

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

REGENERON PHARMACEUTICALS, INC.
Petitioner,

v.

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

Patent Number: 9,220,631

DECLARATION OF HORST KOLLER

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I. Introduction

1. I have been retained by Petitioner Regeneron Pharmaceuticals, Inc. (“Petitioner” or “Regeneron”), as an independent expert witness in the above-captioned *inter partes* review (“IPR”), in which Regeneron has requested that the U.S. Patent and Trademark Office cancel as unpatentable all claims of U.S. Patent No. 9,220,631 (“the ‘631 patent”).

2. This declaration sets forth my analyses and opinions based on my knowledge, experience, and the materials I have considered. As I explain below, it is my opinion that all claims of the ‘631 patent are directed to subject matter that was routine, conventional, and well known in the art before the ‘631 patent priority date. As would be readily appreciated by one of skill in the art, the ‘631 patent is rendered obvious by the combination of prior art references discussed herein.

3. I have reviewed the documents referenced in this declaration. I understand they have been submitted as exhibits in conjunction with Regeneron’s Petitions for IPR.

II. Summary of Opinions

4. Based on my knowledge, experience, and the materials that I have reviewed, it is my opinion that claims 1-23 of the ‘631 patent are obvious. Specifically:

(i) Claims 1-3, 5-9, and 14-22 are obvious based on International Patent Application Publication No. WO 2011/006877 to Sigg et al. (“Sigg”) (Ex. 1007) in view of International Patent Application Publication No. WO 2009/030976 to Boulange et al. (“Boulange”) (Ex. 1008), and if necessary, USP Chapter <789>, titled “Particulate Matter in Ophthalmic Solutions.” (“USP789”) (Ex. 1019);

(ii) Claims 1-3, 5-9, and 14-22 are obvious based on International Patent Application Publication No. WO 2008/077155 to Lam et al. (“Lam”) (Ex. 1029) in view of Boulange, and if necessary, USP789;

(~~iii~~) Claims 4, 10 and 23 are obvious based on Sigg in view of Boulange, further in view of A. Fries, *Drug Delivery of Sensitive Biopharmaceuticals with Prefilled Syringes*, Drug Delivery Technology, Vol. 9, No. 5 (May 2009) (“Fries”) (Ex. 1012), and if necessary, USP789;

(iv) Claims 4, 10 and 23 are obvious based on Lam in view of Boulange, further in view of Fries, and if necessary, USP789;

(~~iii~~) Claims 11-13 are obvious based on Sigg in view of Boulange, further in view of International Patent Application Publication No. WO 2007/149334 (“Furfine”) (Ex. 1021), and if necessary, USP789;

~~(iv) Claims 1-10, and 14-23 are obvious based on Lam in view of Bruno Reuter & Claudia Petersen, *Syringe Siliconization*, 4 TECHNOPHARM 2, 238 (2012) (“Reuter”) (Ex. 1010), and if necessary, USP789;~~

(~~v~~) Claims 11-13 are obvious based on the combination of Lam in view of ~~Reuter~~ Boulange, further in view of Furfine, and if necessary, USP789.

III. Qualifications and Compensation

5. I have a Diplom-Ingenieur (“Dipl.Ing.”) degree in biotechnology from Hochschule Mannheim, which I earned in 1993. A Dipl.Ing is considered equivalent to a master’s engineering degree that would be awarded by a U.S. university. Prior to that I had several years of apprenticeship and work experience as a medical technician in Germany.

6. I am currently the CEO of HK Packaging Consulting, ~~and have held this position since~~which is a consulting company that I formed in 2015. In this role, I consult worldwide on parenteral packaging, which includes consulting on syringe selection and related primary packaging issues, and consulting on the role of primary and secondary packaging in dosage form and drug product development.

7. At HK Packaging Consulting, I provide technical and regulatory support to both primary packaging manufacturers and pharmaceutical companies. For primary packaging manufacturers, I work on choosing pharmaceutical container materials and components (vials, cartridges, and syringes), setting container specifications, ensuring compliance and testing in accordance with compendia such as the U.S., European Pharmacopeias, and the International Organization for Standardization (“ISO”), and providing support for regulatory filings with the U.S. Food and Drug Administration (“FDA”) and the European Medicines Agency (“EMA” or “EMA”). For pharmaceutical companies, I work as a consultant to provide troubleshooting services, including technical support and ~~testing~~test methods relating to primary packaging, design and test manufacturing processes relating to filling and finishing of pharmaceutical containers including syringes, selection and optimization of syringe materials and evaluation of components, and assistance with compendial compliance and testing and regulatory filings.

8. Prior to my current role, I worked at Schott Pharmaceutical Packaging (“Schott”) in Germany and Switzerland from 2000 to 2015. Schott is a well-known manufacturer of both glass and polymer pre-filled syringes. At Schott, I held the following roles in the Syringe Department: Head of Product Technology for New Products from 2000-01; Manager for Research & Development and Quality Management from 2001-03; Head of Scientific and Regulatory Advisory from 2004-07; Manager of Scientific Advisory from 2007-09;

Global Quality Manager for Regulatory Affairs from 2009-11; and finally, Head of Technical and Quality Support for the Syringe Business from 2011-15.

9. At Schott, my responsibilities included support of the global syringe business unit regarding questions of technical product requirements and specifications, and support of the global packaging development group for primary and secondary packaging systems with regard to technical, quality and regulatory requirements. My role also included designing and conducting testing programs for packaging systems, especially for glass and polymer syringe systems, including machine packaging and validation. I coordinated test programs with external partners for extractables and leachables analyses and material testing.

10. After earning my degree and prior to working at Schott, I was the Engineering Supervisor at Abbott GmbH ([“Abbott”](#)) in Germany from 1994 to 1999. At Abbott, I was a Research Technician from 1994-95, and then a Supervisor in Engineering Processes from 1995-99. At Abbott, my responsibilities included maintenance and calibration of equipment for manufacturing and research & development, and optimizing packaging lines for pharmaceutical primary and secondary packaging, including container filling and blister packaging. I also ~~lead~~[led](#) the cleaning and sterilization center for glass equipment at Abbott.

11. During my time at Abbott and Schott I was actively involved in different types of sterilization validation according to ISO requirements for, e.g., steam sterilization, VHP sterilization and decontamination, radiation sterilization (gamma, ebeam and x-ray), and ETO sterilization. My experience includes cycle development, PCD-development, and BI positioning studies as well as cycle confirmation runs. I have performed studies on both empty Container Closure Systems (“CCS”) at the pre-sterilization step prior to filling and on pre-filled CCS products for terminal sterilization. My experience includes such studies

for pre-filled syringe systems, for which I monitored the sterile field application (blister), viscosity adjustments, and sterilization after non-aseptic processes.

12. During my time at Schott and Abbott, I designed and analyzed sterilization techniques and processes for both empty CCS, i.e., pre-sterilization prior to filling (i.e., empty syringes), in addition to terminal sterilization with filled CCS (i.e., sterilization that occurs after the syringe has been filled) depending on the intended use for the pre-filled syringe system. I gained experience with respect to pre-filling sterilization because syringe suppliers typically sterilize syringes before providing them to customers. I also gained extensive experience with respect to the sterilization of pre-filled syringes because syringe suppliers often perform testing on such syringes to ensure that a syringe design will satisfy the downstream needs of customers, including syringes for use with any drug products that were to be terminally sterilized (i.e., sterilized after filling).

~~11~~13. In addition to my work experience, I have ~~many~~13 years of experience participating in professional organizations, standards setting organizations, and pharmacopeias relating to pharmaceutical packaging including syringes. For example, I am an active member of the ISO technical committee, TC 84 on “Devices for administration of medicinal products and catheters,” wherein I am a member of several working groups including WG 3 (needle-based injection systems -injector, container and pen needle) and WG 11 (syringes). I am also an active member of the ISO technical committee, TC 76 on “Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use,” wherein I am a member of several working groups including: WG 2 (rigid container system and related accessories for parenterals and injectables) of which I am the Convenor¹, WG 4 (elastomeric parts and

¹ As convenor, I lead the WG experts participating from 22 member countries (TC76) which have been delegated from national standardization bodies, e.g. ANSI (USA),

components and related secondary packaging), and WG 6 (primary packaging systems for medicinal products). I was *ad hoc* group leader for the WG 2 ISO committee that developed standard 11040-4 for glass syringes and 11040-6 for polymer syringes. I am also the Swiss Medic Delegate for the European Directorate for the Quality of Medicines (EDQM) working group WG 16 on the European Pharmacopoeia Chapter 3 relating to plastics. In addition, I am the faculty head for the area: Transfusion, Infusion and Injection within the German Standardization Body (DIN) for NA 063 Medicine. This faculty leads 6 subgroups related to Injection systems, Transfusion and Infusion container including single use container for IVD, Packaging Systems for filling and application of medicinal products, Fridges and Freezers for medicinal products, Quality Management for Primary Packaging and Elastomers for Primary Packaging.

~~12~~14. In addition to the above, I have given numerous presentations at symposiums, conferences, and other professional organizational meetings, including many presentations over the years that relate to parenteral manufacturing, pre-filled syringes, extractables, leachables, the packaging of syringe systems, and regulatory (FDA/EMA) requirements for the packaging of parenterals.

~~13~~15. My curriculum vitae is attached as ~~Exhibit 1004~~Appendix 1 to my report, and provides further information about my experience, expertise, and presentations.

~~14~~16. Through my professional experience, I have gained extensive expertise in syringe and syringe materials and components, including their manufacturing, testing, siliconization,

which have been delegated from national standardization bodies, e.g. ANSI (USA), AFNOR (France), DIN (Germany), for that group.

characterization, regulatory compliance, sales, and have a deep understanding of the worldwide syringe market. ~~Through this experience,~~ I also have gained knowledge and experience relating to pre-filled syringes, the characterization of syringe stopper movement forces within a syringe, issues relating to syringe component leachables and extractables, issues relating to siliconization, regulatory requirements on particulate matter for parenterals, and sterilization of container closure systems.

~~15~~17. I am being compensated at my standard rate of \$450/hour. My compensation is in no way contingent upon my opinions or the outcome of the proceeding.

IV. Relevant Legal Standards

~~16~~18. I am not an attorney, and therefore my understanding of patent law and the legal standards set forth in this report is based on explanations provided to me by counsel.

~~17~~19. I understand that for any claim of a patent to claim priority to an earlier application (*i.e.*, to benefit from the earlier application's filing date), the claims of the later patent must be fully supported by the disclosure of the earlier patent application to which priority is claimed. I understand that in order for the claims to be supported, the earlier application's disclosure must be sufficient to allow a person of ordinary skill in the art to reasonably conclude that the inventors were in possession of the claimed invention.

~~18~~20. I understand that the '631 patent claims priority to a number of patent applications, the earliest of which are European Patent Application No. EP12174860, filed on July 3, 2012, and European Patent Application No. EP12189649, filed on October 23, 2012. However, as I explain in Section VI.A below, the July 3, 2012 Application No. EP12174860 filing does not support the issued claims of the '631 patent, and therefore the patent claims are not entitled to that priority date, and instead should have a priority date of no earlier than October 23, 2012. Nevertheless,

for the purposes of my opinions, I have considered the state of the art as of and shortly before July 3, 2012, and the level of knowledge that a POSITA would have possessed at that time.

Unless I state otherwise, whenever I refer to any principle or technical subject matter as having been known or understood, this is meant to denote the knowledge and understanding of a

POSITA at or prior to July 3, 2012.⁺²

A. Claim Construction

~~19~~21. It is my further understanding that the numbered paragraphs at the end of the disclosure of a U.S. Patent are the patent “claims” that define the metes and bounds of the alleged invention. I understand that ~~these~~the claims of the ‘631 patent are what is being challenged in the present IPR proceeding.

~~20~~22. I have been informed that, in this proceeding, the Board must determine the scope of the claims by giving the claims their ordinary and customary meaning in light of the specification, as the claims would be interpreted by one of ordinary skill in the art.

~~21~~23. I understand that patent claims generally include a “transitional” term or phrase, such as “consisting” or “comprising,” which may connect the preamble of the claim to the body of the claim. I have been informed that if a claim uses the term “consisting” as a transition term, that means that the claim is a “closed” claim, which means that the claim is limited to the claim features that follow the transition term and nothing else. On the other hand, I understand that the transition term “comprising” denotes an “open” claim, which means that the claim is not limited

⁺²
 It is my opinion that there is no appreciable difference between the state of the art as of July 3, 2012 and as of October 23, 2012, as it relates to the subject matter claimed in the ‘631 patent: ~~To the extent I have cited any references herein whose publication date is after July 3, 2012 (e.g., the Reuter reference), it is my opinion that the subject matter disclosed in such references was well-known in the art prior to July 3, 2012 as well.~~

to only the features recited in the claim, and could encompass the listed elements as well as other unrecited elements.

B. Invalidity

2224. I understand that Regeneron bears the burden of proving that the challenged claims of the '631 patent are invalid, and must prove this by a preponderance of the evidence, which means that invalidity must be shown to be more likely than not.

2325. I have been asked to consider the question of whether the claims of the '631 patent would have been obvious. I understand that this analysis must be conducted from the perspective of the person of ordinary skill in the art, and whether the skilled artisan would consider any differences between the prior art and what is claimed to have been obvious. To make this assessment, I have been informed that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness. I have been instructed that one must not engage in hindsight. Rather, I understand that one should instead consider what the person of ordinary skill in the art would have reason to pursue further, and steps that were routinely done, such as in response to known problems, steps or obstacles.

2426. It is my understanding that the following is a non-exhaustive list of rationales that may support the obviousness of an invention: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; use of a known technique to improve a similar device (method, or product) in the same way; applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; choosing from a finite number of identified,

predictable solutions, with a reasonable expectation of success; and some teaching, suggestion, or motivation in the prior art that would have led a POSITA to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

2527. It is my understanding that the motivation to combine prior art references may be implicit and may be found in the knowledge of one of ordinary skill in the art, or in the nature of the problem to be solved. Specifically, it is my understanding that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the “improvement” is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable or more efficient. It is my further understanding that the motivation to combine references may be found in the nature of the problem to be solved where prior art references are directed to precisely the same problem.

2628. I also understand that prior art may be relied on for its express disclosure and teachings. I also understand that the prior art may be relied upon for a teaching of features that are necessarily present in the prior art reference even if that specific feature is not expressly or explicitly disclosed.

2729. I understand that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of non-obviousness, if any such indicia are offered. These must be considered to ensure that, for example, there were not some unanticipated problems, obstacles or hurdles that may seem easy to overcome in hindsight, but which were not readily overcome prior to the relevant invention date of the patents/claims at issue here. I understand that these objective indicia are also known as “secondary considerations of non-obviousness,” and may include long-felt but unmet need and unexpected results, among

others. I also understand, however, that any offered evidence of secondary considerations of non-obviousness must be ~~comparable~~commensurate with the scope of the challenged claims.

This means that for any offered evidence of secondary considerations of non-obviousness to be given substantial weight, I understand the proponent of that evidence must establish a “nexus” or a sufficient connection or tie between that evidence and the merits of the claimed invention, which I understand specifically incorporates any novel element(s) of the claimed invention. If the secondary consideration evidence offered actually results from something other than the merits of the claim, then I understand that there is no nexus or tie to the claimed invention. I also understand it is the Patent Owner who has the burden of proving that a nexus exists, and I understand that secondary considerations will not overcome a strong showing of obviousness.

C. Person of Ordinary Skill in the Art

2830. I have been asked to review ~~U.S. Patent No. 9,220,631~~ (“the ‘631 patent”) from the perspective of a person of ordinary skill in the art (“POSITA”) as of the earliest claimed priority date for the patent—July 3, 2012. I have been asked to evaluate the disclosure and claims of the ‘631 patent. I have been further asked to consider whether the prior art renders obvious the pre-filled syringe covered by claims 1-23 of the ‘631 patent.

2931. It is my opinion that a POSITA relevant to the ‘631 patent would have had at least an advanced degree (Dipl.Ing, M.S., or Ph.D.), with research experience in mechanical engineering, biomedical engineering, materials science, chemistry, or a related field, or at least 2-3 years of professional experience in one or more of those fields. Furthermore, it is my opinion that a POSITA would have had experience with (i) the design of pre-filled syringes; and (ii) sterilization of drug delivery devices, including those containing sterilization sensitive therapeutics. Such sterilization experience would include experience with microbiology. Based

on my education, training and experience, it is my opinion that I can accurately represent the views of a POSITA as of the earliest claimed priority date of July 3, 2012, as to at least claims 1-23 of the '631 patent. The opinions I provide in this declaration are provided using the viewpoint of the POSITA as of July 3, 2012.

~~30~~32. Claims 24-26 relate to methods of treating a patient suffering from eye disease, by administering an ophthalmic solution using the pre-filled syringe described in claim 1. Because such intravitreal administration must be performed by an ophthalmologist, it is my opinion that a POSITA with respect to claims 24-26 would be an ophthalmologist with experience administering VEGF-antagonist drugs to patients via the intravitreal route. *See* Nema Vol. 1 at 21 (Ex. 1015.036) (“Since an excellent knowledge of the anatomy and function of the eye is required, only an ophthalmologist should attempt these procedures.”).

V. Background of the Technology

~~31~~33. ~~I understand that the~~ The asserted claims of the '631 patent are ~~generally~~ directed to a pre-filled, terminally-sterilized, ~~low-volume~~ 0.5-1 ml glass ~~syringes~~ syringe containing a VEGF-antagonist solution, and having ~~low-amounts-of~~ between about 1-100 µg, about 3-100 µg or about 1-50 µg silicone oil on the barrel, and possessing ~~low~~-break loose and glide forces for the syringe stopper that are less than about 11N or 5N. In this section, I explain the technical concepts underlying the claims of the '631 patent, and also explain how each of these concepts were well known in the art prior to the effective filing date of the '631 patent.

A. Intravitreal Administration of VEGF Antagonists

~~32~~34. “Intravitreal administration” refers to “injection directly into the vitreous cavity of the eye.” Nema Vol. 1 at 20 (Ex. 1015.035). For such injections, “[e]xtreme care and precise

technique are required to minimize or prevent damage to the eye, especially to the corneal endothelium.” *Id.* at ~~036~~21 (Ex. 1015.036). Numerous medical complications could occur from incorrect intravitreal administration, and only small volumes of around 0.1 mL or less should be injected. *Id.* As such, intravitreal injections are typically administered only by ophthalmologists. *Id.*

~~33~~35. Several VEGF-antagonists were known and commercially available, and utilized to various degrees ~~for different reasons beyond the scope of my opinion,~~ before the earliest priority date of the ‘631 patent, including ranibizumab (Lucentis®), aflibercept (Eylea®), and pegaptanib (Macugen®). See Lucentis Label (Ex. 1027), Eylea Label (Ex. 1040), 2008 Macugen Label (Ex. 1009). All three of these VEGF-antagonist drug formulations are intended for intravitreal administration. Because VEGF-antagonist formulations are administered by injection into the eye, they are typically dispensed either in vials to be used with empty disposable syringes (*see* Eylea Label at 14 (Ex. 1040.014),) or in what is known as a pre-filled syringe (*see* 2008 Macugen Label (Ex. ~~1009.001~~1009)).

