silicone oily glass
11 reading from page 15, lines 17 to 21?	11 syringes, usually it pushes away. Due to
12 A. Page 15, line 17 to 21.	12 compression, it pushes away a little bit the
13 Q. Boulange doesn't describe the	13 silicone oil on the surface.
14 accelerated aging testing as worst case in that	14 Then the rubber comes direct
15 paragraph, right?	15 contact with the container surface, and due to
MR. PEPE: Objection. Asked and	16 stickiness of rubber and by pushing the stopper
17 answered.	17 away, it results in typically a break force.
18 A. Boulange is working for BD. So BD is	18 So usually you have a sort of
19 the provider for prefilled syringes. So BD has	19 baked system, then, you know, you should have a
20 knowledge and experience that 40 degrees	20 layer between the rubber and the container surface
21 centigrade for four weeks is reaching a certain	21 because it's like a sort of, you know, siliconized
22 plateau on the break force.	22 layer and that would avoid that the rubber comes in
50	52
1 So this is why it is industry	1 contact with the surface of the container and it
2 standard to use 40 degrees for a month to see what	The second secon
3 the possible outcome can be.	3 that over the shelf life, there is a certain
4 Q. But you don't know what Boulange was	4 increase in the break force.
5 thinking other than what they wrote in this	5 Q. So with the oily, as compared to the
6 application, right?	6 baked-on siliconization, you would expect the oily
7 A. I mean, I guess that he has also some	7 break loose force to go up over time compared to
8 knowledge like me for a POSITA, so I can	8 baked-on, is that right?
9 immediately translate 40 degrees centigrade one	9 A. If the prior art is confirming what I
10 month to a certain worst case scenario.	10 know based on my own experience but depending on
11 Q. I understand you're guessing about it.	11 the type of pistons, that break loose effect might
12 But I am all I'm asking you to confirm this	12 be limited. So it's always a combination between
13 application does not describe the aging as worst	13 the type of rubber and the surface.
14 case, correct?	14 Q. OK. So the break loose effect is not
15 A. It's not describing the aging as worst	15 necessarily limited to the impact of whether the
16 case.	16 silicone is sprayed on or baked on, it also
17 MR. PEPE: We have been going about	17 includes a contribution by the stopper?
18 an hour. If you can find a place for a	And the second of the second o
lead to the second of the seco	18 A. Right.
20 MR. JAMES: This is fine for a break.	19 Q. If you could look back at table 6 of
TORRY MANUFACTURE STATE SATURATION STATES AND STATES AN	20 Boulange, please.
21 (Luncheon recess; 12:49 to 1:20 p.m.)	21 And if you compare 9, scenario 1 and
22	22 scenario 2 results for the A stopper, am I correct

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1 that the break loose force increases more with the	1 table did not cite table 4 in my declaration.
2 baked-on syringe barrel than it does with the oily	2 So table 4 is on – OK.
3 siliconization barrel?	Q. Yeah, it's on page 18.
4 A. Correct.	4 A. OK.
5 Q. So in this instance, the oily	5 Q. Again, the break loose force goes up
6 siliconization exhibits less break loose effect	6 more with the baked-on siliconization than it does
7 than baked-on siliconization?	7 with the oily siliconization comparing these two
8 A. Right.	8 tables, right?
 Q. Which is contrary to the way the break 	9 A. Right.
10 loose effect the way you described the break	10 Q. So at least these two examples that we
11 loose effect a few minutes ago, right?	11 just looked at, tables 4, 5 and 7 in the Boulange
12 MR. PEPE: Object to form,	12 application, they are inconsistent with the
13 mischaracterizes testimony.	13 conclusion that sprayed-on siliconization will
14 A. What I said is that it can show break	14 result in a higher break loose effect than
15 loose effect. There is no need to show break	15 baked-on siliconization, right?
16 loose effect.	16 A. If I leave the spray on to a certain
17 Q. You would agree if there is a break	17 amount? Then yes.
18 loose effect shown as between these two, it's with	18 Q. Let me make sure I understand your
19 baked-on siliconization, right?	19 answer.
20 A. Yes.	20 With the amounts of silicone oil
21 Q. And the same thing is true for the C	21 that are described in these tables, then the answer
22 stopper comparing scenario 1 and scenario 2, the	22 is yes, is that right?
54	56
1 break loose effect, right?	1 A. Does not support the break loose
2 A. Right.	2 effect.
Q. If we look at table 5, how does the	 Q. You would agree that Boulange does not
4 break loose how does the break loose effect	4 disclose testing the syringes with ethylene oxide
5 compare between the baked-on and the oily	5 or vaporized hydrogen peroxide, correct?
6 siliconization?	6 A. It says develop the system which can
7 MR. PEPE: Object to form.	7 withstand sterilization but is — what was your
8 A. Table 5 doesn't have the scenario 2.	8 question again, please?
9 Table 5 only shows the scenario 1 or the baked	9 Q. There is no reference to sterilization
10 siliconization.	10 with ethylene oxide or vaporized hydrogen peroxide
11 But what is missing, what they have is	11 in Boulange?
12 that the silicone on the rubber.	12 A. There is no reference to a specific
13 Q. So it's a different stopper? It has a	13 sterilization method.
14 coating on it?	14 Q. Do you know whether Boulange ever
15 A. It has silicone coating on it.	15 issued as a patent?
16 Q. You pointed out that you can't really	16 A. This is a patent application I have
17 compare with table 5. I guess I was confused	17 here.
18 about that. Thank you.	18 Q. That's correct.
19 So if we compare table 5 and table 4,	19 A. In front of me. So I'm not aware if
20 table 5 is baked-on siliconization, table 4 is	20 there is an actual filed patent.
21 sprayed-on siliconization, right?	21 Q. You just don't know either way?
22 A. Let me read through that because this	22 A. I don't know.
The Let like read this ough that because tills	ZZ IN I WOII CRIIUTT

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Conducted on December 16, 2021 59 Q. Do you know whether Becton Dickinson information you might have, based on publicly ever came out with a syringe using parylene C available information and your work in the coating on the stopper? industry, do you know how much silicone oil was in the BD Hypak Biotech SCF syringe? A. I don't know. Q. You are not aware of one, right? A. I don't know. I would have to look in A. I don't have access to that data to 6 their product specifications. prove that because this is usually not disclosed, Do you know whether the silicone oil depending on how you do your type of submission. 8 was baked on or sprayed on? 9 I don't even know if Becton Dickinson has a drug A. If it's a stake needle syringe, it 10 master file assigned which would describe a 10 needs to be sprayed on. 11 parylene C coated syringe. 11 Q. Is it a stake needle syringe? 12 Q. So you don't know whether Becton 12 A. If it's a stake needle syringe, it's a 13 Dickinson filed a DMF on a parylene C coated 13 stake needling syringe. But Hypak is available 14 stopper or ever had a commercial production with 14 also with luer-lock or luercone. 15 parylene C coated stopper, right? 15 Q. Maybe you could spell that for her? A. Right. A. L-U-E-R and then lock, or 16 16 17 Q. Are you familiar with the BD Hypak or 17 L-U-E-R-C-O-N-E. 18 Biotech SCF syringe? Q. So you are saying that the -- that BD 19 Hypak for Biotech syringe was available with 19 A. Yes, I am. What do you know about that syringe? 20 staked-on needle, a luer-lock or a luer cone, is 20 Q. 21 BD developed the Hypak. That was a 21 that right? 22 trade name for Becton Dickinson. And they have 22 A. I said that it - BD Hypak was 60 1 different rates or different grades and one they 1 available. 2 call Biotech and it's - so, this was usually if 2 I would need to go back - I you talk about Biotech in general terms, they have don't have it top of my head if the BD Hypak 4 low tungsten, they have controlled siliconization Biotech was there because they have different process, and they have more, let's say, controlled grades and I can't just recall when the Biotech dimensions for certain application in the biotech syringe came out on the market. 6 7 industry. But I know if it is a stake needle 8 Q. Do you know whether the BD Hypak for 8 syringe, it is for sure sprayed siliconization and 9 Biotech SCF was available prior to July of 2012? 9 usually Biotech syringes are stake needle syringes 10 A. I know that the Hypak SCF was 10 for certain applications. 11 available prior to 2012. Q. Does a stake needle syringe need to Q. Do you know how much silicone oil it 12 have spray siliconization? 13 had in it? A. Because the needle bonding takes place 14 14 prior to siliconization, and if you do a baking it A. I don't -15 MR. PEPE: I'm going to object to 15 would not survive the 330 degree for half an hour. 16 form. Try to segregate what you know that's Q. Do you know if Becton Dickinson 17 confidential information versus what's 17 promoted the Hypak for Biotech syringe as its best 18 public. But obviously Bausch or anyone else 18 syringe for biotechnology products? 19 associated with Macugen isn't here and 19 MR. PEPE: Object to form. 20 wouldn't want their information disclosed. 20 Are you referring to a special date

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Q.

