UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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REGENERON PHARMACEUTICALS, INC.,
Petitioner

v.

NOVARTIS PHARMA AG,
NOVARTIS TECHNOLOGY LLC,
NOVARTIS PHARMACEUTICALS CORPORATION,
Patent Owners

_____

Case IPR2021-00816
Patent No. 9,220,631

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SUPPLEMENTAL DECLARATION OF KARL R. LEINSING, PE, IN SUPPORT OF NOVARTIS'S PATENT OWNER RESPONSE

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I. INTRODUCTION

1. I am the same Karl Leinsing who submitted a declaration on July 28, 2021 ("Initial Declaration") on behalf of Novartis Pharma AG, Novartis Technology LLC, and Novartis Pharmaceuticals Corp. (collectively, "Patent Owner" or "Novartis") in support of their Patent Owner Preliminary Response. I maintain the opinions set forth in my Initial Declaration and incorporate them by reference here. This supplemental declaration provides further opinions, consistent with those I provided in my Initial Declaration.

2. I understand that Regeneron Pharmaceuticals, Inc. ("Petitioner" or "Regeneron") initiated these proceedings by filing a Petition seeking cancellation of all claims of U.S. Patent No. 9,220,631 ("the '631 patent").

3. The subject of this declaration is the validity of the '631 patent. This declaration is the result of my review and analysis of the petitions, declarations, and prior art submitted by the Petitioner in the above referenced IPR proceeding, and the Board's Institution Decision, as well as additional materials identified herein.

II. SUMMARY OF OPINIONS IN MY INITIAL DECLARATION

4. Based on my knowledge, experience and the reviewed materials, it is my opinion that the '631 patent is not obvious over the prior art cited by the Petitioner in IPR2021-00816 for at least the following reasons:

- A person of skill in the art ("POSA") would not have been motivated to combine the references relied upon by Petitioner to arrive at the claimed invention as claimed in Claims 1–26.
- A POSA would not have reasonably expected to successfully combine the references relied upon by Petitioner to arrive at the claimed invention.
- The prior art relied upon by the Petitioner would not have enabled a POSA to make or use the claimed invention.
- Secondary considerations support the non-obviousness of the '631 patent.

5. European application No. EP 12189649 and U.S. Application No. 13/750,352 demonstrate a constructive reduction to practice of the claimed invention no later than October 23, 2012, and January 25, 2013, respectively.

III. SUMMARY OF ADDITIONAL OPINIONS PRESENTED

6. As set forth in detail below, in addition to the opinions contained in my Initial Report, it is my opinion that the '631 patent is not obvious over the prior art cited by the Petitioner in IPR2021-00816 for at least the following reasons:

- Neither Sigg nor Lam enables terminal sterilization of a PFS while minimizing contact between the drug product and the sterilizing agent.
- Other prior art cited by Petitioner and Mr. Koller would not have taught a POSA the information missing from Sigg and Lam (i.e. how to design a

suitable syringe) to enable the POSA to make the invention of the '631 patent.

- A POSA would not have expected syringes with less than 100 µg of total silicone oil to be suitable for intravitreal injection.
- A POSA would not have been motivated to use Parylene C or the non-Parylene C syringes disclosed in Boulange in a PFS filled with a VEGF-antagonist for intravitreal injection.
- A POSA would not have been motivated to combine Sigg's VHP method or Lam's EtO method with syringes from Boulange.
- A POSA would not have had a reasonable expectation of success in combining Boulange with Sigg or Lam.
- At least dependent claims 14, 17, 21, and 24–26 are non-obvious for additional reasons beyond those applicable to claim 1.

7. Genentech tried and failed to make a PFS filled with the VEGF-Antagonist Lucentis®

8. The Lucentis® PFS marketed in the United States by Genentech embodies claims 1-10 and 14–23 of the '631 patent and is coextensive with the claims.

IV. LEGAL PRINCIPLES

9. In formulating my opinions and conclusions in this proceeding, I have been provided by counsel for Patent Owner with an understanding of the prevailing principles of U.S. patent law that govern the issues of patent validity.

10. In addition to the legal principles outlined in my Initial Declaration, I have been provided with an understanding of the legal principles of enablement and secondary considerations of non-obviousness, as outlined below.

A. Enablement

11. I understand that, to render a claim obvious, the prior art taken as a whole must enable a person of ordinary skill in the art ("POSA") to make and use the claimed invention.

12. I understand that enablement requires that the identified references must collectively teach a POSA how to make and use the claimed invention without undue experimentation.

B. Secondary Considerations of Non-Obviousness

13. I understand that real-world evidence (also referred to as secondary considerations) is a necessary part of an obviousness analysis, and that such evidence can demonstrate non-obviousness. Some secondary considerations that may be considered in such an analysis include, but are not limited to, failure of others to arrive at the invention, commercial success of the patented invention, industry praise, teaching away in the art, long-felt need, skepticism of others

toward the invention, and the taking of licenses under the patent by others. These factors are relevant only if there is a connection, or nexus, between the factor and the merits of the invention covered by the patent claim. I have been informed that nexus may be rebuttably presumed if the product tied to the secondary consideration embodies and is coextensive with the claimed invention. I have been informed that coextensiveness does not require perfect correspondence between the claims and the product, so long as the product is essentially the claimed invention and does not contain substantial unclaimed features that are responsible for the secondary consideration (e.g., commercial success).

C. Person of Ordinary Skill in the Art

14. I understand that whether the claims of a Patent are obvious is evaluated from the perspective of POSA to which the patent pertains as of the priority date of the Patent. I understand that the POSA is a hypothetical person, and that in determining the level of skill such a person would have, I may consider the following factors: (1) the type of problems encountered in the art; (2) the prior art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field.

15. As discussed in my Initial Declaration, I understand that Petitioner has proposed a definition of a POSA for the '631 patent. *See* Ex. 2001 ¶ 61. For

purposes of my Initial Declaration, I did not offer a proposed POSA definition, and simply applied Petitioner's definition. *Id.* ¶ 62. However, Petitioner's definition does not reflect the reality of medical device development as of the priority date, which generally involves collaborative work between persons of ordinary skill in the art and others with complementary skills and experience. For example, in my experience developing medical devices, I have routinely consulted with healthcare providers (e.g., physicians), toxicologists, and microbiologists who specialize in sterilization of medical devices and pharmaceutical products.

16. Therefore, in my opinion a POSA for all claims of the '631 patent would have had an advanced degree (i.e., an M.S., a Ph.D., or equivalent), and at least 2–3 years of professional experience, in mechanical engineering, biomedical engineering, materials science, chemistry, chemical engineering, or a related field, including experience with the design of a PFS and/or the development of ophthalmologic drug products or drug delivery devices. Such a person would have been a member of a product development team and would have drawn upon not only his or her own skills, but also the specialized skills of team members in complementary fields including ophthalmology, microbiology and toxicology.

17. The distinction between this definition of a POSA and Petitioner's does not impact my opinions set forth in my Initial Declaration, and my opinions set forth here would not change if the Board adopted Petitioner's POSA definition.

18. The opinions I provide herein are provided from the perspective of a POSA as of July 3, 2012, which as explained in my Initial Declaration, I understand is the date of the earliest application to which the '631 patent claims priority, and the date relied upon by Petitioner and their expert, Mr. Koller, in arguing obviousness. Ex. 2001 ¶ 28; IPR2021-0816, Paper 1, Petition for Inter Partes Review (Apr. 16, 2021) ("Pet.") at 24; Ex. 1003 ¶ 10. My opinion would not change were the relevant date October 23, 2012, the date to which Mr. Koller admits the '631 can claim priority. Ex. 1003 ¶ 95.

V. FURTHER ANALYSIS OF PETITIONER'S OBVIOUSNESS ARGUMENTS

A. The Prior Art, Including Boulange, Shows That a POSA Would Not Have Expected Syringes With Less Than 100 µg of Total Silicone Oil to Be Suitable for Intravitreal Injection

19. Petitioner and Mr. Koller rely on Boulange for disclosure of syringes with less than 100 µg of silicone oil. However, a POSA would not have understood Boulange, or the prior art as a whole, as teaching that syringes with this amount of silicone oil could be used for intravitreal injections. As explained in more detail below, syringes in the prior art were generally lubricated with silicone oil in amounts well in excess of 100 µg. And contrary to Mr. Koller's opinion, the prior art concerning baked-on silicone oil does not teach that baked on silicone oil uses less *total* silicone oil (as the '631 patent claims), only less *free* silicone oil, i.e., silicone oil that is not tightly bonded to the glass surface. Mr. Koller thus cites

Boulange for disclosure of syringes lubricated with less than 100 µg of silicone oil. *See, e.g.*, Ex. 1003 ¶ 64. But Boulange goes against the overall weight of the prior art with respect to the amount of silicone oil that a POSA would have thought would be necessary for a well-functioning syringe. And Boulange itself—which concludes that use of Parylene C as a novel syringe coating is necessary in order to use amounts of silicone oil in the claimed range in order to have acceptable syringe forces—reflects skepticism that a POSA would have had with syringes that had amounts of silicone oil in the claimed ranges for intravitreal injection. In other words, a POSA would have believed that more than 100 µg of silicone oil would be required to achieve acceptable forces unless a product like Parylene C was also applied.

20. Prior art that addresses siliconization of syringes identifies silicone oil amounts that are well in excess of the claimed amounts. It was generally understood that more silicone oil provided better lubrication, i.e., increasing the amount of silicone oil on a syringe would lead to reduced syringe forces. *See, e.g.*, Ex. 2021, Reuter 2013 at .002 (the "obvious solution" to inadequate lubrication resulting in "the forces in the injection process… be[ing] too high" is "to increase the amount of silicone oil used"). A POSA would have understood that there were disadvantages of using excessive silicone oil, but that a trade-off would thus be needed between providing sufficient lubrication and avoiding problems associated

with having too much silicone oil. In general, the prior art suggested amounts of silicone oil that were far greater than those claimed in the '631 patent. Because of the safety risks of high or inconsistent plunger forces, a POSA would not have traded inferior mechanical function for reduced silicone oil in a PFS for intravitreal injection.

21. For example, Badkar, a 2011 article by Pfizer scientists about "Development of Biotechnology Products in Pre-filled Syringes" reports that a "survey of leading PFS manufactures resulted in our finding that the typical [silicone oil] levels reported vary between 0.5 and 1 mg silicone per syringe," i.e., 500 to 1,000 µg. Ex. 1044, Badkar 2011 at .007. Reuter 2013, an article about syringe siliconization by the Director of Product Development at the syringe manufacturer Gerresheimer Bunde, reports the results of a study showing that in a 1 mL syringe, "the quantity of silicone oil per syringe could be reduced by 40%"—from 800 µg to 500 µg—"without any impairment of the system's functional properties." *See* Ex. 2021.003. Reuter 2013 further states that "[i]nadequate siliconisation of the syringe barrel… can cause slip-stick effects that impair the syringe's function," and that "[t] obvious solution is to increase the amount of silicone oil used to achieve a homogenous coating." Ex. 2021.002. Sacha, a 2010 article entitled "Practical fundamentals of glass, rubber, and plastic sterile packaging systems" by authors from the Research and Development department at

Baxter BioPharma Solutions, states that among the "[p]re-filled syringe options," silicone level "[v]aries, 0.6–1.0 mg per 1 mL syringe," i.e., 600–1,000 µg per syringe. Ex. 2035, Sacha 2010 at .005. Fries, an article entitled "Drug Delivery of Sensitive Biopharmaceuticals With Prefilled Syringes" by the Head of Sales, USA Syringes and Director, Product Management Syringes at Gerresheimer Bunde, states that "[i]n established manufacturing processes on the lines of syringe suppliers, biopharmaceutical companies, and CMOs, syringes are oily siliconized by spraying 0.4- to 1.0-mg silicone oil (e.g., Dow Corning 360, Medical Fluid) into the barrels." Ex. 1012, Fries 2009 at .006.

22. In another example, scientists in the Pharmaceutical Processing and Technology Development department at Genentech reported the results of the development and optimization of a syringe siliconization process. *See* Ex. 2022, Chan 2012. In this report, the Genentech scientists worked to optimize the siliconization of syringes using spray-on oily siliconization with two different siliconization apparatuses. They varied siliconization parameters to apply various amounts of silicone oil and tested the impact of the different silicone oil applications on silicone oil distribution and syringe function, including by measuring glide forces. Ex. 2022.003–.014. Chan determined that "[t]here is a clear trend that, regardless of the spraying condition, the higher the amount of coated silicone, the easier the syringe passes the glide force test." Ex. 2022.011.

By optimizing the siliconization conditions and in view of need to avoid "a high amount of silicone" for biopharmaceutical products, Chan further determined that "[t]he preferred silicone amount for the 1 mL long syringe is in the range of 0.2 to 0.5 mg per syringe." *Id.* Syringes with less than 100 μg of silicone oil were deemed "under-coated." Ex. 2022.007.

23. Genentech is a world leader in biotechnology and the developer of Lucentis. It is notable that, even as late as 2012, these Genentech scientists—despite acknowledging concerns about using high amounts of silicone oil with biopharmaceutical products—were still focused on spray-on siliconization rather than baked-on and had determined that the optimal amount of silicone oil was 2 to 5-fold more than the top of the range claimed by the '631 patent.

24. The disclosures of these prior art references concerning silicone oil levels used in prior art syringes are consistent with [redacted]

[redacted], four-fold above the limit claimed in the ’631 patent.

25. In view of the clear teachings of the prior art that even well-optimized syringes contained silicone oil well in excess of 100 µg, Mr. Koller opines that “[i]t was…well known prior to 2012 that the baked-on siliconization process requires only about one-tenth the amount of silicone oil as oily siliconization to achieve the same break loose and glide force.” Ex. 1003 ¶ 64. But the prior art that Mr. Koller cites does not support his assertion that baked-on siliconization allows use of less *total* silicone oil, but rather focuses on benefits of baked-on siliconization that include reduction of *free* silicone oil—the silicone oil that is not fixed to the glass surface—which is distinct from total silicone oil. Shah explains: “Baking-on the silicone involves heating the silicone-coated syringe to a specific temperature for an appropriate time which results in longer chains that are more

closely adhered to the surfaces they coat. Thus the concentration of silicone in the syringe and its chemical reactivity are both reduced and the product's stability is increased." Ex. 1011, Shah 2009 at .006. Indeed, Mr. Koller acknowledges the distinction between total silicone and free silicone oil. In his discussion of baked-on siliconization, he asserts that baked-on siliconization allows use of less silicone oil (Ex. 1003 ¶ 64), and that "[a]nother benefit" is that it "reduces the amount of 'residual' or 'free' silicone oil, which refers to the quantity of silicone oil that is not affixed to the inner surfaces of the syringe barrel and thus could dislodge from the surface and enter the drug formulation." Ex. 1003 ¶ 65.

26. Other references similarly make clear that "free" silicone oil—not total—was understood in the prior art to be reduced as a result of baked-on siliconization (emphasis added unless noted):

- **Badkar** states that the baking process results in "longer chains of Si that are more closely adhered to the surfaces they coat, thus resulting in a reduced concentration of *free* silicone in these syringes and lower chemical reactivity." Ex. 1044.003. Also, "sprayed-on syringes contained higher *residual-free* silicone compared to baked-on silicone syringes." Ex. 1044.004. Furthermore, despite testing and directly comparing syringes with both spray-on and baked-on silicone oil (*see* Ex. 1044.003), Badkar reports that syringes from "leading PFS manufactures" had silicone oil

levels that "vary between 0.5 and 1 mg silicone per syringe," without distinguishing between spray-on and baked-on syringes (Ex. 1044.007).

- **Fries** explains that baked-on siliconization was "developed to lower the level of *free (non-bound)* silicone oil in prefilled syringes." Ex. 1012.006.
- **Schoeknecht** states that "[b]aking-on the silicone… results in longer chains [of silicone oil] that are more closely adhered to the surfaces they coat. Thus the *concentration* of silicone in the syringe… [is] reduced." Ex. 1013, Schoeknecht 2005 at .004.
- **Overcashier** states that after siliconization, "[s]yringes subsequently may be heated, resulting in so-call 'baked silicone' in an effort to reduce silicone mobility and interaction with the drug product." Ex. 1076, Overcashier 2006, at .003.
- **The Nema textbook (Nema Vol. 1)** states that "[r]ecent developments to minimize free silicone include baking silicone at high heat onto the glass barrels, thereby minimizing the amount of *free* silicone that can interact with drug product." Ex. 1015.330.
- **Sacha** states that "[s]ilicone coatings, typically silicone emulsions, are sometimes applied ('baked') to the inner surfaces of vials to produce a hydrophobic surface." Ex. 2035.0010. In Table 1, "Pre-filled syringe options," Sacha identifies as "Silicone application" options "Silicone oil or

silicone emulsion, Applied at syringe manufacturer, Applied at finished product manufacturer." Ex. 2035.005. For "silicone level," it identifies "Varies, 0.6-1.0 mg per 1 mL syringe." *Id.* Lower levels for syringes using baked-on emulsion are not identified.

The prior art references thus do not suggest that baked-on siliconization generally allows a reduction in total silicone oil.[1] And a POSA would not have known merely from the use of baked-on silicone oil in any particular context how much silicone oil was used.

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[1] The only reference besides Boulange that Mr. Koller cites for his assertion that it was "well known prior to 2012 that the baked-on siliconization process requires only about one-tenth the amount of silicone oil as oily siliconization to achieve the same break loose and glide force" is Chacornac (Ex. 1014). *See* Ex. 1003 ¶ 64. I understand that Chacornac is not prior art because it was filed on October 17, 2011 and published on April 19, 2012, after the inventors had conceived of their invention as of October 2011. *Id*. And, as discussed below, the data in Boulange does not support Mr. Koller's contention. On the contrary, it shows that using baked-on silicone oil with one-tenth the amount results in higher break loose and glide force.

27. It is also notable that the primary reference that Mr. Koller and Petitioner rely on for the use of low silicone oil levels—Boulange—is a patent application that proposes use of a novel stopper coating in conjunction with baked-on silicone oil. Indeed, the need for Parylene C in order to allow reduction of silicone oil is the main premise of Boulange, and Boulange says that the baked-on silicone oil with reduced total amounts alone is unsuitable. Ex. 1008 at 21:4–21:5. This further demonstrates that it was not accepted in the prior art that the silicone oil levels in Boulange that Mr. Koller relies on were able to provide acceptable syringes—particularly in syringe for delicate procedures like intravitreal injection. If less than 100 μg of baked-on silicone oil was understood to be a sufficient amount for syringes to have acceptable forces, there would have been no reason for Boulange and Becton Dickinson to attempt to develop Parylene C as a new stopper coating.