B. Pre-filled Syringes

~~34~~36. As the name suggests, a pre-filled syringe (“PFS”) is a syringe that is packaged and sold with a drug formulation already loaded into the syringe. See Sigg (Ex. 1007) at 1:10-12, 15-17 (“Prefilled containers are a type of medical device that are filled by the manufacturer at the time of assembly and provided to the end user, generally a health-care provider or a patient requiring treatment, in a sterile condition. ... Of the various types of prefilled containers, prefilled syringes are the most common and best suited for parenteral administration of therapeutic products.”). The drug in a pre-filled syringe is typically in a form that is ready to be administered

to a patient. Thus, “[p]refilled syringes are containers and drug delivery systems at the same time.” [Fries at 26](#) (Ex. 1012.006).

[3537](#). Pre-filled syringes are considered to be a type of “primary packaging,” which generally refers to the components of a drug delivery system that are in direct contact with the drug formulation. Primary packaging also includes components such as vials, bottles, closures, etc. Primary packaging can be distinguished from “secondary packaging,” where the latter refers to packaging components such as aluminum caps, cardboard boxes and blister packs that are not intended to come into direct contact with the drug formulation. The following description, taken from FDA’s drug packaging documentation, reflects generally accepted definitions of packaging components:

A primary packaging component means a packaging component that is or may be in direct contact with the dosage form. *A secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form.

A container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

Ex. 1041.005.

[3638](#). A pre-filled syringe comprises certain typical components, such as a syringe barrel, which can be made of glass or plastic, with a front end closure system (such as the Vetter

OVS® system), a plunger rod, ~~or~~and a stopper^{2,3} Shah at 56 (Ex. 1011.002) (describing components of a pre-filled syringe). Pre-filled syringes are also supplied with a needle, referred to as a hypodermic needle, which may be “staked in” (*i.e.*, affixed to the administration end of the barrel), or may be connectable to and detachable from a tapered end of the syringe barrel. *See* Fries at 22 (Ex. 1012.003) (describing components of a pre-filled syringe); Nema Vol. 1 at 319-322 (Ex. ~~1015.344-347~~1015.334-337) (section on “Components for Prefillable Syringes and for Cartridges”); Ex. 1042 (ISO-7864 describing hypodermic needle).

~~37~~39. Connecting a needle to the tapered end of a syringe barrel is most often done by using what is known as a “Luer” connection, which is a type of tapered connection for fitting the tip of the syringe barrel into the bottom of the needle. Luer connections can be either “Luer lock” connections, where the syringe barrel and needle are securely joined together through a screw or tab connection, or a “Luer slip” connection, wherein the barrel and needle are held together by friction at the tapered Luer connection.

~~38~~40. The picture below illustrates how typical components of a syringe may be joined together to create a pre-filled syringe, using the example of a needle with a Luer lock connector.

~~ASSEMBLY INSTRUCTIONS FOR PREFILLED SYRINGE~~

~~Figure 2: Components of pre-filled syringe~~

~~Ex. 1011.002 (Figure 2)~~

~~39~~41. Prior to July 2012, pre-filled syringes were well-known in the art for parenteral administration of therapeutic products, and offered advantages over traditional therapeutic

²~~The stopper can also be referred to as a piston. See e.g. Ex. 1008 at 9:21-25.~~

³~~The stopper can also be referred to as a piston. See, e.g., Boulange (Ex. 1008) at 9:21-25.~~

packaging such as their ease of use, a reduced risk of contamination, elimination of dosing errors, an increase in drug supply, and a reduction in waste. [Shah at 56](#) (Ex. 1011.002); ~~see~~ [Sigg](#) (Ex. 1007) at 1:13-17. Pre-filled syringes began to gain popularity in the early 1980s, and by 2010 their use had become widespread in the injectable therapeutics industry. [Nema Vol. 1 at 314](#) (Ex. 1015.329). While it is possible to use plastic syringe barrels for pre-filled applications, by 2010 glass barreled syringes held a significant market share in ~~pre-filled~~ [prefilled](#) syringes over plastic. *See id.*

~~40~~[42](#). Pre-filled glass syringes had been approved by the FDA prior to 2012 for a variety of applications, including for the intravitreal injection of Macugen[®] (pegaptanib sodium injection), a VEGF antagonist formulation indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD). *See* [2004 Macugen Label \(Ex. 1062\); 2008 Macugen Label \(Ex. 1009\)](#).

~~41~~[43](#). Pre-filled syringes can be made from standard commercially available syringes that are filled by a syringe filler. Such syringes are generally sold in standardized sizes. The most common example of standardized syringe sizes are those prescribed and promulgated by the International Organization for Standardization (“ISO”). For example, ISO-11040-4 sets forth the ISO’s standardized sizes for syringe barrels. *See* [ISO-11040-4](#) (Ex. 1028). In the 0.5 mL to 1.0 mL volume range, [which are the smallest standard sizes](#), there are three ISO standard sets for barrel dimensions, as shown in the table below:

[Adapted from ISO-11040-4 at 4 \(Ex. 1028.008\)](#)

Nominal Volume	Barrel Inner Diameter (d_2)	Barrel Length (l_2 l₁)
0.5 mL	4.65 mm	47.6 mm
1 mL (long)	6.35 mm	54 mm

Nominal Volume	Barrel Inner Diameter (d_2)	Barrel Length (L_1)
1 mL (short)	8.65 mm	35.7 mm

Adapted from Ex. 1028.008

⁴²44. The ISO has also developed a set of needle standards or “gauges,” which may be found in the ISO-~~9626~~9626-1991 (Amendment 1 dated 2001) standard for medical grade tubing (ISO-7864 provides further standards for sterile hypodermic needles made from such tubing). The higher the gauge number, the more fine (*i.e.*, thin or narrow) the needle. For example, a standard 30 G x 0.5 inch needle would have an outer diameter of 0.298 to 0.320 mm, an inner diameter of 0.133 to 0.165 mm, and a length of 0.5 inches. ISO-9626 Am.1 at 2 (Ex. 1043.006). A 25 G x 0.5 inch needle would have an outer diameter of 0.5-0.53 mm, an inner diameter of 0.232 to 0.292 mm, and a length of 0.5 inches. *Id.*

⁴³45. For intravitreal applications, it was understood that “[g]enerally, not more than 0.1 mL may be injected.” Nema Vol. 1 at 21 (Ex. 1015.036). Thus, a smaller volume syringe, such as 0.5 mL or 1 mL,³⁴ is used for intravitreal applications. *See* Furfine (Ex. 1021) at [0059], [0061] (disclosing 1 mL prefilled glass syringe for VEGF-antagonist); Sigg (Ex. 1007) at 21:10-25 (disclosing 0.5 mL prefilled syringe for Lucentis); 2004 Macugen Label at 11 (Ex. 1062.009) (disclosing that Macugen is provided in a 1 mL glass syringe). Similarly, because injecting a drug into the eye is a delicate task, a fine gauge needle would be used for intravitreal applications, generally at least a 27 G needle or a higher numbered gauge (*i.e.*, thinner). *See, e.g.*,

³⁴ The deliverable volume of drug product in the syringe will always be less than the nominal volume of the syringe. ISO-11040-4, which sets forth the ISO’s standardized sizes for syringe barrels, does not provide sizing information for syringes of less than 0.5 mL. ISO-11040-4 at 4 (Ex. 1028.008).

2008 Macugen Label (Ex. ~~1009.007~~ (1009) (Macugen PFS using a 30 G needle for intravitreal injection of ~~Macugen~~ pegaptanib); Ex. 1027 (30 G needle for intravitreal injection of Lucentis)).

C. Syringe Stopper Forces

~~44~~46. As may be readily understood, dispensing medicament from a syringe involves the application of force on the plunger rod, which causes the stopper to move through the syringe barrel and thereby expel the liquid drug formulation out of the needle-end of the syringe barrel.

~~45~~47. Two types of forces are generally used to describe the movement of a syringe stopper through the barrel upon application of force to the plunger rod. The first is the “break loose” force or the stopper “activation” force, which is the force required to start the movement of the stopper from its resting position. The break loose force is ~~only that~~ the amount of force needed to get the stopper to initially start moving, and is thus only a function of the friction between the stopper and the barrel. See Boulange (Ex. 1008) at 15:6-8 (“the friction force B is the force required, under static conditions, to break the contact at the contact region 10 between the piston 3 and the container 2”); Rathore at 469 (Ex. 1087.003) (explaining that break loose force is the “initial force required to set the plunger in motion”).

48. The second type of force is the “gliding” force or “glide” force ~~or~~ (also referred to as “slide” force ~~or~~ “extrusion” force, or “sustaining” force), which is “the force that is needed to sustain movement of the plunger.” Nema Vol. 1 at 343 (Ex. 1015.358) (“When looking at the gliding behavior of syringe plungers one makes distinction between the force that is needed to make the plunger start moving and the force that is needed to sustain movement of the plunger. The former is typically called ‘activation force’ or ‘break-loose force,’ while for the latter the names ‘gliding force’ or extrusion force’ or ‘propagation force’ are used.”); Boulange

(Ex. 1008) at 15:9-12 (describing glide force as “the friction force S is the force required, under dynamic conditions, for moving the piston 3 in the container 2”). The glide or slide force is thus a function of both the friction between the stopper and barrel, and the hydrodynamic force required to expel the fluid out of the syringe (which is a function of, *inter alia*, needle size, stopper speed, and fluid viscosity). See Rathore at 469 (Ex. 1087.003) (explaining that extrusion force (*i.e.*, slide force) is the force needed to sustain plunger movement by overcoming the hydrodynamic pressure and the frictional forces).

~~46~~49. The Nema textbook presents an exemplary force⁵ curve for a pre-filled syringe, below.

Ex. 1015.359

~~47~~50. Based on the shape of the ~~above~~ force curve from Nema, especially the sharpness of the initial peak(s), a POSITA would understand that this is either a force curve generated from actual measurements, or a diagrammatic representation approximating a real force curve, for an aqueous or other low viscosity formulation⁶ because such curves typically reflect a break loose force that spikes and then drops off quickly into a somewhat consistent glide force. Nema describes the above force curve, and the break loose and glide forces depicted therein, as follows:

⁵ The International System of Units has defined the measured unit of “force” as “Newtons” (abbreviated “N”). One N is the force needed to accelerate one kilogram of mass at the rate of one meter/second² in the direction of the applied force.

⁶ I note that the force curve for high viscosity drug formulations could be different. A POSITA would understand, however, that the VEGF antagonists disclosed in the prior art references described below have aqueous formulations, and accordingly have relatively low viscosities.

A typical force curve for the gliding of a plunger in a prefilled syringe is given below.

The curve displays the force that is needed to move the plunger as a function of the distance that the plunger travels into the syringe barrel. From this curve it follows that it needs a certain build-up of force to start the movement of the plunger. Thereafter the force to keep the plunger moving decreases. Gliding forces thus are typically lower than break-loose forces. Break-loose forces must be low enough to guarantee smooth activation of the syringe. Gliding forces equally must be at an acceptably low level.

Moreover gliding forces must be continuous, or without increases and decreases. Should the movement be 'interrupted,' then one speaks of shattering of the syringe. Shattering obviously for the comfort of the patient must be avoided (Fig. 10).

[Nema Vol. 1 at 343](#) (Ex. 1015.358).

⁴⁸[51](#). The break loose force is largely attributable to the ageing of the stopper within the syringe, which is made out of an elastomeric (rubber) material, and will upon ageing ~~over time expand outwards within the~~ [interact with the](#) syringe and become sticky, forming a tighter seal against the inside of the syringe barrel. The tighter seal results in a higher force required to initially displace the stopper, which is the break loose force. Because the break loose force is between the stopper and the inside of the barrel, and is the force required to get the stopper to just about begin moving, the break loose force is largely unaffected by the viscosity of the fluid in the pre-filled syringe.

⁴⁹[52](#). There is no set minimum or maximum force required for break loose or glide forces in a pre-filled syringe. However, a POSITA would have been well aware that commercially available syringes were commonly sold as "10 and 5" syringes, meaning they would have a maximum break loose force of 10 N and a slide force of 5 N. *See, e.g.,* [Fries at 27](#) (Ex.

1012.007) (explaining that “plunger gliding forces in the range of 5 to 10 N” were sufficient to satisfy “syringe functionality” requirements).

While “10 and 5” N are understood to be acceptable forces for such syringes, a POSITA would have understood that the actual tested forces ~~would likely~~ may be lower. For example, as shown above, the exemplary force curves for pre-filled syringes presented in Nema demonstrate break loose forces of approximately 8.25 N and glide forces below 2 N. Nema Vol. 1 at 344 (Ex. 1015.359).

~~50~~53. ~~For~~ A POSITA would understand that for a syringe to function properly, the stopper should be able to glide through the barrel in a relatively smooth manner to dispense the drug formulation contained within. Smooth movement of the stopper is desired to ensure patient comfort and safety during administration of the drug. The smoothness of delivery becomes even more important when the medication is ~~being~~ injected directly into the eye, as with an intravitreally delivered drug formulation. In addition, lower forces are required for intravitreal injection because of the delicate nature of the eye, requiring “[e]xtreme care and precise technique” for a safe injection. Nema Vol. 1 at 21 (Ex. 1015.036. ~~Thus, it is important to reduce the amount of friction between the stopper and the inside of the syringe barrel, in order to have break loose and glide forces that are appropriate for drug delivery and have the stopper move through the barrel with relative ease.~~).

D. Siliconization of Pre-filled Syringe Components

~~51~~54. It was well known before the ‘631 patent priority date that the friction between the stopper and the barrel of a syringe can be reduced by providing an interface between their surfaces. Such an interface can be created by coating the components of the syringe such as the barrel and the stopper with silicone oil, in a process known as “siliconization.” See, e.g., Nema

Vol. 1 at 50 (Ex. 1015.065) (“Silicone oil coating is commonly used on stoppers and on the inside of syringes or cartridges as a lubricant to enable movement of the plunger. . . . Current [baked-on] processes for siliconization of prefilled syringes or cartridges apply well controlled amounts and involves baking of the silicone emulsion.”); id. at 330 (Ex. 1015.345) (“To meet the need for lubricity and sealability, syringe manufacturers use silicone to coat the glass barrels and elastomer components.”).

5255. Silicone oils are one of the most common and preferred lubricants for use in syringes because they are “viscous, inert materials with excellent characteristics as hydrophobic lubricants.” Fries at 26 (Ex. 1012.006). Silicone oils generally consist of a mixture of polydimethylsiloxane (PDMS) molecules with Si-O chains, varying in length and number of OH groups. *See* Fries at 26 (Ex. 1012.006); Nema Vol. 1 at 299 (Ex. 1015.314). The molecular structure of silicone oils “determines how silicone oil layers are adsorbed onto glass surfaces and the distribution, thickness, composition, and uniformity of the layers.” Fries at 26 (Ex. 1012.006).

5356. Siliconization is recommended for syringe components that experience dynamic friction, including the inside of syringe ~~barrel~~barrels and potentially also on the surface of elastomeric components such as the plunger stopper. *Id.*; Nema Vol. 1 at 315 (Ex. 1015.330) (“Silicone facilitates ease of movement of pistons in filling and stoppering equipment, and allows pistons to glide smoothly on activation of syringes.”). In pre-filled syringes, not only the siliconization of the plunger, but also the siliconization of the inside of the barrel is important. Nema Vol. 1 at 343 (Ex. 1015.358) (“The degree and way of siliconization of the plunger, the degree and way of siliconization of the inside of the barrel and the homogeneity of siliconization

of the inside of the barrel over the total path length of the plunger strongly influence break-loose and gliding forces.”).

⁵⁴57. Further, because stoppers are generally made from elastomeric materials, which may be sticky, siliconization can be used to prevent the sticking of rubber stoppers to the syringe barrel. *Id.* at 341 (Ex. 1015.356) (“Siliconization of rubber closures is necessary to overcome the stickiness that is inherent to typical rubber formulations that are used for parenteral stoppers.”); *id.* at 330 (Ex. 1015.345) (“To meet the need for lubricity and sealability, syringe manufacturers use silicone to coat the glass barrels and elastomer components.”).

1. “Oily” or “Spray-on” Siliconization

⁵⁵58. One known method of siliconization involves spraying silicone oil directly onto the inside of the syringe barrel to form a lubricant coating on the inside of the barrel. This process is known as “oily” siliconization or “spray-on” siliconization. *See, e.g., Fries at 26* (Ex. 1012.006) (“oily”); Schoenknecht at 10 (Ex. 1013.004) (“oily”); Badkar at 566 (Ex. 1044.003) (“sprayed-on”). For a typical 1 mL syringe, oily siliconization requires about 0.4 mg to 1.0 mg of silicone oil to be deposited on the inner surface of the syringe barrel. *See Chacornac* (Ex. 1014) at [0026]; For example, as explained in Badkar, 0.5 mg to 0.8 mg (500 µg to 800 µg), according to syringe manufacturers, was typical for staked-in needle syringes. Badkar at 566 (Ex. 1044.003).

⁵⁶59. While the oily method is a relatively cheap and effective way to deposit silicone oil on syringe components, oily siliconization has long been known to have several shortcomings, especially when used in pre-filled syringes. One such shortcoming occurs when the rubber stopper within a pre-filled syringe over time starts to displace the silicone coating on the inside of

the barrel and comes into direct contact with the inner glass surface, causing what is known as the “break loose effect.” [Schoenknecht at 10](#) (Ex. 1013.004) (“[B]reak loose effect ... can occur during storage when the rubber closure, inside the syringe barrel, expands outwards so that eventually it displaces the low friction silicone coating and comes into direct contact with the inner glass surface.”); [Shah at 56](#) (Ex. ~~1011~~ [at 61011.006](#)). The break loose effect causes the stopper to essentially stick to the barrel, requiring higher forces to displace the stopper (*i.e.*, higher break loose or activation forces).

This break loose effect is undesirable, and potentially dangerous to the patient, as described by the Schoenknecht article:

The user cannot detect the problem until the point of administration when they try to depress the plunger. Because the rubber closure is essentially stuck to the inside surface of the syringe, a high initial force is needed to shift it. The needle has already penetrated the patient’s skin and the tip is positioned in their tissue at this point, so the lack of control as the extra force is applied and the potential for a sudden movement as the rubber closure is freed up, is clearly undesirable.

[Schoenknecht at 10](#) (Ex. 1013.004). As can be readily understood, the break loose effect is even more undesirable and potentially dangerous when a pre-filled syringe is being used for intravitreal administration of a drug, on account of the danger posed to the patient’s sensitive eye structures once the needle has penetrated the eyeball and entered the vitreous humor. *See* [Nema Vol. 1 at 21](#) (Ex. 1015.036) (detailing the potential negative consequences of imprecise intravitreal administration).