21

22

A.

Q.

Right.

Setting aside any confidential

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Well, do you know at any date?

21 for promoting or is it in general terms?

63 A. BD is the main supplier. So BD is the 1 Q. Was Hypak the trade name for the 2 Becton Dickinson prefillable syringes? 2 forerunner of all PFS development out in the field. So whatever, you know, is out, BD was A. BD developed the prefillable syringes first. as a ready-to-use system and their - one of the 4 first name was BD Hypak. Q. What does the Hypak indicate to a So I have different, as I explained, they have different grades in place. person of skill? MR. PEPE: Object to form. Right. So Hypak is Hypak SCF is a certain It has to do something with packaging A. 10 and maybe high expectation. I don't know what 10 trade name for a certain sterile clean fill. This 11 is a ready-to-use syringe. And based on that, 11 the -12 Q. You don't actually know what the – if 12 they do offer different type of syringes intended 13 for different use in application. 13 Hypak was a trade name that was associated with 14 any particular kind of syringe for any particular Q. OK, so sorry if this seems like the 15 same question, but prior to July of 2012, do you 15 use, is that right? 16 MR. PEPE: Same objection. 16 know if Becton Dickinson was promoting the BD 17 Hypak for Biotech SCF as its best syringe for 17 A. Right. 18 Q. You don't know if Hypak was limited to 18 biotechnology products? 19 prefillable syringes or if it could also be used 19 MR. PEPE: Object to form. 20 as a trade name for syringes that could be used to 20 A. It's - Biotech is a sort of trade 21 name. There might be a syringe out which might do 21 extract from a vial and inject, is that right? Hypak SCF is a ready-to-use system. 22 the job for a biotech application which is not 62 64 1 called a Biotech syringe. Q. So Hypak SCF, sterile clean fill is a 2 So it - this is a trade name 2 prefillable syringe? 3 which says, according to my customer, I get the A. Right. 4 syringe with certain specification, and even if 4 Q. Now, going back to talk a little bit 5 this – if it says it is a Biotech syringe does not more about Boulange, and parylene C, did you necessarily mean that my drug product which is a investigate whether parylene C would actually stay biotech product is compatible with the type of bonded to rubber stoppers over time? 8 syringe. A. During my time at Schott, we had a So you always need to check on 9 product development, which is called Ingentle, 10 that one. It could be that my biotech product is 10 where we coated one of the rubber components and 11 on a standard syringe available because it might 11 we needed to verify that the rubber, if the 12 not be silicone sensitive, tungsten sensitive, or 12 parylene C stays on the system and if it's doing 13 might not require special cosmetic issues or 13 the job as designed for this specific need. 14 dimension or specifications. Q. And in that Ingentle system, the 15 Q. Do you know if the BD Hypak Biotech 15 parylene C was not used on the stopper of the 16 was available with luer-lock prior to July 2012? 16 syringe, right? A. I don't know the exact date. I know 17 A. Right. It was used in the place which 18 that BD luer-lock - I mean, BD luer-lock syringes 18 is in direct drug product contact. 19 and luer cone syringes with OBS or with a certain And as far as you know, that syringe 20 luer-lock adapter have been available in the 20 has not been commercialized for use with any

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21 product, right?

A.

21 market. But I cannot refer to a certain date

22 without having proof or evidence.

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In 2015, until I left Schott, right.

Q. If you look at the figure in 1 what I did in my time at Schott without having 2 Boulange -- before I ask you questions about this 2 patents in place which made it to the market. the figure, if the -- excuse me -- if the Boulange Q. You don't have to have a patent in application was abandoned by Becton, would you order to work on a product? assume that the product had not been A. Yes. commercialized? Q. But if you have a patent application 6 MR. PEPE: Object to form. Calls for 7 that covers a product that you're commercializing, wouldn't it be fair for a person of skill in the 8 speculation. A. I don't know if it was abandoned and I 9 art to assume you wouldn't abandon that patent if 10 don't know if the invention still has been used. 10 you had a commercial product? 11 Sometimes people using invention without claiming 11 MR. PEPE: Same objection. 12 a patent out of that one. 12 The question, what you want to do with A. Q. Would you say that it's more likely 13 the patent. So as a POSITA, if I look through and 14 than not that if a company has a commercial 14 I say, as a POSITA, I would, you know, the 15 product that's covered by a patent, that they will 15 technical information out of that patent. 16 continue to prosecute the patent? Isn't that your Based on the technical 17 experience? 17 information, I could use that for development to my 18 MR. PEPE: Same objection. 18 own purposes. If the patent is there, I might, you 19 A. I can't answer that. I would need to 19 know, take the risk of infringing or look to see if 20 speculate. I don't know what the patent structure 20 it's not there, I might be able to take that one 21 of the company would mean - what they do. 21 and still develop my syringe. If the patent is But have you -- do you have experience 22 abandoned, it doesn't mean it is actually a 66 1 with a company giving up its patent protection 1 nonfunctional system that I could not use for my where it had a commercial product covered by the purposes. 2 3 patent application? Q. But if a company has a commercial A. Not knowingly. I might have. Might product, they wouldn't abandon the patent cross my desk that I work with something like protection for that product, right? MR. PEPE: Objection, calls for that. 6 6 7 Q. Would you agree that a person of skill speculation. 8 in the art would think that if the patent A. Again, there is the patent – did she 9 application was abandoned, that the company did 9 have a patent where I say - I don't know, if it's 10 not have a commercial product covered by the 10 not really helping me to have that patent. 11 patent? Q. But from a -- as a company, having a 12 MR. PEPE: Object to form. Calls for 12 patent protect your product would help you, right? 13 speculation. 13 A. It could help you, yes. 14 Not necessarily. It wouldn't make economic sense to 15 That would be a logical conclusion for 15 abandon it if you have a commercial product, 16 the POSA to come to though, right? 16 correct? 17 MR. PEPE: Same objection. 17 A. As I said, it depends. It could make A. It could be product development still 18 18 economic sense not to proceed with the system if

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21 patent strategy.

19 taking place without following up the patent.

21 stuff is not limited to having a patent in place.