B. A POSA Would Not Have Been Motivated to Combine Boulange with Sigg or Lam and Would Not Have Had a Reasonable Expectation of Success in Doing So

28. As discussed in my Initial Declaration, a POSA would not have been motivated to combine Boulange with Sigg or Lam (Ex. 2001 ¶¶ 106–49, 166–71), and also would not have had a reasonable expectation of success in doing so (Ex. 2001 ¶¶ 150–65, 172–74). First, as discussed in my Initial Declaration (Ex. 2001 ¶¶ 175–85) and in more detail below (at §§ V.C and V.D), the prior art (including

Sigg and Lam) would not have enabled a POSA to use the sterilization methods discussed in Sigg and Lam to terminally sterilize a syringe that both has the characteristics of Boulange's syringes and is filled with a VEGF-antagonist. A POSA would have recognized the gaps in the prior art disclosures and as a result neither would have been motivated to fill Boulange's syringes with a VEGF-antagonist and then attempt to sterilize them using Sigg or Lam's methods, nor would have expected to succeed in the endeavor.

29. Second, Boulange's substantial shortcomings are inconsistent with both a motivation to combine Boulange with Sigg or Lam and a reasonable expectation of success in doing so. Because of the deficiencies associated with syringes disclosed in Boulange—both with and without Parylene C—a POSA would not have selected any of Boulange's syringes to attempt to make a PFS filled with a VEGF-antagonist that is terminally sterilized using Sigg or Lam's methods.

1. A POSA Would Not Have Been Motivated to Use Parylene C in a PFS Filled with a VEGF-Antagonist

30. Boulange is a patent application about the use of Parylene C as a novel coating for pistons in medical devices. *See, e.g.*, Ex. 1008 at abstract ("Abstract: The invention relates to a medical device comprising at least one first part coated with a coating having a composition comprising at least one polymer material comprising [parylene]." (references to annotated figure omitted)). *See*

also Ex. 2001 ¶¶ 81–84, 91 (my Initial Declaration providing an overview of Boulange). The premise of the Boulange application is that Parylene C coating on a piston can "improve the slip" between medical device components, and that using Parylene C makes it possible to use less silicone oil to lubricate medical devices, for example in the barrel and on the stopper of a syringe. *See, e.g.*, Ex. 1008 at 1:27–2:6 ("In order to improve the slip between" parts of a medical device that are in contact with and move relative to one another, "it has been proposed for the entirety of the developed surface of one of the parts to be coated with a coating consisting of at least one polymer material" comprising parylene). *See also* Ex. 2001 ¶¶ 85–91, 109–11 (my Initial Declaration discussing Boulange's focus on use of Parylene C and conclusion that Parylene C allows reduction of silicone oil). Boulange states that "*with the medical device of the invention*, [i.e., a device with at least a parylene-coated part], it is possible to decrease the total amount of lubricant, for example silicone oil, that is necessary in such a medical device." Ex. 1008 at 6:23–25 (emphasis added).

31. As discussed in my Initial Declaration, Boulange specifically teaches that syringes containing stoppers without the Parylene C coating are not satisfactory when used with the low levels of silicone oil proposed by Mr. Koller and Petitioner. *See* Ex. 2001 ¶¶ 87–89, 110, 143–44. For example, Boulange states, based on the data disclosed, that the pistons without Parylene C were

"markedly inferior" and not "acceptable for a medical device." Ex. 1008 at 19:6–7, 21:4–5. A POSA would have therefore understood that Boulange suggests using syringes with 4 μg/cm^2 silicone oil on the barrel interior (i.e., about 40 μg per syringe) only in conjunction with stoppers coated with Parylene C.

32. However, as discussed in my Initial Declaration, a POSA would not have been motivated to use Parylene C in a terminally sterilized PFS filled with a VEGF-antagonist for intravitreal injection. *See* Ex. 2001 ¶¶ 112–32. On the contrary, a POSA would have avoided Parylene C for numerous reasons. *See id.* ¶¶ 92–96, 112–21.

33. First, neither Boulange, nor Sigg, nor Lam provide any information or assurances about the suitability of Parylene C for a syringe intended for intravitreal injection of a biologic drug product, and neither Mr. Koller nor Petitioner has identified any evidence that Parylene C was used as a coating on a VEGF-antagonist PFS in the prior art or that Becton Dickinson (the owner of the Boulange application) had, as of the priority date of the '631 patent, marketed any syringe comprising Parylene C. *See* Ex. 2001 ¶¶ 113–14; Ex. 2189 at 157:1–16. There is also no evidence that Parylene C was used in a Macugen PFS, despite Petitioner's contention that a POSA would have been motivated to resolve issues with silicone oil. *See* Ex. 2001 ¶ 115. Indeed, the Parylene C coated syringes tested in Boulange are all used with water alone, not with a biologic drug or any

drug at all. A POSA would not have inferred suitability for use with biologic drugs from experiments using just water.

34. Furthermore, as discussed in my Initial Report and in more detail by Dr. Dillberger, a POSA would have known that there are stringent requirements that materials must satisfy to be used in primary packaging of drugs, and that the concern is particularly acute for materials used in primary packaging of injectable or ophthalmic drugs. *See* Ex. 2001 ¶¶ 117–21; Ex. 2202 ¶¶ 13–51. But Petitioner and Mr. Koller have not identified any prior art disclosing use of Parylene C as a primary packaging material for an injectable, ophthalmic, and/or biologic drug, or investigating its suitability for that purpose. *See* Ex. 2001 ¶¶ 117–21. Mr. Koller's reliance on prior art concerning use of fluoropolymer coatings does not support use of Parylene C; Parylene C is not a fluoropolymer. *See* Ex. 2001 ¶¶ 117–21122–128; *see also,* Ex. 2202 ¶¶ 52–58. Furthermore, as discussed in my Initial Report and in further detail by Dr. Dillberger, Parylene C has been shown to have high protein adsorption, meaning that proteins adhere to Parylene C surfaces. *See* Ex. 2001 ¶¶ 129–30; Ex. 2202 ¶¶ 66–67. This property is desirable for other biomedical applications of Parylene C, but is a significant detriment to its use in primary packaging for a biologic drug because it can lead to degradation of the drug or depletion of the drug from solution. *See* Ex. 2001 ¶¶ 129–30; Ex. 2202 ¶¶ 45, 62, 66–67. Furthermore, Parylene C was also known in the prior art to have

increased coefficient of friction upon treatment with hydrogen peroxide, creating a risk that Parylene C coated stoppers would be mechanically compromised upon VHP treatment. *See* Ex. 2001 ¶ 132; Ex. 1075, Wolgemuth 2002 at .004.

35. Moreover, nothing in Sigg, Lam, or Boulange suggests that the syringes with Parylene C-coated stoppers are compatible with terminal sterilization of a filled syringe using the methods discussed in Sigg and Lam. Notably, as discussed in detail below in Paragraphs 130-133, Boulange's brief mention of sterilization (Ex. 1008 at 4:3–5) is about sterilization of individual syringe components with radiation prior to aseptic filling, not terminal sterilization of already-assembled and filled syringes, and the degradation that Boulange mentions refers to degradation of the rubber in the stoppers, not degradation of drug products contained within a filled syringe. A POSA would not have interpreted this discussion as suggesting that syringes with Parylene C-coated stoppers could be terminally sterilized with VHP or EtO.

36. For these reasons, a POSA would have been deterred from using Parylene C to coat the stoppers in a terminally sterilized PFS filled with a VEGF-antagonist for intravitreal injection. A POSA developing such a syringe would not have had an incentive to use a novel lubricant coating like Parylene C that was unproven as a pharmaceutical packaging material and had a variety of potential drawbacks including (as discussed above and by Dr. Dillberger) toxic leachables

and destructive interactions with drug compounds and formulations, especially where long-established lubricants (i.e., silicone oil) were available and worked well. *See* Ex. 2202 ¶ 59–65. Medical device and drug developers and manufacturers had decades of experience using silicone oil as the standard lubricant for medical devices and pharmaceutical packaging. Despite some concerns about use of excessive silicone oil, silicone oil was known to be an effective lubricant that is both safe and compatible with most drugs and sterilization methods. A POSA would not have replaced silicone oil—whose drawbacks were known and manageable—with Parylene C, thereby introducing a variety of new and uncertain problems associated with Parylene C. A POSA would be even less motivated to use Parylene C in a syringe that still had silicone oil present—as in the Parylene C syringes that Petitioner and Mr. Koller rely on Boulange for—thus introducing Parylene C's problems without eliminating the silicone oil.

37. The POSA therefore would not have been motivated to combine Boulange with Sigg or Lam because use of Parylene C as a stopper coating is the essential premise of Boulange.

2. A POSA Would Not Have Been Motivated to Use the Non-Parylene C Syringes Disclosed in Boulange

38. As discussed in my Initial Report, Boulange is a reference about the use of Parylene C as a stopper coating to allow use of less silicone oil to lubricate

the barrel of a syringe. *See* Ex. 2001 ¶¶ 81–91, 142. The premise of Boulange ties the potential to reduce silicone oil to the use of Parylene C, and by describing stoppers without Parylene C (i.e., stoppers A and C) as not "acceptable for a medical device" and "markedly inferior," Boulange expressly discourages a POSA from using such stoppers in syringes with less than 500 µg of silicone oil on the barrel. *See* Ex. 1008 at 19:6–7, 21:4–21:5; Ex. 2001 ¶ 143. Further, Boulange expressly emphasizes to a POSA the importance of using syringe components with "surface characteristics, including the coefficient of friction, of the region of contact between the two parts of the medical device, [that] can be maintained over time, even after prolonged storage." Ex. 1008 at 4:15–20. In other words, Boulange makes clear the importance of maintaining low syringe forces throughout the shelf life of a syringe, and credits the use of Parylene C as allowing for stable syringes, in contrast to the non-Parylene control syringes.

39. Mr. Koller nevertheless asserts that "Boulange also discloses stopper designs that do not use a Parylene C coating that would be desirable to use with Sigg," i.e., stopper C. Ex. 1003 ¶ 178. I disagree. A POSA would not have relied on Boulange while ignoring its main premise, and thus would not have been motivated to use the non-Parylene C stoppers in a PFS, particularly a PFS for a delicate application that requires low and consistent forces over the shelf-life of a product, such as intravitreal injection. *See* Ex. 2001 ¶¶ 141–49.

40. According to Mr. Koller, a POSA would have looked past Boulange's express teachings discouraging the use of non-Parylene C stoppers in low-silicone oil syringes because the data reported in Boulange from the characterization of the non-Parylene C syringes would not have discouraged their use. I disagree. The data does not support Mr. Koller's contentions concerning the use of syringes without Parylene C-coated stoppers. Rather, a POSA would have interpreted the data in Boulange for the non-Parylene C syringes as supporting Boulange's conclusions that those syringes are markedly inferior and unsuitable. Moreover, a POSA would have recognized and agreed with Boulange's emphasis of the importance of maintaining the characteristics of syringe components "including the coefficient of friction" over time "even after prolonged storage," (Ex. 1008 at 4:16–18), and would have understood that the data for the non-Parylene C stoppers is inconsistent with this objective.

41. As discussed in my Initial Declaration (*see* Ex. 2001 ¶ 145), Boulange's data shows that piston C, the stopper without Parylene C that Mr. Koller says a POSA would have used, performed substantially worse in syringes with 40 µg of baked-on silicone oil than in syringes with 500 µg of oily silicone oil, particularly with respect to the break loose effect (the increase in break loose force over time) and the gliding force S. Example 2 and Example 3 of Boulange are identical experiments except that in Example 2 the syringes had 500 µg of oily

silicone oil on the interior of the barrel, while in Example 3 the syringes had 40 µg of baked-on silicone oil. In each example the silicone oil was also applied to the stoppers in amounts ranging from 5 to 50 µg/cm^2. The results of the break loose force ("BLF") measurements (Force B) from the two experiments for the two non-Parylene stoppers are compiled below:

Piston	Si Oil on Piston	Si Oil on Syringe	BLF at T=0 (N)	BLF at T=1 (N)	Increase in BLF (N)	% BLF Increase
C	5 µg/cm^2	500 µg	3.8	5.0	1.2	32%
		40 µg	**4.7**	**8.4**	**3.7**	**79%**
	15 µg/cm^2	500 µg	3.6	4.7	1.1	31%
		40 µg	**4.2**	**7.5**	**3.3**	**79%**
	50 µg/cm^2	500 µg	3.6	4.8	1.2	33%
		40 µg	**3.9**	**7.8**	**3.9**	**100%**

See Ex. 1008 at 17:25–19:10 (Tables 4 and 5). The break loose forces and increases over time are even greater for stopper A. *Id.* Boulange thus observed significantly greater increases in break loose force in the syringes with 40 µg of baked-on silicone oil than in the syringes with spray-on silicone oil. For pistons A and C, at all time points the gliding force S was also much higher in the syringes with 40 µg of silicone oil than in the syringes with 500 µg of silicone oil. *Compare* Ex. 1008 at 17:25–18:1 (Table 4) *with* 19:1–3 (Table 5).

42. Example 5 of Boulange discloses the results of a similar experiment, except no additional silicone oil was applied to the stoppers (only the syringe barrels had silicone oil applied). In this experiment, the difference in the break

loose effect between the syringes with 500 µg of oily silicone oil and those with 40 µg of baked-on silicone oil was even more dramatic:

Piston	Si Oil on Piston	Si Oil on Syringe	BLF at T=0 (N)	BLF at T=1 (N)	Increase in BLF (N)	% BLF Increase
C	0	500 µg	4.2	5.4	1.2	29%
		40 µg	**3.9**	**14.4**	10.5	**269%**

See Ex. 1008 at 21:1–3 (Table 7). The results were similar for piston A, and, again, for both pistons A and C the gliding force S was also much higher in the syringes with 40 µg of silicone oil than in the syringes with 500 µg of silicone oil. *See id.*

43. The premise of Petitioner's argument and Mr. Koller's opinions concerning Boulange is that a POSA would have relied on Boulange to reduce the amount of silicone oil used in syringes from typical prior art levels, i.e., from well above 100 µg (e.g., 500 µg) to below 100 µg as claimed in the '631 patent. But according to Boulange, without Parylene C, the syringe forces, particularly the increase in break loose force after just one month of aging,[2] are substantially worse

[2] As I explained in my Initial Declaration, the aging conditions used in Boulange were standard accelerated aging conditions used for testing shelf-life stability of drug products and medical devices, and not "extreme conditions… to assess the worst-case performance" of the PFS as Mr. Koller stated in his declaration. *See*

when the silicone oil is reduced from 500 µg per syringe to 40 µg, even when using baked-on silicone oil. These data would have deterred a POSA from using those syringes in a PFS filled with a VEGF-antagonist for intravitreal injection because physicians need syringes with low and consistent forces in order to safely administer intravitreal injections. Moreover, a POSA would have known that the break loose force may continue to rise over the shelf life of the PFS. Indeed, the only data in Boulange for longer time points—measured forces for stopper A after three and five months (i.e., T=3 and T=5) disclosed in Table 7—shows just such a continued increase in break loose force over time, reaching 17.2 N and 20.5 N after three and five months, respectively. *See id*.

44. Furthermore, the data in Boulange are inconsistent with the reasons that Mr. Koller provides for why a POSA would be motivated to use baked-on siliconization. According to Mr. Koller, "[b]aked-on siliconization reduces the amount of silicone oil that is applied to the syringe tenfold" and a "baked-on syringe… retains the break loose and slide forces achieved by an oily syringe, but

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Ex. 2001 ¶ 86 n.8 (addressing Ex. 1003 ¶ 143). In his deposition, Mr. Koller confirmed that Boulange's use of accelerated aging is a standard approach and that the one-month timepoint approximates the effect of three months of storage in normal conditions. Ex. 2189 at 134:14–135:15.

provides the benefit that the break loose force remains relatively constant over time (even after storage), which is not true of an oily syringe." Ex. 1003 ¶ 71. Mr. Koller further states that it would have been understood by a POSA that "reducing the break loose effect is generally desirable in a pre-filled syringe, but is particularly relevant for intravitreal administration on account of the potential damage that can occur in the eye." *Id.* ¶ 166. Based on the data in Boulange, however, the "break loose and slide forces achieved by an oily syringe" were not retained when the amount of silicone oil on the barrels was reduced to 40 μg per syringe using baked-on silicone oil. And significantly, the break loose effect was substantially *worse* in the low-silicone oil baked-on syringes, which, as Mr. Koller observed, would have been particularly relevant for intravitreal administration. In his deposition, Mr. Koller confirmed that the data in Boulange show a greater break loose effect for Boulange's baked-on syringes with 40 μg of silicone oil than for the oily silicone syringes with 500 μg of silicone oil. *See* Ex. 2189 at 151:4–156:2.

45. Much of Mr. Koller's opinions concerning a POSA's motivation to rely on Boulange are based on Boulange's use of baked-on silicone oil and general benefits of baked-on siliconization. But Mr. Koller relies on several benefits of baked-on siliconization as motivating a POSA to use the Boulange's baked-on syringes that—like the reduction of free silicone oil—do not depend on the use of

reduced amounts of total silicone oil.[3] And the data in Boulange suggest that the benefits of baked-on siliconization may *not* be realized when total silicone oil is reduced. *See* Ex. 1003 ¶¶ 163–65. Therefore, even if a POSA would have been generally motivated to use baked-on siliconization to achieve the benefits identified by Mr. Koller, Boulange would not have motivated the POSA to do so with the amount of total silicone oil that Boulange used. For example, as discussed above, Mr. Koller asserts that reduction of the incidence of the break loose effect would motivate a POSA to use baked-on siliconization. But, as discussed above, the Boulange data shows that without Parylene C, this benefit is not just lost but reversed when less silicone oil is used. Mr. Koller also asserts that "[b]aked-on siliconization as disclosed in Boulange was also known to be specifically advantageous to protein formulations (such as VEGF-antagonist solutions) because the baking attaches the silicone oil to the inner surface of the syringe barrel, which reduces the amount of 'residual' or 'free' silicone oil that can enter the protein formulation and cause negative effects." Ex. 1003 ¶ 165. But, as discussed above,

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[3] Mr. Koller's opinions appear to equate use of baked-on silicone oil with use of less total silicone oil. But, as discussed above, the prior art does not support this inference; the prior art focuses on reduction of free, i.e., non-bonded silicone oil, not total silicone oil. *See* § V.A, above.