~~57~~[60](#). Utilizing a larger amount of silicone oil is not an acceptable solution to the break loose effect. Oily siliconization already uses a relatively high amount of silicone oil (greater than 200

~~μg~~ug), and this ~~high~~higher level of silicone oil (and potentially further increasing the amount of silicone oil) creates other undesirable problems. Possibly the most significant problem with higher levels of silicone oil is that silicone oil “can interact with drug formulation components.” Nema Vol. 1 at 315 (Ex. 1015.330). This is especially problematic for protein therapeutics, because “[s]ub-visual silicone oil particles are thought to promote protein aggregation which can increase the severity of immune responses and reduce the drug’s tolerability.” Schoenknecht at 10 (Ex. ~~1010.004~~; Ex. 1013.004) (“One particularly common problem has been that [protein therapeutics] can react with the oily form of silicone, which is used as a lubricant to coat the sliding components of the syringe.”). Thus, a POSITA would want to avoid higher levels of silicone oil in pre-filled syringes containing sensitive protein formulations such as VEGF antagonists, because of potential “incompatibilities includ[ing] aggregation, deformation, and inactivation of native protein structures.” Fries at 26 (Ex. 1012.006).

~~58~~61. Moreover, with oily siliconization, it had also been postulated that silicone oil can flow within the syringe barrel from areas of thicker coverage. Chacornac (Ex. 1014) at [0024]. “Detachment of silicone oil in water-filled syringes is possible and can result in particulate matter and clouding phenomenon.” Nema Vol. 1 at 315 (Ex. 1015.330). Silicone oil droplets in injectable formulations are ~~especiall~~y problematic in the case of drugs for intravitreal administration, because in addition to potentially causing protein instability from aggregation, injecting silicone oil droplets into the eye could cause visual impairment including the perception of “floaters” in the eye and an increase in intra-ocular pressure. *See, e.g.,* ~~Ex. 1001 at 50-55~~ (“However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including ‘floaters’ and an increase in Leys at 697-

698 (Ex. 1065.005-006) (“Silicone oil complications, including elevated intraocular pressure
.”)”; .. are not uncommon and can be vision threatening.... Removal of these droplets may
help decrease symptomatic floaters and other complications.”); Nema Vol. 1 at 21 (Ex.
1015.036) (explaining the precautions necessary for intravitreal administration); Liu at 1033
(Ex. 1025.011) (“silicone contaminants, when injected into the vitreous cavity at the time of
anti-VEGF injections, could cause persistent elevations in [intraocular pressure]”).

5962. Thus, prior to 2012, a POSITA would have been well aware of the drawbacks of
oily siliconization, and would have had strong motivation to utilize alternative methods of
applying silicone oil on the syringe barrel.

2. “Baked-On” Siliconization

6063. It was well known in the art prior to 2012 that siliconization could be performed
to achieve a more homogeneous and thinner coating of silicone oil, while reducing the amount of
silicone oil required, through a process known as “baked-on” siliconization, which “involves
application of a silicone oil emulsion and “heating the silicone-coated syringe to a specific
temperature for an appropriate time.” Schoenknecht at 10 (Ex. 1013.004); see, e.g., Nema Vol.
1 at 315 (Ex. 1015.330) (describing siliconization achieved by “baking silicone at high heat onto
the glass barrels”); Shah at 54 (Ex. 1011.004) (same); Fries at 26 (Ex. 1012.006) (same).

6164. It was also 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. For example, U.S. Patent Publication No. 2012/0091026 (~~Ex. 1014~~)
“Chacornac”⁷ explains, with respect to baked-on siliconization, that “the siliconizing operation

⁷ Chacornac was filed on October 17, 2011.

comprising a polymerization step (i) is more precise and more homogenous than [sic] a simple standard siliconizing operation; and (ii) *makes it possible to reduce the amount of silicone that is used...by about a factor of 10 without any loss of lubricating effect.*” Chacornac (Ex. 1014) at [0026] (emphasis added). Similarly, Boulange (~~Ex. 1008~~ published in 2009) at Table 7 shows ~~the low break loose and slide forces for~~ that a pre-filled syringe including 4 ~~µg~~ µg/cm² silicone on the syringe barrel (prepared using the baked-on method), ~~whereas 50 µg/cm² is used in Example 5 for the spray-on method.~~ Fries (Ex. 1012) achieved comparable break loose and slide forces compared to pre-filled syringes which included 50 µg/cm² silicone oil on the syringe barrel (prepared using a spray-on method). See Boulange (Ex. 1008) at Table 7; see also id. at 20:15-21 (describing that Scenario 1 had 4 µg/cm² baked-on silicone lubricant, while Scenario 2 had 50 µg/cm² sprayed on silicone lubricant). Fries also reports that such baked-on siliconized syringes having “low levels” of silicone oil (*i.e.*, those that reduce “[t]he amount of extractable silicone oil . . . below the detection limit (0.03 mg [*i.e.*, 30 ~~µg~~ µg])”) maintained syringe functionality, with “plunger gliding forces in the range of 5 to 10 N.” ~~Ex. 1012.006-007. Similarly, Badkar (Ex. 1044) discloses that “baked-on syringes . . . approximately contain ten-fold less free silicone oil” and “showed no deleterious impact on product quality.” Ex. 1044.008.~~ Fries at 26-27 (Ex. 1012.006-.007).

6265. Another benefit of baked-on siliconization is that the heat treatment affixes a thin layer of silicone oil lubricant—possibly of single layer thickness—to the inner surface of glass syringe barrels, which helps to prevent the silicone oil from breaking off from the inside of the syringe barrel and entering the drug formulation. Fries at 26 (Ex. 1012.006) (“Mono-layers of the lubricant are affixed to the glass surface.”). This feature of baked-on siliconization 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. See [Shah at 54](#) (Ex. 1011.004) (“Baked Silicone: Binding the silicone to the glass barrel through a proprietary technology reduces the level of free silicone. This is a clear benefit for silicone-sensitive drugs.”); [Nema Vol. 1 at 315](#) (Ex. 1015.330) (“Recent 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.”); [Badkar at 571](#) (Ex. 1044.008) (“baked-on syringes . . . approximately contain ten-fold less free silicone oil” and “showed no deleterious impact on product quality.”).

~~63~~66. As explained above, [a POSITA would understand](#) there are numerous reasons to avoid silicone oil in protein drug formulations, including to avoid protein aggregation, and, in the case of intravitreal injections, to avoid increasing intraocular pressure and causing vision problems. [For example, a 2008 Article published in the Journal of Retinal and Vitreous Diseases describes “a need to review the methods of injections and utilization of syringes to decrease the amount of silicone oil that is inadvertently injected.” See Bakri at 1000](#) (Ex. [1067.005](#)). This problem ~~is~~was known to be especially acute in pre-filled syringes, because such devices come prepackaged with drug formulation contained in the device, and as such the drug formulation is in contact with the silicone oil for an extended period of time while the device is in storage. [See Kocaberra \(Ex. 1080\) \(2010 article explaining that intravitreal contamination by silicone oil droplets associated with intravitreal injection of Pegaptanib is due to the use of a pre-filled syringe\)](#). However, in syringes prepared using the baked-on siliconization method, the silicone oil molecules are believed to be held to the inner surface of glass syringe barrels by forces that “range from van de Waals forces to covalent Si-O bonds.” [Fries at 26](#) (Ex. 1012.006). Such bonds, especially the covalent bonds, which are known to be relatively strong,

hold the silicone oil to the glass surface relatively tightly as compared to oily siliconization. *See id.* (depicting the conversion of silicone oil into an Si(R)O coating which increases fixation to the glass). Thus, reducing the amount of residual silicone oil is an added benefit of baked-on siliconization.

~~6467. Reducing~~ Using less silicone oil in a syringe was well-known to be advantageous because such a syringe is less likely to negatively affect the quality of a drug product. For example, reducing the amount of ~~sub-visual~~ silicone oil particles in protein formulations ~~is~~ was known to be beneficial because such particles can increase the aggregation potential of proteins. Badkar at 570 (Ex. 1044.007). ~~Reducing~~ And as explained above, reducing the amount of ~~sub-visual particles is especially important for ophthalmologic applications, since sub-visual particle requirements are stringent, as discussed in Section V. F below~~ silicone oil in a syringe was known to be desirable for an ophthalmic application to minimize the quantity of silicone oil that may be injected into the eye. Thus, baked-on siliconization ~~is~~ was especially recommended for sensitive protein formulations such as VEGF antagonists for intravitreal administration. *See* Badkar at 569 (Ex. 1044.006) (“Overall data suggested that the baked-on silicone process was better suited for protein formulation development in PFS as it represented a lesser degree of risk for the formation of subvisible particulate matter as well as minimized any potential for protein precipitation on the Si-oil droplets.”).

~~6568.~~ It was also known that ~~baked-on~~ baked-on siliconization can reduce the incidence of the “break loose effect.” Schoenknecht at 10 (Ex. 1013.004) (“The second benefit of baked-on silicone is that it reduces the frequency of the ‘break loose’ effect.”). Specifically, as shown in the Figures 1a and 1b below, taken from ~~the Schoenknecht article (Ex. 1013),~~

comparing oily and baked-on siliconization, “baked-on silicone provides a more consistent coating of the syringe walls, which prevents the expanding rubber closure from touching the glass wall. Lubrication is maintained so that the initial force required to inject using prefilled syringes with baked-on silicone remains consistently low before and after storage.” Schoenknecht at 10 (Ex. 1013.004).

Ex. 1013.004 (Figure 1) (annotated in orange)

~~66~~69. Thus, a POSITA would understand that baked-on siliconization achieves a thinner layer of silicone oil on the inside of a syringe barrel as compared to oily siliconization. Fries discloses that a baked layer of silicone thickness on glass cartridges measured a mean of 76.83 nm ~~and~~while oily layer of silicone thickness measured a mean of 232.67 nm. Fries at 26 (Ex. 1012.006). Schoenknecht also notes that the concentration of silicone oil in the baked-on syringe is reduced. Schoenknecht at 10 (Ex. 1013.004).

~~67~~70. ~~Baked-on~~It was also known in the art that baked-on siliconization uses silicone oil emulsions such as Dow Corning 365, 35% Dimethicone⁴⁸ NF Emulsion (“DC 365”), a well-known grade of silicone oil emulsion comprising Dow Corning 360 silicone oil diluted in highly purified water (see DC365 FAQ (Ex. 1034)), which is then sprayed into syringe barrels that undergo heat treatment. See Fries at 26 (Ex. 1012.006) (“The baked siliconization method uses emulsions of silicone oil (eg, Dow ~~Coming~~Corning 365, 35% Dimethicone NF Emulsion, diluted in HPW)”; ~~Ex. 1001~~‘631 patent at 5:9-14 (“Various types of silicone oil are available, but typically either DC360 (Dow Corning®; with a viscosity of 1000 cP) or ~~DC-365~~DC365 emulsion (Dow Corning®; DC360 oil with a viscosity of 350 cP) are used for syringe

⁴⁸ Dimethicone is also referred to as polydimethylsiloxane, or PDMS, as stated in ~~52~~61, above.

~~siliconization~~siliconisation.”). The viscosity of the DC 360 silicone oil in the DC 365 emulsion is 350 cP. *Id.*

~~68~~71. In summary, a POSITA would understand that baked-on siliconization provides a number of benefits over ~~spray-on~~spray-on siliconization. Baked-on siliconization reduces the amount of silicone oil that is applied to the syringe ~~ten-fold~~tenfold. For example, the prior art discloses that a 0.5-1 mL baked-on syringe may utilize 40-100 µg of silicone as compared to 400-1000 ~~µg~~µg for the same size oily syringe. The baked-on syringe also retains the break loose and slide forces achieved by an oily syringe, but provides the benefit that the break loose force remains relatively constant over time (even after storage), which is not true of an oily syringe. Finally, the thin silicone layer created by baked-on siliconization adheres to the glass barrel of the syringe in a monolayer, thereby reducing the amount of free silicone oil, which ~~reduces the number of sub-visual particles. This makes~~a POSITA would recognize would reduce the potential for protein aggregation and risk of injection of silicone oil into the patient, as I explained above. This made baked-on siliconization particularly suited for protein-based therapeutics, ~~which are known to aggregate in the presence of sub-visual particles, and even more so, those intended for~~ and intravitreal ~~administration~~applications.

3. Coated, Uncoated, and Siliconized Stoppers

~~69~~72. One of skill in the art would also understand that the characteristics of the syringe stopper itself plays an important role in achieving low break loose and glide forces, while also avoiding break loose effect. Since the stopper (also called the plunger or piston) is in contact with and must slide along the syringe barrel, a POSITA would have understood that:

During the drug shelf life the plunger must maintain an adequate seal on the inner side of the barrel. However, at the time of administration of the drug to the patient, the plunger

also must exhibit efficient gliding behavior in the barrel to adequately transfer the syringe contents into the patient.

Nema Vol. 1 at 330 (Ex. 1015.345).

~~70~~73. Stoppers are generally made from elastomeric materials (*i.e.*, rubbers) because “[f]or a plunger for a prefilled syringe the seal is formed between the ribs of the elastomeric plunger and the inside surface of the glass or plastic barrel,” *id.* at ~~355~~ (Ex. 1015.370), and “the elasticity of such materials allows for preservation of the sterility of the packaged drug.” *Id.* at ~~339~~ (Ex. 1015.354). “P plungers for prefillable syringes are standardized by ISO 11040-5.” *Id.* at ~~346~~ (Ex. 1015.361).

~~71~~74. In order to maintain the seal between the stopper and the inside of the syringe barrel and to improve lubricity, stoppers are often themselves siliconized.

Id. at ~~341~~ (Ex. 1015.356) (“Siliconization of rubber closures is necessary to overcome the stickiness that is inherent to typical rubber formulations that are used for parenteral stoppers.”).

~~72~~75. However, as is a consistent theme in the art, pre-filled syringes were known to have additional concerns as compared to disposable syringes in relation to the stoppers used therein, because the stopper in a pre-filled syringe is in constant contact with the drug formulation throughout the storage shelf life of the drug product. Thus, a POSITA would have been aware that minimizing extractables and avoiding high levels of silicone oil are additional features that may be desirable for pre-filled syringe stoppers, as described in the following passage from the Nema textbook:

A very important difference between the plungers in prefillable and in disposable syringes however is the contact time with the drug. For a prefillable syringe this

time is expressed in years, whereas for a disposable syringe plunger it will be minutes or hours. This difference has a large impact on the type of material that the plunger is made of.

A prefillable syringe plunger will be designed to ensure adequate gliding behavior as well as to aim for low levels of material that could be extracted from the rubber into the drug product as a leachable, while disposable syringe plungers will be designed primarily to ensure acceptable administration behavior.

Id. at :347 ([Ex. 1015.362](#)) (emphasis added).

~~73~~76. It was well known prior to 2012 that providing a coating on the ~~syringe~~ stopper was a potential solution for preventing the leaching of extractables into drug formulations, as well as for reducing break loose and glide forces. *See id.* at :330 ([Ex. 1015.345](#)) (“Use of these coated stoppers provides lubricity for machinability and reduces piston clumping in feeder bowls. Additional benefits, depending on the coating used, include a decrease in particle generation and a reduction of extractables from the elastomer.”). Coated stoppers are especially useful in ~~pre-filled~~[prefilled](#) syringes for protein formulations (such as VEGF-antagonists), because the leaching of extractables would be especially problematic due to possible interactions with the sensitive drug proteins. *Id.* at :350 ([Ex. 1015.365](#)) (“Worth mentioning in this respect are biotech drugs that are used in very small quantities per dose and where no absorption by the vial stopper is allowed. ... For such applications, solutions are offered to the market in the form of coated vial stoppers and coated syringe plungers.”); *see also* [Furfine](#) (Ex. 1021) at [0059], [0061] (disclosing examples of pre-filled glass syringes with coated stoppers containing a VEGF-antagonist).

~~74~~77. Moreover, certain types of stopper coatings help reduce or eliminate the need for siliconization of the stopper, which is also desirable for pre-filled syringes containing protein formulations such as VEGF-antagonists due to the potential interactions with silicone oil. Nema Vol. 1 at 335 (Ex. 1015.350) (“Since the coating is nontacky in itself, these closures do not require any surface siliconization, which in applications where the drug is sensitive to silicone of course is of highest value.”). ~~Such coated stoppers could nevertheless achieve low break loose and glide forces without the need for additional silicone oil.~~

~~75.~~ For example, ~~the Boulange reference~~Furfine discloses pre-filled glass syringes comprising the VEGF-antagonist aflibercept that includes a FluroTec coated plunger. Furfine (Ex. 1021) at [0059]. Other stopper coatings were also known in the art. Boulange, for example, teaches that using baked-on siliconization in the syringe barrel can achieve low break loose and glide forces, and that these forces may be lowered even further through the use of ~~coated stoppers, as described further in Section VII C below. Ex. 1008 at 21:1-19. Baked-on siliconization was also known as a means to reduce or avoid the need for siliconization of the stopper. Ex. 1014 at [0026]. By avoiding siliconizing~~stoppers coated with Parylene C. Boulange (Ex. 1008) at 19-4:10. Thus, using a coated stopper was known to allow a syringe designer to minimize the use of silicone oil on the stopper, which results in less silicone oil ~~would~~that can come into contact with the drug formulation in a ~~prefilled syringe, which is desirable, as I have described above~~pre-filled syringe. As I explained above, it was well-known in the art that minimizing the amount of silicone oil used in a pre-filled syringe was highly desirable.

E. Sterilization of Pre-filled Syringes

7678. The FDA, in its guidance on aseptic filling, indicates that “terminal sterilization” is required when possible. See Ex. 1036.007. Although sterility is a general requirement for many drug products, the FDA and EMA specifically require all ophthalmic products to be sterile, including pre-filled syringes for intravitreal injection. *See, e.g., Ex. 1036.007*; 21 C.F.R. § 200.50 (a)(1) (“Informed medical opinion is in agreement that all preparations offered or intended for ophthalmic use, including preparations for cleansing the eyes, should be sterile. It is further evident that such preparations purport to be of such purity and quality as to be suitable for safe use in the eye.”).

7779. Medical products can be sterilized using, for example, “steam sterilization, radiation sterilization, gas sterilization (*e.g.*, with ethylene oxide), and chemical sterilization.” Lam (Ex. 1029) at 1:14-16. In the case of a drug product, the means used for sterilization must be compatible with the drug. *See Leventon at 1* (Ex. 1045.001) (“When deciding on a sterilization method, one of the first considerations should be product compatibility.”). Relevant to the instant case, it was known in the art prior to 2012 that protein drug formulations are sensitive to both high temperatures and interactions with certain types of radiation and substances used, for example, ~~in~~ gas sterilization, such that these sterilization techniques could affect the structure and function of the protein. *See Sigg* (Ex. 1007) at 7:29-8:2; Lam (Ex. 1029) at 1:18-25; Metzner (Ex. 1018) at [0010][0011]. For the VEGF-antagonist solutions recited in the ‘631 patent claims, high temperature sterilization processes would be disfavored, as would any contained closure system (in this case, a ~~prefilled~~pre-filled syringe) which allowed substantial quantities of a sterilizing gas to interact with the drug inside the container closure system.