So a product development type of

22 I can develop, you know, a functional syringes - I

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19 this was too much. I mean, this is — I cannot

20 speculate what other people might do on their

Q. Just talking about parylene C for a

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1 moment, is there any information in Boulange	1 intravitreal, but based on the function and
2 demonstrating compatibility of parylene C with a	2 performance, as a POSITA, I would know that I
3 VEGF antagonist?	3 could use the syringe based on this functional
4 A. There is no specific mentioning in the	4 explanation for intravitreal injection.
5 examples on the MTVGF product.	5 Q. But there is no information in the
6 Q. Is there any information in the	6 documents you are alluding to demonstrating the
7 Boulange application demonstrating the safety of	7 safe use of parylene C as a primary container
8 parylene C for intravitreal use?	8 closure for an intravitreal injection, right?
9 MR. PEPE: Object to form.	9 MR. PEPE: Object to form.
10 A. It's generally –	10 A. It doesn't say the same for the
11 MR. PEPE: Sorry, Horst. Go ahead.	11 silicone, so.
12 I'm done.	12 Q. Whether it says the same for silicone
13 A. General information of a suitable,	13 or not, my question is relating to parylene C.
14 safe development here, independent if this can be	14 MR. PEPE: You need to stop
15 used for intravitreal application.	15 interrupting the witness when he is
16 So what Boulange is claiming that he has	16 answering a question. OK. It's got to
17 a low silicone oil, gas tight PFS, glass PFS with	
18 low enough break loose glide forces in order to use	The state of the s
19 that in combination with the sterilization method as	
20 described in Sigg or Lam as a syringe for	Q. Yes. There is nothing in the
21 intravitreal injection. This would be my motivation	
22 to combine as a POSITA.	22 that the safety of parylene C as a primary
70 1 Q. Is there any information in Boulange	1 container closure for intravitreal injection,
2 demonstrating the let me strike that.	2 correct?
3 Is there any information in Boulange	3 MR. PEPE: Object to form.
4 relating to extractables that could be that	4 A. Again, what I explained again, and I
5 could result from parylene C?	5 do it again, if I look at the data, as a POSITA, I
6 A. Boulange says that you need to have	6 have a read-out that based on functional
7 certain container closure system like also	7 performance, I can use it for intravitreal
8 viscoelastic material for the wrapper components	8 injection, given the intravitreal injection might
9 which allows you to store the product and storing	9 not be explicitly mentioned in the Boulange
10 means keeping it safe over shelf life as well as	10 document.
11 still have a functional system.	11 So this is the know-how of a
12 So and of course, if I would use	12 POSITA to combine prior art and use prior art to
13 parylene C, what we have discussed before, for sure	13 get to a certain, get to a certain result.
14 Boulange has enough data on hand to show and prove	14 Q. Whether or not you can make certain
15 that parylene C is biocompatibility was P class 6	15 inferences, my question is, there are no data
16 and parylene C and that's prior art in the SCS	16 demonstrating the safety of parylene C for an
17 documentation that parylene C was used for syringes	17 intravitreal syringe prior to July of 2012,
18 and medical devices prior to 2012.	18 correct?
19 Q. None of that information relates to	19 MR. PEPE: Objection, asked and
20 it's use for intravitreal administration, correct?	20 answered.
CONTRACTOR	21 A. I don't understand your question.
22 A. That's not specifically mention	22 What is the information you are looking for?

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1 Q. We talked about are you finished?	1 A. Could assume that.
2 A. Yes.	2 Q. Now, if you look in on page 29 of
3 Q. We talked about the fact that a person	3 Exhibit 1008, the figures and there it shows
4 of skill in the art would do safety studies and	4 that the parylene C is in figure 3 shows the
5 that they would do extractable testing and that	5 close-up and it's let me strike that.
6 they would do leachable testing to demonstrate	6 In figure 2, there is a little bubble
7 that there was nothing in the product or in the	7 with a close-up of the stopper and it shows
8 compounds that come into contact with the product	8 parylene C coating the ribs of the stopper. Is
9 that could cause toxicity, you recall that?	9 that right?
10 A. I recall that.	10 A. That's right.
11 Q. There are no such data in the prior	11 Q. And I think you testified before that
12 art that you are referring to demonstrating the	12 you had some experience where Teflon was used to
13 safety or compatibility of parylene C for	13 coat a stopper in that same manner, right?
14 intravitreal use? That's my question. Is that	14 A. Right.
15 correct?	15 Q. And in that instance, the stopper
16 A. Boulange is from Becton Dickinson.	16 didn't form a gas tight seal with the syringe
17 They are one of the main leader for PFS, and they	17 barrel, correct?
18 for sure followed the container system closure	18 A. Wrong.
19 guidelines from 1999.	19 Q. What's wrong about that?
20 So if I set up a system like	20 A. I said there was one stopper out which
21 that, for sure, they need to follow certain	21 did not form a tight seal. So that is why they
22 guidelines. Otherwise, I would not be able to do a	22 made the reinvention of the so-called top face
74	76
1 good job.	1 cover for FluroTec.
 Q. You can't point me to any safety data 	2 There was another coated stopper
3 or compatibility data for parylene C in an	3 out which has similar type of Teflon coating, but
4 intravitreal syringe prior to July of 2012,	4 not laminated which was tight.
5 correct?	5 Q. OK. So for one kind of Teflon
6 A. Correct.	6 coating, it didn't work, and for the other, it
7 Q. So I just want to go back to the	7 did, is that right?
8 question of whether or not this patent application	8 A. That's right.
9 issued as a patent.	9 Q. Why was it that the Teflon coating
10 You mentioned a moment ago you're	10 failed to form seal on between the stopper and
11 offering opinions that the person of skill in the	11 the barrel?
12 art. Would a person of skill in the art assume	12 A. Based on my knowledge, the Teflon
13 that Becton Dickinson did not commercialize	13 coating – the laminate was not flexible enough
14 parylene C if this patent was this patent	14 and Boulange describes that the coating needs to
15 application was abandoned?	15 be flexible enough in order to be squeezed and
16 MR. PEPE: Objection, asked and	16 show functional performance.
17 answered.	17 Q. Have you done any – let me strike
18 A. I don't know.	18 that.
19 Q. If it was abandoned, would the person	Do you know how the flexibility of
20 of skill in the art assume that the product was	20 parylene C compares to the flexibility of the
21 not commercially available?	21 Teflon that you are referring to?
22 MR. PEPE: Same objection.	22 A. Parylene C is coated as a plasma, as a
22 Mic. I Di D. Suine Objection.	A I at yiene C is coated as a plasma, as a

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plasma chemical vapor deposition. 1 Do you see that? 2 And Teflon is usually used as a A. I see that. 3 laminate. So this is a film and the film, you Q. And we talked about this earlier, but know, to stretch it around the edges of such a 4 you agree that products can be designated sterile wrapper needs to have a certain, like I said, even when they are handled using aseptic flexibility. processing, correct? 6 7 MR. PEPE: Object to form. There are systems out that would 8 show it depends on the thickness of the laminate. A. Sterile filling is a part of aseptic 9 There is not one laminate out which would fail. It 9 processing, yes. Q. A product can be manufactured and 10 depends on the thickness and some flex models on 10 11 this, you know, laminate in order to make it work 11 designated as sterile even if it's manufacture is 12 or fail. 12 done using aseptic processing, correct? 13 The next exhibit is IPR Exhibit 1036. 13 MR. PEPE: Object to form. 14 It's a document entitled "Guidance for Industry, A. I would need to go through this 14 15 Sterile Products Produced by Aseptic Processing, 15 document in a bit more detail to define what type 16 Good Manufacturing Practice " Actually it says 16 of aseptic processing they would mention in the 17 guideline. 17 "Current Good Manufacturing Practice." 18 (Exhibit 1036, document entitled Q. OK, if you look at page 2 to 3 -- let 19 19 me just ask you a general question. "Guidance for Industry, Sterile Products Produced by Aseptic Processing, Current In aseptic processing, the 20 20 21 Good Manufacturing Practice" marked 21 individual components of a product are sterilized 22 previously for identification.) 22 and then the device is assembled, and if necessary, 78 Q. Mr. Koller, is this a document that 1 filled under aseptic conditions, right? you relied on in your declaration? 2 A. So aseptic filling means that you have A. It says — I know the guide, but I three sterilized components filled it under ISO class 5 clean room environment. 4 don't know the top of my head if I cited this in my IPR. Q. So for a prefilled syringe, that would Q. And you look at your list of 6 mean that you would have sterile drug product 6 materials, I can get it for you, I think, but the going into a barrel and having a stopper and a tip exhibit number indicates that it's a Regeneron cap, for example, all of which were sterile ahead 9 exhibit and it was cited in your declaration. I 9 of time, sterilized ahead of time, right? 10 only have a couple of questions about it. If you 10 A tip cap would be already 11 turn to page 1. 11 preassembled on the syringe, but it would be 12 12 presterilized on the syringe. A. Yes. 13 Q. Before we start there, this guidance 13 Q. Sorry, there was one question about 14 is about aseptic processing, right? 14 Boulange I forgot to ask you. 15 A. Right. Can you go back to Exhibit 1008 16 for just a moment. If you could turn to page 4? And the introduction in the first 16 17 sentence says, "This guidance is intended to help 17 18 manufacturers meet the requirements in the 18 The first paragraph, it says that the 19 agency's current good manufacturing practice, 19 first sentence talks about how the viscoelastic 20 cGMP, regulations" -- there is a cite to the CFR 20 material that the piston is made of is generally 21 -- "when manufacturing sterile drug and biological 21 an elastomeric material which alters in particular 22 products using aseptic processing." 22 degrades chemically over time.