"residual" or "free" silicone oil is distinct from total silicone oil, and thus this benefit does not require the use of less silicone oil overall. This benefit, therefore, would not have motivated a POSA to use a syringe with baked-on silicone oil in the amounts of Boulange's 4 μg/cm^2 syringes. A POSA would have understood that these benefits could be achieved by using baked-on silicone oil with higher total amounts, which would not have risked the deleterious effects of the low-levels of baked-on silicone oil that Boulange observed.

46. Furthermore, regardless of whether the claims of the '631 patent require the syringes to maintain the claimed break loose force over time, a POSA would not be motivated to use a PFS for intravitreal injection unless it had at least some shelf-life stability. It takes time for a PFS to reach physicians and patients after manufacturing is complete, and the PFS and its contents must be sufficiently stable over this time period. Otherwise it would be impossible to actually supply the usable PFS to a physician. In his deposition, Mr. Koller agreed that it would realistically take at least a week after a PFS is filled, packaged, and terminally sterilized for it to reach a physician, and often much longer than that. *See* Ex. 2189 at 104:14–106:18. Therefore, the need for at least some stability would impact a POSA's motivation to rely on Boulange to make a PFS filled with a VEGF-antagonist. A POSA would not have been motivated to use a syringe that deteriorates to the extent that the non-Parylene C syringes in Boulange did.

3. A POSA Would Not Have Been Motivated to Combine Sigg's VHP Method with Syringes From Boulange

47. Mr. Koller and Petitioner argue that a POSA would have been motivated to use the VHP sterilization method discussed in Sigg to sterilize Boulange's syringes filled with a VEGF-antagonist. Pet. at 27, 31; Ex. 1003 ¶¶ 127, 159–60. I disagree. As discussed in my Initial Declaration, a POSA would have recognized that Sigg expressly limits the applicability of the VHP method to "very few" syringes, but does not teach the POSA how to identify or design a suitable syringe. *See* Ex. 2001 ¶¶ 106–08.

a. *Terminal Sterilization with Sterilizing Gases Requires a Different Level of Seal Integrity to Protect the Drug Product Than Is Required for General Syringe Function*

48. As discussed in my Initial Declaration, there is an important distinction between the tightness of seal required to have a usable syringe (i.e., a syringe capable of normal syringe function with acceptable plunger forces) and the tightness needed for terminal sterilization of a PFS using sterilizing gases. *See* Ex. 2001 ¶¶ 134, 156–59. In all working syringes, including PFSs, the interface between the stopper and the syringe barrel must create a seal that is tight enough to prevent liquid from leaking out the back of the syringe (i.e., through the interface between the stopper and barrel) when the syringe is used. Normal use of a syringe entails depressing the plunger to force the liquid contained inside through a needle with smaller diameter than the interior of the syringe barrel. This is done by

exerting force on the back of the plunger, which transmits it to the stopper (e.g., the user's thumb presses the back of the plunger). This force puts pressure on the liquid inside the syringe, forcing it out through the needle. The seal between the plunger and the barrel must be tight enough such that this pressure does not cause the liquid to leak out the back of the syringe through the interface of the stopper and the barrel, and instead goes out of the syringe only through the needle at the opposite end. A PFS must also remain airtight under normal storage conditions to prevent evaporation of water and exposure of the drug to oxygen.

49. However, there is a distinction between the seal necessary for a functional syringe and the seal necessary for terminal sterilization of a PFS. Gases such as VHP and EtO that are used in terminal sterilization can penetrate into some spaces that liquids such as water cannot. Water has a relatively high surface tension, which means that aqueous solutions in particular are less susceptible to leaking than pressurized gases. During sterilization processes, medical devices being sterilized are generally exposed to sterilizing gases under elevated pressures, which further acts to force gases into tight spaces such as the interface between the stopper and syringe barrel of a PFS. To achieve high levels of sterility, the sterilization process must be designed such that the gas fully accesses all exterior spaces that might be non-sterile at the outset, but may be difficult for gases to access. *See* Ex. 1016, Nema Vol. 2 at .211, .227–.228; Ex. 1045, Leventon at .002.

For example, sterilizing agents must reach the spaces in and around the exterior of the luer-lock tip and tip cap, the interior of the syringe behind the stopper (i.e., within the syringe barrel but outside the drug compartment), and throughout the interior of any secondary packaging being used. This requirement limits the extent to which concerns about gas ingress can be addressed by reducing the harshness of sterilization conditions.

50. Moreover, in addition to the potential for sterilizing gases to permeate through the interface between the stopper and syringe barrel, another aspect of the "tightness of the system" needed to allow terminal sterilization is avoiding movement of the stopper in the barrel during sterilization. *See* Ex. 1001, '631 patent at 2:64–3:14. Stopper movement during sterilization can undermine the sterilization process and/or cause damage to the drug product. For example, stopper movement could cause the stopper to cover portions of the barrel that need to be sterilized such that they are not sufficiently exposed to sterilizing gas for complete sterilization. If the movement is significant enough, the drug product within the syringe may be exposed to portions of the syringe barrel interior that had been behind the stopper and may be non-sterile, resulting in "breaching of the sterility zone" and possible contamination of the drug product. *See* Ex. 1001 at 3:9–11.

51. As the ’631 patent explains, stopper movement can result from changes in volume of bubbles inside the syringe caused by changes in pressure during the sterilization process. Ex. 1001 at 3:4–9. Air bubbles are often trapped inside PFSs,[4] and VHP sterilization involves substantial changes in pressure as part of the sterilization process. *See, e.g.*, Ex. 1016.221; Ex. 1007 at 3:17–19, 14:9–14. Furthermore, problems associated with stopper movement are exacerbated by greater fluctuations in pressure, and one of the main disclosures of Sigg with respect to VHP sterilization is the use of pressure variations during sterilization, including exposing the syringes to vacuum conditions, to minimize the presence of residual VHP and reduce ingress. *See* Ex. 1007 at 3:19-21, 14:9–14, 15:1–5, 15:21–23. Yet Sigg neither accounts for this problem nor provides any solution. The potential for stopper movement during sterilization is also particularly

[4] *See, e.g.*, Ex. 1001 at 3:4–9; Ex. 1011, Shah at .005 (stating that “conventional methods [of syringe filling] leave a gas bubble inside the syringe”); Ex. 1009, 2008 Macugen Label at .007 (instructing user to expel all bubbles from the syringe prior to injection); Ex. 2197, Eylea 2019 PFS Label at 5–6 (instructing the same); Ex. 2044, U.S. Lucentis® PFS Administration Flashcard (instructing the same).

pronounced in syringes with very low friction forces because less force resulting from pressure changes is required to move the stopper.[5]

52. A POSA also would have known that vaporized hydrogen peroxide is toxic, and terminal sterilization using sterilizing gases can also cause degradation of syringe materials and components, and the sterilant can be absorbed into syringe materials and leave toxic residues on syringe surfaces. Ex. 1016.049; Ex. 2175, Ex. 2175, Akers 2010 at .270-71. And even traces of sterilants such as VHP and EtO can cause degradation of biologic drugs. *See* Ex. 1015.248. Therefore, syringe materials must be compatible with the sterilizing agent and the sterilization process must adequately remove the sterilizing agent, which often involves exposing the articles being sterilized to vacuum and significant variations in pressure. Ex. 2175.270-271; Ex. 1007 at 3:17–19; Ex. 1045.004.

53. Based on these considerations, a POSA would have understood that a terminal sterilization process for a PFS containing a biologic product must sterilize the medical device while at the same time minimizing contact between the drug

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[5] At his deposition, Mr. Koller agreed that pressure changes during VHP sterilization can cause stopper movement, and that syringes with low break loose force are more susceptible to such movement. Ex. 2189 at 49:17–50:8, 51:14–52:22.

product and the sterilizing agent to avoid degradation of the drug product, avoid degradation of the syringe components, and avoid leaving traces of toxic substances.

54. As such, there is a critical distinction between the seal necessary for a functional syringe (i.e., one which is tight enough to prevent liquid from leaking out) and the seal necessary for terminal sterilization of a PFS (i.e., one which is tight enough to prevent sterilizing gases from contacting the drug solution and to prevent the stopper from moving).

b. *Sigg Focuses on Sterilization Processes, Not Syringe Design Necessary to Accomplish It without Impact to the Drug Product*

55. Despite the importance of the seal protecting the drug product during terminal sterilization of a PFS, Sigg is entirely focused on the sterilization *process*, i.e., the steps involved in performing the sterilization method on a filled container such as a syringe, but provides essentially no information about the container (e.g., the syringe) itself. For example, Sigg states that "[i]t has been discovered that by varying the parameters of the antimicrobial treatment, for example — temperature, humidity, treatment duration, pressure, etc., conditions are generated that prevent the leaching of VHP into the syringes." Ex. 1007 at 3:17–19. Sigg similarly states that "[i]t has now been discovered that applying post-treatment, or post-application, measures reduces or prevents the adverse effects of VHP on sensitive

solutions," and that "[p]ost application measures" can be "application of a vacuum at the end of the antimicrobial treatment in the chamber to inverse the diffusion direction of hydrogen peroxide vapors" and "neutralizing the oxidative ability of hydrogen peroxide vapors." Ex. 1007 at 14:3–18. As another example, Sigg also states that "described herein is terminal sanitization or sterilization and surface decontamination of prefilled containers within secondary packaging by tunable electron beam (low-energy beta-ray) irradiation technologies" and "the penetration depth of electron beam radiation is tunable by adjustment of the accelerator voltage of the irradiation generator." Ex. 1007 at 4:1–3, 4:8–9. Indeed, Mr. Koller's discussion of the disclosures of the Sigg reference are focused on process steps (*see* Ex. 1003 ¶¶ 83–89), as is the Board's analysis of Mr. Koller's opinions concerning the Sigg disclosures. IPR2021-0816, Paper 13, Institution Decision (Oct. 26, 2021) ("Inst. Decision") at 63–65.

56. That process information, however, would not have been sufficient for a POSA to practice the VHP sterilization method on a PFS filled with a VEGF-antagonist for intravitreal injection. As the Board determined in the Institution Decision, "terminally sterilized" as used in the '631 patent refers to sterilization of the outside of a PFS while minimizing contact between the drug product within the PFS and the sterilizing agent being applied. Inst. Decision at 34. By 2012, VHP sterilization was a well-known method for sterilization of medical devices in

general. While the procedural steps for conducting the sterilization are important for a POSA, a POSA would also need to know how to design a syringe that could withstand the sterilization process while minimizing contact between the sterilizing agent and the VEGF antagonist drug contained within and balance this requirement with low syringe plunger force and adequate sterilization. Sigg does not provide any such design information. Nor does any other art relied upon by Petitioner or Mr. Koller.

57. The existence of the problem that is the focus of the Sigg reference—ingress of sterilizing gases into the syringe interior—underscores the importance of syringe design to practice the terminal sterilization method on a PFS. As part of the background discussion, Sigg acknowledges that although "[v]arious methods of sterilization of medical devices are known,… not all methods work with syringes, especially syringes prefilled with a drug or protein solution." Ex. 1007 at 1:18–19. With respect to cold sterilization using ethylene oxide ("EtO") or VHP in particular, Sigg states that "[d]iffusion of gas into the product container affects the stability of the drug product through chemical modification by gas vapors, such as alkylation and oxidation." Ex. 1007 at 2:11–12. *See also* Ex. 1007 at 13:30–14:2 ("It has been determined that with sensitive solutions, such as protein solutions, leaching of vaporized-hydrogen peroxide into the prefilled container is detrimental to the molecular integrity of the solutions because hydrogen peroxide vapors that

enter the container cause chemical modifications of the solution, such as oxidation."). A POSA reading these statements would have understood that syringes that are able to function as containers for a drug product, i.e., have sufficient integrity as a container to hold the drug product without leaking, may nevertheless be unable to prevent diffusion of gases into the syringe interior during or after sterilization. As a result, Sigg states that "[d]ue to the sensitive nature of certain drug products, such as proteins, it is not possible to perform terminal sterilization and surface decontamination of containers filled with such products using current methods, like… cold sterilization." Ex. 1007 at 2:20–23.

c. *Sigg Does Not Provide Information That Would Be Necessary to Successfully Terminally Sterilize a PFS Filled with a Sensitive Drug*

58. In addition to describing efforts to develop process steps to help reduce ingress of sterilizing agents into drug containers, Sigg also states that it "has been found that among the commercially available primary packaging components, there are only very few packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gases into the pharmaceutical liquid enclosed by the prefilled container." Ex. 1007 at 3:27–30. As discussed in my Initial Declaration, Sigg thus recognizes and makes clear that most syringe designs are not suitable for use with the described VHP methods, but

Sigg does not identify any examples of suitable syringes or even features of syringes that are suitable. *See, e.g.*, Ex. 2001 ¶¶ 70–73, 108, 152.

59. A POSA would have understood that Sigg's discussion of commercially available packaging components also acknowledges the distinction between the tightness of seal required to achieve basic syringe function versus the seal required for terminal sterilization with VHP. A POSA would have understood that, in this context, "commercially available primary packaging components" includes commercially available prefilled syringe systems and prefilled syringe components, such as "off the shelf" prefilled syringe systems. A POSA would further expect any commercially available syringe to have the basic functional properties needed to perform its intended function. For prefilled syringes, this would mean providing a tight enough seal to contain a liquid in the syringe and expel the liquid during injection without leaking out the back of the syringe and remain airtight to protect the contents under normal storage conditions.

60. A POSA would have thus understood Sigg's acknowledgement of the existence of commercially available syringes that are able to function as syringes but do not "provide the required tightness of the system such as to avoid ingress of sterilizing gasses" as confirmation that there is a difference in the seals required for these different functions. Accordingly, a POSA also would have understood that all but "very few" syringes satisfy the requirements of the former but not the latter.

Mr. Koller's statement that "components that are capable of making the tight seal required for terminal sterilization" were "readily available" (*see* Ex. 1003 ¶ 124 n.15) is thus inconsistent with Sigg itself.

61. Notably, although Sigg acknowledges that terminal sterilization requires greater "tightness of the system" than syringes generally, Sigg does not teach a person of skill in the art how to identify syringes that would work with the disclosed sterilization process. As discussed in my Initial Declaration, Sigg's disclosures thus do not include teachings that would be necessary for a POSA to terminally sterilize a PFS filled with a sensitive drug such as a VEGF-antagonist, particularly a PFS with low syringe forces for intravitreal injection, while minimizing contact between the drug and the sterilizing agent. Ex. 2001 ¶¶ 106-108, 175–79.[6]

62. Mr. Koller's further assertion that "Sigg teaches a POSITA that the VHP technique is broadly applicable to pre-filled syringes" (Ex. 1003 ¶ 184 (citing Ex. 1007 at 8:21–25)) contradicts Sigg's clear statement to the contrary. Mr. Koller misreads the only passage from Sigg that he cites in support of his assertion.

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[6] At his deposition, Mr. Koller agreed that Sigg does not provide any specifics about packaging material combinations and that the examples do not disclose a variety of aspects of the syringe design. Ex. 2189 at 48:6–49:16, 53:1–54:16.

The cited passage states that "Fig. 1 [a cartoon of a PFS] shows one exemplary prefilled container, however, it will be understood by those skilled in the art that various containers, *other than a syringe*, are also suitable." Ex. 1007 at 8:24–26 (emphasis added). This statement in Sigg does not negate the clear disclosure that "very few" syringe components are compatible, or suggest that the sterilization methods are "broadly" applicable to pre-filled syringes, but is rather a statement that, in addition to the "very few" suitable syringes, the VHP method can be used to sterilize *other* kinds of containers. Sigg defines "container" as including "vials, syringes, bags, bottles, or other means useful for storage of medical treatments, such as drug products, whether in solid or liquid form, and other biological agents, such as peptides, proteins or recombinant biologicals, whether in solid or liquid form." Ex. 1007 at 5:30–6:2. Notably, the sterilization of the other types of containers listed does not pose the same challenges associated with maintaining mechanical function of a syringe (e.g., low and consistent plunger forces) while also establishing the necessary "tightness of the system" required for terminal sterilization.

d. *Sigg Does not Teach That the VHP Sterilization Was Successful*

63. Moreover, Mr. Koller and Petitioner's arguments regarding Sigg are based on use of the VHP sterilization method. *See, e.g.*, Pet. at 26–27; Ex. 1003 ¶ 127. But Sigg discusses two different sterilization methods: the VHP method used

in Example 1 (*see* Ex. 1007 at 20:10–21:11), and the beta irradiation method used in Example 2 (*see* Ex. 1007 at 21:12–23:20). Neither Petitioner nor Mr. Koller suggests that a POSA would have considered using beta irradiation, but neither provides any rationale for why a POSA would have selected the VHP method over beta irradiation.

64. Example 1, which uses VHP, provides virtually no information about the VHP sterilization process used—the only information was that there were untreated control syringes, and syringes that were "treated with a vaporized hydrogen peroxide sterilization treatment in a chamber, either by a single pass through a VHP sterilization procedure or two passes … through a VHP sterilization procedure." Ex. 1007 at 21:10–21:14. Example 1 also provides no characterization of the sterilization—no data concerning the amount of VHP to which the syringes were exposed, and no data concerning the sterility of the syringes following VHP treatment. Ex. 1007 at 21:10–22:11. A POSA would not know from Sigg's disclosure in Example 1 what level of exposure to VHP the syringes had received, nor even whether the process actually worked to kill microbial contamination and to what degree. In contrast, Example 2, which discusses sterilization by beta irradiation of various containers made of different materials, at least discloses characterization of the radiation dose that reached the interiors of some of the containers.

65. A POSA would have recognized the deficiencies of Sigg's teachings, and would not have been motivated to use Sigg's VHP sterilization method to terminally sterilize a particular PFS (such as those used in Boulange) without the missing information about whether the syringe would be suitable. Furthermore, Boulange mentions nothing about using VHP to sterilize its syringes. As discussed below in Section V.C.3.d, the only sterilization method mentioned in Boulange is "ionizing radiation," and that discussion is in the context of sterilizing syringe components prior to aseptic filling, not terminal sterilization. *See* Ex. 1008 at 4:3–5. Nothing in Boulange suggests that the authors had considered terminal sterilization of any of the syringes they used, or that the syringes would be suitable for terminal sterilization. A POSA would not assume that any syringe was compatible with VHP sterilization unless specifically designed for that purpose. The brief mention of sterilization of syringe components in Boulange would not have motivated a POSA to terminally sterilize any syringe from Boulange.