7880. Several sterilization processes were known that did not require high temperatures, including sterilization using ethylene oxide (“EtO”) gas or vaporized hydrogen peroxide (H₂O₂)

(“VHP”), which were both known at least by 2008. See Carter at 42 (Ex. 1046.001) (“Until 2008, there were three options for these purposes; ethylene oxide (EO), gas plasma, and ozone systems.”); *id.* at ~~.002~~43 (Ex. 1046.002) (“Vaporized hydrogen peroxide (VHP) technology was originally developed by STERIS Corporation and introduced in the early 1990s. It soon became a ‘gold standard’ for pharmaceutical sterilization, in critical environments where drugs are produced and packaged.”). EtO sterilization has been used since the 1950s and VHP systems since at least the 2000s to sterilize heat and ~~moisture-sensitive~~moisturesensitive medical devices. *Id.* at ~~.001-.002~~42-43 (Ex. 1046.002-003). EtO and VHP can be applied to medical devices to achieve a type of sterilization referred to in the ‘631 patent as “terminal sterilization,” which, as used therein, refers to the sterilization of the outside surface of the final container (*i.e.* pre-filled syringe) and secondary packaging containing the drug product.

~~79~~81. “Terminal sterilization” traditionally means that the sterilization of the container closure system **and** the drug product within it may be achieved in a single process. For drugs that are not heat sensitive, the drug and packaging may be sterilized at once, for example by steam sterilization, negating the need for aseptic fill. However, a POSITA would understand that EtO or VHP sterilization of pre-filled syringe containing a drug formulation inside ~~would~~should avoid contact between a drug and EtO gas or VHP, and instead, the objective is sterilizing the outer surface of the syringe. In the case of a pre-filled syringe, in order to ensure a sterile drug formulation, the syringe would be filled under aseptic conditions, in a process known as “aseptic fill.” But, although filled under aseptic conditions, ~~pre-filled~~prefilled syringes are not packed into their secondary packaging in an aseptic environment. Thus, the exterior surfaces are likely to be microbiologically contaminated ~~and in.~~ In one method to ensure sterility, the exterior surfaces (and any secondary packaging) are sterilized via EtO or VHP sterilization following the aseptic

fill. Sigg (Ex. 1007) at 2:13-19. As explained in greater detail below, the term “terminal sterilization” in the ‘631 patent includes this latter type of sterilization wherein the outer surface of the pre-filled syringe is sterilized after the syringe is filled with the drug product. See ~~Ex. 1001~~ ‘631 patent at 9:49, 55-56; 10:2-4 (emphasis added) (“[t]he package is exposed to the sterili[z]ing gas until the *outside* of the syringe is sterile,” and “it is a requirement that significant amounts of the sterili[z]ing gas should not enter the variable volume chamber of the syringe.”). Throughout this ~~declaration~~report, I will use the term “terminal sterilization” to refer to the context in which it is used in the ‘631 patent, unless otherwise specified.

~~80~~82. Because a POSITA would understand that one of the goals when applying EtO or VHP sterilization to a pre-filled syringe would be to keep the sensitive drug formulation from interacting with these chemicals, keeping the container closure system as impermeable to EtO and VHP as possible is important. A pre-filled syringe disclosed in U.S. Patent No. 2005/0182370 to Hato, entitled “Prefilled Syringe with Plunger Backward Movement Limiting Mechanism,” has a mechanism that limits plunger movement, as well as a 3-ribbed stopper, both of which aid in achieving the integrity of the syringe. See Hato (Ex. ~~1047.002 (Fig. 3)~~1047) at Fig. 3. As shown below the mechanism for limiting plunger movement in Hato comprises a disk 76 on the plunger rod that engages a flange on the end of the syringe barrel furthest from the needle:
Hato (Ex. 1047) at [0028] (“The withdrawal-limiting member 76 in a disc form is fixed to the plunger rod 24 at the distance of d from the rear-end annular plate 82 of the withdrawal-limiting flange 56. In this mode of the invention, by fixing the withdrawal limiting member at a proper location in the axial direction of the plunger rod 24 depending on the quantity of the injection liquid to be filled in the prefilled syringe, it is possible to

provide the withdrawal-limiting member 76 at the distance of d from the rear-end annular plate 82 of the withdrawal limiting flange.”). Hato describes that this design configuration prevents inadvertent withdrawal of the plunger, which can otherwise result in contamination. Hato (Ex. 1047) at [0034] (“If the plunger is inadvertently withdrawn beyond the predetermined position, the injection liquid sealed in the liquid-filled area in the barrel may contact with the surface of the liquid-unfilled area (which bacteria etc. possibly adhere to), resulting in a risk of contamination.”).

~~81~~83. As of July 2012 (and before July 2011), the prior art discloses the use of cold sterilization⁵⁹ processes using EtO or VHP to terminally sterilize the outside of pre-filled syringes containing a drug formulation. ~~The~~ such as a VEGF-antagonist. Sigg ~~application~~ describes “a terminal sterilization and surface decontamination treatment of prefilled containers, specifically for sterilization of prefilled containers containing sensitive solutions, such as drug product or biological therapeutic, within secondary packaging.” Sigg (Ex. 1007) at 3:8-16. Sigg further notes that “[t]erminal sterilization of prefilled containers in secondary packaging is one way to provide the device to an end user with a low bio-burden and low risk of contaminants.” *Id.* at 2:15-17. Sigg also explains that the VHP sterilization methods would be applied to pre-filled syringes containing sensitive protein formulations such as VEGF-antagonists in order to sterilize the outside surface of the syringe (and not the drug formulation itself). *Id.* at 2:13-15 (“Prefilled syringes, although filled under aseptic conditions, are not packed into their secondary packaging in an aseptic environment and are therefore likely to be microbiologically contaminated at their

⁵⁹ Cold sterilization refers to processes that sterilize a product without requiring high temperatures, which would damage sensitive drug formulations.

outside.”). Thus, “terminal surface sterilization” is desirable for the disclosed prefilled syringe.
Id. at 2:31.

8284. Sigg describes the VHP sterilization method as:

treating prefilled containers within secondary packaging with controllable vaporized-hydrogen peroxide (VHP). The principle is the formation of a vapor of hydrogen peroxide in containment and a subsequent removal or inactivation of vapors in a controlled manner. Prior to removal or inactivation, VHP condenses on all surfaces, creating a microbiocidal film that decontaminates the container surface.

Id. at 3:11-16.

8385. ~~The~~Moreover, the Nema textbook, ~~for example,~~ describes ~~EtO~~ cold sterilization using EtO. Nema characterizes EtO as “[t]he most prevalent gas utilized for sterilization” such that “sterilization using other agents is based on methods used for ETO.” Nema Vol. 2 at 245-246 (Ex. 1016.260-261). Nema also describes the process sequence used for EtO sterilization. *Id.* at 261.

(Ex. 1016.276)84. Similarly, Lam describes an EtO gas “terminal sterilization” of a VEGF antagonist solution in a pre-filled syringe (that is, a sterilization performed post-filling that avoids interaction of the EtO with the VEGF antagonist protein) that allows the protein solution to maintain its stability throughout the sterilization process. *See* Lam (Ex. 1029) at 13:9-16:8.

8586. U.S. Pat. Appl. Pub. No. 2003/0003014 (“Metzner”) describes a “terminal sterilization” procedure using hydrogen peroxide plasma, another form of H₂O₂ sterilization, that “permits sensitive biological and therapeutic products to be sterilized externally in the solid or liquid state in their final container (primary packaging).” Metzner (Ex. 1018) at [0010]-[0011],

[0038]-[0039]. The procedure is shown to achieve sterility of the outer surfaces of glass carpules containing a protein fibrinogen solution, without affecting the stability of the fibrinogen. *Id.*

8687. EtO acts as a sterilization agent by oxidizing the biological molecules of microorganisms. See Nema Vol. 2 at 245-246 (Ex. ~~1016.260-.261~~ 1016.260-261). This effect, while beneficial for killing microorganisms, also will ~~oxidize~~damage biologic drug products if they are exposed to EtO gas during the sterilization process. While VHP works by a different mechanism than EtO, it still has the potential to damage biologic drug products. Thus, for pre-filled syringes, 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. Sigg, for example, describes that removal of VHP vapors “ensures that the long-term stability of the protein is not compromised.” Sigg (Ex. 1007) at 3:24-27.

8788. For similar reasons, anyone handling the drug products would want to avoid direct contact with the sterilization agents. Health authorities, for example, have implemented regulations to minimize the amount of sterilizing agent residue that is permissible to individuals to be exposed to. See OSHA Guidelines (Ex. 1048) (OSHA guidance limiting EtO exposure to 1 ppm in an 8-hour period). To prevent interaction of EtO and VHP with handlers of the sterilized pre-filled syringes, the gas or vapor must be allowed to sufficiently exit the secondary packaging of pre-filled syringe after the sterilization process is over. For example, the VHP sterilization disclosed in Sigg includes a step to remove VHP by “applying post-treatment measures, within a decontamination chamber.” Sigg (Ex. 1007) at 10:5-6.

8889. The measure of the probability that an individual article may not be sterile is referred to as the sterility assurance level, or SAL, and would have been routine for a POSITA to

determine prior to July 2012. For example, Sigg defines both the SAL and the term “sterility,” and recommends a SAL of ~~10⁻⁶~~10⁻⁶ for health care products:

“Sterility” as used herein is meant to refer to complete absence of microbial life as defined by a probability of non-sterility or a sterility assurance level (SAL). The required SAL for a given product is based on regulatory requirements. For example, required *SALs for health care products are defined to be at least 10⁻⁶*, i.e. a chance of less than 1:1 million of a non-sterile product for aseptically manufactured and terminally sterilized products, respectively.

Sigg (Ex. 1007) at 7:8-13 (emphasis added); See also Nema Vol. 2 at 548 (Ex. 1016.563) (“Thus, the 10⁻⁶ survivor level or SAL or a 12-spore log reduction (SLR) represents a one-in-one million probability of one microorganism surviving the process... Products intended to come in contact with compromised tissue, those with a sterile fluid pathway claim or those that are surgically implanted generally are validated to a 10⁻⁶ SAL. For other products not intended to come in contact with compromised tissue, for topicals, mucosal contact products or nonfluid pathway surfaces of sterile products an SAL of 10⁻³ can be used. It should be pointed out, however, that for sale of product labeled ‘sterile’ in Europe an SAL of 10⁻⁶ is required used.”).

F. Particulate Content

~~89~~90. As explained above, ophthalmic solutions for injection into the human eye have strict requirements for the number of sub-visual particles they may contain. Regulatory authorities require ophthalmic formulations in pre-filled syringes to have sufficiently low particulate content to avoid complications upon administration. See Nema Vol. 2 at 129 (Ex. 1016.144) (explaining that “[a] new U.S. guideline for ophthalmic products was [made] official

in 2004”); Scypinski (Ex. 1017) at 10:14-11:13 (“There are also strict controls on sub-visible particulate matter for ophthalmic injections.”); ~~Ex. 1001~~ ‘631 patent at 2:1-4 (“For ophthalmic injections, it is particularly important for the ophthalmic solution to have particularly low particle content.”). The applicable limits on particulate content are set forth in USP789.⁶¹⁰ See USP789 at 328-329 (Ex. ~~1019.005-.006~~; 1019.005-006); Scypinski (Ex. 1017) at 10:19-22 (“United States Pharmacopoeia (USP) Chapters <788> *Particulate Matter in Injections* and <789> *Particulate Matter in Ophthalmic Solution* describe physical tests for the purpose of enumerating extraneous particles within specific size ranges.”).

~~9091~~. Particulate matter in USP789 is defined as “mobile, randomly sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis because of the small amount of material they represent and because of their heterogeneous composition.”

USP789 at 328 (Ex. 1019.005). Specifically, USP789 provides two methods of detecting particulate matter in ophthalmic solutions, the light obscuration and microscopic procedures. *Id.*

at ~~.005-.006~~ 328329 (Ex. 1019.005-006). The test approach using these procedures is two-stage— first, the light obscuration method is used, which has its own set of test limits. If the light obscuration method is not able to be used for some reason, or if the test fails, the microscopic method must be used. *Id.* The following are the requirements for the number of particles detected by each method: for the light obscuration test, the limit of particles of diameter > 10 ~~µm~~ µm is 50 per mL and the limit of particles of diameter > 25 µm is 5 per mL; and for the

⁶¹⁰ USP is a nonprofit scientific organization founded in 1820 that develops and disseminates public compendial standards for drug products. Nema Vol. 2 at 93-94 (Ex. ~~1016.108-.109~~ 1016.108-109). Here, the USP sets forth the standard for particle size and number, which ~~is an element which~~ were copied as limitations in the ‘631 patent ~~attempts to claim~~ claims.

microscopic particle count test, the limit of particles of diameter > 10 µm is 50 per mL, the limit of particles of diameter > 25 µm is 5 per mL, and the limit of particles of diameter > 50 µm is 2 per mL. *Id.*

~~91~~92. While the USP is not legally binding, it ~~is~~was well known in the art that USP specifications are de facto requirements for regulatory approval of a drug product. Ex.

~~1057~~1057.001 (“The U.S. Federal Food, Drug, and Cosmetics Act designates the USP-NF as the official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the standards in USP-NF to avoid possible charges of adulteration and misbranding. The USP-NF is also widely used by manufacturers wishing to market therapeutic products worldwide. Meeting USP-NF standards is accepted globally as assurance of high quality.”); *see also* 21 U.S.C. §§ 321(j), 351(b). Thus, a POSITA would have understood that it is effectively a requirement for all ophthalmic products to meet the USP789 guidelines, including VEGF-antagonists for intravitreal administration.

VI. The ‘631 Patent

A. The Claims

~~92~~93. I understand that the petition challenges all of the claims of the ‘631 patent. Independent claim 1 of the ‘631 patent is directed to a terminally sterilized pre-filled glass syringe for intravitreal injection, of 0.5 mL to 1 mL volume, having between 1 µg to 100 ~~µg~~µg of silicone oil in the barrel and a stopper break loose force of less than about 11N, and containing a VEGF-antagonist with no more than 2 particles >50 ~~µm~~µm in diameter per mL. As I explain in this Declaration, a POSITA, in and prior to 2012, would have understood that there was nothing inventive about this combination of features, which were well known in the art at the time. Such pre-filled syringes having baked-on siliconization with low amount of silicone oil and low forces

were known and available at the time, and it would have been a routine application of such syringes to add any of the known VEGF-antagonist formulations to the syringe and then terminally sterilize the product. Claim 1 is reproduced below:

1. 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 μ g to 100 μ g silicone oil,
 - (c) the VEGF-antagonist solution comprises no more than 2 particles >50 μ m in diameter per ml and wherein the syringe has a stopper break loose force of less than about 11N.

| 9394. The '631 patent claims priority to a European patent publication, EP12174860 (Ex. 1035), which was filed on July 3, 2012. However, EP12174860 does not contain any examples, and does not contain any disclosure of specific *break loose* forces for any syringe disclosed therein. Instead, EP12174860 merely discloses that the *glide* force for certain embodiments of the syringe is "less than about 11N or less than 9N, less than 7N, less than 5N or between about 3N to 5N":

During testing it was found that, for syringes having small dimensions, such as those discussed above, and particularly those described in conjunction with the Figures below, the
| break loose

10 and sliding forces for the stopper within the syringe are substantially unaffected by reducing the siliconisation levels far below the current standard to the levels discussed here. In

one embodiment the glide force for the stopper within the pre-filled syringe is less than about 11N or less than 9N, less than 7N, less than 5N or between about 3N to 5N. Having too great a force required to move the stopper can cause problems during use for some users, for example accurate dose setting or smooth dose delivery may be made more difficult if significant strength is required to move, and/or keep in motion, the stopper.

[EP12174860](#) (Ex. 1035) at 6:8-16

⁹⁴95. However, because the independent claim of the '631 patent requires that the *break loose* force is less than about ~~11N~~11 N, and this is required for all of the claims of the '631 patent, a POSITA would not be able to reasonably conclude that the inventors had possession of an invention consisting of a pre-filled syringe with the claimed break loose force based on the disclosure in EP12174860. Thus, the claims of the '631 patent are not entitled to the July 3, 2012 filing date due to this lack of disclosure, and are instead entitled to a priority date of October 23, 2012 at the earliest.

⁹⁵96. The dependent claims can be grouped as follows, based on the additional features that they add. As I further explain in this Declaration, the features added by these dependent claims were also well-known at or prior to 2012, and a POSITA would have understood that there was nothing inventive about the combination of features recited in these claims.

⁹⁶97. Claims 2-4, 22 and 23 require a range of silicone oil thickness (450 nm or less), narrower ranges for the amount of silicone oil (3-100 µg or 1-50 ~~µg~~µg), the type of silicone oil (DC365 emulsion), and the silicone oil viscosity (350 cP viscosity).

⁹⁷98. Claim 5 requires certain particle content limitations for the VEGF-antagonist solution that are set forth in USP789, while claim 6 requires that the solution meets USP789.

⁹⁸99. Claims 7-9 require that the VEGF-antagonist is an anti-VEGF antibody,

or more specifically ranibizumab.

~~99~~100. Claim 10 combines the particle content limitations of claim 5 and the silicone oil viscosity limitation of claim 23.

~~100~~101. Claims 11-13 require that the VEGF-antagonist is a non-antibody VEGF-antagonist, or more specifically aflibercept.⁷¹¹

~~101~~102. Claims 14-16 require a stopper break loose force of less than 5 N, a stopper slide force of less than 5 N or 11 N, and require a stopper traveling speed (190 mm/min) and needle type at which the force should be measured.

~~102~~103. Claims 17-21 include limitations relating to sterilization: the syringe is sterilized using H₂O₂ or EtO; the outer surface of the syringe has 1 ppm H₂O₂ or EtO residue; the total H₂O₂ or EtO residue is 0.1 mg; less than or equal to 5% of the VEGF-antagonist is alkylated; and the syringe is sterilized with a Sterility Assurance Level of at least 10⁻⁶.

~~103~~104. Claim 24 is a method of treating a patient suffering from one of several ocular diseases comprising the step of administering an ophthalmic solution using a pre-filled syringe according to claim 1. Dependent claim 25 requires the step of depressing the plunger to align the stopper with a priming mark. Dependent claim 26 requires that the VEGF-antagonist administered is a non-antibody VEGF-antagonist and the patient previously received treatment with an antibody VEGF-antagonist.

B. Overview of Specification

- 1. The '631 patent fails to disclose a process for applying ~~low~~the
claimed levels of silicone oil**

⁷¹¹ Aflibercept was developed by Regeneron and is marketed under the trade name EYLEA®.