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Do you see that?	1 supplied the syringe and needle for Macugen PFS."
A. I see that.	2 Do you see that?
Q. Then the second sentence says, "This	A. Um-hm. I see that.
4 possible degradation is sometimes initiated by the	Q. And then there is a citation to
5 processes used to sterilize the medical devices	5 Exhibit 1017 which is the Sapinski application and
6 containing them, for example, bringing into	6 you said "describing BD syringes for use with
7 contact with ionizing radiation."	7 Macugen."
8 Do you see that?	8 Do you see that?
9 A. I see that.	9 A. I see that.
10 Q. The degradation that's referred to in	10 Q. Was that your understanding at the
11 that sentence is the degradation of the stopper	11 time in July of 2012 that Macugen used a Becton
12 material, right?	12 Dickinson syringe?
13 A. It says sterilized medical devices	13 A. Do you have to the Exhibit 1017
14 containing them, so by ionization, radiation. So	14 available for me so I can verify –
15 this could also be a polymer syringe, not	15 Q. I do, but just
16 necessarily a glass syringe which you would then	16 A. – the statement.
17 irradiate by gamma E-beam or x-ray.	17 Q. You say in that sentence that the
18 Q. Well, just looking back at the first	18 POSITA would have been aware that Becton Dickinson
19 sentence again, it's talking about the	19 supplied the syringe and needle for Macugen PFS.
20 viscoelastic material that the piston is made of,	20 Do you see that?
21 it says it is generally an elastomeric material	21 A. Um-hm, I see that.
22 which degrades chemically over time, right?	22 Q. Is that an accurate statement?
82 1 A. Um-hm.	1 A. Accurate statement.
2 Q. Then the next sentence refers to that	2 Q. Were you aware that Macugen employed
3 by saying this possible degradation is sometimes	3 the Becton Dickinson syringe?
4 initiated by the process used to sterilize the	4 A. If I was looking at the PFS – Macugen
5 medical devices.	5 PFS?
6 Do you see that?	6 Could you please rephrase your
7 A. I see that, yeah.	7 question.
8 Q. The degradation in that sentence is	8 Q. Yes, in 2012, were you personally
9 referring to the degradation of the piston,	9 aware that Macugen employed the Becton
10 correct?	10 Dickinson strike that.
11 A. Correct.	11 Were you aware in 2012 that
12 Q. That's not a reference to degradation	12 Macugen employed a Becton Dickinson syringe?
13 of the drug product that would be eventually	13 A. The Macugen was developed in the early
14 stored in the syringe, right?	14 2000s and one of the only — maybe not the only
15 A. Not a reference of the drug product.	15 one, but the main syringe supplier was Becton
16 Q. Can you look in your declaration at	16 Dickinson.
17 paragraph 164; in particular, you can look at any	17 Q. For Macugen?
18 part of it obviously to answer my question, but in	18 A. For PFS in general.
19 particular, the part of the paragraph on page 98,	19 Q. Do you know how much silicone oil was
20 there is a sentence that begins "for example."	20 in the Macugen syringe?
21 It says, "For example, a POSITA	21 A. According to prior art, .821
22 would have been aware that Becton Dickinson	22 milligram. But I would point out to the exhibit.

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85	87
Q. Let me show you the Macugen label.	1 Q. There is no express reference to
Next exhibit is Regeneron Exhibit	2 terminal sterilization in the label, right?
3 1009. It's a printout from Drugs.com on Macugen.	3 A. Right.
4 Mr. Koller, is that a document that	4 Q. Now, in addition to that change where
5 you relied on offering your opinions in this	5 they reference the sterile foil pack, they also
6 matter?	6 made another change to the label where they
7 A. This is a document I relied on.	7 indicated that the there was a sterile package
8 Q. Do you know the date of that document?	8 BD single-use 30-gauge needle, correct?
9 A. So on page number 11 of 11, it says	9 A. Correct.
10 that marketing information for this is the NEA on	10 Q. And although the Macugen 2008 label
11 2017 2004 — 2004 Macugen label.	11 indicates that the foil pouch is sterile, you
12 Q. So it is your understanding that this	12 would agree that you can achieve sterility using
13 label came out in 2004?	13 aseptic processing in addition to terminal
14 A. No, it says the NDA was in 2004. The	14 sterilization, correct?
15 label is established down there was revised in	15 A. I don't agree with that statement.
168/2008 from the Eyetech Inc., the company	16 Q. You don't agree that you can have a
17 producing Macugen.	17 product that's designated sterile that's
 Q. If you could turn in your declaration 	18 manufactured using aseptic processing?
19 then to paragraph 149.	MR. PEPE: Object to form.
20 A. Yes.	20 Mischaracterizes testimony.
Q. And sorry, paragraph 150.	21 A. So I need to go back a step.
Do you have a side-by-side there	Compared to label 4 and 5, the
1 or one above the other comparison of the 2004 2 Macugen label and the 2008 Macugen label which is 3 Exhibit 1009 that we were just looking at. 4 Do you see that? 5 A. I see that. 6 Q. Now, the 2004 label let me strike 7 that. Just look at the 2008 label. 8 It says that "Macugen, pegaptanib 9 sodium injection, is supplied in a sterile foil 10 pouch." 11 Correct? 12 A. Correct. 13 Q. And it's your opinion that from that a 14 person of skill in the art can derive that Macugen 15 was terminally sterilized, is that right? 16 A. Right. 17 MR. PEPE: Object to form. 18 Q. But you'll agree with me that the 19 label does not say how the Macugen was sterilized	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
20 in the 2008 label, correct? 21 A. It does not specifically say	20 Q. OK, you would agree with me that in
A CONTRACTOR OF THE PROPERTY O	21 that 2008 Macugen label, where it says sterile
22 sterilized by terminal sterilization.	22 foil pouch, there is no reference to any