4. A POSA Would Not Have Been Motivated to Use Lam's EtO Method With Syringes From Boulange

66. Mr. Koller and Petitioner argue that a POSA would have been motivated to use the EtO sterilization method discussed in Lam to sterilize Boulange's syringes filled with a VEGF-antagonist. Pet. at 55; Ex. 1003 ¶¶ 248,

250.[7] I disagree. As discussed in my Initial Declaration, Lam expressly limits the EtO sterilization method to objects having an "ethylene-oxide-impermeable interior space," but does not teach the POSA how to identify or design a syringe that satisfies this requirement. *See* Ex. 2001 ¶¶ 76–80, 167–68. A POSA would have recognized Lam's shortcomings and would not have been motivated to use the EtO sterilization method of Lam to sterilize syringes as described in Boulange and filled with a VEGF-antagonist.

a. *Lam Focuses on the Process of EtO Sterilization, Not Syringe Design*

67. Like Sigg, Lam is entirely focused on the sterilization *process*, i.e., the steps involved in performing the sterilization method on a filled container such as a syringe, but provides little information about the container itself.

68. For example, Lam states that its "invention relates to *methods* for surface-sterilizing objects containing ethylene oxide-sensitive, temperature-sensitive compounds, such as biological molecules." Ex. 1029, Lam at 2:1–2

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[7] Petitioner and Mr. Koller both assert that a POSA would have been motivated to combine Lam and Boulange for the same reasons as Sigg and Boulange. Pet. at 55; Ex. 1003 ¶ 248. Neither Petitioner nor Mr. Koller articulate any separate basis for a POSA to combine Lam and Boulange.

(emphasis added). Lam further explains that the work disclosed in the patent application entailed "experiments to identify whether there were *parameters for EtO sterilization* that would effectively sterilize the surface of an object but which do not damage an ethylene-oxide-sensitive, temperature-sensitive compound contained inside" (*id.* at 13:12–14) that resulted in "the surprising discovery of ethylene-oxide-based *sterilization conditions* that will effectively sterilize the surface of an object" but which do not damage compounds contained inside (*id*. at 2:4–6) (emphasis added).

69. However, Lam does not provide sufficient information for a POSA to practice the EtO sterilization method to sterilize any particular syringe (including any syringe with characteristics discussed in Boulange) that is filled with a VEGF-antagonist for intravitreal injection, and that minimizes contact between the drug product and the sterilizing EtO gas. Like VHP sterilization, sterilization with EtO was well-known for sterilization of medical devices in general. And like VHP, EtO is toxic, and sterilization using EtO can cause degradation of syringe materials and components, and EtO can be absorbed into syringe materials and leave toxic residues on syringe surfaces. Ex. 1016.049; Ex. 2175, Akers 2010 at .270-71; Ex. 1015, Nema Vol. 1 at .366–.367; Ex. 1016 at .221–.222, .259–.264; Ex. 2196, ISO 10993-7 (2008). The known procedural steps for conducting EtO sterilization are important for a POSA to practice such sterilization on a PFS, but not sufficient. A

POSA would also need to know how to design a syringe that could withstand the sterilization process while minimizing contact between the sterilizing agent and the drug contained within and without interfering with adequate sterilization.

70. In addition to describing a single example of experiments to identify parameters for EtO sterilization of an object that are compatible with sterilization of the object's surface without damaging the contents, Lam makes clear that an "object" that can be sterilized with Lam's method must have "an ethylene-oxide(EtO)-impermeable interior space." *See* Ex. 1029 at 2:7–9, 3:17–18.

71. As discussed in my Initial Declaration, Lam, like Sigg, thus recognizes and makes clear that not all drug containers are suitable for use with the described EtO method. But Lam does not identify examples of suitable syringes or features of syringes that are suitable, and provides essentially no information about how to design a syringe that is suitable. *See, e.g.*, Ex. 2001 ¶¶ 77–80, 166–71. Mr. Koller asserts that "Lam teaches a POSITA that the EtO technique is broadly applicable to pre-filled syringes." Ex. 1003 ¶ 250 (citing Ex. 1029 at 2:7–9, 2:29). The passage from Lam that he cites, however, makes clear that the EtO method is limited to "object[s] having an ethylene-oxide (EtO)-impermeable interior space," a significant limitation that excludes many syringes and other containers. Ex. 1029 at 2:7–8.

72. The problem that is the focus of the Lam reference—damage to sensitive active ingredients in pharmaceutical compositions by sterilization agents such as ethylene oxide—underscores the importance of syringe design to practice the terminal sterilization method on a PFS. In the "Background of Invention" section, Lam acknowledges that sterilization of "[o]bjects used in medical applications" can be "accomplished by a variety of methods including, e.g., steam sterilization, radiation sterilization, gas sterilization (e.g. with ethylene oxide), and chemical sterilization," but those "treatments cannot be used for objects containing pharmaceutical compositions because their active ingredients are typically sensitive to them." Ex. 1029 at 1:14–18. Lam also states that "[c]onsequently, pharmaceutical compositions are generally sterilized by an alternative method, e.g. by filtration, and then packaged into separately sterilized objects," i.e., by aseptic processing. *Id.* at 1:22–23. Implicit in these statements is that attempts to use established gas-based sterilization methods to sterilize filled syringes (i.e., syringes that are able to function as containers for a drug product and have sufficient integrity to hold the drug product without leaking) have resulted in damage to the drug product caused by ingress of gases into the syringe interior. Thus, according to Lam, there "remain[ed] a need for efficient and cost-effective methods of surface-sterilizing objects containing ethylene-oxide-sensitive, temperature-sensitive compounds, such as biological molecules, without a significant adverse

effect on their activity or integrity." *Id*. at 1:29–32. This objective depends on use of an "object" that is able to prevent ingress of the ethylene oxide during the sterilization method.

b. *Lam Does Not Describe a PFS that Could Be Terminally Sterilized While Minimizing Contact between a Sensitive Drug Product and the Sterilizing Agent*

73. As discussed above, terminal sterilization with sterilizing gases requires a different level of seal integrity than is required for general syringe function. However, Lam does not provide any guidance concerning how to design a suitable syringe.

74. Lam presumes that a container, such as a filled syringe, that is suitable for sterilization with the EtO method has an "EtO impermeable interior space." Ex. 1029 at 2:7–9, 3:17–19. But Lam does not tell a POSA how to identify or design such a syringe. As discussed above, and as demonstrated by the difficulties experienced by Genentech, providing a sufficiently tight seal in a syringe is not a trivial problem. At his deposition, Mr. Koller agreed that not every combination of components would work to protect the drug product from the ingress of sterilizing gases and that a POSA would have to select suitable components. Ex. 2189 at 73:15–74:15. But he further agreed that Lam does not provide any information about the design of the syringe barrel, stopper, or plunger rod, information regarding brand or composition of the syringe barrel, or the presence or amount of

silicone oil. Ex. 2189 at 92:13. Lam thus omits critical teachings that a POSA would have needed to apply the EtO method to syringes in general, and particularly to syringes with very low syringe forces or syringes as disclosed in Boulange.

75. Moreover, Lam provides two specific examples of materials that were used for the stopper, including "a stopper comprising D777-7 laminated with FluroTec" (*see* Ex. 1029 at 2:30), and no other information about the design of the stopper (or any other part of the syringe) (Ex. 2189 at 92:13–94:11). For the syringes used in the Example, Lam does not disclose whether the syringe barrels were made of glass or some other material. Lam also provides no information about whether the barrels contained silicone oil, and if they did, what quantity.

76. Regeneron's argument and Mr. Koller's opinions that a POSA would have combined Boulange's stopper B (which is coated with Parylene C) with the method in Lam depend on replacing the stoppers used in Lam with a Parylene C-coated stopper. But neither reference provides a basis to believe that would work. FluroTec is a conventional fluoropolymer coating, which is typically applied to syringe stoppers only on the surface that is in contact with the drug product in the syringe, not on the sides of the stopper that are in contact with the barrel. Ex. 2035, Sacha 2010 at .015. Parylene C is applied to a stopper by a plasma deposition process, which results in coating the entire surface of the stopper. *See*

Ex. 1008 at 2:25–3:13; Ex. 2189 at 95:20–96:6. Mr. Koller says that a POSA would have put the Parylene C coating over the FluroTec coating on Lam's stoppers. Ex. 2189 at 95:3–19. But this makes little sense.

77. A POSA would not have believed that two different coatings could be used on a single stopper (i.e., using FluroTec *and* Parylene C on the same stopper), and putting a second coating over the FluroTec coating would rending the FluroTec ineffective and pointless. And as discussed in my Initial Declaration, a POSA would not have believed that FluroTec and Parylene C are interchangeable or that the use of FluroTec in Lam would support use of Parylene C in its place. *See* Ex. 2001 ¶¶ 122–28. Moreover, there is no indication that a fundamental change in the container, like using a stopper with Parylene C coating at the interface between the stopper and the glass barrel, would be consistent with providing an EtO impermeable interior space. Indeed, the modification required by the teachings of Boulange changes the very aspect of the device that is most relevant to achieving an "EtO impermeable interior space"—the interface between the stopper and the barrel.

78. There is also no discussion in Lam about the mechanical function of syringes, syringe forces that are suitable for intravitreal injection, or the need to maintain syringe function after sterilization. There is thus no indication in Lam that the tested syringes exhibited any particular break loose force (including the 11

N break loose force required by claim 1). Nor is there any indication that the syringe forces had been measured or even considered. A POSA would have understood that the need for a syringe to have a sufficiently tight seal to prevent EtO ingress into the drug solution during sterilization conflicts with the need to provide sufficiently low break loose and slide forces for safe intravitreal injection. In general, a tighter seal is provided by stronger interaction between the stopper and syringe barrel (e.g., by using a stopper with a tighter fit into the syringe), but the stronger interaction (and tighter seal) would tend to result in greater plunger forces, which are detrimental to use of the syringe for intravitreal injection into the human eye. A POSA must therefore balance the opposing requirements of complete sterilization, avoidance of product contamination and degradation by EtO and residues, and acceptable syringe forces for intravitreal injection. Lam provides no disclosures to a POSA regarding how to achieve this balance.

79. Like Sigg, Lam also does not address the possibility of stopper movement during sterilization, nor does Lam provide any solutions to this problem. This omission is particularly significant because Lam's method calls for multiple rounds of pressure changes as part of the sterilization process, including twice evacuating the sterilization chamber to about 5.0" HgA, i.e., subjecting the syringes to a vacuum of about one-sixth atmospheric pressure. Ex. 1029 at 13:17–

21. This level of vacuum creates a substantial risk of stopper movement, especially in a syringe with low break loose and slide force.

80. Furthermore, as Dr. Miller explains in detail, Lam does not disclose a process that can achieve an SAL of 10^{-6}. *See* Ex. 2203 ¶¶ 75–81, 89–90. On the contrary, Lam's disclosures are consistent with much less stringent levels of sterility assurance, and suggest that further sterilization would result in unacceptable damage to the drug product. *Id.* ¶ 77–78.

81. Furthermore, as discussed below with respect to enablement in Section V.C.3, neither a POSA's general knowledge nor other references that Mr. Koller cites would have filled in the gaps in information necessary to enable a POSA to practice Lam's method on a syringe from Boulange filled with a VEGF-antagonist.

5. A POSA Would Not Have Been Motivated to Make a VEGF-Antagonist Solution Having No More Than 2 Particles Greater Than 50 µm in Diameter per Milliliter

82. Mr. Koller asserts that a POSA would have "been aware of and motivated to comply with USP789" because "compliance with USP789 was highly desirable if not mandatory" in order to achieve regulatory approval. Ex. 1003 ¶ 168. Mr. Koller also asserts that it would have been obvious that "the combination of Sigg and Boulange would result in a pre-filled syringe comprising a VEGF-antagonist solution with no more than 2 particles > 50 µm in diameter per mL"

because a POSA would know that "a VEGF-antagonist solution for intravitreal administration would need to comply with USP789 for regulatory approval and thus it would need to meet the microscopic particle count test as set forth in USP789 which requires no more than 2 particles of diameter ≥ 50 μm per mL." *Id.* ¶¶ 203, 205. *See also id*. ¶¶ 265–67 (making the same assertion for the combination of Lam and Boulange). Mr. Koller does not identify any basis for motivation to achieve a solution with no more than 2 particles greater than 50 μm in diameter per milliliter or obviousness of such a solution other than the requirements of USP789. *See, e.g.*, *id.* ¶¶ 90–92, 168–70, 203–06, 252–54, 265–69. But Mr. Koller is incorrect about the requirements of USP789; having fewer than 2 particles greater than 50 μm in diameter per milliliter is not a requirement.

83. USP789 is the section of the United States Pharmacopeia about "Particulate Matter in Ophthalmic Solutions." *See* Ex. 1019.005. USP789 explains that the "tests described herein are physical tests performed for the purpose of enumerating extraneous particles within specific size ranges" in ophthalmic solutions. *Id.* USP789 describes two different methods for measuring the particle content of a solution: the "light obscuration particle count test" and the "microscopic particle count test." *See id*. Compliance with USP789 involves "a test approach in two stages": "The ophthalmic solution is first tested by the light obscuration procedure (stage 1). If it fails to meet the prescribed limits, it must

pass the microscopic procedure (stage 2) with its own set of test limits." *Id.* In other words, the two methods for measuring particle content of an ophthalmic solution have two different sets of limits, and the limits for the microscopic method are only applicable if a solution fails to meet the limits for the light obscuration method. The microscopic method limits are inapplicable to a solution that meets the prescribed limits using the light obscuration test, and such a solution need not even be tested using the light obscuration method.

84. The prescribed limits for the light obscuration test are as follows:

Table 1. Light Obscuration Test Particle Count

	Diameter	
	≥ 10 µm	≥ 25 µm
Number of particles	50 per mL	5 per mL

Id. The light obscuration test only has limits on particles greater than 10 µm in diameter (i.e., 50 per milliliter) and 25 µm in diameter (i.e., 25 per milliliter). There is no specific limit on the number of particles greater than 50 µm in diameter (other than the limits based on the smaller-sized particles), and a solution with more than two particles of 50 µm in diameter per milliliter can satisfy these limits. In contrast, USP789's limits for the microscopic particle count method are as follows:

Table 2. Microscopic Method Particle Count

	Diameter		
	≥ 10 µm	≥ 25 µm	≥ 50 µm
Number of particles	50 per mL	5 per mL	2 per mL

Ex. 1019.006. Therefore, USP789 only has a specific limit on particles greater than 50 μm in diameter for solutions that fail to satisfy the light obscuration test. And USP789 states that "[i]t is expected that most articles will meet the requirements on the basis of the light obscuration test alone." Ex. 1019.005. Mr. Koller has not provided any basis for a POSA to expect that the VEGF-antagonist solution contained in Sigg would be among the minority of solutions that would not satisfy the particle limits of the light obscuration test and then be subject to the microscopy test and its additional requirement. Mr. Koller's discussion of USP789 thus does not provide a motivation for a POSA to meet the requirement of claim 1 that the VEGF-antagonist solution have no more than 2 particles greater than 50 μm in diameter per milliliter.

6. A POSA Would Not Have Had a Reasonable Expectation of Success in Combining Boulange with Sigg or Lam

85. In addition to not being motivated to combine Sigg or Lam with Boulange, a POSA also would not have had a reasonable expectation of success in combining Boulange with Sigg or Lam to make a terminally sterilized PFS filled with a VEGF-antagonist for intravitreal injection. A POSA would have recognized the express limitations of the sterilization methods discussed in Sigg and Lam—i.e., that the methods are limited only to syringes that provide sufficient tightness to avoid sterility breach and ingress of damaging gas. Because neither Sigg nor Lam addresses how to design a syringe that is suitable for terminal sterilization—

particularly one with sufficiently low syringe forces to be suitable for intravitreal injection—a POSA therefore would not have reasonably expected to succeed in applying Sigg and Lam's sterilization methods. And nothing in Boulange would provide a POSA with a reasonable expectation of success. Boulange does not suggest that its syringes were specifically designed for terminal sterilization after filling or that its syringes are suitable for that purpose, and Boulange does not provide the design details missing from Sigg or Lam that are needed to make a PFS that can be terminally sterilized in accordance with the claims of the '631 patent.

86. The invention described in Boulange is the use of Parylene C coated stoppers, and a POSA would not have expected to succeed in using Parylene C-coated stoppers in a PFS filled with a VEGF-antagonist that would be suitable for intravitreal injection. As discussed above and in my Initial Declaration, materials must meet a variety of stringent requirements to be suitable for use in primary packaging for pharmaceuticals, particularly for sensitive applications such as for injectable drugs, ophthalmic drugs, and biologic drugs. *See* Ex. 2001 ¶¶ 117–21; § V.B.1, above. But, as discussed in my Initial Declaration, a POSA would not have had a basis in the prior art to expect that Parylene C would meet a number of different requirements to be suitable for use in a PFS containing a biologic drug such as a VEGF-antagonist that would be used for ophthalmic injection, and in fact

information in the prior art indicates that Parylene C would not be suitable for a number of reasons. Ex. 2001 ¶ 121.

87. I have reviewed the declaration of Dr. John Dillberger. Dr. Dillberger is a toxicologist with experience in safety evaluation of drug products and pharmaceutical packaging. Ex. 2002 ¶¶ 3-8, Exhibit A. He is a type of person that a POSA designing a syringe would consult with as part of the development of a PFS like the one claimed in the '631 patent.[8] In my experience, I have consulted with experts in toxicology like Dr. Dillberger on questions of the suitability of materials for use in medical devices and related concerns about toxicity, leachables, and extractables. In his Declaration, Dr. Dillberger has further elaborated on the requirements of a primary packaging material for this application and the reasons why a POSA would not have reasonably expected Parylene C to satisfy them. *See generally,* Ex. 2202. And for a syringe that would be terminally sterilized by VHP or EtO, Parylene C would further need to be compatible with the gases and to provide a sufficiently tight seal to prevent gas ingress despite pressure

[8] In his deposition, Mr. Koller confirmed that companies developing PFSs generally have toxicologists "in-house" to address questions concerning potentially toxic compounds that can be extracted from packaging materials. *See* Ex. 2189 at 109:5–110:3.

variations during the sterilization process. The prior art identified by Mr. Koller and Petitioner do not provide a POSA with a reasonable expectation that Parylene C would be compatible.