~~104~~105. The '631 patent claims a syringe ~~with between~~having about 1 andμg to 100 μg of silicone oil on the syringe barrel and break loose and slide forces for the syringe stopper that are less than ~~HN~~about 11 N. However, the '631 patent does not contain any disclosure of how a POSITA would achieve ~~these low~~the claimed amounts of silicone oil in the barrel. As I have explained herein, it was well-known at the time that using baked-on siliconization results in ~~relatively low~~a syringe having an amount of silicone oil in the barrel that falls within the ranges claimed and also results in break loose and glide forces ~~while still~~ using low levels of silicone oilwithin the ranges claimed. To the extent that ~~the Patent~~ OwnerNovartis were to argue that the '631 patent is directed to a particular method of applying silicone oil that allowed them to achieve the claimed features in a way that was different from the well-known baked-on processes disclosed in the prior art, that alleged teaching of siliconization is not disclosed anywhere in the '631 patent and would not be discernable to a POSITA reading the '631 patent.

~~105~~106. Similarly, while the '631 patent says that using ~~lower~~the claimed levels of silicone oil ~~and~~while achieving ~~similar low~~the claimed break loose and glide forces as compared to those achieved via an oily siliconization was “surprising,” a POSITA would understand that there was nothing surprising about this result. Instead, as explained above in **Section V.D.2**, this result would have been expected in 2012 given that baked-on siliconization was known to use about 10 times less silicone oil as compared to oily siliconization while still achieving the same break loose and slide forces. As described in more detail below, Boulange discloses a pre-filled syringe comprising the claimed silicone oil levels in conjunction with the claimed break loose and slide forces. See VII.C below.

2. The ‘631 patent fails to disclose ~~the~~ process details for terminal sterilization

~~106~~107. ~~Likewise, the~~The ‘631 patent explains that “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~~‘631 patent 1:31-36. The ‘631 patent says that the sterilization it discloses may be done via “known” methods, such as VHP or EtO, but no details are provided regarding the sterilization process itself. *Id.* at 9:49-54. Instead, the remaining description sets forth only the desired results—how long the syringe remains sterile, the Sterility Assurance Level, the alkylation of the product, and the amount of chemical residue remaining—and no process steps to achieving them. *Id.* at 9:55-10:22. In my opinion, the disclosure in the ‘631 patent does not add anything new to the art of sterilizing a pre-filled syringe.

108. I understand that Novartis has contended that the design of the plunger/stopper and plunger rod described in the ‘631 patent specification are features that enable a pre-filled syringe comprising a VEGF-antagonist to be terminally sterilized. As an initial matter, the claims of the ‘631 patent are not directed to a particular stopper or plunger rod design, and instead encompass any stopper and plunger rod. See ‘631 patent at Claim 1. Accordingly, these unclaimed features (a plunger rod comprising a disk and stopper having certain spacing between the ribs) do not distinguish the claims of the ‘631 patent from the prior art I have analyzed below.

109. In any event, the stopper and plunger rod design disclosed in the ‘631 patent specification were already known in the art by 2011. For example, a plunger rod comprising a disk to minimize rearward movement of the stopper to prevent

contamination of the drug product in a pre-filled syringe is described in U.S. Patent Publication No. 2005/0182370 (“Hato”), which is a patent publication filed by Becton Dickinson in 2003. The figure on the left below highlights the disk 32 on the plunger rod described in the ‘631 patent, while the figure on the right highlights disk 76 on the plunger rod in Hato:

Hato specifically describes that the disk 76 should be positioned so as to ensure that the stopper movement is less than the space between the first and last rib of the stopper, which ensures that the drug product within the syringe does not become contaminated. Hato (Ex. 1047) at [0022], [0034]. These 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. For example, the 2008 Macugen Label describes that the user must remove a clip from the syringe prior to use. Ex. 1009.007. A POSITA 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.

110. Similarly, it would be a matter of routine optimization for a POSITA to develop a stopper comprising at least 3 ribs with at least 3 mm spacing between the first and last rib. See ‘631 patent at 3:23-32 (describing a stopper having 3 ribs with at least 3 mm spacing). As explained above, Hato discloses three ribs and describes that the spacing between the ribs on the stopper should be greater than the distance that the plunger rod can inadvertently move to prevent contamination. Hato (Ex. 1047) at [0022], [0034]. Thus, a POSITA would have considered it a matter of routine optimization to set the rib spacing at a distance greater than the distance the plunger rod could potentially move after the

pre-filled syringe has been assembled. See also ISO 11040-5 (Ex. 1028) (ISO standard dated January 15, 2012 showing typical plunger designs, all of which have three ribs); Ex. 1008 (Boulangé disclosing a three-rib stopper). The precise spacing would depend on the other dimensions of the syringe, but in any event there nothing inventive about a stopper comprising at least 3 ribs with at least 3 mm spacing between the first and last rib.

111. I also disagree that the plunger rod and stopper design described in the ‘631 patent would have been necessary to successfully terminally sterilize a prefilled syringe. For example, a POSITA would understand that Macugen PFS was terminally sterilized by 2008, but instead of a plunger rod comprising a disk it utilized a syringe clip to minimize movement of the stopper, as described below. See VII.D below.

C. ~~Meaning of the Claim Terms~~ Prosecution History

112. The application that resulted in the ‘631 patent (Application No. 13/750,352) was filed on January 25, 2013. In the application as filed, claim 1 required a syringe barrel with less than about 500 µg silicone oil, but included no requirements for terminal sterilization or break loose forces. See Ex. 1002.0020, 0078. On May 14, 2014, the examiner rejected all the claims based on various anticipation and obviousness grounds. Ex. 1002.1245-1253. In response, Novartis amended the claims to require 1 µg to 500 µg of silicone oil. Ex. 1002.1270. In response, the examiner again rejected the claims based on obviousness grounds. Ex. 1002.1284-1285.

113. In response to the second rejection, Novartis amended the claims to require from about 1 µg to 100 µg of silicone oil, and a break loose force of less than about 11 N. Ex. 1002.1294. In conjunction with this amendment, Novartis argued to the examiner that the “applicants have shown for the first time that you can reduce the silicone so far below

previous standards and still obtain a usable syringe,” and that the “applicants have surprisingly found that the application of less silicone resulted in lowered sliding and break forces.” Ex. 1002.1298-1299. Novartis further argued that this finding “flies in the face of conventional wisdom, which suggests that the way to reduce these forces is to use more lubricant.” In response to these amendments and arguments, the examiner again rejected the claims. Ex. 1002.1310. With respect to Novartis’s assertion of unexpected results for using less silicone oil, the examiner asserted that it would have been “common sense to use as little as possible to achieve the desired effect.” Ex. 1002.13101311. I agree with the examiner’s assertion. It was not only common sense to use less silicone oil at that time, but well-known that using less silicone oil applied via baked-on siliconization would result in a usable syringe, as demonstrated by the prior art (*e.g.*, Boulange), and as explained in more detail below. *See also* Section V.D.2 above.

114. In response to the examiner’s rejection of Novartis’s unexpected results argument, Novartis asserted that the claims of the ‘631 patent should be allowed because the disclosed syringe was terminally sterilized. Ex. 1002.13531354. In response, the examiner again rejected the claims because they did not require a prefilled syringe that was terminally sterilized. Ex. 1002.1358-1359. In response, Novartis for the first time amended the claims to require a “pre-filled, terminally sterilized syringe.” Ex. 1002.1370. It was only after this amendment that the examiner allowed the claims. Ex. 1002.1458-1459. In particular, the examiner determined that the “prior art of record fails to disclose either singly or in combination the claimed device of a prefilled glass syringe with 1-100 µg of silicone oil that is prefilled with a VEGF antagonist and is terminally sterilized.” Ex. 1002.1458.

115. Accordingly, the examiner only allowed the claims because there was no prior art of record during prosecution that disclosed a pre-filled syringe comprising a VEGF-antagonist that was terminally sterilized. Notably, there is no indication that the examiner was aware of Sigg, Lam, or Macugen PFS during examination of the claims of the ‘631 patent. Each of these references and products discloses a terminally sterilized pre-filled syringe comprising a VEGF antagonist, as explained in more detail below.

116. I understand that Novartis argued in the previously filed *inter partes* review proceeding that several prior art references before the examiner disclose terminal sterilization that is pertinent to the claims of the ‘631 patent, including WO 2007/084765 and WO 97/44068. I disagree that these references disclose terminal sterilization of a pre-filled syringe comprising a VEGF-antagonist. There was nothing disclosed during the prosecution of the ‘631 Patent with respect to terminal sterilization which was cumulative of the disclosures provided in Sigg and Lam, as explained in further detail below.

117. With respect to WO 2007/084765, Novartis argued to the PTAB that it discloses terminal sterilization because it states that “sterilization can be performed after manufacture.” See IPR2020-01317, Paper 14 at 11 (Ex. 1051.020). In context, however, this statement clearly refers to sterilizing a drug composition after manufacturing it—not sterilizing a prefilled syringe after it is filled and assembled. The paragraph below also states that it is preferable to sterilize “devices and instruments to be used for administration to the eye,” but does not describe sterilizing a syringe after it is filled with a drug product (*i.e.*, terminal sterilization as claimed in the ‘631 Patent).

[00255] Preferably any composition to be administered to the eye is sterile. The composition can be made from sterile components, or sterilization can be performed after

manufacture. Methods of sterilization include irradiation, heat, etc. Preferably, the sterilization method used does not substantially reduce the activity or biological or therapeutic activity of the therapeutic agents. Devices and instruments to be used for administration to the eye are also preferably sterile, at least to the extent they will enter the eye.

WO 2007/084765 (Ex. 1088) at [00255]. As to WO 97/44068, the Abstract states that the syringe can be filled and then sterilized in a sterilizing chamber, but is silent as to the type of drug product in the syringe. WO 97/44068 (Ex. 1089) at Abstract. WO 97/44068 therefore does not appear to disclose terminal sterilization of a pre-filled syringe comprising a VEGF-antagonist. In sum, the prior art I address below is materially different from any sterilization prior art that was before the examiner during prosecution of the '631 patent.

118. I understand that Novartis has also argued in the previously filed *inter partes* review proceeding that Boulange was cumulative of the baked-on siliconization art before the examiner. I disagree. Boulange discloses a pre-filled syringe with both silicone oil and break loose and glide forces in the ranges claimed by the '631 Patent. The examiner did not have the benefit of one reference which contained all of the key silicone oil limitations. For example, Hioki only disclosed a wide range of silicone oil amounts, and did not disclose the break loose or glide forces. See Hioki (Ex. 1020).

D. Claim Construction

119. I understand that the words of the claims of patent are generally given the ordinary and customary meaning as interpreted by a person of ordinary skill in the art at the time of invention. I have been informed that patent claims are construed in light of the

claim language, the specification (including the drawings), and the prosecution history (including the references cited during the prosecution of the patent).

~~407~~120. The ‘631 patent claims a “**terminally sterilized**” pre-filled syringe and discloses in the specification that according to its “terminal sterilisation” methods, “[t]he package is exposed to the sterilising gas until the outside of the syringe is sterile,” but also that “it is a requirement that significant amounts of the sterilising gas should not enter the variable volume chamber of the syringe.” ~~Ex. 1001~~‘631 patent at 9:49, 55-56; 10:2-4. Thus, a POSITA would understand that the term “terminally sterilized” as used in the ‘631 patent includes the sterilization of the outside of a ~~prefilled~~pre-filled syringe (*i.e.*, primary packaging component) while minimizing contact between the drug product within the pre-filled syringe and the sterilizing agent being applied.

121. The term “stopper¹² break loose force” is the force required to make the stopper move from the resting position in the syringe barrel, while the term “stopper slide force”¹³ is the force required to sustain movement of the stopper in the syringe barrel after movement has begun. Nema Vol. 1 at 343 (Ex. 1015.358).

¹² The ‘631 patent uses the term “stopper,” while other prior art uses the term “piston.” Both of these terms refer to the same component of the syringe, which is pushed by the plunger and forces the drug solution through the needle. A POSITA would understand these terms are used interchangeably in the art.

¹³ Based on its use in the specification (‘631 patent at 5:27-50, 12:21-45), a POSITA would understand that synonyms for “stopper slide force” would include “gliding force,” “glide force,” and “sustaining force.”

The break loose and slide forces are illustrated below in a figure from Nema, where the initial peak is the break loose force and the lower relatively constant force is the slide force:¹⁴

~~108. The ‘631 patent uses the term “stopper⁸break loose force” consistently with its well-understood meaning in the art, which is the minimum force required to make the stopper start moving from the resting position in the syringe barrel, as I have explained in Section V.C. While break loose force changes over time, for baked-on syringes the amount the break loose force change over time is known to be less than for oily syringes. The change in break loose force over time is known as the “break loose” effect, which more specifically refers to the sticking of the stopper to the syringe barrel because of displacement of the silicone oil layer upon ageing of the syringe stopper.~~

~~109. The ‘631 patent uses the term “stopper slide force” (or “glide” force) consistent with its well-understood meaning in the art, which is the minimum force required to sustain the movement of the stopper in the syringe barrel (after movement has already begun), as I have explained in in Section V.C. Unlike the break loose force, the glide force does not typically change substantially over time.~~

~~110. I note that the ‘631 patent does not specify when the stopper break loose force or the stopper glide force is measured, i.e., whether the forces are measured when the syringe is~~

¹⁴ 14 As noted above, the precise shape of this graph would depend on the viscosity of the solution within the syringe.

⁸ The ‘631 Patent uses the term “stopper,” while other prior art uses the term “piston.” Both of these terms refer to the same component of the syringe, which is pushed by the plunger and forces the drug solution through the needle. A POSITA would understand these terms are used interchangeably in the art.

~~newly siliconized or after storage for a period of time. As explained above in Section V.C, a POSITA would understand that break loose force can increase over time as the syringe ages, and the break loose force may especially increase on account of the break loose effect in oily siliconized syringes. Thus, while it is common to define the storage time of the piston in the syringe when discussing the measured stopper forces, a POSITA would understand that the stopper force-related claim terms would include such forces measured at any time given the lack of specificity in the ‘631 patent.~~

VII. The Prior Art to the ‘631 Patent

A. “Sigg” -WO 2011/006877

~~111~~122. Sigg (~~Ex. 1007~~) is a patent application publication that lists the same lead inventor as the ‘631 patent, and is assigned on its face to the same entity -Novartis AG. Sigg discloses terminally sterilized, low volume (0.5 -1.0 mL) pre-filled glass syringes containing an ophthalmic solution that is a VEGF-antagonist intended for intravitreal injection. I understand that Sigg was not of record during the prosecution of the application that became the ‘631 patent.

~~112~~123. Sigg discloses embodiments of terminally sterilized 0.5 mL syringes for intravitreal injection containing the VEGF-antagonist ranibizumab (Lucentis). Sigg (Ex. 1007) at 9:11-14; 20:17-21. Example 1 of Sigg discloses “prefilled syringes [that] were treated with a vaporized-hydrogen peroxide sterilization treatment,” wherein the syringes contained “protein solutions,” and more specifically, “[a] formulation as described in U.S. Patent No. 7,060,269,” which is a patent disclosing ranibizumab. *Id.* at 20:11-18; see also Ex. 1023 at 2:14-19 (U.S. Patent No. 7,060,269 to Genentech describing “anti-VEGF antibodies”). The syringes tested

in Example 1 of Sigg were “0.5 mL syringes” which a POSITA would understand refers to the size, and therefore the nominal fill volume of the syringe. *Id.* at 20:20.

~~113~~124. Sigg discloses glass syringes. See Sigg (Ex. 1007) at 2:1-6 (disclosing that sterilizing using gamma rays can cause discoloration to glass as a reason for adopting different sterilization methods, *e.g.*, VHP sterilization), 22:8-11 (disclosing glass syringe in Example 2). While Sigg does not explicitly state the syringes in Example 1 were glass, it would be obvious to a POSITA to use glass syringes in Example 1 for a number of reasons. First, the VEGF-antagonist (Lucentis) within the syringe is sensitive to degradation by VHP. See *id.* at 2:~~27-29~~2729 (“oxidizing gases, while efficient for killing bacterial contamination, also harm biological molecules in sensitive therapeutic solutions”); 3:27-30 (“It further has been found that among the commercially available primary packaging components, there are only very few packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gasses into the pharmaceutical liquid enclosed by the prefilled container.”¹⁵). It was well known in 2012 that glass is impermeable to gas and vapors. See e.g., Lam (Ex. 1029) at 3:19. I also understand that during prosecution of the application that led to the ‘631 patent, Novartis argued that pre-filled syringes for protein formulations such as VEGF-antagonists must be made out of the glass. See Ex. 1002.1274-1275 (during prosecution, Novartis argued that “syringes which are prefilled with ~~biologies~~biologics are comprised of glass

¹⁵ I note that although Sigg states that “very few” syringe components are capable of making the tight seal required for terminal sterilization, such components were well-known and readily available to those of ordinary skill in the art before the ‘631 patent. As described below, a POSITA would understand that Macugen PFS was terminally sterilized by 2008, while an EYLEA PFS terminally sterilized with VHP was approved in Australia by February 2012. See Sections VII.D, VIII.B below.

barrels,” and made this argument in order to distinguish the ‘631 patent application claims from the prior art). Furthermore, the use of glass syringes for VEGF antagonist solutions was well known in the art. Drugs.com Macugen Label at 8 (Ex. ~~1009.001~~1009.008) (disclosing that Macugen is supplied in a pre-filled glass syringe); Furfine (Ex. 1021) at [0059], [0061] (disclosing examples of pre-filled glass syringes containing a VEGF-antagonist). Thus, it would have been obvious to a POSITA to use a glass syringe in the ~~pre-filled~~prefilled syringe embodiment of Example 1.

~~114~~125. A POSITA would understand that the sterilization disclosed in Sigg is “terminal sterilization” as that term is used in the ‘631 patent, because according to the Sigg sterilization method, the drug formulation was ~~first sterilized separately, Ex. 1007 at 20:19-20 (“solution was filtered through a 0.22 µm syringe filter”), then~~ filled into syringes under sterile conditions, *i.e.*, filled via aseptic fill- ~~(~~id. at 20:20-21 (“[f]illing of 0.5 mL syringes was performed in a sterile lab for hydrogen peroxide treatment”)), and ~~only~~ then ~~was~~ VHP sterilization was applied to the syringe outer surface. *Id.* In addition, Sigg explicitly states that the “invention relates to a method and system for *terminal sterilization of the outer surface and/or surface decontamination of prefilled containers in secondary packaging*, wherein the prefilled container contains a pharmaceutical or biological drug product.” *Id.* at 1:5-8 (emphasis added). Juergen Sigg, the lead inventor on both Sigg (the prior art reference) and the ‘631 Patent, submitted a declaration during the prosecution of the U.S. patent application corresponding to Sigg stating that “[t]he present application disclosed for the first time, and contrary to conventional thinking, that it is possible to obtain sufficient sterilization of the outer surface of a syringe in secondary packaging at ambient pressure.” Sigg Declaration at 4 (Ex. 1070.004).