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particular SAL, correct? 1 Selecting a Sterility Assurance Level, SAL, For 2 Products Labeled Sterile." A. You would not state on the label that you have a sterile coating to 10 to the minus 6. A. I can't remember if I cited this one Sterile is claimed in the product specification. 4 in my IPR. So it could be 10 to the minus 6. It could be Q. You did not, no. I'm just asking you whatever they claim and verify. 6 if you know about that document. Q. It could be 10 to the minus 3, A. No. I might have crossed it because I 8 correct? 8 did some validation for sterilization myself for Again, industry expectations for a 9 different original areas. But it doesn't ring a 10 terminal sterilization of system on components 10 bell. 11 that are allowed to do that, the expectation is 11 Q. Do you know if there are provisions 12 available for helping companies or -- let me 12 that you would have a 10 minus 6. Q. I understand that's your opinion that 13 strike that. 14 it's an expectation. But you could also have a 14 Do you know if there are guidelines 15 reference to a sterile product that was sterilized 15 for companies who are seeking to get an SAL lower 16 to an SAL of 10 minus 3 correct? 16 than 10 to the minus 6 where it s required for 17 MR. PEPE: Objection, asked and 17 that particular product? 18 18 MR. PEPE: Object to form. answered. 19 A. A POSA so would not go for that. He 19 A. I don't know. 20 would for sure go 10 to the minus 6. This is the 20 Q. Would you agree that in a case where 21 official sterile claim in the pharmaceutical 21 you couldn't achieve 10 to the minus 6 without 22 industry. With exemptions. He would need to 22 degrading the product, that a company would either 1 prove that you could not do a 10 to the minus 6 in 1 need to redesign their product or seek from the 2 the first place. And prior art shows that by 2 FDA a lower SAL of 10 to the minus 3? doing ETO, it could go to a 10 to the minus 6 A. Option 1 has that you would start to without damaging the product. redesign to see option - or basically option 2, So if the FDA would look into 5 if you say you need to go to the FDA. 6 such document, they would for sure let you do the They would not say that you, you 10 to the minus 6 validation compared to the 10 to know, would immediately could go to the 10 to the minus 3. You would need to prove data, and then, the minus 3 if it's feasible and that was proven. MR. PEPE: We have been going about 9 you know, let them know what is the risk involved 10 an hour if you find a good spot for a break. 10 and they might then give you such a suggestion on a 11 MR. JAMES: Why don't we break right 11 certain acceptability after they verified all the 12 here. 12 submission data that would prove the sterilization 13 (Recess; 2:33 to 2:48 p.m.) 13 technique used for a lower log reduction than 10 14 Q. Mr. Koller, have you heard of a 14 minus 6. 15 document referred to as ANSI/AAMI ST67? 15 Q. Have you heard of situations where a A. I don't know about the number for 16 company has presented data to the FDA or the EMA 17 sure. Can you let me know the title of that 17 about sterilization where they demonstrated a 18 document? Please. 18 lower bioburden in conjunction with a lower SAL to 19 Q. I will try. 19 receive a sterility designation? 20 It's from American National A. I haven't heard ever from the EMA or 21 Standard and it's called, "Sterilization of 21 FDA because these submission documents are always

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22 Healthcare Products, Requirements and Guidance for

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22 confidential and publicly not accessible.

Conducted on December 16, 2021 93 95 Q. You don't have any experience with 1 that you have to purchase them, is that fair? 2 that sort of thing? 2 That's fair. A. I don't have any experience. Q. If we can go back to the Macugen document we were talking about a moment ago, I O. Do you actually know, going back to my think you still have it in front of you? question about that document, what the ANSI American National Standards -- do you know what A. Yes. Could a POSA understand that the that is? 8 sterility achieved for the Macugen product as A. I mean, could be the organization which, you know, is involved in ISO, but I would reflected in that 2008 label was achieved using an 10 autoclave or beta radiation? 10 need to verify. 11 MR. PEPE: Object to form. Q. What about the AAMI, do you know what A. So depending on the sensitivity to 12 that organization is? 12 13 American Association -- AAIM? 13 different sterilization products, and as described 14 was in prior art, beta radiation would be AAMI. 14 Q. 15 A. AAMI. For American Association - no. 15 something or - so they would have - how do I 16 I mean, I know the abbreviation, but I don't know 16 answer the question. 17 the spelled name. 17 Beside gas are different known 18 sterilization methods in the market, yes. 18 Q. What does ISO do? Q. I didn't understand -- the side cast 19 A. ISO does harmonization of existing 20 are different -- I didn't understand what you said 20 standards into ISO document which gives then a 21 guideline for, you know, worldwide guideline. As 21 there, sorry. 22 an example, for ISO 11135 or 11137 for irradiation 22 I mean beside gas sterilization. 96 1 or ETO sterilization guidelines on how to validate 1 Beside gas sterilization, thank you. and check your validation system. 2 A. VHP or ETO or maybe other plasma Q. Does ISO have guidelines on setting an systems, irradiation or steam, hot steam is - are 4 SAL? typical sterilization methods. A. For sure there is a description in the Q. So based on this prior art document ISO standard for SAL explanation and how to get that you cited to, a person of skill in the art there, but I can't -- top of my head, I can't talk would not be able to tell how the sterility of about detail about the approach there. The ISO this product was achieved, right? MR. PEPE: Object to form. 9 guidelines would be typically used to validate 10 your system. 10 A. I mean, maybe through terminal 11 Q. And a person of skill in the art would 11 sterilization because it is after filling. 12 have had access to the ISO documents, correct? Q. I understand that that's your position A. You have free access to an abstract 13 that it's terminal sterilization. But assume 14 that's true for a moment, you wouldn't be able to 14 and then through your notified standard could be 15 the AAMI or something, you could buy them through 15 tell whether it was terminally sterilized using 16 that notice standard -- the American 16 ethylene oxide, vaporized hydrogen peroxide, 17 standardization body in Switzerland, it would be 17 autoclave or beta radiation, correct?

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Q.

22

21 sterilization is used.

18 like the Swiss Normen Group or Germany, it would 19 be the DIN. This is where you normally get access

20 for this. But you need to buy them. They are not

Q. They are publicly available except

21 publicly available, only in abstract.

A. There is no additional evidence in the

19 label describing the foil pouch that could give

20 you an indication on what is - what kind of

You could -- go ahead.

 A. Tyvek is used – Tyvek pouches or 1 and the plunger rod. If it would not have a 2 foils or blisters are used for, you know, 2 certain function or feature, then the clip would sterilization with gas because it needs to have a not be added. 4 certain permeability to gas to sterilize and then Q. Let me show you the next exhibit, get the gas out. Whereas if you do irradiation, Exhibit 1081, which is a document you cited in your declaration. It's another version of the the Tyvek window could be there, but it's not necessarily required. Macugen label. Q. In the Sigg application we looked at 8 (Exhibit 1081, Macugen label 9 9 earlier, the second example was about beta marked previously for identification.) 10 radiation, correct? It's Exhibit 1008, I 10 Is this a document you cited in your 11 believe -- I'm sorry, it's 1007. 11 declaration? 12 A. Example 2 is using beta irradiation. 12 A. Yes. 13 Q. And in the first paragraph of the 13 Q. If you look at the first page, about 14 example, they talk about using, in the last 14 halfway down, it says number 1, "Remove the 15 sentence, polyethylene bag with a foil thickness 15 syringe from the plastic clip." 16 of 50 microns, an aluminum bag with foil thickness A. Um-hm. 16 17 of 0.1 millimeter. 17 Q. Do you see that? 18 Do you see that? 18 A. I see that. Q. It doesn't say where the clip is 19 A. I see that. 19 Q. So you're saying, without further 20 attached, right? 20 21 information in that Macugen label, you could not 21 A. Um-hm. 22 determine what method was used to achieve It doesn't say remove the clip from 98 1 the syringe. It says remove the syringe from the 1 sterility, correct? 2 clip, right? A. The Macugen label explicitly claims a clip with two functions that is unique to remove Yes, it says that. the clip in order to make the syringe function. Q. It doesn't say the clip is attached to So I can move the piston. And it also says if you 5 the plunger rod? are opening the pouch and the clip is removed, A. No. don't use the syringe. It doesn't say that the clip has to be removed to achieve functionality? So a POSITA would know that the clip is 9 usually used if you have pressure differentiations 9 A. No. 10 which would not occur if you do radiation in the 10 Q. Right? 11 system. A. It says remove the syringe from the 11 12 So the likelihood that I use a 12 plastic clip. 13 gas system, VHP or ETO because I cannot use steam 13 Right. That is all it says? 14 That is all it says. 14 because of the heat sensitivity of the system, then 15 a POSA would get to the conclusion that it could be 15 Q. It doesn't say anything about terminal 16 sterilization? 16 either VHP or ETO, but not say exactly which type 17 of gas could be used. 17 A. No. 18 Q. The label does not indicate what the Q. Now, if you were using a foil bag or a 18 19 clip is. It just refers to it as a plastic clip. 19 foil pouch with beta radiation, you mentioned that 20 Tyvek window earlier, you wouldn't need a Tyvek 20 MR. PEPE: Object to form. 21 A. It describes the function to remove 21 window with a foil pouch that was used with beta 22 the clip prior to use. So it fixes the syringe 22 radiation, right?