88. Mr. Koller responds by asserting that a POSA would have expected to succeed by using the control syringes disclosed by Boulange, i.e., the syringes that do not include Parylene C. I disagree. A POSA also would not have reasonably expected to succeed in using those syringes either. Boulange found the syringes to be markedly inferior and not acceptable for a medical device, as discussed in my Initial Report. *See* Ex. 2001 ¶ 89. Mr. Koller agreed at his deposition that, at a minimum, a POSA would not have found these statements to be motivating. Ex. 2189 at 147:8–148:4. Not only does Boulange expressly tell the POSA that the non-Parylene C syringes are not acceptable, but the data show that those syringes have significantly higher forces than the Parylene C syringes, and that the forces increase dramatically during just one month of aging. A POSA would have known that for patient safety, a PFS for intravitreal injection must have low and consistent forces. Ex. 2204 ¶¶ 67-73.[9] A POSA would have further known that, after

[9] Dr. Calman is an ophthalmologist who regularly administers VEGF antagonists to patients by intravitreal injection as part of his practice. Ex. 2204 ¶¶ 3-12. A POSA

manufacturing, it takes time for a PFS to reach healthcare providers and patients—they simply cannot be used immediately after manufacturing is complete. Ex. 2189 at 104:14–106:18. And a POSA would have further known that viable drug products and medical devices must have some reasonable shelf life during which the properties and functions of the products are consistent and acceptable. A POSA would not have reasonably expected a PFS whose forces change as dramatically as Boulange's non-Parylene C syringes do to be usable in a PFS with a VEGF-antagonist for intravitreal injection. Ex. 2204 ¶¶ 71-73.

89. Petitioner also argues that a POSA would have expected Boulange's syringe to be "compatible with known sterilization processes" and that "Parylene C would not interact negatively with drug products (e.g., VEGF-antagonists)" because Boulange is a patent application owned by Becton Dickinson, "a world leader in pre-filled syringe design." Pet. at 38. Petitioner's argument ignores the fact that Becton Dickinson, one of the largest syringe manufacturers in the world, makes many different syringes for many different purposes. And specialized syringe designs are often required for specialized applications, especially applications that involve particular challenges such as prefilled syringes for

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developing a PFS for intravitreal injection of a VEGF antagonist would have consulted with a person with Dr. Calman's qualifications.

sensitive biologic drugs that are terminally sterilized and used for delicate modes of administration like intravitreal injection. That Boulange is a Becton Dickinson patent application (which never issued as a patent) would not have suggested to a POSA that the syringes discussed therein, including the Parylene C syringes, are suitable for any particular purpose (e.g., containing a VEGF-antagonist or being terminally sterilized) that is not expressly discussed in the application.

90. Mr. Koller also cites to a patent by Wittland as support for a reasonable expectation of success in using Lam's EtO terminal sterilization method. *See* Ex. 1003 ¶ 250 (citing Ex. 1026). But Wittland addresses a completely different issue—the use of EtO to sterilize unfilled syringe barrels *prior to filling*, such that the barrels are ready to be filled under aseptic conditions. *See, e.g.*, Ex. 1026 at 1:16–17 ("The invention relates to a method for producing *prefillable* syringes.") (emphasis added), 4:9–19 (describing "syringe bodies," i.e., *unfilled syringe barrels*, being placed in a tray and being "sterilized, in particular with gas, for example ethylene oxide"), 4:37–54 (claim 1, the sole independent claim claiming "a method for producing *prefillable* syringes," i.e., syringes designed for use as a PFS but not yet filled) (emphasis added). Wittland says nothing about the challenges of terminally sterilizing a prefilled syringe containing a VEGF-antagonist and having low syringe forces and gives a POSA no indication that its disclosures are applicable to terminal sterilization. As discussed above and

in my Initial Declaration, the use of EtO and other sterilizing gases to sterilize syringe components prior to assembly and filling of the syringes was well-known in the art. *See* Ex. 2001 ¶¶ 45, 49–50; *see also* Ex. 1015.315. Wittland thus adds nothing to a POSA's expectation of success in combining Lam and Boulange to arrive at the invention claimed in the '631 patent.

91. For all of the reasons stated above, it is my opinion that a POSA would not have been motivated to combine Sigg or Lam with Boulange to make the invention of independent claim 1 of the '631 patent, nor would they have had a reasonable expectation of success in doing so. Accordingly, claim 1 would not have been obvious. I further understand that dependent claims incorporate all of the limitations of the independent claim from which they depend, and that if the independent claim is not obvious, its dependent claims are likewise non-obvious for at least the same reasons. As all of claims 2–26 depend from claim 1, those claims would likewise not have been obvious.

C. Sigg Does Not Enable Terminal Sterilization of a PFS While Minimizing Contact between the Drug Product and the Sterilizing Agent

92. Sigg concerns methods for terminally sterilizing the exteriors of pre-filled containers containing pharmaceutical products. *See* Ex. 1007. Mr. Koller's opinions that the claims of the '631 patent are obvious are premised on his mistaken understanding that a POSA would have been able to apply the

sterilization method discussed in Sigg to PFSs for intravitreal injection of VEGF antagonists in small volume syringes, having unconventionally low levels of silicone with reliable mechanical forces as required by the claims, and that a POSA would thus have been able to design a syringe suitable for this purpose. But, as discussed in my Initial Declaration and above with respect to motivation to use Sigg's VHP method, Sigg does not teach a POSA how to do this.

93. As discussed above, terminal sterilization with sterilizing gases such as VHP requires a different level of seal integrity to protect the drug product than is required for general syringe function. For terminal sterilization, the syringe must prevent gas ingress and stopper movement despite exposure to high and low pressure extremes. Sigg acknowledges that only "very few" syringe components provide the necessary seal, but Sigg focuses only on the sterilization process, not the syringe design necessary to accomplish it without impact to the drug product. And the other prior art cited by Petitioner and Mr. Koller does not supply the missing information. Thus, the prior art (including Sigg) do not provide information that would be necessary to successfully terminally sterilize a PFS filled with a sensitive drug such as a VEGF antagonist.

94. Furthermore, real-world evidence demonstrates the difficulty with designing a syringe tight enough for a VHP process. Mr. Koller's assertions that the invention claimed in the '631 patent is the result of a simple combination of

known technologies (Sigg and Boulange), and that a POSA would have expected success, are at odds with the objective evidence of the difficulty companies actually faced in developing a terminally sterilized PFS for intravitreal administration of a VEGF-antagonist. The real-world experiences of companies trying (and failing) to develop terminally sterilized PFSs demonstrates, for example, the significance of the distinction between the "tightness of the system" needed for general syringe function and the tightness needed to terminally sterilize a PFS filled with a sensitive drug and having low syringe forces and shows how Mr. Koller's analysis of the prior art is based on hindsight that ignores the actual difficulty facing a POSA at the time.

1. Novartis's unsuccessful attempts to implement Sigg's VHP process

95. Dr. Sigg's and Novartis's experience developing a terminally sterilized Lucentis PFS demonstrates the shortcomings of Sigg's disclosures. Dr. Sigg's declaration and the documents that he cites therein show that, despite considerable effort, Novartis was actually unsuccessful in its efforts to develop a Lucentis PFS that is terminally sterilized using the VHP sterilization method discussed in Sigg. Ex. 2206 ¶¶ 30–40. Novartis's unsuccessful attempts to implement Sigg's VHP process confirm that a POSA would not have been able to make and use the claimed invention based on the disclosures of Sigg.

96. [redacted]

97. When Dr. Sigg and Novartis originally filed the Sigg application, they thought that it might be possible that the VHP sterilization would work in view of the information included in the application. Ex. 2206 ¶ 33. [redacted]

[10] The earliest priority application for Sigg was filed in June 2009. Ex. 1007.001.

[redacted] Novartis abandoned both the efforts to use VHP sterilization with the syringes they were using at the time, and the Sigg patent application, and instead focused on developing EtO sterilization. Ex. 2206 ¶ 38.

98. Therefore, despite about two years of additional work after the filing of the Sigg application, Novartis was unable to devise a working VHP sterilization process derived from the process disclosed in the Sigg application. This failure demonstrates that undue experimentation would have been required for a POSA—and even for Dr. Sigg, author of the Sigg reference—to use the VHP sterilization method discussed in Sigg to terminally sterilize a PFS with a VEGF-antagonist for intravitreal injection. As discussed below, it was not until after Novartis redesigned the stopper and plunger rod of the syringe that the inventors were able to achieve a validated sterilization process for syringes with low forces and an adequate sterility assurance level.

99. The inventors of the ’631 patent eventually overcame the critical challenges associated with terminal sterilization of a VEGF-containing PFS for intravitreal administration and disclosed in the ’631 patent key elements of their efforts that enabled their successful development of Novartis’s Lucentis PFS. In

contrast, the Sigg application neither addresses syringe design issues nor provides any enabling disclosure with respect to design of a suitable syringe.

100. [redacted]

101. The ’631 patent explains these problems:

> For small volume syringes, for example those for injections into the eye in which it is intended that about 0.1 ml or less of liquid is to be injected the sterilisation can pose difficulties that are not necessarily associated with larger syringes. Changes in pressure, internal or external to the syringe, can cause parts of the syringe to move unpredictably, which may alter sealing characteristics and potentially compromise sterility.
>
> …
>
> Furthermore, certain therapeutics such as biologic molecules are particularly sensitive to sterilisation, be it cold gas sterilisation, thermal sterilisation, or irradiation. Thus, a careful balancing act is required to ensure that while a suitable level of sterilisation is carried out, the syringe remains suitably sealed, such that the therapeutic is not compromised.

Ex. 1001 at 1:21–36. The Sigg application, in contrast, does not address these issues at all.

102. [redacted]

103. [redacted]

[redacted]

104. [redacted]

[redacted]

[redacted]

[redacted] *See also* Ex. 1001 at Fig. 5, 3:23–36, 12:11-21, 12:27-

29 ('631 patent disclosing stopper design). [redacted]

105. [redacted] The inventors' syringe design thus allowed them to develop an acceptable terminal sterilization process that provided sufficient sterility assurance without exposing the drug to excessive sterilizing gases. *Id.*

106. The '631 patent also describes these innovations and their significance for terminal sterilization. *See* Ex. 1001 at 2:57–3:62, 11:14–36, 12:15, 12:27–29,

Figs. 2, 3, 5. For example, the specification describes the backstop shoulder on the plunger rod and its purpose, (Ex. 1001 at 2:64–3:14), as well as the use of stoppers with ribs with increased spacing to create an "enhanced sterility zone" in order to facilitate sterilization and "reduce the potential exposure of the medicament to the sterilising agent." *Id.* at 3:23–36.

107. Unlike the '631 patent, Sigg provides no disclosures about the design of a syringe that is suitable for terminal sterilization after filling with a VEGF-antagonist. Furthermore, other than the simple observation that most commercially available primary packaging components do not provide the required tightness of the system needed to avoid ingress of sterilizing gases into the drug product, Sigg has no discussion of the issues related to syringe design that are important for a POSA to actually practice the VHP sterilization method. It took Dr. Sigg and the other inventors of the '631 patent years of diligent additional work after the Sigg application was filed to complete development of the Lucentis PFS, and without disclosures like those in the '631 patent, a POSA would have similarly needed to conduct undue experimentation to use the VHP method discussed in the Sigg application to sterilize a PFS filled with a VEGF-antagonist based on the teachings of Sigg.

2. Genentech's unsuccessful efforts

108. As discussed in more detail below in Section VI.A, Genentech also spent several years attempting to develop a terminally sterilized PFS for Lucentis® (i.e., a PFS filled with the VEGF-antagonist ranibizumab). Genentech is a large biotechnology company with a motivation to make a successful PFS for its Lucentis product. [redacted] There is no indication, however, that during development of its own PFS, Genentech ever had a problem with drug solution leaking from the syringes despite having inadequate tightness to prevent ingress of EtO.

109. Similarly, as discussed in more detail above, Dr. Sigg's and Novartis's efforts to develop a VHP sterilization method based on the work disclosed in Sigg were unsuccessful, and Novartis's eventual success in developing a terminally sterilized PFS involved significant design changes to the syringe components to address syringe tightness issues, as disclosed in the '631 patent. *See* § V.C.1.

3. Neither a POSA's General Knowledge nor Other References Cited by Mr. Koller Would Have Enabled a POSA to Practice Sigg's Method on a Syringe from Boulange

110. Mr. Koller acknowledges that to use gas sterilization on a PFS, "the syringe itself would have to be sufficiently closed off to prevent substantial amounts of the sterilizing gas from coming into contact with the drug formulation within." Ex. 1003 ¶ 87. But, notwithstanding Sigg's clear disclosure that only particular syringes are compatible with the sterilization method and that most commercially available syringes are not, Mr. Koller asserts that components "capable of making the tight seal required for terminal sterilization… were well-known and readily available to those of ordinary skill in the art before the '631 patent." Ex. 1003 ¶ 124 n.15.

111. If, as Mr. Koller suggests, suitable syringes were "well-known and readily available," there would be no problems associated with gas ingress during terminal sterilization—the exact problem that Sigg purports to address. Contrary

to Mr. Koller's assertion, identifying a syringe that can be sterilized according to the sterilization method discussed in Sigg would not have been straightforward as he suggests, particularly when constrained to the syringes as disclosed in Boulange, i.e., a syringe with the specific combinations of a Parylene C-coated stopper, the specific levels of silicone oil, and the measured syringe forces.

112. Mr. Koller cites two examples as support for his assertion that suitable syringes were "well-known and readily available," the Macugen PFS and an Eylea PFS that was purportedly "approved in Australia," (Ex. 1003 ¶ 124 n.15), both of which the Board relied on in finding Mr. Koller's opinions sufficient for purposes of institution. Inst. Decision at 65. But neither example supports Mr. Koller's assertion for the reasons explained below. Furthermore, other references that Mr. Koller relies on to fill in the gaps in Sigg's disclosures also would not have enabled a POSA to practice Sigg's VHP sterilization method on syringes described in Boulange.

a. *The Macugen Label*

113. As discussed in my Initial Declaration and in further detail in Dr. Miller's report, the 2008 Macugen Label on which Mr. Koller relies does not provide any information about how the Macugen PFS was sterilized and a POSA would not have inferred from the Macugen Label that the Macugen PFS was

terminally sterilized. Ex. 2001 ¶¶ 98–101; Ex. 2203 ¶¶ 95–103.[11] Moreover, even if a POSA had made the inference suggested by Mr. Koller that the Macugen PFS was terminally sterilized (which is, in my opinion, unsupported), the Macugen Label does not provide information that a POSA would need to design a terminally sterilizable syringe. Not only does the Macugen Label not provide information about how the syringe was sterilized, it also does not describe design elements that allow terminal sterilization without contact between the drug product and the sterilizing agent.

114. Mr. Koller asserts that a POSA would have understood from a minor change in the description of the secondary packaging for the Macugen PFS from "foil pouch" to "sterile foil pouch" in subsequent versions of the Macugen Label that the Macugen PFS was terminally sterilized. Ex. 1003 ¶¶ 151–153. Mr. Koller's assertion is not based on any information in the prior art he relies on. As discussed in my Initial Declaration, I disagree that a POSA would have reached

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[11] Dr. Miller is a microbiologist with extensive experience in sterilization of pharmaceutical products and medical devices. *See* Ex. 2203 ¶¶ 2–16, Appendix A. A person with Dr. Miller's qualifications would be a typical member of a medical device development team.

that conclusion or that the disclosures of the Macugen Label support such a conclusion. *See* Ex. 2001 ¶¶ 98–101.

115. First, the Macugen label says nothing about how sterility was achieved. A POSA would have known that there are multiple ways to manufacture sterile products, including aseptic filling and packaging. Furthermore, aseptic processing was common practice, particularly in the manufacture of biologic drugs, and was well-known to be able to achieve sterility in a variety of contexts. *See, e.g.*, Ex. 1036, FDA Guidance: Sterile Drug Products Produced by Aseptic Processing (September 2004) at .006–.007; Ex. 2175, Akers at .324-38. Publicly available information indicated that Macugen had been processed using aseptic filling since its launch in 2004.[12] A POSA would not have inferred that the

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[12] *See* Ex. 2056, EMA Macugen European Public Assessment Report ("EPAR") at .003 (stating that "[d]ue to the instability of the active substance to terminal sterilisation, an aseptic, filter sterilisation process has been developed…. The solution is sterilized by filtration and filled into syringes under aseptic conditions. The syringes are labelled and then packaged into a foil pouch."). The Macugen EPAR Scientific Discussion (Ex. 2056) is publicly available on the European Medicines Agency's website at https://www.ema.europa.eu/en/documents/scientific-discussion/macugen-epar-

Macugen syringe was terminally sterilized merely from the phrase "sterile foil pouch." In fact, a POSA would have believed from this phrase that the syringe was not terminally sterilized because foil is impermeable to sterilizing gases such as EtO and VHP. It would therefore not be possible to use these methods to terminally sterilize a PFS contained in a pouch made solely of foil.

116. The only rationale that Mr. Koller provides for his opinion that a POSA would think that the Macugen PFS described in the Macugen Label was terminally sterilized is the assertion that "aseptic filling and packaging of a foil pouch would be prohibitively expensive for a commercial product, if not technically infeasible." Ex. 1003 ¶ 150. But Mr. Koller provides no support for this assertion, nor any explanation for why such a process would be prohibitively expensive or technically infeasible. And Mr. Koller's assertion is contradicted by the fact that Macugen had been approved for sale using aseptic filling. *See* Ex. 2056.003.

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scientific-discussion_en.pdf. The EMA EPAR record indicates that the Scientific Discussion was first published on May 31, 2007. *See* Ex. 2279, Macugen EPAR website at .004 (available at https://www.ema.europa.eu/en/medicines/human/EPAR/macugen).

117. Furthermore, even if the Macugen Label did indicate to a POSA that the Macugen PFS was terminally sterilized, the Macugen Label still does not identify any particular sterilization method[13] and would not have helped the POSA practice the sterilization method discussed in Sigg. The Macugen Label does not describe design elements of the syringe that would be necessary to use Sigg's terminal sterilization method, nor has Mr. Koller identified any such disclosures. The Macugen Label also does not provide any information about the silicone oil content of the syringes.[14] The mere statement that a product had been terminally sterilized would not provide a POSA with any useful information on how to design a syringe to accomplish successful sterilization or any reasonable expectation of success that any particular design would be successful. And even if a Macugen PFS had been terminally sterilized prior to 2012, neither Mr. Koller nor Petitioner have identified any information about how much experimentation was needed to develop that process. As discussed above, the inventors of the '631 patent were

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[13] Mr. Koller agreed that the Macugen Label does not disclose what kind of sterilization was used. Ex. 2189 at 196:5–197:7.