~~115~~126. Sigg also explains that the disclosed VHP sterilization methods would be applied to pre-filled syringes containing sensitive protein formulations such as VEGF-antagonists: “Prefilled syringes, although filled under aseptic conditions, are not packed into their secondary packaging in an aseptic environment and are therefore likely to be microbiologically contaminated at their outside.” *Id.* at 2:~~13-15~~. Thus, “terminal surface sterilization” is desirable. *Id.* at 2:31. However,1315. Sigg explains that prior techniques of sterilizing the surfaces of container closure systems, such as temperature steam and gamma irradiation, cannot be applied to sensitive biologic drug solutions because the sterilization methods risked denaturing or chemically modifying the active ingredient of the drug. *Id.* at 2:~~20-29~~2029; *id.* at 7:29-8:1 (“terminal-sterilization methods suitable for prefilled containers containing sensitive products, such as biotech (biological) drug solutions, which can otherwise be compromised when using classical terminal sterilization processes”). Thus, Sigg teaches a VHP sterilization method that is specifically intended “for sterilization of prefilled containers containing sensitive solutions, such as a drug product or biological therapeutic, within secondary packaging.” *Id.* at 3:9-11. Sigg further notes that “[t]erminal sterilization of prefilled containers in secondary packaging is one way to provide the device to an end user with a low bio-burden and low risk of contaminants.” *Id.* at 2:15-17.

~~116~~127. Sigg taught two methods for sterilizing pre-filled syringes: “treatment of prefilled containers in secondary packaging by an application of vaporized-hydrogen peroxide, in which vapors are controllable by certain post-treatment measures, and exposure to tunable-beta radiation, in which the depth of penetration of beta rays into secondary packaging are controllable.” *Id.* at 8:8-12. The VHP sterilization disclosed in Sigg, which is the method relevant here, includes “applying post-treatment measures, within a decontamination chamber” that ensure

full removal of VHP residue and thus protection of the sensitive biologic product. *Id.* at 10:5-6.

In this way, Sigg proposes that the hydrogen peroxide is able to fully sterilize the exterior and secondary packaging of the product, without risking exposure to the sensitive biologic drug product.

~~117~~128. The disclosure of Sigg is silent as to the amount of silicone oil used in the tested pre-filled syringes, or the resultant break loose or glide forces that the ~~prefilled~~pre-filled syringes would exhibit when tested. Nevertheless, a POSITA would understand that because the pre-filled syringes in Sigg contain ranibizumab, which is a VEGF-antagonist for intravitreal administration, it would be advantageous and desirable to minimize the amount of silicone oil used in the pre-filled syringe to avoid negative interactions between the silicone oil and the VEGF-antagonist protein. As explained above in **Section V.D.~~21~~2**, a POSITA would understand that the amount of silicone oil in a pre-filled syringe can be minimized by using baked-on siliconization, which also reduces the risk of the break loose effect, while still providing low break loose and glide forces as would be required for intravitreal administration. As explained above in **Section V.D.3**, a POSITA would also understand that using coated stoppers would be further advantageous because the stopper coatings help prevent leaching of extractables into the drug formulation upon storage, and further reduce the amount of silicone oil needed.

B. “Lam” -International Pat. Appl. Pub. No. WO 2008/077155

~~118~~129. Lam (~~Ex. 1029~~) is a patent application publication that is assigned on its face to Genentech, Inc. Lam discloses terminally sterilized pre-filled glass syringes containing a VEGF-antagonist intended for intravitreal injection. I understand that Lam was not of record during the prosecution of the application that became the ‘631 patent.

~~119~~130. Lam discloses examples in which EtO sterilization is performed on syringes containing Lucentis (ranibizumab), which is a VEGF-antagonist drug formulation that was on the market prior to 2012. Lam (Ex. 1029) at 13:14-15 (“We performed EtO sterilization on syringes containing a ranibizumab solution...”). Lam also teaches that the syringes could be filled with Macugen, another VEGF-antagonist. *Id.* at 11:9-11. A POSITA would understand that both Lucentis and Macugen are injected intravitreally. Lam also teaches EtO sterilization of the object in its secondary packaging such as an EtO-permeable material. *Id.* at 2:1-33.

~~120~~131. A POSITA would understand that the syringes being sterilized in Lam were “pre-filled syringes” as that term would be understood by a POSITA at the time, because the syringes already contained a drug formulation within the syringe, optionally along with a tip cap to close off the tapered end of the syringe barrel. *See id.* at 13:14-15 (describing the syringes as containing Lucentis); *id.* at 15:12-17 (describing the tip cap added to the syringes being tested).

~~121~~132. Lam discloses glass syringes. Lam (Ex. 1029) at 2:29-31, 3:17-19, claim 21. While Lam does not explicitly state the syringes in the testing on pages 15 and 16 were glass, it would be obvious to a POSITA to use glass syringes in the testing for a number of reasons. First, the VEGF-antagonist within the syringe is sensitive to degradation by EtO. *See id.* at 13:14-15 (“We performed EtO sterilization on syringes containing a ranibizumab solution... .”); *id.* at 2:7-11 (disclosing that the objects to be sterilized must have “an ethylene-oxide (EtO)-impermeable interior space”). It was well known in 2012 that glass is impermeable to gas and vapors.

Lam (Ex. 1029) at 3:19 (“As [sic] EtO-impermeable object my [sic] comprise, e.g., glass”). Lam also teaches that its disclosed methods of EtO sterilization can be applied to

syringes wherein “[i]n some embodiments *the syringe comprises glass* and comprises a stopper comprising D777-7 laminated with FluroTec®....” *Id.* at 2:~~333~~3-33 (emphasis added). In the testing on pages 15 and 16 of Lam, the coated stopper tested corresponds to the aforementioned described embodiment of a glass syringe with a D777-7 laminated stopper. *See generally id.* at 15-16. I also understand that during prosecution of the application that led to the ‘631 patent, Novartis argued that ~~pre-filled~~prefilled syringes for protein formulations such as VEGF-antagonists must be made out of the glass. *See* Ex. 1002.1274-1275 (~~during prosecution~~, Novartis ~~argued~~arguing that “syringes which are prefilled with biologics are comprised of glass barrels;” ~~and made this argument in order~~ to distinguish the ‘631 patent application claims from the prior art). Furthermore, the use of glass syringes for VEGF antagonist solutions was well known in the art. 2008 Macugen Label at 8-9 (Ex. ~~1009.001~~1009.008-009) (disclosing that Macugen is supplied in a ~~pre-filled~~prefilled glass syringe); Furfine (Ex. 1021) at [0059], [0061] (disclosing examples of pre-filled glass syringes containing a VEGF-antagonist). Thus, it would have been obvious to a POSITA to use a glass syringe in the pre-filled syringe embodiment in the Example disclosed in Lam.

~~122~~133. The pre-filled syringes disclosed in Lam are for intravitreal administration, and therefore, it would be obvious to a POSITA that the syringes are small volume syringes, for example 0.5-1 mL in volume. *See* Nema Vol. 1 at 21 (Ex. ~~1015.036~~1015.36) (administration volume for intravitreal injection is “generally <0.1 mL”); Furfine (Ex. 1021) at [0059], [0061] (disclosing a VEGF-antagonist in a 1 mL prefilled glass syringe); 2004 Macugen Label at 11 (Ex. 1062.009) (disclosing that Macugen is provided in a 1 mL glass syringe).

~~123~~134. A POSITA would understand that the sterilization disclosed in Lam is “terminal sterilization” as that term is used in the ‘631 patent, because according to the Lam

sterilization method, the drug formulation is first sterilized separately and packaged into sterilized primary packaging whose surface may then be sterilized by the disclosed EtO sterilization methods. *See* [Lam](#) (Ex. 1029) at 1:22-33 (“Consequently, pharmaceutical compositions are generally sterilized by an alternative method, *e.g.* by filtration, and then packaged into separately sterilized objects. ... In many circumstances it would be advantageous to sterilize the surfaces of these objects in order to reduce the risk of contamination during subsequent handling. ... Thus, there remains 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.”).

~~124~~[135](#). Lam explains that the EtO sterilization methods disclosed therein are especially suitable for drug formulations that contain active ingredients that may be damaged by the high temperatures, radiation, or chemical gases used in some sterilization processes. *See id.* at 1:18-23. Thus, Lam applied the EtO sterilization method to sterilize the outer surface of a pre-filled syringe containing the VEGF-antagonist Lucentis. [Id. at 2:24](#).

~~125~~[136](#). Lam also explains why a POSITA would wish to terminally sterilize a pre-filled syringe for intravitreal administration. Specifically, Lam teaches that “it would be advantageous to sterilize the surfaces of these objects [*i.e.*, objects containing pharmaceutical compositions] in order to reduce the risk of contamination during subsequent handling,” and specifically that “there is an increased risk of endophthalmitis after intraocular injection if the surface of the syringe used for injection is not sterilized.” *Id.* at 1:26-29.

~~126~~[137](#). A POSITA reading Lam would understand the disclosed terminal sterilization is compatible with a pre-filled syringe having a coated stopper. Specifically, Lam “also tested several different syringe components: where the stopper on the plunger comprised ...”

coating of FluroTec® barrier film .” and taught that despite the added coating on the stopper “the percentage of protein in the basic peak was not statistically different from control.” *Id.* at 15:12-14, 24-25. Lam’s testing showed that the residual EtO on pre-filled syringe embodiments having a coated stopper was even lower than if coated stoppers were not used, which shows that, if anything, the terminal sterilization results were even better when coated stoppers were used. *See id.* at 16:1-2 (Table 3).

~~127~~138. The disclosure of Lam is silent as to the amount of silicone oil used in the tested pre-filled syringes, or the resultant break loose or glide forces that the pre-filled syringes would exhibit when tested. Nevertheless, a POSITA would understand that because the pre-filled syringes in Lam contain Lucentis, which is a VEGF-antagonist for intravitreal administration, it would be advantageous and desirable to minimize the amount of silicone oil used in the pre-filled syringe to avoid negative interactions between the silicone oil and the VEGF-antagonist protein. As explained above in **Section V.D.2**, a POSITA would understand that the amount of silicone oil in a pre-filled syringe can be minimized by using baked-on siliconization, which reduces the risk of the break loose effect, while still providing low break loose and glide forces as would be required for intravitreal administration.

C. “Boulangé” -International Pat. Appl. Pub. No. WO 2009/030976

~~128~~139. Boulangé (~~Ex. 1008~~) is a published patent application that was filed by Becton-Dickinson, ~~a well-known~~one of the world leader’s in syringe ~~manufacturer~~design and manufacturing. I understand that Boulangé was not of record during prosecution of the ‘631 patent.

~~129~~140. Boulangé discloses force testing conducted on pre-filled syringes with glass barrels and coated or uncoated¹⁶ stoppers (called “pistons” in Boulangé). Boulangé (Ex. 16) I note that Boulangé describes coated and uncoated stopper with respect to the effect that the stopper coating has on break loose and slide forces. This refers to coating (or not

1008) at 13:11-12 (“The container 2 is a glass syringe body accommodating a piston 3 able to move translationally...”); 14:19-21 (“tests were applied on containers filled with 1 mL of demineralised water and each plugged with one piston to be tested (coated or uncoated)”).

Boulangé specifically discloses a 1 mL syringe with 40 µg of baked-on silicone that has break loose and slide forces of less than 11 N and less than 5 N, as explained below.

~~130~~141. Table 1 of Boulangé describes the different configurations of stoppers (pistons) used in the testing in Boulangé, which are labeled A, B1, B2 and C.

Piston and stopper are used interchangeably by those skilled in the art. Pistons B1 and B2 include a polymer coating, while pistons A and C do not.

Table 1 : configurations of pistons A, B1 and C

[Boulangé \(Ex. 1008\) at 14:1-3 \(Table 1\)](#)

Piston reference	Viscoelastic substrate	Coating	Coating thickness	Surface finish
A (comparative)	Bromobutyl rubber	No		Smooth Ra -0.7 µm Rt = 11.4 µm
B1 (Invention)	Bromobutyl rubber	Yes	3 µm	Smooth Ra = 0.9 µm Rt =12.0 µm
B2 (comparative)	Bromobutyl rubber	Yes	3 µm	Rough Ra = 31 µm Rt = 24.0 µm
C (comparative)	Chlorobutyl rubber	No		Smooth Ra= 0.7 µm Rt = 11.0 µm

[that the stopper coating has on break loose and slide forces. This refers to coating \(or not coating\) the sides of the stopper that interface with the inner surface of the syringe barrel. A POSITA would recognize that even an “uncoated” stopper as described in Boulangé could include a laminate or film \(i.e., a tip coating\) on the portion of the surface that contacts the drug product within the syringe. The laminate or film on the stopper tip does not impact break loose and glide forces, but serves to prevent the stopper material from leaching into the drug product. See V.D.3 above.](#)

~~131~~142. The testing in Boulange disclosed measurements of break loose force, labeled in Boulange as “friction force B.” *Id.* at 15:6-8 (“the force required, under static conditions, to break the contact at the contact region 10 between the piston 3 and the container 2”). Boulange also discloses measurements of glide forces, labeled in Boulange as “friction force S” and “friction force F,” both of which are types of slide forces, measured at different points along the syringe barrel. *Id.* at 15:9-11 (“the friction force S is the force required, under dynamic conditions, for moving the piston 3 in the container 2. The friction force S is measured half way of the piston travel.”), 15:13-15 (“the friction force F is the force required, again in dynamic mode, to move the piston 3 when it reaches the end of its travel in the container 2”).

~~132~~143. In Example 5, Boulange compares the break loose force and slide force of syringes with the silicone oil either ~~baked-on~~baked-on (“Scenario 1”) or ~~sprayed-on~~ (~~“sprayed-on~~ (“Scenario 2”) to the barrel. *Id.* at 20:15-21. The ~~baked-on~~baked-on silicone was applied to the syringe body at “a rate of 40 µg for a surface area of 10 cm²,” while the ~~sprayed-on~~sprayed-on silicone was applied “at a rate of 500 ~~µg~~µg for a surface area of 10 cm².” *Id.* No silicone oil was applied to the piston in either Scenario 1 or Scenario 2. *Id.* As shown in Table 7 reproduced below, regardless of the configuration of the piston (A, B1 or C), the unaged syringes (T=0)⁹¹⁷ for the “~~baked-on~~baked-on” silicone method resulted in break loose and slide forces of less than 7 N. The syringe configured with the coated piston (B1) exhibited break loose and slide forces below 5 N for both the unaged (T=0) and aged (T=1) syringe.

⁹¹⁷ In Table 7 of Boulange, the subscript T refers to the age of the syringe (i.e., T=0 is unaged, T=1 is aged one month, etc.). The “aged” syringes were stored in a chamber for a period of time before testing at extreme conditions (i.e., 40° C) to assess the worst-case performance of the syringe over its shelf-life.

~~Ex. 1008 at 21:1-3 (Table 7) (annotated)~~

~~133~~144. Thus, as can be seen from Boulange Table 7, above, testing conducted on a pre-filled syringe with uncoated stopper C showed a stopper break loose force of 3.9 N and a stopper glide force as low as 3.9 N. Similarly, the coated stopper B1 showed a stopper break loose force of 2.1 N and a stopper glide force as low as 2.5 N. Table 5 likewise discloses testing of syringes having baked-on silicone oil on the syringe barrel. In contrast to Table 7, the stoppers for the syringes in Table 5 also included a coating of silicone oil, which was and still is commonly used to coat stoppers in pre-filled syringes:

As ~~explained above in Section VLC, because~~shown above, the stopper configurations in Table 5 comprised break loose forces as low as 2.2N, and slide forces as low as 2.7N.

Because the ‘631 patent is silent as to when the stopper break loose force and glide forces are measured, or where along the syringe barrel the glide force is measured, a POSITA would understand that these forces could be measured at any time and glide force can be measured at any place along the syringe barrel.

~~134~~145. Boulange provides motivation to a POSITA to use the baked-on siliconized syringes disclosed, because Boulange discloses that “with the medical device of the invention, it is possible to decrease the total amount of lubricant, for example silicone oil, that is necessary in such a medical device” and “[i]n consequence, the medical device of the invention allows to limit the risk of interaction between... silicone oil, and the therapeutic molecules potentially stored in the container of the medical device.” Boulange (Ex. 1008) at 6:23-29.

~~135~~. Thus, Boulange is directed to optimizing the functionality of low volume syringes for ease of use by practitioners, while minimizing the amount of silicone oil. *Id.* at 1:~~3-7~~37, 14:19-20. Specifically, Boulange claims polymer coated pistons to further improve upon already

existing pre-filled syringes utilizing ~~low levels~~ less than 50 µg of silicone oil. Boulange discloses that the invention provides decreased break loose and slide forces while preserving the tight seal of the container, as well as decreased levels of silicone oil, thereby limiting the risk of interaction between the silicone oil and any therapeutic drug stored in the syringe. *Id.* at 6:10-32.

~~136~~146. Additionally, I note that the break loose and glide force testing results in Boulange's Example 5 showed improved lubricity from using the coated stopper B1, ~~with B1~~ ~~showing the best results in Table 7~~. *Id.* at 21:1-3 (Table 7). This is consistent with what would have been expected by a POSITA at the time, as I explain above in **Section V.D.3**, because it was known that using a coated stopper could increase lubricity and, when combined with baked-on siliconization, minimize or potentially eliminate the need for siliconization of the stopper. *See, e.g.,* Chacornac (Ex. 1014) at [0026]. Moreover, it was known that using a coated stopper could have specific advantages in pre-filled syringes containing sensitive protein formulations, including reducing extractables and leachables that could enter the drug formulation during storage, and reducing the amount of silicone oil, which was known to cause protein aggregation. Nema Vol. 1 at 315 (Ex. 1015.330) ("Additional benefits, depending on the coating used, include a decrease in particle generation and a reduction of extractables from the elastomer."); *id.* at :350 (Ex. 1015.365) ("Worth mentioning in this respect are biotech drugs that are used in small quantities per dose and where no absorption by the vial stopper is allowed. ... For such applications, solutions are offered to the market in the form of coated vial stoppers and coated syringe plungers."); *id.* ("Since the coating is nontacky in itself, these closures do not require any surface siliconization, which in applications where the drug is sensitive to silicone of course is of highest value;").

~~137~~147. This is especially advantageous for intravitreally administered protein ~~drug~~drugs, such as the VEGF-antagonist solutions recited in the claims of the '631 patent, because of the dangers that silicone oil, extractables, and aggregated protein could pose to the eye. For example, in the Furfine patent publication, which disclosed testing of glass pre-filled syringes containing a VEGF-antagonist, the syringes had coated stoppers. Furfine (Ex. 1021) at [0059], [0061]. ~~Thus, in addition to being motivated to use the uncoated stopper C from Boulange, a~~ POSITA would have been motivated by the foregoing to use the coated stopper B1 because of the ~~additional~~ benefits described in Boulange. A POSITA also would have been motivated to use the conventional stopper design C coated with silicone oil disclosed in Table 5, which reflected a design that was and still is typically used in the art.