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20	203
1 A. For the pure sense of irradiation with	1 This is a copy of a portion of the 2011 version of
2 beta, you would not need a foil pouch.	2 USP 34-NF29.
3 If you have a system which	3 (Exhibit 1019, 2011 version of
4 undergoes certain pressure differentiations, like	4 USP 34-NF29 marked previously for
5 in a sort of air transport or something, then it is	5 identification.)
6 strongly recommended to use still a foil pouch with	6 Q. Is that a document that you relied on
7 the Tyvek window because otherwise, the	7 in offering your opinions in this matter?
8 differentiation in pressure might cause the pouch	8 A. Yes.
9 to break open and then you would have a container	9 Q. What is it?
10 closure integrity breach.	10 A. The document is an extract out of the
11 Q. If you can turn to paragraph 109 in	11 United States Pharmacopeia 34 based on 2011 which
12 your declaration, in particular, the portion of	12 describes certain specific tests, how to perform
13 the paragraph that's on page 63, toward the end.	13 tests for certain type of drug products and the
14 At the end of that paragraph, you	14 let's say monograph or chapter 789 describes
15 mentioned that the 2008 Macugen label described	15 particulate matter in ophthalmic solutions. And
16 that the user must remove a clip from the syringe	16 it gives references to test method as well as to
17 prior to use.	17 test limits.
Do you see that?	18 Q. I just want to walk through this for a
19 A. Yes.	19 minute.
20 Q. And then the next sentence, you say,	20 So USP 789 is a test for
21 "A POSITA would recognize that the clip would	21 particulate matter in ophthalmic solutions, right?
22 serve to prevent the plunger from moving after it	22 A. Right.
202	204
1 is placed in a blister pack, including during a	1 Q. And there are two tests that are
2 terminal sterilization process and during	2 referred to in USP 789, correct?
3 transportation."	3 A. Correct.
4 A. Right.	4 Q. And the way that USP 789 works is
5 Q. Do you see that?	5 that let me strike that.
6 A. I see that.	6 The two tests are light
7 Q. So the clip can also be there to	7 obscuration particle count test and a microscopic
8 protect the syringe during transportation, right?	8 particle count test, right?
9 A. Yes.	9 A. Right.
10 Q. Now, in your analysis of this case,	10 Q. Each of the two tests has its own
11 you have not examined an actual Macugen syringe	11 conditions for passing the test, right?
12 that was available between 2008 and 2012, right?	12 A. The microscopic particle count has an
13 A. Right.	13 additional condition a compared to the light
14 Q. And to your understanding, when the	14 obscuration test. So it is asking for taking 50
15 makers of Macugen changed their label in 2008,	15 micrometer particles, and not only larger equal 10
16 they did not lower the amount of silicone oil in	16 or larger equal 25.
17 the syringe, correct?	17 Q. I guess my questions was a little
18 A. Correct.	18 different. The light obscuration test has two
19 Q. And to the best of your knowledge, the	19 conditions for passing. One is the number of
20 makers of Macugen never adopted parylene C, right?	20 particles greater than 10 microns and the other is
21 A. To the best of my knowledge, right.	21 number of particles greater than 25 microns,
22 Q. The next exhibit is IPR Exhibit 1019.	22 right?
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205 A. Right. 1 it by light obscuration, and it has fewer than 50 Q. And then the microscopic particle 2 particles greater than 10 microns and fewer than count test has a different set of conditions, five particles greater than 25 microns, then the the -- it has the same limit on the number of material passes USP 789, right? MR. PEPE: Object to form. particles greater than 10 microns, same limit on number of particles greater than 25 microns, but A. So again, this is based on the certain then also has a limit on the number of microns -pooling of container tests. It's usually not -8 particles greater than 50 microns, right? because the equipment, like light obscuration from A. Right. 9 HIAC Royco as an example, usually requires a 10 Q. Have you ever done this test? 10 certain amount, pooled volume in order to do the 11 A. Yes. 11 measurement. 12 12 Q. As I understand it, the way the test So like in 788, it describes to 13 is done is that the product to be tested is tested 13 say, OK, depending on the system, you should pool 14 by the light obscuration test first. Is that 14 so many, let's say, containers that you get at a 15 right? 15 least up to 25 mls. And then if you put that on 16 the machine, then it flushes the first time to 16 A. That is right. 17 If the material passes the light 17 clean the system because you prepared the system 18 obscuration test, there is no reason to do the 18 with purified water particle measurement as 19 microscopic particle count test, right? 19 described in 788. With that, you clean all 20 A. Right. 20 basically the components coming apart with such a 21 O. So a material could have less than --21 solution. 22 let me strike that. And then you know, it says, OK, then it 206 If you had a material you were testing 1 does doing 3 or 4 measurements depending on the 2 and you did the light obscuration particle count volume, each 5 mls and then it gives you, out of test and you had less than 50 particles greater four measurements, gives an average regarding the than 10 microns and less than 5 particles greater particle size per ml. than 25 microns, the material would pass USP 789, So for 788, this is slightly 6 right? different because then you need to calculate that A. I mean, this is not material testing. one according to the container because 788 also These are container testing. Because depending on describes volume up to 100 mls. 9 the volume needed for the test, which is described So 789, you do some pooling, as 10 in 788 which has the two channels, large or equal 10 low as possible, let's say, and then do the 11 10 and 25, it gives you a description how to 11 repeated testing here. If you pass -- if you have 12 prepare certain standards, and then you need to 12 enough -- one milliliter -- if the system could 13 pool in order to be able to measure a certain 13 work only on one ml, and you would need to pull 5 14 amount and then it gives you an average count for 14 and it gives you an average of the five syringes. 15 the channel. Q. OK. But if you do the pooling and you So if you pass light obscuration like a 16 get an average per ml that is less than 50 for 10 16 17 container pull, if you pull 10 or 15 syringes then 17 micron particles and less than 5 for 25 micron 18 there would be no need to do microscopic. 18 particles, the material passes USP 789, correct? 19 O. So I want to make sure I'm on the same 19 You have a solution that passes 789, 20 page with you. 20 yes.