[14] At his deposition, Mr. Koller agreed that the Macugen PFS had more than 100 µg of silicone oil, and indeed many times that. Ex. 2189 at 44:19–21, 184:19–22.

eventually able to make a gas sterilization process work on a syringe enabled by the specification and with the other elements of the claims of the '631 patent, but only after years of experimentation.

118. Mr. Koller also relies on the 2008 Macugen Label for its reference to a "clip." Ex. 1003 ¶ 109. Mr. Koller states that "the 2008 Macugen Label describes that the user must remove a clip from the syringe prior to use," and asserts that a POSA "would recognize that the clip would serve to prevent the plunger from moving after it is placed in its blister pack, including during a terminal sterilization process and during transportation." *Id.* (citing Ex. 1009.007). There is simply no basis in the 2008 Macugen Label for this assertion. Rather, the 2008 Macugen Label merely indicates that there is a clip somewhere on the syringe, and that the syringe should be removed from the clip before use. Ex. 1009.007. The Label provides no description of the "clip" beyond it being a "clip," which could refer to a variety of structures attaching to the syringe at multiple locations for a variety of purposes. Not only does the Macugen Label not suggest that the clip has anything to do with terminal sterilization, it does not even indicate that the clip contacts the stopper or plunger, or is able to prevent stopper movement. Mr. Koller's assertion that the "clip" that is mentioned in the label in the context of instructions for preparing the syringe for use is related to terminal

sterilization of the syringe is entirely disconnected from the Macugen Label that he relies on.

b. *The Australian Public Assessment Report for Eylea PFS*

119. Mr. Koller also relies on an Australian Public Assessment Report for aflibercept as support for his assertion that "suitable syringes were "well-known and readily available." *See* Ex. 1003 ¶¶ 124 n.15, 186 (citing Ex. 1066). I disagree. First, the Australian Public Assessment Report ("Eylea AusPAR") that Mr. Koller cites is not prior art. It is dated July 30, 2012 (*see* Ex. 1066.002), after the July 3, 2012 filing date of the earliest application to which the '631 patent claims priority;[15] less than six months before the filing date of the application that led to the '631 patent, (*see* Ex. 1001.001); and well after the inventors of the '631 patent had conceived of the invention. *See* Ex. 2001 ¶¶ 193–211; Ex. 2002. The Eylea AusPAR therefore would not have been available to a POSA and could not have contributed to enablement of Sigg's VHP method.

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[15] The '631 patent indicates that the earliest priority application, EP 12174860, was filed on July 30, 2012 (Ex. 1001.001), but I understand that this is a typographical error and the actual filing date was July 3, 2012. *See* Ex. 1035, EP 12174860 at .002.

120. Second, like both Sigg and the Macugen Label, the Eylea AusPAR provides no details to a POSA about an Eylea PFS syringe that would have enabled a POSA to design a terminally sterilized syringe. No design elements that would have been necessary for a POSA to conduct terminal sterilization are mentioned or disclosed in the Eylea AusPAR, and Mr. Koller has identified none. Furthermore, there is no indication in the document Mr. Koller identifies that the syringe met the other requirements of the claims of the '631 patent.

121. Furthermore, the AusPAR is ambiguous about the sterilization method that would be used to sterilize the Eylea PFS. *See* Ex. 1066.007. The AusPAR states that "[b]listers containing the syringe are either hydrogen peroxide (H_2O_2)-sterilised or ethylene oxide (ETO)-sterilised." *Id.*

122. Finally, there is no evidence that the Australian syringe that Mr. Koller points to was ever launched or that the makers were actually successful in making a syringe that could be marketed to physicians to treat patients. Notably, I understand that, just like in the United States and Europe, no Eylea PFS was actually marketed in Australia until years later, no earlier than 2019. *See* Ex. 2278 (2020 article discussing Bayer's recent announcement of the "introduction of the prefilled syringe" for Eylea in Australia); Ex. 2036 (same). Mr. Koller provides no evidence that the syringe was available and confirmed at his deposition that it was not available to physicians in 2012. Ex. 2189 at 45:15-46:4. My understanding is

that such a syringe (i.e., the device itself) could not be used as prior art in the context of an IPR in any event.

c. *Purported Disclosures of Syringe "Backstops"*

123. As discussed above, the disclosures of the '631 patent underscore the deficiencies of Sigg's disclosures for enablement of using the VHP method to terminally sterilize a small-volume syringe for intravitreal injection of a VEGF-antagonist. The '631 patent discloses key design elements that allowed the inventors to overcome challenges associated with terminal sterilization of a syringe with very low syringe forces, including use of a redesigned stopper with increased distance between the circumferential ribs and a plunger rod with a shoulder that interlocks with a backstop shoulder on the finder flange. These innovations allowed minimized stopper movement and enabled sterilization to a high level of sterility assurance without breaching the sterility zone of the syringe or compromising the integrity of the interior holding the drug product despite pressure changes during sterilization. *See, e.g.*, Ex. 1001 at 2:57–3:61, 11:14–36. These types of syringe design elements are conspicuously missing from the disclosures of Sigg and Boulange.

124. Mr. Koller nevertheless asserts that the plunger rod design disclosed in the '631 patent was "already known in the art by 2011," and that "[t]hese kinds of backstops were well-known in the art, and prevented inadvertent stopper

movement due to handling by the user as well as any changes of pressure, whether during terminal sterilization or air transportation." Ex. 1003 ¶ 109. The only support that Mr. Koller has identified for these assertions is Hato, a patent application directed to a safety mechanism to prevent user error, and the 2008 Macugen Label, which vaguely alludes to the presence of a "clip" that Mr. Koller ascribes to terminal sterilization without support in the reference. *Id.* (citing Ex. 1047, Hato, and Ex. 1009). But these references do not support his assertion.

125. As discussed in my Initial Report, Hato relates to mechanisms for preventing microbial contamination of liquids in syringes *resulting from user error*. Ex. 2001 ¶ 180 n.25 (emphasis added) (citing Ex. 1047.004, .006). Hato explains that its design "prevents accidental withdrawal of the plunger due to mishandling," which can reduce "risk of contamination," and "prevent the occurrence of medical malpractice attributable to the contamination." Ex. 1047.006. Mr. Koller's suggests that, based on similarity between the '631 patent inventors' plunger rod design that facilitates terminal sterilization, and the mechanism disclosed in Hato, a POSA would have relied on the Hato reference when attempting to design a syringe that can be terminally sterilized with VHP or EtO. *See* Ex. 1003 ¶¶ 108–109. In my opinion, contrary to Koller's assertions, and unlike the '631 patent, nothing in Hato suggests using its syringe design for terminally sterilized syringes. In fact, Hato explains that its design is intended to

be used for syringes that *cannot* be terminally sterilized or as a less costly alternative to terminal sterilization. *Id.* Hato thus expressly teaches away from using its syringe for terminal sterilization.

126. A POSA would have had a wide variety of syringe designs and commercially available syringe components to choose from—potentially thousands of different combinations. Mr. Koller has not identified anything in either Sigg or Hato would have pointed a POSA to this particular syringe design. Without the '631 patent as a guidepost, there would have been no way for a POSA to identify this design as potentially solving a problem that is unrelated to the express motivation of Hato (i.e., preventing user error).

127. Mr. Koller also cites the 2008 Macugen Label as an "example" of a backstop used in the prior art to prevent "inadvertent stopper movement." Ex. 1003 ¶ 109. As discussed above, there is no basis in the Macugen Label for a POSA to determine the nature or purpose of the clip mentioned in the Macugen Label, or to conclude that it had any relation to sterilization of the Macugen PFS.

128. I therefore disagree with Mr. Koller's contention that the '631 inventors' design was "well known." None of the prior art identified by Mr. Koller links the use of a "backstop" mechanism to terminal sterilization.

d. *Boulange*

129. As discussed in my Initial Declaration, Boulange neither suggests that the syringes discussed in Boulange are among the "very few" that are suitable for terminal sterilization after filling, nor provides the information that a POSA would have needed to apply Sigg's terminal sterilization method to the syringes. *See, e.g.*, Ex. 2001 ¶¶ 151, 156–64; Ex. 1008, Boulange. Boulange does not address terminal sterilization at all, including the challenges associated with terminal sterilization of syringes filled with sensitive drugs such as VEGF-antagonists. Boulange also provides none of the information that is missing from Sigg about the design of a syringe that would allow terminal sterilization of syringes filled with sensitive drugs and having the characteristics of the syringes discussed in Boulange on which Mr. Koller relies for his opinions concerning obviousness. Boulange thus adds nothing to a POSA's ability to terminally sterilize a syringe filled with a VEGF-antagonist beyond the disclosures of Sigg.

130. Boulange does not mention sterilization of syringes with VHP or EtO. Rather, Boulange contains a single reference to sterilization and it is unrelated to the use of sterilizing gases. *See* Ex. 1008 at 4:3–5. This discussion in Boulange that mentions "processes used to sterilize the medical devices" is not about terminal sterilization of filled syringes, but rather sterilization of syringe components prior to assembly and filling. *See id*. Mr. Koller appears to suggest in

his declaration, however, that Boulange's discussion relates to terminal sterilization and that Boulange addresses "degradation" of drug products in prefilled syringes. *See* Ex. 1003 ¶ 186. *See also* Pet. at 37–38, Inst. Decision at 69. I disagree.

131. The paragraph in which Boulange's sole reference to sterilization appears begins by noting that "[t]he viscoelastic material of which the piston of a medical device such as a syringe may be made is generally an elastomeric material which alters, in particular degrades chemically over time." Ex. 1008 at 4:1–3. In other words, elastomeric materials of which stoppers are usually made, such as rubber, tend to chemically degrade over time. Boulange then explains that "[t]his possible degradation is sometimes initiated by the processes used to sterilize the medical devices containing them, for example bringing them into contact with ionizing radiation." *Id*. at 4:3–5. A POSA would have understood this statement to be referring to the known phenomenon that some types of rubber are susceptible to chemical degradation that can be initiated by treatment with radiation. *See, e.g.*, Ex. 1015.366; 1016.306. In other words, the degradation mentioned in Boulange refers to degradation of the elastomeric material of the stopper, not degradation of the drug product contained within a syringe. At his deposition, Mr. Koller agreed that the cited passage in Boulange relates to sterilization and potential degradation of the stopper and not to degradation of the drug product. Ex. 2189, Koller IPR

Deposition Transcript at 182:2–15. As such, the brief mention of degradation of rubber by exposure to radiation does not, as Petitioner suggests, support Petitioner's assertion that a POSA "would have expected Parylene C would have been suitable for use in a pre-filled syringe comprising a VEGF-antagonist." Pet. at 37–38. On the contrary, the statement in Boulange about stopper degradation is unrelated to suitability for use in a PFS comprising a VEGF-antagonist.

132. Boulange proceeds to explain that degradation of rubber pistons can lead to problems associated with interactions with drug products or deterioration of the pistons' mechanical properties, (Ex. 1008 at 4:6–10), and that potential effects may occur "over time" as a result of the degradation of rubber pistons:

> Over time, *that is to say as soon as the medical device has been filled with the medical product*, and in particular when it is used or operated, it is therefore necessary for a coating to effectively isolate the region of contact between on one hand a first part of the device made of such a viscoelastic material and on the other hand the medical product or a second part of the device, intended to cooperate with said first part, so that the surface characteristics, including the coefficient of friction, of the region of contact between the two parts of the medical device, can be maintained over time, even after prolonged storage, regardless from the fact that the properties of said viscoelastic material may have been adversely affected over time.

Ex. 1008 at 4:10–20 (emphasis added). A POSA would have understood that this passage refers to filling of the medical device with "medical product" *after* chemical degradation of the rubber piston is initiated by irradiation. The POSA would have recognized this as referring to the common practice of sterilizing

individual syringe component prior to assembling and filling syringes under aseptic conditions. *See, e.g.*, Ex. 1015.315 ("Prefillable syringes can be supplied as 'bulk' (unprocessed) containers intended to be rinsed, siliconized and sterilized just prior to filling… there also is a significant and growing market for prefillable syringes that have been rinsed, siliconized, suitably packaged and then sterilized by the syringe manufacturer."), .353 ("steam sterilizing the stoppers… is usual for aseptic filling"); Ex. 1036.006 ("In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together.").

133. The discussion in Boulange that mentions sterilization thus relates to sterilization of the syringe pistons individually prior to assembly and filling of the syringe, not terminal sterilization. A POSA would have known that sterilization of syringe components prior to filling would be needed for almost any prefilled syringe, and would not equate this process with the much more specialized and uncommon practice of sterilizing the syringe exterior after filling with a biologic drug.

134. As further discussed in my Initial Declaration, Boulange's discussion of "preserving the tightness at the contact region" between a piston and a container refers to the tightness required to ensure that "all of the product to be administered escapes only via the distal end of the container and does not leak out of said

container via the piston at the proximal end of the container." Ex. 1008 at 6:14–19; Ex. 2001 ¶ 157. A POSA would have understood that this reference to "tightness" in Boulange refers to the level of tightness needed for the basic function of any syringe (i.e., a sufficiently tight seal to contain a liquid such as to prevent it from leaking out the back of the syringe during use of the syringe), not the tightness needed for terminal sterilization. *See id.*

135. Mr. Koller asserts that Boulange "describes that its syringe is suitable for storing a drug product in a gaseous phase, which means that it must have sufficient tightness to prevent gas from exiting or entering the syringe." Ex. 1003 ¶ 172. But a POSA would not have interpreted Boulange's passing reference to a medical product in the "gaseous" phase to mean that Boulange discloses a syringe that provided sufficient "tightness of the system" to allow terminal sterilization with sterilizing gas. First, Boulange makes clear that its disclosures relate to medical devices and "container[s]"—not just syringes—and it is only in the more general category of "container" that Boulange states can "accommodate a medical product in the… gaseous… phase." *See* Ex. 1008 at 1:14–18, 9:21–29. Gases are usually stored in other types of containers, not syringes, and there is no suggestion in Boulange that syringes with Parylene C-coated stoppers—or any syringes or any container with Parylene C coated components of any kind—were actually tested for their ability to contain a gas without leaking. A POSA would have been

skeptical that the Boulange syringes could be used for this purpose. Moreover, even if a syringe were nominally gas-tight such that it could hold a gas under normal storage conditions, it would not necessarily be able to prevent gas ingress during the pressure variations involved in terminal sterilization with sterilizing gases.

136. Furthermore, as discussed above, in addition to whether a syringe can prevent gases from ingressing through the interface between the stopper and syringe barrel, potential movement of the stopper during or after sterilization is another aspect of the "tightness of the system" required for terminal sterilization. But Boulange does not recognize this problem, or even mention terminal sterilization or unintended stopper movement. Boulange certainly does not suggest that its syringes would not be susceptible to this problem or suggest any solution to it. And Boulange discloses that the syringes with Parylene C-coated stoppers in particular had low syringe forces, so the stoppers would be particularly susceptible to stopper movement during sterilization. The disclosures of Boulange therefore would have provided a POSA with no assistance in designing a syringe with the characteristics of Boulange's that could be terminally sterilized.

137. And indeed, neither Mr. Koller nor Petitioner have identified any prior art reference that provides the necessary information about the design of a syringe

specifically for use as a prefilled syringe filled with VEGF-antagonist that would help a POSA practice the sterilization method discussed in Sigg.

[redacted] Lam Does Not Enable Terminal Sterilization of a PFS While Minimizing Contact between the Drug Product and the Sterilizing Agent

138. Like Sigg, Lam concerns methods for terminally sterilizing the exterior of pre-filled containers containing pharmaceutical products. Mr. Koller's opinions that the claims of the '631 patent are obvious are premised on his assertion that a POSA would have been able to apply the sterilization method discussed in Lam to PFSs with the other properties required by the claims, and that a POSA would thus have been able to design a syringe suitable for this purpose. But, as discussed in my Initial Declaration (*see* Ex. 2001 ¶¶ 166–171) and above with respect to a POSA's motivation to use Lam's EtO sterilization method and enablement with respect to Sigg, neither Lam nor the other references that Mr. Koller cites teach a POSA how to do this. A POSA therefore would have required undue experimentation to use Lam's EtO method to sterilize a PFS filled with a VEGF antagonist.

1. Genentech's Failure to Develop a Lucentis PFS Demonstrates that Lam is Not Enabled

139. [redacted]

[redacted] This failure supports my opinion that the information disclosed in Lam is insufficient to enable a POSA to use Lam's EtO method to terminally sterilize a PFS filled with a VEGF-antagonist.

140. [redacted] emphasizes the significance of Lam's own disclosures concerning the high levels of degradation that result from Lam's method (as I discussed in my Initial Declaration). *See* Ex. 2001 ¶ 179 n.24 (citing Ex. 1029.003, .018). According to Lam, the sterilization method of the Lam application sterilizes the surface of a container holding "a compound with… EtO-sensitive activity" while "the compound retains *at least 50%* of said activity." Ex. 1029 at 2:7–11 (emphasis added). In other words, the sterilization process may result in reduction of activity by *as much as 50%*. Lam further states that in "some embodiments, the compound retains at least 90% of said activity," i.e., as much as 10% reduction is possible.

Ex. 1029 at 2:18. No threshold above 90% retained activity is identified in Lam, which would have signaled to a POSA that this is the highest threshold that the inventors had confidence in claiming. But, as noted in my Initial Declaration, these levels of degradation would not be acceptable for a drug product, and thus a POSA would not have used a sterilization method that would result in a 10% reduction in the activity of the active ingredient in a drug product.[16, 17] Ex. 2001 ¶

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[16] *See, e.g.*, Ex. 2033, Remington 2006 at .004 ("Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level."); Ex. 2034, Nema 2006 at .009 ("Therefore, the aggregate level in commercial intravenous immunoglobulin products is limited to less than 5% based on the WHO standards."); Ex. 2228, FDA Guidance: Stability Testing of New Drug Substances and Products (2003) at .014 (defining "significant change" in part as "[a] 5% change in assay from its initial value").

[17] Note that in my Initial Declaration, among the references that I cited concerning drug degradation is FDA Guidance: Stability Testing of New Drug Substances and Products, cited as Exhibit 2027. I understand that the incorrect document was filed as this exhibit (a duplicate of Ex. 2048, the substantively identical ICH Guideline).

179 n.24. A process in which the drug product is exposed to EtO such that the drug's activity is reduced by 10% or more has not minimized the contact between the sterilizing agent and the drug product. Lam's disclosure of a sterilization method that cannot guarantee less than 10% reduction of drug activity cannot enable terminal sterilization of a PFS filled with a biologic drug for intravitreal injection.