~~D. "Reuter" Bruno Reuter & Claudia Petersen, Syringe Siliconization, 4 TECHNOPHARM 2,238 (2012)~~

~~138. Reuter (Ex. 1010) is an article on pre-filled syringe siliconization that lists Gerresheimer Bunde GmbH as the authors' employer. Gerresheimer is a well-known syringe manufacturer. Reuter was published in August of 2012. Reuter was not of record during the prosecution of the '631 patent application.~~

~~139. Reuter discloses methods for the siliconization of syringes and also provides background on siliconization, including chemical and physical descriptions of the siliconization process. Reuter discloses 1 mL long syringes siliconized via oily siliconization that have low break loose and glide forces. Specifically, Reuter teaches that "[s]tudies on 1 ml long syringes have revealed considerable potential for reducing the amount of silicone oil required," and discloses two force curves for a "standard 1 ml long syringe" using 800 mg and 500 µg of silicone oil, respectively, where the respective break loose forces were reported to be 2.5 N and~~

1.7 N, and the respective glide forces were 1.7 N and 0.5 N. Ex. 1010.004-005. The forces curves from that Reuter study are reproduced below.

D. 2008 Macugen Label

148. Macugen is a non-antibody VEGF Antagonist that was first marketed and administered to patients in the United States in late 2004 for the treatment of neovascular (wet) age-related macular degeneration (wet AMD). See, e.g., Ex. 1071 (FDA Approval letter for Macugen dated December 17, 2004 stating that this “new drug application provides for the use of Macugen (pegaptanib sodium injection) for the treatment of neovascular (wet) age-related macular degeneration”); 2004 Macugen Label (Ex. 1062) (Macugen label dated December 2004); 2008 Macugen Label at 11 (Ex. 1009.011) (indicating that Macugen marketing started on December 17, 2004, and that the label was revised in August 2008); Ex. 1081 (same). I understand that Dr. Szilard Kiss personally administered Macugen in a pre-filled syringe in the United States from 2006-2008.

149. From a review of the FDA approved labels, a POSITA would understand that the Macugen PFS was terminally sterilized by 2008. In particular, the August 2008 Macugen PFS label describes that Macugen PFS was supplied “in a sterile foil pouch as a single used glass syringe pre-filled with 0.3 mg of Macugen in a nominal 90 uL deliverable volume pack. A sterile packaged BD single use 30G x 1/2” Precision Glide Luer Lok need is supplied in a separate pouch.” 2008 Macugen Label at 8-9 (Ex. 1009.008-009); Ex. 1081.003.

150. The Macugen PFS label from 2004 relative to the revised label from 2008 are re-produced below, which indicate how the design of Macugen PFS changed in 2008:

2004 Macugen Label at 9 (Ex. ~~1010.005~~ (Fig. 5 ~~1062.007~~)):

HOW SUPPLIED

Macugen (pegaptanib sodium injection) is supplied in a single use 1 mL glass syringe with a gray rubber plunger containing 0.3 mg in a 90 µL deliverable volume. Each syringe is fitted with a fixed 27 gauge needle covered with a gray rubber needle shield and a rigid plastic outside sheath. All are contained in a foil pouch. The accompanying polystyrene plunger rod and white flange are in a separate foil pouch. The two foil pouches are packaged in a carton.

~~140. With respect to the above force curves, Reuter teaches that even with oily siliconization, the “quantity of silicone oil per syringe could be reduced by 40% without any impairment in the system’s functional properties.” *Id.* at .004. Thus, Reuter shows that even with oily siliconization, using a diving nozzle to spray on the silicone (*i.e.*, the nozzle moves within the barrel during siliconization) as compared to a fixed nozzle, can result in lower break loose and glide forces and lower amounts of silicone oil being used. *Id.* For a 1 mL syringe, Reuter teaches that 500 µg of silicone oil can produce break loose forces of around 1.7 N and glide forces of 0.5 N.~~

~~141. Reuter teaches that “the main objective in siliconization is to achieve the most homogenous possible coating with the minimum possible quantity of silicone oil.” Ex. 1010.004. Reuter further teaches that baked-on siliconization can be used to achieve an “extremely thin layer of silicone,” which “in conjunction with the low quantity of silicone oil used in the emulsion minimizes free silicone in the syringe and ensures that the required quality of finish is achieved.” *Id.* at .005. Specifically, Reuter teaches that the amount of silicone oil in the syringe barrel resulting from baked-on siliconization is far less than for oily siliconization, because baked-on siliconization results in a layer of silicone oil on the inside of the barrel that “measures 15 [to] 50~~

nm,” whereas “the average layer thickness with oily siliconization is 500 [to] 1,000 nm.” *Id.* This is consistent with the understanding of a POSITA at the time, that in addition to reducing the quantity of free silicone oil, baked-on siliconization also uses 10% of the amount of silicone oil as compared to oily siliconization, but still results in similar forces. *See, e.g.,* Ex. 1014 at [0026] (baked-on siliconization “makes it possible to reduce the amount of silicone that is used ... by about a factor of 10 without any loss of lubricating effect.”). Reuter similarly teaches that “[b]aked-on siliconization reduces the measurable quantity of free silicone oil to approx. 10% of the normal value.” Ex. 1010.005.

142. Reuter explains that “[t]here is a trend towards reduced silicone systems or baked-on siliconization in glass syringe finishing” and provides several reasons for this shift in preferences. *Id.* at .007. Specifically, Reuter explains that by reducing the “measurable quantity of free silicone oil to approx. 10% of the normal value,” baked-on processes result in “fewer sub-visual and visual silicone oil particles in the solution.” *Id.* at .005. Reuter teaches that “[s]ub-visual silicone oil particles are thought to promote protein aggregation which can increase the severity of immune responses and reduce the drug’s tolerability.” *Id.* at .004. Thus, Reuter explains that baked-on siliconization, which reduces silicone oil content and residual silicone oil, “is therefore recommended for use with sensitive protein formulations,” and specifically “also advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.” *Id.* at .005. A POSITA would understand this reference to particle contamination requirements in Reuter to include the requirements disclosed in USP789. Thus, Reuter provides motivation to a POSITA to use baked-on siliconization in syringes containing “sensitive protein formulations,” such as VEGF-antagonists.

143. Reuter also explains other advantages of baked-on siliconization, including increasing “the stability of the mechanical properties of the filled syringe throughout its shelf life.” *Id.* Reuter teaches that baked-on siliconization can ensure that the “breakloose force remains practically constant over the entire storage period.” *Id.* This improvement in the break loose effect is illustrated via Figure 7 of Reuter, reproduced below. These graphs compare the break loose and slide forces before and after storage for an oily siliconized syringe (left side of Figure 7) and a baked-on siliconized syringe (right side of Figure 7). I have annotated the figure below to point out the break loose force on the graphs. Figure 7 clearly depicts that the break loose and slide forces of the baked-on siliconized syringe will be comparable to the break loose and slide force of the oily siliconized syringe before storage (the graph on the left for each type of syringe), but that unlike the oily siliconized syringe, “the breakloose force remains practically constant over the entire storage period” for the baked-on siliconized syringe, while the break loose force increases after storage for the oily siliconized syringe. Ex. 1010.005-006. Given that Reuter discloses a break loose force of 1.7 N and a slide force of 0.5 N for an oily syringe in Figure 5, a POSITA would understand that the break loose force and slide force for the baked-on syringe (containing 10% the amount of silicone oil) would also be less than 5 N. Reuter’s teaching of a reduction or avoidance of the break loose effect is an additional motivation to a POSITA to use baked-on siliconization (particularly in intravitreal applications where a loss of control due to a higher force required to initiate an injection could result in damage to the anatomical structures in the eye):

2008 Macugen Label at 8-9 (Ex. 1010.006 (annotations in orange 1009.008-009)):

144. Additionally, with respect to the stoppers of pre-filled syringes, Reuter suggests that using a coating on the stopper can further reduce the amount of silicone oil required to

achieve functional break loose and glide forces. *See id.* at .007 (“The gliding properties of the fluoropolymer coating on specially developed plunger stoppers eliminate the need to siliconize plastic syringes.”). A POSITA would understand that if a coated stopper can reduce the amount of silicone oil needed in a plastic syringe, it would have the same effect in a glass syringe.

145. Reuter also teaches that DC 365, a silicone oil emulsion, is typically used for baked-on siliconization, rather than DC 360 (pure silicone oil) which is used for regular oily siliconization. *Id.* at .003 (“For the so call ed oily siliconization of the syringe barrel DOW CORNING® 360 with a viscosity of 1,000 cSt is used. The DOW CORNING® 365 siliconization emulsion is often used in the baked-on siliconization process.”).

HOW SUPPLIED

Macugen (pegaptanib sodium injection) is supplied in a sterile foil pouch as a single-use glass syringe pre-filled with 0.3 mg of Macugen® in a nominal 90 µL deliverable volume pack. A sterile packaged BD® single use 30G x 1/2” Precision Glide® Luer Lok® needle is supplied in a separate pouch. The foil pouch and needle are packaged together in a carton. Note that the 2008 label indicates that Macugen pre-filled syringe is supplied “in a sterile foil pouch.” In contrast, the 2004 label indicates only that the Macugen prefilled syringe was supplied “in a foil pouch.” A POSITA would understand that this difference is due to a terminal sterilization treatment utilized for Macugen PFS as of 2008, because aseptic filling and packaging of a foil pouch would be prohibitively expensive for a commercial product, if not technically infeasible.

151. As described in the 2008 Macugen label, the Macugen PFS included a “dosing line,” or priming mark, to assist in expelling excess drug and air bubbles.

2008 Macugen Label at 1-2 (Ex. 1009.001-.002); Ex. 1081.003. The dosing line from the prescribing information is shown below:

152. A POSITA would understand that this act of priming the syringe would effectively reset the break loose force to be at or closer to the glide force, because priming would break the initial contact between the stopper and the inside of the barrel that had developed over time during storage.

153. The 2008 Macugen Label reflects the design of Macugen PFS that was on sale and in public use in the United States as of August 2008, as indicated by the Revision Date on the Label. For example, the Macugen PFS label was available on the Drugs.com website as of March 2011, which confirms that Macugen PFS was available in the United States in the form described on the August 2008 label by no later than March 2011. See Drugs.com Macugen Label (Ex. 1009); see also Declaration of Christopher Butler [Ex. 1037] (explaining that the Drugs.com Macugen Label was available on Drugs.com as of March 8, 2011). Drugs.com was known as the “most popular, comprehensive and up-to-date source of drug information.” Ex. 1038.001. Moreover, I understand from the declaration of Dr. Szilard Kiss that he personally used Drugs.com in his professional capacity to find prescribing information and data about drugs, and that physicians in general would have known that Drugs.com was a source for prescribing information as of 2011. Thus, the presence of the August 2008 Macugen PFS label on the Drugs.com website as of March 2011 demonstrates that the August 2008 label reflects the design of Macugen PFS administered in the United States at that time. This includes, *inter alia*, the “sterile foil pouch” resulting from the terminal sterilization process, and a glass syringe using a 30 G x 1/2” needle.

E. “Fries” -A. Fries, *Drug Delivery of Sensitive Biopharmaceuticals with Prefilled Syringes*, Drug Delivery Technology, Vol. 9, No. 5

~~146~~154. Fries (~~Ex. 1012~~) is an article on the use of pre-filled syringes with biopharmaceuticals. Fries at 22 (Ex. 1012.003). Fries recognizes that the silicone oil used to lubricate pre-filled syringes has been shown to have “interactions with sensitive biopharmaceuticals,” such as “aggregation, deformation, and inactivation of native protein structures.” *Id.* at ~~006~~26 (Ex. 1012.006). To that end, Fries describes that the baked-on siliconization process was developed “to lower the level of free (non-bound) silicone oil in prefilled syringes.” *Id.*

~~147~~155. Fries explains that the baked-on siliconization process involves spraying an emulsion of silicone oil such as Dow Corning 365 into the syringe barrel followed by heat treatment, which “enables the lubricant to spread out evenly over the glass surface and creates a thin, uniform film.” *Id.* Fries also reports that such syringes having “low levels” of silicone oil (*i.e.*, those that reduce “[t]he amount of extractable silicone oil . . . below the detection limit (0.03 mg [*i.e.*, 30 µg])”) maintained syringe functionality, with “plunger gliding forces in the range of 5 to 10 N.” *Id.* at ~~006-007~~26-27 (Ex. 1012.006-007).

F. “Furfine” -WO 2007/149334

~~148~~156. Furfine (~~Ex. 1021~~) is a patent publication assigned to ~~Petitioner~~ Regeneron. Furfine describes “[o]phthalmic formulations of a vascular endothelial grow factor (VEGF)-specific fusion protein antagonist . . . suitable for intravitreal administration to the eye.” Furfine (Ex. 1021) at Abstract. The VEGF-specific proteins (*i.e.*, VEGF-antagonists), called “VEGF trap” in Furfine, include the active ingredient that later became known as aflibercept

(EYLEA). *Id.* at [0002] [0005], [0006], [0036], [0045], [0059]; ~~see Ex. 1001~~ ‘631 patent at 6:38-42.

~~149~~157. Furfine discloses two examples, Examples 4 and 6, which tested embodiments of a “1 ml prefilled luer glass syringe with 4023/50 FluroTec coated plunger” containing 40 mg/mL of a VEGF-antagonist. “VEGF Trap.” Furfine (Ex. 1021) at [0059], [0061]; *see also id.* at [0036];

~~G. “Macugen Label”-Macugen® Prescribing Information~~

~~150. The Macugen Label (Ex. 1009) contains information published online at Drugs.com in 2011 from the FDA-approved label for Macugen (pegaptanib sodium), a VEGF antagonist in a glass pre-filled syringe that was initially approved in 2004 for treating wet AMD via intravitreal injection. Ex. 1009.001, .011.~~

~~151. The Macugen prefilled syringe included a “dosing line,” or priming mark, to assist in expelling excess drug and air bubbles. *Id.* at .001, .007. A POSITA would understand that this act of priming the syringe would effectively reset the break loose force to be at or closer to the glide force, because priming would break the initial contact between the stopper and the inside of the barrel that had developed over time during storage.~~

VIII. ~~Petition 1~~, Ground 1: Sigg in View of Boulange Renders Obvious Claims 1-3, 5-9, and

14-22

~~152~~158. As set forth in detail below, claims 1-3, 5-9, 14, and ~~14-22~~16-22 of the ‘631 patent are rendered obvious by Sigg in view of Boulange. and the knowledge of a POSITA.¹⁸ The discussion below specifies where each element of the aforementioned claims is

¹⁸ The knowledge of a POSITA includes, for example, the prior art USP789.

found in the applied references, and includes a detailed explanation of the significance of the quotations and citations from the applied references.

A. Motivation to Combine Sigg and Boulange

1. Silicone Oil and Break Loose / Slide Forces

~~153~~159. As detailed in **Section VII.A** above, Sigg teaches a pre-filled terminally sterilized glass syringe containing a VEGF-antagonist for intravitreal injection with a nominal maximum fill volume of between 0.5 mL and 1 mL. Because Sigg discloses that the pre-filled syringe can contain a sensitive protein or biologic drug product, such as a VEGF-antagonist solution, a POSITA would have been motivated to minimize the amount of silicone oil used in the syringe barrel in order to reduce or avoid the negative interactions that were known to occur between silicone oil and protein or biologic formulation. See Schoenknecht at 10 (Ex. 1013.004) (“One particularly common problem has been that [biotechnology formulations] can react with the oily form of silicone, which is used as a lubricant to coat the sliding components of the syringe.”).

~~154~~160. A POSITA would be further motivated to lower the amount of silicone oil, because pre-filled syringes are both “containers and drug delivery systems at the same time,” Fries at 26 (Ex. 1012.006), and therefore the silicone oil in the syringe would be in contact with the protein formulation for an extended period of time, which would heighten ~~the~~protein stability concerns. As such, a POSITA would look at avoiding higher levels of silicone oil in pre-filled syringes containing sensitive protein formulations such as VEGF antagonists, because of potential “incompatibilities ~~includ[ing]~~including” aggregation, deformation, and inactivation of native protein structures.” *Id.* ~~at .006~~.

~~155~~161. Moreover, it was known that silicone oil “can flow away from the inner surface [of a syringe barrel] and pass into the container’s content;” (Chacornac (Ex. 1014) at [0024]), and such “detachment of silicone oil in water-filled syringes is possible [] and can result in particulate matter and clouding phenomenon.” Nema Vol. 1 at 315 (Ex. 1015.330). Thus, a POSITA would be especially ~~motived~~motivated to lower the amount of silicone oil used in pre-filled syringes for intravitreal injection to avoid injecting silicone oil into the eye, which could cause floaters and/or an increase in intra-ocular pressure. *See, e.g.,* Liu at 1033 (Ex. 1025.011) (“silicone contaminants, when injected into the vitreous cavity at the time of anti-VEGF injections, could cause persistent elevations in [intraocular pressure]”); ~~Ex. 1001 at 4:50-55~~ (“However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including ‘floaters’ and an increase in intra-ocular pressure.”); ~~Ex. 1015.036~~Nema Vol. 1 at 21 (Ex. 1015.36) (explaining the precautions necessary for intravitreal administration); see also Section V.D.1-2 above.

~~156~~162. As explained in **Section V.D.~~1~~1-2** above, there is abundant evidence in the prior art of the risks of silicone oil for biologic products in general, as well as specifically for ophthalmic injections. For example, Nema warns that “[s]ilicone, however, can interact with drug formulation components” and recommends “baking silicone at high heat onto the glass barrels, thereby minimizing the amount of free silicone that can interact with drug product.” Nema Vol. 1 at 315 (Ex. 1015.330-). And as explained above, it was well-documented in the prior art that it was desirable to minimize the amount of silicone oil introduced into the eye via intravitreal injection. See Section V.D.1-2 above. Thus, a POSITA would have been

motivated to use a syringe comprising baked-on silicone oil, as disclosed in Boulange, to reduce the amount of silicone oil injected into a patient's eye.

~~157~~163. ~~Thus, a~~A POSITA would have looked to reduce or minimize the amount of silicone oil used in the pre-filled syringe of Sigg by using the teachings of Boulange, which discloses baked-on siliconization of a pre-filled syringe, resulting in low break loose and slide forces. A POSITA would have looked to Boulange because it discloses that “with the medical device of the invention, it is possible to decrease the total amount of lubricant, for example silicone oil, that is necessary in such a medical device” and “[i]n consequence, the medical device of the invention allows to limit the risk of interaction between.. silicone oil, and the therapeutic molecules potentially stored in the container of the medical device.” Boulange (Ex. 1008) at 6:23-29. Moreover, a POSITA would have been motivated to employ the baked-on syringes disclosed in Scenario 1 of Example 5 of Boulange because those syringes retain low break loose and slide forces while using approximately ~~one-tenth~~onetenth the amount of silicone oil in comparison to the sprayed-on syringes in Scenario 2 of Example 5 of Boulange. Boulange (Ex. 1008) at 20:11-21:19 (Example 5). A POSITA would have been particularly motivated to select a syringe with a coated stopper (B1) because it showed the best results in Example 5. Boulange (Ex. 1008) at 21:1-3 (Table 7). A POSITA also would have been motivated to select a syringe having a low amount of silicone oil with stoppers coated in silicone oil (e.g., Table 5 of Boulange), as such stoppers were commonly used in the art of pre-filled syringes and also resulted in low break loose and slide forces.