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21

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21

How ever much volume you need to test,

22 if you test your container with your material in

And there is no reason then to look

22 for particles greater than 50 microns in that

209	2
1 material, right?	1 ml, right?
2 A. Right.	2 A. Right.
3 Q. The material could have more than two,	3 Q. If you look at the bottom of that
4 three, four particles greater than 50 microns and	4 page, 127, there is a sentence that begins
5 still pass USP 789, correct?	5 "specifically."
6 A. Correct.	6 It says, "Specifically, a POSITA
7 Q. There is nothing in the prior art that	7 would know that a VEGF antagonist solution for
8 would suggest to a person of skill in the art that	8 intravitreal administration would need to comply
9 you would have to use the microscopic test on a	9 with USP 789 for regulatory approval, and thus, it
10 VEGF antagonist, right?	10 would need to meet the microscopic particle count
11 A. Depending on the type of VGF, if it's	11 test as set forth in USP 789 which requires no more
12 in such a way that it's cloudy, torpidity, and	12 than two particles of diameter greater than 50
13 cannot be handled by light obscuration, then	13 microns per ml."
14 membrane method is the only one you can use then	14 Right?
15 for release. And then you have the 50 micrometers	15 A. Right.
16 included in the MM method.	16 Q. But, in fact, a VEGF antagonist
17 Q. I understand that some conditions	17 solution would not necessarily have to meet the
18 could exist where you would think, oh, I can't use	18 requirement of no more than two particles greater
19 light obscuration, I have to use microscopic. I	19 than 50 microns if it met the light obscuration
20 think that's what you are saying.	20 test, correct?
21 My question is a little different. Is	21 A. Yes, but this is not what I described
22 there anything in the prior art that suggests that	22 here. There is no reference here to only the
2 0	2 2
1 the VEGF antagonist would have to be tested by	1 light obscuration testing.
2 microscopic particle tests?	2 It says 789 and 789 has this
3 A. No. It says it needs to be tested	3 second method in it, the interpretation of what I
	The state of the s
4 according to 789.	4 need to do, following step. So if I cannot and
5 Q. Right. And 789 only requires light	5 if I don't know what type of VEGF it would be, then
Q. Right. And 789 only requires lightobscuration if you pass the light obscuration,	THE TRANSPORT OF THE PROPERTY
5 Q. Right. And 789 only requires light	5 if I don't know what type of VEGF it would be, then
 Q. Right. And 789 only requires light obscuration if you pass the light obscuration, right? A. Yes. 	 5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the
 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 	 5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP
 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 	5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right?
 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 	 5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right? 11 A. It states if I pass USP 789, then
 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? 	5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right? 11 A. It states if I pass USP 789, then 12 there would be no requirement to test on 50 ml
 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 	5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right? 11 A. It states if I pass USP 789, then 12 there would be no requirement to test on 50 ml 13 sorry, for 50 micron pieces.
 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 	5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right? 11 A. It states if I pass USP 789, then 12 there would be no requirement to test on 50 ml 13 sorry, for 50 micron pieces. 14 Q. Do you know when the Lucentis
 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 	5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the as I said is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right? 11 A. It states if I pass USP 789, then 12 there would be no requirement to test on 50 ml 13 sorry, for 50 micron pieces. 14 Q. Do you know when the Lucentis 15 prefilled syringe was first approved by the FDA in
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Q. Right. And 789 only requires light 6 obscuration if you pass the light obscuration, 7 right? 8 A. Yes. 9 Q. You agree there is nothing in the Sigg 10 or Lam references that suggest that the products 11 would have to be tested by the microscopic 12 particle test, right? 13 A. I would need to go back to Sigg and 14 Lam to verify — I can't — Sigg and Lam talks 15 about sterilization. It doesn't talk about 16 particulate matter. 17 Q. If you would turn to paragraph 205 of 18 your declaration, please. 19 A. Yes.	5 if I don't know what type of VEGF it would be, then 6 if I can't do light obscuration, then membrane is 7 the — as I said — is the only way to do so. 8 Q. But it is not necessary to do the 9 microscopic particle test in order to meet USP 10 789, right? 11 A. It states if I pass USP 789, then 12 there would be no requirement to test on 50 ml — 13 sorry, for 50 micron pieces. 14 Q. Do you know when the Lucentis 15 prefilled syringe was first approved by the FDA in 16 the United States? 17 A. I think I cited it in my document. 18 I'm not sure about the exact date, so I would — I 19 would need to go back to verify the exact date.

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produced with the production of the production o	ecember 10, 2021
But in any event, at some point,	1 A. Right.
2 the Lucentis prefilled syringe was approved for use	2 Q. And that difference between the two
3 in the United States, right?	3 includes the fact that the prefilled syringe has a
4 A. Yes.	4 barrel and a stopper and a plunger rod, right?
5 Q. And before that, it was available in a	5 MR. PEPE: Object to form.
6 vial presentation, right?	6 A. Like a single use syringe would have
7 A. Right.	7 as well. You know, if you transfer it from the
8 Q. And the vial is the vial	8 vial into the injection device, then a single use
9 presentation is the drug in a vial with a rubber	9 syringe has a barrel, a flange and a plunger rod.
10 stopper on the top, right?	10 Q. And the Lucentis syringe has a low
11 A. Right.	11 amount of silicone oil, right?
12 Q. And the physician has to take a	12 MR. PEPE: Object to form.
13 syringe, puncture that rubber stopper, draw out	13 A. Lucentis claims a certain amount of
14 the solution, switch needles and then inject it	14 silicone oil in the syringe.
15 into the patient, correct?	15 Q. And it's less than 100 micron silicone
16 A. Correct.	16 oil, right?
17 Q. And with the prefilled syringe, the 18 drug is already in the syringe, right?	17 A. According to the claim, it's less than 18 100 microns.
And the second of the second s	19 Q. And the prefilled syringe has
	20 exhibits forces of less than 11 newtons for break
	THE TRANSPORT OF THE WAS A CONTROL OF THE TRANSPORT OF TH
21 it reduces the steps and is more convenient for	21 loose force, right?
22 the doctor, correct?	22 MR. PEPE: Object to form. That is
1 A. Correct.	what this claim anticipated.
2 Q. But the drug inside the prefilled	2 Q. And the Lucentis prefilled syringe
3 syringe is the same as the drug that was inside	3 also has less than two particles per ml of greater
4 the vial, right?	4 than 50 microns, right?
5 MR. PEPE: Object to form.	5 A. The syringe?
6 A. The active ingredient could be the	6 Q. Yes.
7 same. I'm not sure about the formulation because	7 A. Might not have.
8 you have silicone oil in the system and so the	8 Q. You don't know?
9 formulation might need to be adjusted. So I'm not	9 A. If you don't do the testing, you don't
10 sure about that one.	10 know.
11 Q. Whether there are minor differences in	11 Q. So sitting here today, you don't know
12 the formulation or not, the active ingredient, the	12 whether Lucentis meets that particle size
13 ranibizumab is the same in the vial and the	13 limitation, right?
14 prefilled syringe, right?	14 A. I know it is passes 789. So if it
15 A. Right.	15 fails, then they do MM, and if it then have less
16 Q. Both of them contain the same VEGF	16 than two particles, they release the final drug
17 antagonist, right?	17 product.
18 A. Right.	18 So it would not be released to
19 Q. So the difference between the vial and	19 the market if they would fail 789 in total which
20 the prefilled syringe is that the container that	20 includes both methods if needed.
20 the prefined syringe is that the container that	
21 the drug is supplied in is in a prefilled syringe	21 Q. Other than the things that we have

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1 there any other feature of the prefilled syringe	Did you see there is a sentence
2 that is sold with Lucentis in it?	2 that begins with break loose?
3 MR. PEPE: Object to form. Vague.	
4 A. Please repeat the question.	4 Q. It says, "Break loose in slide forces
Q. Other than the parts of the syringe	5 for prefilled syringes known in the art are
6 that I've just gone through, are there any other	6 typically in the region of the less than 20
7 features or parts of the Lucentis prefilled	7 newtons."
8 syringe?	8 A. Yes.
9 MR. PEPE: Same objection.	9 Q. I think you referred to this in your
10 A. You have the prefilled syringe comes	10 testimony earlier, right?
11 with a finger flange and which acts as a backstop	11 A. Right.
12 device. Or plunger.	12 Q. Now, that sentence refers to prefilled
13 Q. OK, all right.	13 syringes, but it doesn't refer to prefilled
14 Anything else?	14 syringes for intravitreal injection, right?
MR. PEPE: Same objection.	15 A. Right.
16 A. I would need to see an actual package	16 Q. Could you turn in your declaration to
17 of the Lucentis in order to verify what's around	17 paragraph 94, please.
18 the glass barrel.	18 A. Can you just give me one second.
19 Q. You mean in terms of like labeling or	19 Q. Yeah, of course.
20 something like that?	20 A. So I was referring to the 20 newton on
21 A. For sure I know it must have a label	21 column number 1, line 65 – or 60.
22 because of regulatory requirements. But	22 So it says, "In one embodiment
2 8	220
1 additional components around the glass barrel, a	1 the syringe is suitable for ophthalmic injections,
2 feature –	2 more particularly intravitreal injections, and as
3 Q. Such as what? Give me an example of	3 such, has a suitably small volume. The syringe may
4 something that might be there.	4 also be silicone oil free or substantially silicone
5 A. For sure it needs to have a plunger	5 oil free or may comprise a low level of silicone
6 rod. It needs to have finger flange extension.	6 oil as lubricant. In one embodiment, despite the
7 It depends on the intended use of the molecule, if	7 low silicone oil level, the stopper break loose and
8 you use the finger flange or not. And it comes	8 slide force is less than 20 newton."
9 with, according to the claim, it comes with a sort	9 Q. But there is no claim in the patent
10 of backstop feature in combination with the	10 that is limited to 20 newtons, right?
11 plunger rod.	11 A. There is no claim on 20 newton.
12 Q. To prevent the backward movement of	12 Q. Can you turn to paragraph 94 in your
13 the stopper?	13 dec, please.
14 A. Right.	14 A. Yes.
15 MR. JAMES: Why don't we take a short	15 Q. And in paragraph 94, you are talking
16 break. Off the record.	16 about the '631 patent claiming priority to a
17 (Recess; 3:39 to 3:43 p.m.)	17 European patent application that was filed on
18 Q. Mr. Koller, do you have the '631	18 July 3, 2012, right?
19 patent in front of you?	19 A. Right.
20 A. Yes.	and the second of the second o
TO SOLVE STATE STA	20 Q. And you say, in the second sentence,
	21 that that European patent application does not
22 Line 34.	22 contain any examples and does not contain any