E. Additional Reasons Why Claims 17, 21, and 24–26 Are Non-obvious

141. In addition to the reasons discussed above and in my Initial Declaration for why independent claim 1 is not obvious over the prior art cited by Petitioner and Mr. Koller, several of the dependent claims are separately non-obvious for additional reasons, as set forth below.

1. Dependent Claim 14 Would Not Have Been Obvious

142. Claim 14 recites a pre-filled syringe according to claim 1, and adds a lower limit on the break loose force of less than about 5 Newtons (N) and a limit on the slide force of less than about 5 Newtons (N). As for claim 1, Mr. Koller and Petitioner rely on Boulange for teaching syringes with the claimed forces. *See* Pet.

The FDA Guidance has now been filed as Exhibit 2228. Citations in my Initial Declaration to Ex. 2027 actually refer to Ex. 2228.

at 49–50; Ex. 1003 ¶¶ 221–224. A POSA would not have been motivated to use a stopper with Parylene C (i.e., piston B) and would not have had a reasonable expectation of success in doing so for the reasons discussed above.

143. The slide force for piston C, the non-parylene C stopper that Mr. Koller and Petitioner say a POSA would have used, has a slide force above 5 N even at the initial timepoint T=0. A POSA would not have been motivated to use a syringe that had a measured slide force greater than 5 N to make a PFS with a slide force of less than 5 N, nor would a POSA have reasonably expected it to succeed. Mr. Koller opines that a POSA would have been able to lower the slide forces through "routine optimization," but offers no suggestion about how this could be done other than by modifying the experimental conditions by which the force is measured. Ex. 1003 ¶ 222. A POSA would not consider modifying the force measurement parameters to be "optimization" of the syringe or the plunger forces, and would not have considered this to be a sensible approach to the problem of excessive sliding force.

144. On the contrary, the most straightforward way for a POSA to optimize the syringe to address excessive slide force would have been to increase the lubrication of the syringe by increasing the amount of silicone oil. *See* discussion above at § V.A; Ex. 2021.002. Indeed, the data in Boulange bears this

out. The slide forces for Piston C are dramatically lower when 500 µg of silicone oil was used as compared to 40 µg:

Piston	Si Oil on Piston	Time Point	Force S (N) with **500 µg Si Oil**	Force S (N) with **40 µg Si Oil**	% Difference in Force S with reduced Si Oil
C	0 µg/cm^2	T = 0	1.0	6.6	660%
		T = 1	1.3	4.8	369%
	5 µg/cm^2	T = 0	0.8	6.5	812%
		T = 1	1.0	8.3	830%
	15 µg/cm^2	T = 0	0.8	6.0	750%
		T = 1	1.1	8.3	754%
	50 µg/cm^2	T = 0	0.8	5.2	650%
		T = 1	1.0	6.2	620%

Ex. 1008 at .020–.021, .023 (Tables 4, 5, and 7). A POSA thus would not have expected to be able to achieve lower slide forces with the claimed level of silicone oil by routine optimization.

2. Dependent Claim 17 Would Not Have Been Obvious

145. Dependent claim 17 recites a blister pack comprising a pre-filled syringe according to claim 1, and adds that "the syringe has been sterilized using H_2O_2 or EtO." A POSA would not have found claim 17 obvious for all of the reasons discussed above with respect to claim 1, but in addition, it would not have been obvious for a POSA to carry out sterilization using either of the recited agents based on the prior art raised by the Petitioner.

146. First, a POSA would not have been motivated to use H_2O_2 (VHP) or EtO to terminally sterilize the pre-filled syringe of claim 1. As discussed above,

Boulange only refers to the use of ionizing radiation, and only in the context of an aseptic filling process. *See* § V.C.3.d, above; Ex. 1008 at 4:3–5. Boulange does not suggest terminal sterilization of any sort, and there is no mention in the reference of VHP or EtO. Additionally, the prior art suggested that exposure of the Parylene C coating to at least one of the gases – EtO – would negatively impact Parylene C's coefficient of friction, which would negatively impact the function of the syringe. *See* Ex. 2001 ¶ 132; Ex. 1075, Wolgemuth 2002 at .004. This art would discourage a POSA from combining stoppers coated in Parylene C with EtO. Second, as discussed by Dr. Miller, a POSA would not have been motivated to use the VHP process discussed in Sigg for the additional reason that the reference provides no evidence that its VHP process worked to sterilize the tested syringes. *See* Ex. 2203 ¶¶ 59–62, 66. By contrast, Sigg expressly states that the beta radiation method of Sigg achieved an SAL of 10^{-6}. *See* Ex. 2203 ¶¶ 63–65; Ex. 1007 at 18:10–14. Thus, a POSA would not have been motivated to use VHP or EtO according to claim 17 to terminally sterilize a blister pack containing any of the syringes discussed in Boulange.

147. In addition, and as discussed above, there is nothing in Sigg, Lam, or Boulange providing a reasonable expectation of success in implementing terminal sterilization of the Boulange syringes using VHP or EtO. Boulange provides no suggestion that Parylene C would be compatible with exposure to either of those

gases, Sigg provides no evidence that the VHP process actually sterilized the tested syringes, and the prior art suggests that exposure to EtO will negatively impact the functionality of Parylene C. Further, as discussed above and below, objective evidence shows that Genentech and Novartis were not able to successfully make a PFS as claimed in the '631 patent using the methods disclosed in Sigg (VHP) and Lam (EtO). This evidence further supports the conclusion that claim 17 would not have been obvious to a POSA. *See* § V.C.1, above and § VI.A, below. For these additional reasons, claim 17 would not have been obvious to a POSA over the combination of Sigg and Boulange or Lam and Boulange as asserted by Mr. Koller.

3. Dependent Claim 21 Would Not Have Been Obvious

148. Claim 21 depends from claim 17 and adds the limitation that the PFS sterilized with H_2O_2 or EtO has "a Sterility Assurance Level of at least 10^{-6}." Claim 21 would not have been obvious for the reasons set out above with respect to claims 1 and 17, and also for the following additional reasons.

149. Dr. Miller explains that a Sterility Assurance Level ("SAL") is a term referring to the probability of finding a single non-sterile unit following the completion of a validated terminal sterilization process (*see* Ex. 2203 ¶¶ 40-51), and that an SAL of at least 10^{-6} means there is a 1 in 1,000,000 chance of finding a non-sterile unit following sterilization (*see* Ex. 2203 ¶ 41).

150. Dr. Miller further explains that neither Sigg nor Lam suggest that the disclosed VHP and EtO sterilization processes can be used to achieve an SAL of 10^{-6}. *See* Ex. 2203 ¶¶ 62, 67, 69, 78, 89-90. Dr. Miller provides an analysis of the Sigg disclosure and concludes, among other things, that "[t]here is no disclosure in Sigg that suggests the VHP method can achieve an SAL of 10^{-6}." *See id.* ¶ 68. He likewise analyzes the disclosure of Lam and concludes that Lam does not disclose a process that achieves an SAL of 10^{-6}. *See id.* ¶ 89. Further, Dr. Miller explains that it would not have been "routine" optimization for a microbiologist to achieve an SAL of 10^{-6} using the processes described in Sigg and Lam. *See id.* ¶¶ 71-74, 82-88, 94. In my opinion, a POSA would not have been motivated to use the VHP or EtO processes discussed in Sigg and Lam to terminally sterilize the PFS of claim 1 to achieve an SAL of 10^{-6}. *See id.* ¶¶ 68-74, 91-94. Nor would the POSA have had a reasonable expectation of success in doing so. *See id.* For these additional reasons, claim 21 would not have been obvious to a POSA over the prior art as asserted by Mr. Koller. Moreover, as further explained by Dr. Miller, Mr. Koller's opinions to the contrary are contradicted by the failed attempts of Novartis and Genentech to use the methods disclosed in Sigg and Lam to terminally sterilize a VEGF-filled PFS to achieve an SAL of 10^{-6}. *See id.* ¶¶ 72-74, 94. Such evidence supports my opinion that the claims would not have been obvious over the prior art.

4. Dependent Claims 24–26 Would Not Have Been Obvious

151. Claim 24 depends from claim 1, and further requires treating a patient suffering from specified "ocular diseases" by administering an ophthalmic solution using the PFS of claim 1. Claims 25 and 26 depend from claim 24, and therefore include this same additional limitation. Claims 24–26 would not have been obvious for the reasons set forth with respect to claim 1, above, and also for the following additional reasons.

152. A POSA would have recognized that a PFS would need to meet more stringent requirements to be suitable for *administration* to a patient, even if one were to assume that it would have been obvious to *make* such a PFS. For example, before deciding whether to administer an ophthalmic solution using Boulange's syringe with a Parylene C-coated stopper B1, a POSA would have needed to balance the potential efficacy of the drug against the potential safety concerns of Parylene C, described above. *See* Ex. 2204 ¶¶ 61-66. *See also, generally*, Ex. 2202 (Dillberger Decl.). Additionally, a POSA would have known that a PFS could not be used to administer a drug until the PFS reaches a physician, which takes time after manufacturing of the PFS is complete. Mr. Koller agreed that it would realistically take at least a week after a PFS is filled, packaged, and terminally sterilized for it to reach a physician, and often much longer than that.

See Ex. 2189 at 104:14–106:18. For any use to treat patients, the PFS and its contents must be sufficiently stable over this time period.

153. A POSA would also know that a PFS could be administered at any point during its shelf-life, and therefore would have needed to reasonably expect it to remain safe until its expiration for claims 24–26. A POSA would also have similarly needed to confirm that a syringe would have an acceptable force profile and retain its potency over its expected shelf-life. As explained in the declaration of Dr. Calman, an ophthalmologist would not have been motivated to use a syringe for intravitreal administration of an ophthalmic solution unless these concerns were addressed. Ex. 2204 ¶ 130-137.

154. As set forth above in Section V.B.1, a POSA would not have expected a PFS containing a Parylene C-coated stopper (like Boulange's stopper B1) to be safe for intravitreal administration. Nor would a POSA have expected a PFS containing a non-Parylene C-coated stopper (like Boulange's stopper C) to maintain a consistent force profile over time. *See* § V.B.2, above. Furthermore, Sigg provides data concerning degradation of the active ingredient only at T_0, i.e., immediately after exposure to VHP, and a POSA would have expected VHP to cause further degradation of the product over time. A POSA would therefore not have been motivated to administer to a patient the PFS of claim 1 with a reasonable

expectation of success, and so claims 24–26 are nonobvious for these additional reasons.

VI. FAILURE OF OTHERS

A. Genentech Tried and Failed to Develop a Lucentis® PFS

155. The Lucentis® PFS is a pre-filled syringe product containing the VEGF-antagonist, ranibizumab. The Lucentis® PFS is approved for intravitreal injection and is marketed in the United States by Genentech, Inc. ("Genentech"). *See* Ex. 2173 (NOVITC(US)00752928 (2018 Prescribing Information)).

156. [redacted]

157. [redacted]

158. [redacted]

---

18 [redacted]

159. [redacted]

160. [redacted]

161. [redacted]

162. [redacted]

[redacted]

163. [redacted]

[redacted]

164. [redacted]

165. Using Novartis's patented technology, Genentech was finally able to develop a Lucentis® PFS. *See* Genentech Press Release (Oct. 14, 2016).

VII. GENENTECH'S LUCENTIS® PFS PRODUCT EMBODIES AND IS CO-EXTENSIVE WITH AT LEAST CLAIMS 1–10 AND 14–23 OF THE '631 PATENT

166. I understand that Novartis has identified certain "secondary considerations" that support the non-obviousness of the '631 patent based on the Lucentis® PFS that is sold by Genentech in the United States. I further understand that whether the Lucentis® PFS embodies and is co-extensive with the claims of the '631 patent is relevant to these secondary considerations. As set forth below, I have reviewed documents concerning the Lucentis® PFS and, in my opinion, it embodies and is coextensive with at least claims 1-10 and 14-23 of the '631 patent.

167. Genentech received approval from the FDA in 2016 to market the Lucentis® PFS and began selling the product in the United States in 2017. Ex. 2160, Lucentis® PFS Approval Letter and Label, Oct. 2016 at .004–.007.[19] The first approved dosage for the Lucentis® PFS was 0.5 mg. Ex. 2160.004. In 2018, the FDA approved a 0.3 mg dosage in the Lucentis® PFS. *See* Ex. 2117, Genentech Press Release, Mar. 21, 2018.

168. As described in the currently approved FDA label, "Each LUCENTIS® 0.5 mg carton (NDC 50242-080-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 10 mg/mL [or 6 mg/mL for the 0.3 mg dosage form] ranibizumab solution." Ex. 2125, Lucentis Prescribing Information (revised Mar. 2018) at .027. "Each prefilled syringe is sterile and is packed in a sealed tray." Id. "Each prefilled syringe is sterile and is packed in a sealed tray." *Id.*

169. I understand that Genentech provided sBLA documents to the FDA to describe the Lucentis® PFS that is now marketed in the United States. [redacted]

[19] The October 2016 FDA Approval Letter and Label are publicly available and can be found at the Drugs@FDA database at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125156Orig1s110.pdf.

[redacted]

A. Claim 1

170. Claim 1 of the ’631 patent recites:

> A pre-filled, terminally sterilized syringe for intravitreal injection, the syringe comprising a glass body forming a barrel, a stopper and a plunger and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein: (a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml, (b) the syringe barrel comprises from about 1 µg to 100 ug silicone oil, (c) the VEGF antagonist solution comprises no more than 2 particles >50 µm in diameter per ml and wherein the syringe has a stopper break loose force of less than about 11N.

1. pre-filled, terminally sterilized syringe for intravitreal injection

171. The prescribing information for the Lucentis® PFS (revised March 2018) states that Lucentis® (ranibizumab) is provided in a pre-filled syringe presentation for intravitreal injections:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection) for intravitreal injection
Initial U.S. Approval: 2006

----------**DOSAGE FORMS AND STRENGTHS**----------
- Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:
  - 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
  - 6 mg/mL solution (LUCENTIS 0.3 mg) (3)

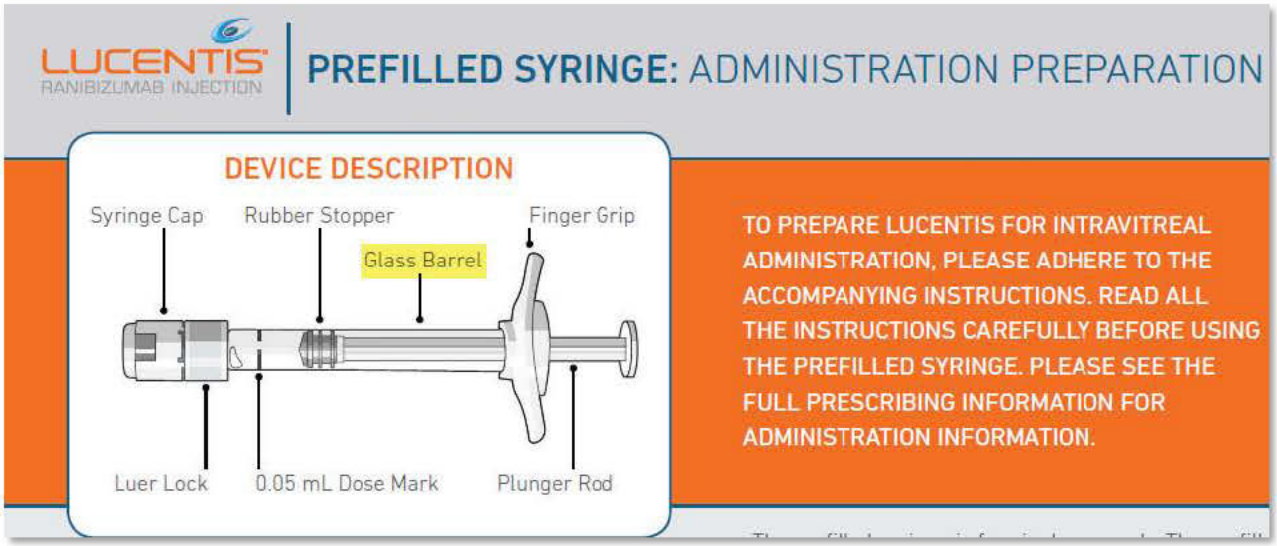
Ex. 2125.001 (annotated); *see also* Ex. 2160.009 (Lucentis® PFS Approval Letter and Label, Oct. 2016).

172. [redacted]

173. Thus, Lucentis® PFS is a pre-filled, terminally sterilized syringe for intravitreal injection.

2. the syringe comprising a glass body forming a barrel, a stopper and a plunger and

174. The Lucentis® PFS Administration Flashcard (dated April 2018) illustrates that the syringe of the Lucentis ® PFS comprises a glass body forming a barrel. Ex. 2044.002 (annotated):



175. [redacted]

176. The Prescribing Information for Lucentis® PFS (revised March 2018) depicts a stopper and a plunger rod):

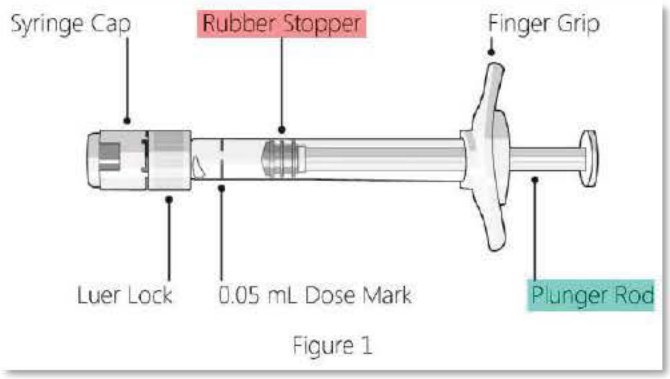


Figure 1

Ex. 2125.004 (annotated); *see also* Ex. 2160.011 (Lucentis® PFS Approval Letter and Label, Oct. 2016) (same).

177. [redacted]

178. [redacted]

179. Thus, the syringe of the Lucentis® PFS comprises a glass body forming a barrel, a stopper, and a plunger.

3. [the syringe] containing an ophthalmic solution which comprises a VEGF-antagonist, wherein

180. I understand that in previous proceedings, Petitioner and Novartis have agreed that the term "VEGF-antagonist" means "a substance capable of blocking or inhibiting the biological action of vascular endothelial growth factor." The '631 patent identifies "ranibizumab (Lucentis®)" as a VEGF-antagonist. *See* Ex. 1001 at 6:32–36 ("VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF-antagonists have been approved for human use, namely ranibizumab (Lucentis®) ...").

181. An ophthalmic solution is a solution that is used for the eye. The prescribing information for the Lucentis® PFS indicates that the Lucentis® PFS

contains ranibizumab, a VEGF-antagonist, in a solution for injection into the eye.

See Ex.2125.001, Lucentis Prescribing Information, revised March 2018

(annotated):

LUCENTIS® (ranibizumab injection) for intravitreal injection
Initial U.S. Approval: 2006

----------**RECENT MAJOR CHANGES**----------

Indications and Usage, Diabetic Retinopathy (1.4)	04/2017
Dosage and Administration (2)	03/2018
Dosage Forms and Strengths (3)	03/2018

----------**INDICATIONS AND USAGE**----------

LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

----------**DOSAGE AND ADMINISTRATION**----------

For ophthalmic intravitreal injection only (2.1)

----------**DOSAGE FORMS AND STRENGTHS**----------

- Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:
  - 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
  - 6 mg/mL solution (LUCENTIS 0.3 mg) (3)

See also Ex. 2125.015 (disclosing that ranibizumab is a VEGF-antagonist)

(annotated):

11 DESCRIPTION

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

See also Ex. 2160.009, .020 (Lucentis® PFS Approval Letter and Label, Oct. 2016).

182. Thus, the Lucentis® PFS contains an ophthalmic solution which comprises a VEGF-antagonist.

4. (a) the syringe has a nominal maximum fill volume of between about 0.5 mL and about 1 mL,

183. [redacted]

184. Thus, the Lucentis® PFS syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml.

5. (b) the syringe barrel comprises from about 1 µg to 100 ug silicone oil,

185. [redacted]

[redacted]

[redacted]

186. Thus, the syringe barrel of the Lucentis® PFS comprises from about 1 µg to 100 µg silicone oil.

6. (c) the VEGF-antagonist solution comprises no more than 2 particles > 50 µm in diameter per mL

187. [redacted]

[redacted]

188. [redacted]

[redacted]

189. [redacted]

190. Accordingly, the VEGF-antagonist solution in the Lucentis® PFS comprises no more than 2 particles >50 μm in diameter per ml.

7. wherein the syringe has a stopper break loose force of less than about 11N

191. [redacted]

[redacted]

192. Thus, the Lucentis® PFS has a stopper break loose force of less than about 11N.

193. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 1 of the '631 patent.

B. Dependent Claims

1. Claim 2

194. Claim 2 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450 nm or less.

195. The syringe barrel of the EU Lucentis® PFS has an internal coating of silicone oil that has an average thickness of 450 nm or less. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

196. [redacted]

[redacted]

197. [redacted]

[redacted]

198. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 2 of the ’631 patent.

2. Claim 3

199. Claim 3 of the ’631 patent recites:

> A pre-filled syringe according to claim 1, wherein the syringe barrel has an internal coating of from about 3 μg to about 100 ug silicone oil.

200. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

201. [redacted]

202. Thus, the syringe barrel of the Lucentis® PFS has an internal coating of from about 3 μg to about 100 ug silicone oil.

203. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 3 of the ’631 patent.

3. Claim 4

204. Claim 4 of the ’631 patent recites:

> A pre-filled syringe according to claim 1, wherein the silicone oil is DC365 emulsion.

205. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

206. [redacted]

207. [redacted]

208. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 4 of the '631 patent.

4. Claim 5

209. Claim 5 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the VEGF antagonist solution further comprises one or more of (i) no more than 5 particles ≧25 μm in diameter per ml, and (ii) no more than 50 particles ≧10 μm in diameter per ml.

210. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

211. [redacted]

212. [redacted]

[redacted]

213. [redacted]

214. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 5 of the ’631 patent.

5. Claim 6

215. Claim 6 of the ’631 patent recites:

> A pre-filled syringe according to claim 1, wherein the VEGF antagonist solution meets USP789

216. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

217. [redacted]

218. [redacted]

219. [redacted]

220. Accordingly, the Lucentis® PFS also contains a VEGF-antagonist and meets USP <789>. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 6 of the '631 patent.

6. Claim 7

221. Claim 7 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the VEGF antagonist is an anti-VEGF antibody.

222. The VEGF-antagonist in the Lucentis® PFS is ranibizumab, an anti-VEGF antibody. *See* Ex. 2125.001, Prescribing Information for Lucentis® PFS (revised March 2018) (annotated):

LUCENTIS® (ranibizumab injection) for intravitreal injection
Initial U.S. Approval: 2006

----------**RECENT MAJOR CHANGES**----------

Indications and Usage, Diabetic Retinopathy (1.4)	04/2017
Dosage and Administration (2)	03/2018
Dosage Forms and Strengths (3)	03/2018

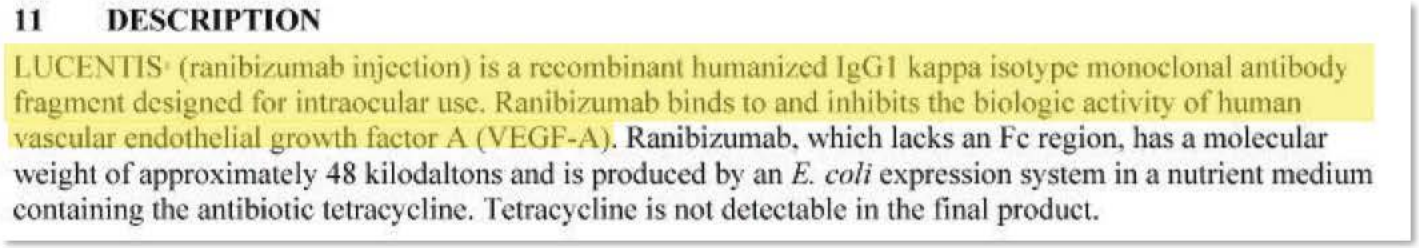
----------**INDICATIONS AND USAGE**----------

LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

See also Ex. 2160.009 (Lucentis® PFS Approval Letter and Label, Oct. 2016).

223. Ranibizumab is an anti-VEGF antibody. For example, the prescribing information for Lucentis® PFS (revised March 2018) discloses that ranibizumab is as anti-VEGF antibody):



11 DESCRIPTION

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

Ex. 2125.015; *see also* Ex. 2160.020 (Lucentis® PFS Approval Letter and Label, Oct. 2016); Ex. 1001 at 6:32–36 ("VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF-antagonists have been approved for human use, namely ranibizumab (Lucentis®) ...").

224. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 7 of the '631 patent.

7. Claim 8

225. Claim 8 of the '631 patent recites:

> A pre-filled syringe according to claim 7, wherein the anti-VEGF antibody is ranibizumab.

226. The anti-VEGF antibody in the Lucentis® PFS is ranibizumab. *See* Ex. 2125.001 (Prescribing Information for Lucentis® PFS (revised March 2018)) (annotated):

LUCENTIS® (ranibizumab injection) for intravitreal injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage, Diabetic Retinopathy (1.4)	04/2017
Dosage and Administration (2)	03/2018
Dosage Forms and Strengths (3)	03/2018

----------INDICATIONS AND USAGE----------

LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

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- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)
- Myopic Choroidal Neovascularization (mCNV) (1.5)

Ex. 2160.020 (Lucentis® PFS Approval Letter and Label, Oct. 2016).

227. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 8 of the '631 patent.

8. Claim 9

228. Claim 9 of the '631 patent recites:

> A pre-filled syringe according to claim 8, wherein the ranibizumab is at a concentration of 10 mg/ml.

229. The ranibizumab in the 0.5 mg Lucentis® PFS is at a concentration of 10 mg/ml. *See* Ex. 2125.001 (Prescribing Information for Lucentis® PFS (revised March 2018)) (annotated):

----------DOSAGE FORMS AND STRENGTHS----------

- Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:
  - 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
  - 6 mg/mL solution (LUCENTIS 0.3 mg) (3)

See also Ex. 2160.020 (Lucentis® PFS Approval Letter and Label, Oct. 2016).

230. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 9 of the '631 patent.

9. Claim 10

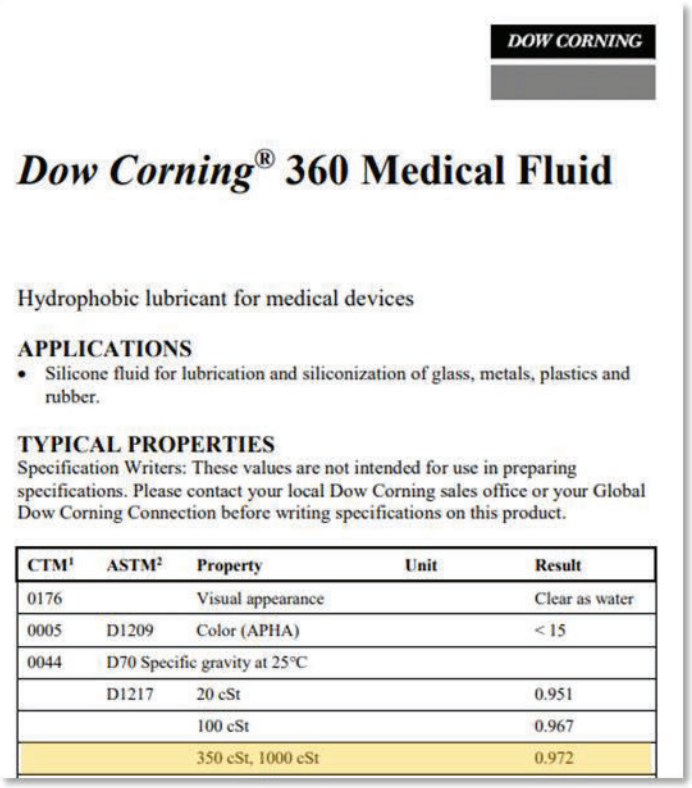
231. Claim 10 of the '631 patent recites:

> A pre-filled syringe according to claim 8, wherein the silicone oil has a viscosity of about 350 cP, and the VEGF antagonist solution further comprises one or more of (i) no more than 5 particles ≧25 μm in diameter per ml, and (ii) no more than 50 particles ≧10 μm in diameter per ml.

232. The silicone oil in the Lucentis® PFS has a viscosity of about 350 cP.

[redacted]

See also Ex. 2152, Dow Corning® 360 Medical Fluid at .001 (NOVITC(US)00000788) (annotated):



DOW CORNING

Dow Corning® 360 Medical Fluid

Hydrophobic lubricant for medical devices

APPLICATIONS

- Silicone fluid for lubrication and siliconization of glass, metals, plastics and rubber.

TYPICAL PROPERTIES

Specification Writers: These values are not intended for use in preparing specifications. Please contact your local Dow Corning sales office or your Global Dow Corning Connection before writing specifications on this product.

CTM[1]	ASTM[2]	Property	Unit	Result
0176		Visual appearance		Clear as water
0005	D1209	Color (APHA)		< 15
0044	D70	Specific gravity at 25°C		
	D1217	20 cSt		0.951
		100 cSt		0.967
		350 cSt, 1000 cSt		0.972

233. 350 cSt is about 350 cP. To convert from viscosity measured in cSt (centistokes) to cP (centipoise), we multiply the viscosity in cSt by the density of the fluid, which is equivalent to its specific gravity multiplied by the density of water at a given temperature. As shown above, the specific gravity of the DC 360 silicone oil fluid found in the DC 360 emulsions at 350 cSt viscosity and 25 degrees Celsius is 0.972. Ex. 2152.001. The density of water at that temperature is 0.997 g/mL. Thus, 350 cSt x 0.972 x 0.997 = 339.180 cP, which is about 350 cP, so the silicone oil of the Lucentis® PFS has a viscosity of about 350 cP.

234. Additionally, the VEGF-antagonist solution in the Lucentis® PFS further comprises one or more of (i) no more than 5 particles ≧25 μm in diameter per ml, and (ii) no more than 50 particles ≧10 μm in diameter per ml. *See* claim 5, above at ¶¶ 210-214.

235. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 10 of the '631 patent.

10. Claim 14

236. Claim 14 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the syringe has a stopper break loose force of less than about 5N, and wherein the syringe has a stopper slide force of less than about 5N.

237. The Lucentis® PFS has a stopper break loose force of less than about 5N, and wherein the syringe has a stopper slide force of less than about 5N. [redacted]

[redacted]

238. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 14 of the ’631 patent.

11. Claim 15

239. Claim 15 of the ’631 patent recites:

> A pre-filled syringe according to claim 14, wherein the stopper break loose force or stopper slide force is measured using a filled syringe, at a stopper travelling speed of 190 mm/min, with a 30 G×0.5 inch needle attached to the syringe.

240. The Lucentis® PFS has a stopper break loose force or stopper slide force that is measured using a filled syringe, at a stopper travelling speed of 190 mm/min, with a 30 G×0.5 inch needle attached to the syringe.

241. [redacted]

[redacted]

242. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 15 of the '631 patent.

12. Claim 16

243. Claim 16 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the syringe has a stopper slide force of less than about 11N.

244. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

245. [redacted]

246. Thus, the Lucentis® PFS has a stopper slide force of less than about 11N.

247. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 16 of the '631 patent.

13. Claim 17

248. Claim 17 of the '631 patent recites:

> A blister pack comprising a pre-filled syringe according to claim 1, wherein the syringe has been sterilised using H_2O_2 or EtO.

249. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

250. The prescribing information for the Lucentis® PFS (revised March 2018), Ex. 2125.004, .0028 (annotated), shows that the Lucentis® PFS is packed in a sealed tray:

Step 1: Prepare

- Make sure that your pack contains a sterile prefilled syringe in a sealed tray.
- Peel the lid off the syringe tray and, using aseptic technique, remove the syringe.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and a CLEAR finger grip. Each prefilled syringe is sterile and is packed in a sealed tray.
- Each LUCENTIS 0.3 mg carton (NDC 50242-082-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 6 mg/mL ranibizumab solution. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and an ORANGE finger grip. Each prefilled syringe is sterile and is packed in a sealed tray.

See also Ex. 2160.011–.012, .032 (Lucentis® PFS Approval Letter and Label, Oct. 2016).

251. [redacted]

[redacted]

252. Thus, the syringe of the Lucentis® PFS is packaged in a blister pack and sterilized using EtO.

253. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 17 of the '631 patent.

14. Claim 18

254. Claim 18 of the '631 patent recites:

> A blister pack comprising a pre-filled syringe according to claim 17, wherein the outer surface of the syringe has ≦1 ppm EtO or H2O2 residue.

255. [redacted]

[redacted]

256. [redacted]

[redacted]

257. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 18 of the '631 patent.

15. Claim 19

258. Claim 19 of the '631 patent recites:

> A blister pack comprising a pre-filled syringe according to claim 17, wherein the syringe has been sterilised using EtO or H_2O_2 and the total EtO or H_2O_2 residue found on the outside of the syringe and inside of the blister pack is ≦0.1 mg.

259. As explained above, it is my opinion that the Lucentis® PFS is packaged in a blister pack comprising a pre-filled syringe according to claim 17. *See* claim 17, above at ¶¶ 249-253.

260. [redacted]

[redacted]

261. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

262. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

263. [redacted]

[redacted]

[redacted]

[redacted]

264. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 19 of the '631 patent.

16. Claim 20

265. Claim 20 of the '631 patent recites:

> A blister pack comprising a pre-filled syringe according to claim 18, wherein ≦5% of the VEGF antagonist is alkylated.

266. As explained above, it is my opinion that the Lucentis® PFS is packaged in a blister pack comprising a pre-filled syringe according to claim 18. *See* claim 18, above at ¶¶ 255-257.

267. [redacted]

268. [redacted]

[redacted]

269. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 20 of the ’631 patent.

17. Claim 21

270. Claim 21 of the ’631 patent recites:

> A blister pack comprising a pre-filled syringe according to claim 17, wherein the syringe has been sterilised using EtO or H_2O_2 with a Sterility Assurance Level of at least 10^{-6}.

271. As explained above, it is my opinion that the Lucentis® PFS is packaged in a blister pack comprising a pre-filled syringe according to claim 17. *See* claim 17, above at ¶¶ 249-253.

272. [redacted]

[redacted]

273. [redacted]

274. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 21 of the '631 patent.

18. Claim 22

275. Claim 22 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the syringe barrel has an internal coating of from about 1-50 µg silicone oil.

276. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

277. As discussed above with respect to the silicone oil amount limitation of claim 1, above ¶¶ 185-186, [redacted]

[redacted]

278. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 22 of the '631 patent.

19. Claim 23

279. Claim 23 of the '631 patent recites:

> A pre-filled syringe according to claim 1, wherein the silicone oil has a viscosity of about 350 cP.

280. As explained above, it is my opinion that the Lucentis® PFS is a pre-filled syringe according to claim 1. *See* claim 1, above at ¶¶ 171-193.

281. As explained above with respect to claim 4, [redacted]

282. DC 365 contains silicone oil in the form of a dimethicone fluid sold as DC 360 medical fluid, which has a viscosity of 350 cSt. *See* Ex. 2154.003 (NOVITC(US)00000795).

283. As explained above with respect to claim 10, 350 cSt is about 350 cP. *See* above at ¶¶ 232-235.

284. Thus, the silicone oil in the Lucentis® PFS has a viscosity of about 350cP.

285. It is therefore my opinion that Lucentis® PFS meets all claim limitations of claim 23 of the ’631 patent.

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286. For the reasons explained above, it is my opinion that Lucentis® PFS meets all the claim limitations of at least claims 1–10 and 14–23 and therefore embodies these claims.

287. Moreover, based on my review of all the evidence related to this product, it is my opinion that Lucentis® PFS is coextensive with these claims because the claims cover the entirety of the marketed pre-filled syringe product and the product does not contain substantial unclaimed features. As discussed in detail above, the Lucentis® PFS comprises a syringe body with a VEGF antagonist contained within. The syringe body includes a barrel, a stopper, and a plunger, and the PFS has the other elements of the claims (as outlined above). The Lucentis® PFS is not a component of a larger product, nor is it marketed as a part of a kit with another substantial component. A POSA comparing the claims with Lucentis® PFS would recognize that the product is essentially the invention in these claims.

288. Furthermore, I understand that certain claimed features of the Lucentis® and Regeneron® PFS—for example, terminal sterilization and low silicone oil levels, were necessary in order to obtain FDA approval, further supporting that the commercial success of these products is attributable to the

claimed features and that a nexus exists between the claims and the marketed products for purposes of non-obviousness. [redacted]

VIII. DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: January 18, 2022

By: 
Digitally signed by Karl R. Leinsing
Date: 2022.01.18 21:52:16 -05'00'

Karl R. Leinsing, M.S.M.E., P.E.