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Conducted on December 16, 2021 223 disclosure of specific break loose forces for any 1 away from that sentence about glide forces syringe disclosed therein, right? anything about break loose forces, is that right? A. Right. MR. PEPE: Object to form. Q. Instead, you note that it discloses A. Right. only glide force for certain embodiments is less Q. If you could turn to paragraph 313 in than about 11 newtons or less than 9 newtons, less your declaration, please. than 7 Newton, less than 5 newtons or between 3 A. Yes. 8 newtons to 5 newtons, right? Q. In that paragraph, you say that with A. Right. 9 respect to the claimed break loose and glide 10 Q. And then you have the material from 10 forces, syringes commercially available before the 11 the prosecution history excerpted there in that 11 critical date of the '631 patent were commonly 12 paragraph, right? 12 sold as 10 and 5, syringes meaning they would have 13 A. Right. 13 a maximum break loose force of 10 newtons and 14 Q. And then in paragraph 95, say that 14 slide force of 5 newtons squarely within the 15 because the independent claim in the '631 patent 15 ranges claimed. 16 requires that the break loose force is less than 16 Do you see that? 17 about 11 newtons and this is required for all the 17 A. I see that. 18 claims of the '631 patent, a POSITA would not be 18 Q. And you're citing Fries, right? 19 able to reasonably conclude the inventors had 19 A. Right. Q. I'll hand you the next exhibit which 20 possession of an invention consisting of a 20 21 prefilled syringe with the claimed break loose 21 is IPR Exhibit 1012. It's a 2009 article from 22 force based on the disclosure of EP 12174860. 22 Drug Delivery Technology with the first author 222 1 Right? 1 Arnold Fries called "Drug Delivery of Sensitive Biopharmaceuticals with Prefilled Syringes." 2 Right. A. Q. So your opinion as stated there is 3 (Exhibit 1012, article "Drug 4 that because all that was stated were slide Delivery of Sensitive Biopharmaceuticals 5 forces, the POSITA could not conclude anything with Prefilled Syringes" marked 6 about possession of a break loose force, right? 6 previously for identification.) A. Right. Or had possession of inventing Q. Just take a look at that and confirm consisting of prefilled syringe with the claimed 8 that that is a Fries article that you were citing 9 break force. 9 in paragraph 313? A. Yes. 10 Q. So when you look at that excerpted 10 11 portion where it talks about these glide forces, 11 O. It was? 12 you don't read the highest number as the break 12 It was. 13 loose force in that sentence? 13 Q. If you turn to page 1012.006. 14 MR. PEPE: Object to form. 14 15 A. So it says in one embodiment the glide It says, at the bottom, "The amount of 16 extractable silicone oil could be reduced below 16 force for the stopper within the prefilled syringe 17 is less than about 11 newton or less than 9 17 the detection limit (0.03 milligrams of ICPAES 18 newton, less than 7, less than 5 or between about 18 according to EN ISO 11885," and then it says, 193 and 5. And it says, embodiment, the glide force 19 "with low levels of lubricant quantity, the 20 specified syringe functionality was fulfilled, 20 for the stopper. So in this sentence, it does not 21 mention the break force. 21 plunger gliding forces in the range of 5 to 10

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22 newtons."

So in your opinion, you can't take

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Do you see that?	1 page 15?
2 A. I see that.	2 A. Yes.
Q. So in that parenthetical at the end,	3 Q. And after you after directing you
4 it's only referencing gliding forces, right?	4 to that excerpt of Lam, Mr. James asked you
5 A. Plunger gliding forces, right.	5 whether Lam disclosed a glass syringe.
6 Q. And they are all greater than 5	6 Do you recall that?
7 newtons, correct?	7 A. I recall it.
8 A. In the Fries article.	8 Q. I would like you to now turn to page 2
9 Q. I'm sorry, in that parenthetical, when	9 of Lam. And I'm going to direct you to the
10 he says, "The gliding forces are in the range of 5	10 paragraph starting at line 29.
11 to 10 newtons," that means all the gliding forces	11 Do you see it says in some
	12 embodiments, the object is a syringe?
12 were greater than 5 newtons, right?	
MR. PEPE: Object to form.	Do you see that?
14 A. 5 to 10 newtons, right.	14 A. On page 2?
15 Q. It means above 5, right?	15 Q. Page 2, line 29.
16 A. Above 5 and below 10.	16 A. Some embodiments, the object is a
MR. PEPE: Object to form.	17 syringe.
18 Mischaracterizes the document.	18 Q. Can you read that paragraph to
19 A. Between 5 and 10.	19 yourself.
20 Q. That parenthetical doesn't say	20 A. Yes.
21 anything about break loose force, right?	Q. What does that paragraph describe with
22 A. Right.	22 respect to the material used for the syringe
226	228
1 Q. You can't glean anything about break	1 barrel disclosed in Lam?
2 loose force from the recitation of those plunger	2 A. So it says that a glass syringe has 3 been used in combination with a D777 laminated
3 gliding forces, right?	
4 A. Right.	
5 MR. JAMES: I have no further	5 Fluro Tec, so — the used syringe material is 6 glass.
6 questions for the witness.	
7 MR. PEPE: Why don't you just give me	A second
a couple of minutes and then we can step out	8 questions. 9 MR. JAMES: Thank you.
9 for a second.	10 (Time noted: 4:00 p.m.)
10 (Recess; 3:54 to 3:56 p.m.)	
11 EXAMINATION BY	11 12
12 MR. PEPE:	HORST KOLLER
13 Q. Mr. Koller, can you take out Exhibit	13
14 1029 which would be on the top of your stack.	14 Subscribed and sworn to
Do you recall that that is the	15 before me this day
16 Lam publication?	16 of MO , 2021.
17 A. Yes.	17 , 2021.
18 Q. I would like you to turn to page 15.	18
19 A. 15?	19
20 Q. Yes.	20
21 Do you recall earlier that	21
22 Mr. James directed you to lines 12 through 17 on	22
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_	Conducted on By
1	CERTIFICATE 229
2	
3	I, MARY F. BOWMAN, Certified Reporter and
4	Notary Public within and for the State of New Jersey
5	do hereby certify:
6	
7	That Horst Keller, the witness whose
8	deposition is hereinbefore set forth, was duly sworn
9	by me before the commencement of such deposition and
10	that such deposition was taken before me and is a true
11	record of the testimony given by such witness.
12	
13	I further certify that the adverse party,
14	was represented by counsel at the deposition.
15	
16	I further certify that the deposition of
17	Horst Keller, occurred at the offices of
18	Weil, Gotshal & Manges LLP at 767 Fifth Avenue,
19	New York, New York 10153 on Thursday,
20	December 16, 2021, commencing at 9:00 a.m. EST to
21	4:00 p.m. EST
22	
	230
1	I further certify the inspection, reading
2	and signing of said deposition were not waived by
3	counsel for the respective parties and by the witness.
4	
5	I further certify that I am not related to
6	any of the parties to this action by blood or
7	marriage, I am not employed by or an attorney to any
8	of the parties to this action, and that I am in no way
9	interested, financially or otherwise, in the outcome
10	of this matter.
11	
12	IN WITNESS WHEREOF, I have hereunto set my
13	hand this 29th day of December 2021.
14	
15	May 7. Sn
16	- Ivac
17	
18	NOTARY PUBLIC IN AND FOR THE
19	STATE OF NEW JERSEY
20	
21	
22	

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