164. It is also my opinion that a POSITA would have looked to Boulange specifically because the application was filed by Becton Dickinson, one of the leading manufacturers of pre-filled syringes, including prefilled syringes used for intravitreal

injection. For example, a POSITA would have been aware that Becton Dickinson supplied the syringe and needle for Macugen PFS. Ex. 1017 at 3:16-21, 9:13-20 (describing BD syringes for use with Macugen). A POSITA would have been aware that BD was a world leader in the syringe space, with extensive expertise in the design of pre-filled syringes and pre-filled syringe components. As such, it would have been natural for a POSITA to look to prior art from BD when looking to optimize a pre-filled syringe.

¹⁵⁸165. Baked-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 ~~interactions~~effects. See Shah at 54 (Ex. 1011.004) (“Baked Silicone: Binding the silicone to the glass barrel through a proprietary technology reduces the level of free silicone. This is a clear benefit for silicone-sensitive drugs.”); Nema Vol. 1 at 315 (Ex. 1015.330) (“Recent 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.”). Thus, it was known that “the baked-on silicone process was better suited for protein formulation development in PFS as it represented a lesser degree of risk for the formation of subvisible particulate matter as well as minimized any potential for protein precipitation on the Si-oil droplets.” Badkar at 569 (Ex. 1044.006).

¹⁵⁹166. Additionally, it was known that the baked-on process could reduce the incidence of the break-loose effect, as described in **Section V.D.2** above, because the baked-on siliconization process results in a more homogeneous coating of silicone oil on the inside of the syringe barrel. Fries at 26 (Ex. 1012.006) (in ~~baked-on~~baked-on siliconization the “[r]emoval

of water enables the lubricant to spread out evenly over the glass surface and creates a thin, uniform film”); [Schoenknecht at 10](#) (Ex. 1013.004) (“The second benefit of baked-on silicone is that it reduces the frequency of the ‘break loose’ effect.”). Thus, with baked-on siliconization, “[l]ubrication is maintained so that the initial force required to inject using prefilled syringes with baked-on silicone remains consistently low before and after storage.” [Schoenknecht at 10](#) (Ex. 1013.004). As would have been readily understood by a POSITA, 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. *See, e.g., Nema Vol. 1 at 343* (Ex. 1015.358) (“Moreover gliding forces must be continuous, or without increases and decreases. Should the movement be ‘interrupted,’ then one speaks of shattering of the syringe.”). [A POSITA would have recognized that reducing the break loose effect also improves the accuracy of dosing the medicine within the pre-filled syringe, as the clinician typically advances the plunger initially to prime the syringe and align the stopper with the dosing mark.](#)

~~160~~[167](#). As explained in **Section V.D.3** above, it was well known prior to the earliest priority date of the ‘631 patent that using coated stoppers was advantageous for protein formulations in pre-filled syringes, because a coating on the stopper could potentially prevent leaching of extractables from the rubber into the sensitive protein formulation. *See, e.g., Nema Vol. 1 at 315* (Ex. 1015.330) (“Use of these coated stoppers provides lubricity for machinability and reduces piston clumping in feeder bowls. Additional benefits, depending on the coating used, include a decrease in particle generation and a reduction of extractables from the elastomer.”); *id.* at 350 ([Ex. 1015.365](#)) (“Worth mentioning in this respect are biotech drugs that are used in very small quantities per dose and where no absorption by the vial stopper is allowed. ... For

such applications, solutions are offered to the market in the form of coated vial stoppers and coated syringe plungers.”); *see also* [Furfine](#) (Ex. 1021) at [0059], [0061] (disclosing examples of ~~prefilled~~[pre-filled](#) glass syringes with coated stoppers containing a VEGF-antagonist). Additionally, certain types of stopper coatings could help reduce or eliminate the need for siliconization of the stopper, which is also desirable for pre-filled syringes containing protein formulations such as VEGF-antagonists due to the potential interactions with silicone oil. [Nema Vol. 1 at 335](#) (Ex. 1015.350) (“Since the coating is nontacky in itself, these closures do not require any surface siliconization, which in applications where the drug is sensitive to silicone of course is of highest value.”). Such coated stoppers could nevertheless achieve low break loose and glide forces ~~without the need for additional~~[with minimal](#) silicone oil, as shown by the testing of Boulange discussed above which shows that the lowest forces were experienced with coated stoppers.

2. Particulate Content

168. Sigg discloses a pre-filled syringe that includes a VEGF-antagonist, such as ranibizumab, for intravitreal injection. A POSITA would understand that the ranibizumab solution disclosed in Sigg is an ophthalmic solution. When making a pre-filled syringe including a VEGF-antagonist for intravitreal injection, such as the ophthalmic ranibizumab solution disclosed in Sigg, a POSITA would have been aware of and motivated to comply with USP789, which is prior art and sets forth particulate content requirements for ophthalmic solutions. Those particulate content requirements from USP789 were directly copied into the claims of the ‘631 patent. In order to achieve regulatory compliance and approval, which is ultimately the goal for most if not all pharmaceutical formulations, a POSITA would have understood that compliance with USP789 was highly desirable if not mandatory.

169. A POSITA would have had a reasonable expectation of success that the combination of Sigg and Boulange would result in a pre-filled syringe containing a VEGF-antagonist for intravitreal injection that meets the particulate matter requirements of USP789. A POSITA would understand that the ophthalmic ranibizumab solution disclosed in Sigg should meet the USP789 requirements. The '631 patent provides no information regarding how a VEGF-antagonist solution is prepared such that it complies with the USP789 requirements, thus conceding such a preparation would have been known to a POSITA. Furthermore, a POSITA would understand that ophthalmic solutions of VEGF-antagonists were already known in the art—*i.e.*, Macugen®, Lucentis®, and Eylea®—and that the methods of preparing these solutions such that they meet the requirements of USP789 would be known to one of ordinary skill in the art.

170. With respect to meeting the requirements of USP789, the '631 patent states only that “the syringe has low levels of silicone oil sufficient for the syringe to meet USP789.” '631 patent at 6:28-30. As explained above, Boulange discloses a syringe siliconized using baked-on siliconization that has low levels of silicone oil falling within the ranges claimed in the '631 patent. Accordingly, a POSITA would have expected that the combination of Boulange and Sigg would result in a pre-filled syringe meeting the particulate content requirements of USP789.

3. Stopper Configurations

171. I understand that Novartis has argued that a POSITA would not be motivated to combine Sigg and Boulange because in one embodiment, the stopper of the Boulange syringe is coated with Parylene C. Novartis contends that Boulange does not disclose whether Parylene C is compatible with proteins or ocular drugs, and that it is unknown whether a Parylene C coated stopper would ensure sufficient tightness for VHP

sterilization. For the reasons explained below, a POSITA would have understood that Parylene C would be compatible with a terminally sterilized syringe comprising a VEGF-antagonist, and that it would provide sufficient tightness for terminal sterilization, as disclosed in Sigg and Lam.

172. A POSITA would understand from the disclosure in Boulange that the disclosed stopper configurations, including a Parylene C coating, would be compatible with the teachings of Sigg and Lam (i.e., a syringe comprising a sensitive drug product that is terminally sterilized). First, Boulange explicitly acknowledges that Parylene C coating is impervious to gases and thus attractive for use in medical applications. Boulange (Ex. 1008) at 2:21-24 (describing that Parylene C is impervious to gases, which makes it “particularly attractive for use in numerous biomedical applications”). Boulange further acknowledges the need for a stopper design to maintain sufficient tightness to seal the portion of the syringe comprising the drug product while maintaining acceptable operational forces. Boulange (Ex. 1008) at 1:18-21 (“The piston is preferably made at least partially from a viscoelastic material so as to ensure tightness in the region of contact between the container and the piston.”), 3:20-27 (describing that with Parylene C coating on the stopper “tightness in the region of contact between the piston and the container can be guaranteed to be maintained”); *see also* Boulange (Ex. 1008) at 4:21-32 (explaining that the disclosed coating ensures tightness and enables “gliding between the two parts intended to cooperate together and also tightness between these two parts at the contact region”). Thus, a POSITA would understand from the disclosure in Boulange that stoppers coated with Parylene C would provide low operational forces while ensuring that the drug product in the syringe is properly sealed by the interface between the glass barrel and

stopper. And a POSITA would certainly recognize that such a design with a tight seal and a coating such as Parylene C that is impervious to gases would be suitable for terminal sterilization. In fact, Boulange explicitly 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.

Boulange (Ex. 1008) at 1:14-15. Moreover, a POSITA would have known that it was conventional that a pre-filled syringe should be gas-tight to protect certain drug products from exposure to oxygen and degradation. See, e.g., Furfine (Ex. 1021) at [0049] (explaining that a liquid formulation comprising a VEGF antagonist can be stored in an oxygen-deprived environment comprising an inert gas such as nitrogen).

173. Second, Boulange also explicitly acknowledges that it is necessary for the stopper design to prevent “possible degradation [that] is sometimes initiated by the processes used to sterilize the medical devices containing them, for example bringing them into contact with ionizing radiation” that “may cause inadequate interactions with the medical product potentially present in the medical device.” Boulange (Ex. 1008) at 4:4-8. Boulange further describes that it is necessary for the coating of the stopper “to effectively isolate the region of contact” between the stopper and the drug product. Boulange (Ex. 1008) at 4:12-16. Thus, Boulange encourages the use of Parylene C with the understanding that the coating must not negatively impact the drug product, must withstand the sterilization process that pre-filled syringes were known to undergo (e.g., VHP or EtO sterilization)¹⁹, and must ensure a tight seal to protect the drug product while ensuring low

¹⁹ A POSITA would also recognize that because Boulange’s syringe is gas tight, any sterilizing gas would not interact with the Parylene C coating on the stopper, which is inside the syringe (i.e., located where the sterilizing gas cannot enter).

operational forces. Accordingly, it would have been clear to a POSITA that the syringe and stopper design disclosed in Boulange would be suitable for a sensitive drug product contained in a pre-filled syringe subject to terminal sterilization, as disclosed in Sigg.

174. It was well-known that Parylene C was suitable for use in medical applications. See SCS at 10 (Ex. 1074.010) (explaining that Parylene C has “been tested according to the Biological Evaluations requirements of ISO 10993,” that it has “been demonstrated in a wide range of medical coating applications over the past three decades”). Accordingly, a POSITA would have reasonably expected that Parylene C would be suitable for use with a terminally sterilized syringe with a VEGF antagonist for intravitreal injection. For example, a 2007 publication explains that Parylene C has very low permeability to moisture and corrosive gasses, and that Parylene C had been tested for compatibility with different sterilization methods, including VHP and EtO. See SCS at 2 (Ex. 1074.002) (explaining that Parylene C has “a very low permeability to moisture and corrosive gasses”); *id.* at 4 (explaining that the water vapor transmission rates “for Parylene C [are] superior to most common polymeric materials.”), *id.* at 6 (discussing sterilization compatibility, including with hydrogen peroxide plasma and ethylene oxide).

175. A 2012 publication further describes that Parylene C is desirable and “widely applied” to pre-filled syringes. Ex. 1072.001 (explaining that Parylene C is one of the available Parylene coatings that “provides barrier protection for the syringe barrel, plunger and seals, and for the drug.... It is also highly lubricious, eliminating sticky plungers.. Parylene is widely applied on syringes to make their use easier and more precise.”). It further describes that Parylene “is an excellent barrier coating, protecting the container, including caps and seals, and also protecting the drug from any unwanted

leaching or extractions.” *Id.* at .002; see also Ex. 1075.004 (describing that the results of sterilizing Parylene C with EtO and H2O2 “were quite favorable”).

176. I also know from my own work experience that Parylene C was used as a coating for rubbers in commercial syringes that were to be sterilized with EtO. In particular, Schott in 2010 developed the InJentle Syringe System, which comprises a rubber coated with Parylene C that acts as a seal during shelf life. In addition, I note that the tightness of the seal was easily tested and optimized using a helium leakage test. Helium testing involves smaller molecules than either VHP or EtO, and could be routinely used to optimize the tightness of a stopper comprising a Parylene C coating.

177. A POSITA would also expect that Parylene C would be a suitable coating for pre-filled syringes containing protein formulations such as VEGF-antagonists because Parylene C was known to be chemically inert and would not react with drug formulations. For example, Boulange explicitly describes that the purpose of its invention is to prevent interaction between lubricants and drug products. Boulange (Ex. 1008) at 6:26-29 (“[T]he medical device of the invention allows to limit the risk of interaction between a lubricant, for example silicone oil, and the therapeutic molecules potentially stored in the container”). It would make little sense for Boulange to address a problem of limiting interaction between a lubricant and therapeutic molecule by proposing the use of a coating (Parylene C) that would negatively interact with a drug product.

178. Boulange also discloses stopper designs that do not use a Parylene C coating that would be desirable to use with Sigg. For example, Table 5 discloses stoppers coated with a small amount of silicone oil (5 µg/cm²) that do not have Parylene C (Stopper C), which achieves low break loose and slide forces:

179. I understand that Novartis has argued that Boulange discourages the use of stoppers that do not have Parylene C (i.e., stopper C). I disagree with this interpretation of Boulange. For example, Novartis notes that for Table 5, Boulange describes that Stopper C was “markedly inferior” to Stopper B1 (i.e., the Parylene C coated stopper), but that is only because the break loose and slide forces for Stopper C increased over time. See Boulange (Ex. 1008) at 19:4-10 (“The results obtained with a piston having no coating (piston C) are markedly inferior. After one month of ageing, the friction forces B and S increase...whereas they remain practically unchanged and below 4 N in the case of inventive piston B1”). A POSITA would understand, however, that Stopper C in Table 5 still provided acceptable operational forces and represents a design that was conventional in the art at the time of Boulange and the effective filing date of the ‘631 patent (i.e., stoppers coated with silicone oil but no Parylene C). Thus, even if Parylene C could not be used in combination with Sigg (which is incorrect), a POSITA would have recognized that the conventional stopper such as configuration C in Table 5 could be used instead while still providing acceptable break loose and slide forces. Notably, Stopper C provided break loose and slide forces well within the claimed ranges (less than 11 N) at both T = 0 and T = 1.

180. Stopper C in Table 5 exhibited force characteristic consistent with what one of ordinary skill would have expected for a pre-filled syringe prior to 2012. For example, Configuration C in Table 5 had break loose and slide forces less than 5N at T=0, and still maintained break loose and slide forces less than 10 N at T=1. As I explained above, syringes are typically sold as 10 and 5, meaning that they have break loose forces less than 10 N and slide forces less than 5 N. See V.C above; see also

Overcashier at 81 (Ex. 1076.006) (describing break loose and slide force test results of 5-10 N for “Pre-filled Syringes for Protein Products”). Thus, the results for Configuration C in Table 5 are consistent with typical industry expectations. In fact, the ‘631 Patent specification acknowledges that prior art syringes used for intravitreal injection had forces of less than 20 N. Ex. 1001 at 5:34-36 (“Break loose and slide forces for pre-filled syringes known in the art are typically in the region of less than 20N....”). The results for Stopper C in Table 5 are substantially less than 20 N.

181. With respect to the results disclosed in Table 7, Boulange states that the forces for Stoppers A and C were “something which does not appear to be acceptable for a medical device.” Ex. 1008 at 21:4-5. As an initial matter, I note that Stoppers A and C in Table 7 had break loose and slide forces within the claimed ranges at T=0, and forces no greater than about 20 N at T=1 (which the ‘631 Patent specification describes was generally used in the prior art). Nonetheless, a POSITA would have recognized that Boulange describes that Stoppers A and C in Table 7 do “not appear to be acceptable” because they were rubber stoppers with no coating on them at all (no Parylene C or silicone oil).²⁰ It was well-understood that a stopper requires a coating of some type to achieve acceptable break loose and slide forces. See Section V.D.3. As such, a POSITA would recognize that Stoppers A and C would be acceptable for use in a pre-filled syringe for intravitreal injection if a coating of silicone oil were applied to them, as disclosed in Table 5 of Boulange.

²⁰ A POSITA would recognize that Boulange only tested configurations A and C in Table 7 (no coating at all) to provide a baseline for assessing the improvements that can be attributed to the use of a Parylene C coating. Boulange (Ex. 1008) at 21:4-14.

B. Reasonable Expectation of Success

~~161~~182. A POSITA would have a reasonable expectation that the combination of Sigg and Boulange would result in a terminally sterilized, low volume, pre-filled glass syringe having an amount of silicone oil and break loose and slide forces falling within the ranges claimed in the '631 patent. First, Boulange explicitly discloses a syringe having 40 µg silicone oil for a 1 mL syringe (*i.e.*, 4 µg/cm²) and resulting break loose and slide forces of less than 3N. Boulange (Ex. 1008) at 20:15-21:14. A POSITA would understand that the break loose forces disclosed in Table 7 of Boulange would remain substantially the same even when a ~~VEGF-antagonist~~VEGF-antagonist such as ranibizumab is contained in the syringe rather than water because the viscosity of the fluid does not affect the break loose force.

Specifically, as explained in **Section V.C** above, because the break loose force is the force required to get the stopper to just about begin moving, ~~and because the force is between the stopper and barrel and therefore a function of siliconization, and stopper material and coating, the measured~~the break loose force is ~~effectively~~the force required to overcome the friction between the stopper and syringe barrel, and is thus independent of the viscosity of the fluid within the ~~prefilled~~pre-filled syringe (which impacts the hydrodynamic force the stopper must overcome).

~~162~~183. In addition, while the viscosity of the solution does affect the slide force, the viscosity of a VEGF-antagonist solution such as ranibizumab (1.3 cp) will be sufficiently close to the viscosity of water (1 cp) that the use of ranibizumab instead of water would not substantially affect the slide forces disclosed in ~~Table~~Tables 5 and 7 of Boulange. The Hagen-Poiseuille formula can be used to calculate how a change in viscosity would impact the slide force based on the change in hydrodynamic force. Below is the Hagen-Poiseuille

formula which shows how the forces (P) needed to expel 1ml of water through a defined syringe outlet vary with respect to the other inputs. The following definition apply: inner radius needle = r , v is the mean flow velocity, P is the pressure (*i.e.*, the measured force), p is the dynamic viscosity, and l is the length of the needle):

See also Overcashier at 82-83 (Ex. 1076.007-.008) (describing Hagen-Poiseuille equation with respect to estimating stopper slide force). In the Hagen-Poiseuille formula, the dynamic viscosity of the fluid, p , varies proportionally with pressure, P , and pressure varies proportionally with force ($P = F / A$, where A is area), so the slide forces would be only 1.3 times greater, for example, if a ranibizumab solution is used in place of water in Example 5 of Boulange.

Moreover, a POSITA would readily understand from the equation above that the slide forces disclosed in Boulange could be maintained by decreasing the stopper speed (v) to compensate for the increase in viscosity associated with ranibizumab. Boulange, for example, describes testing stoppers at a speed of 380 mm/min. Ex. 1008 at 16:13-15. Testing the syringes at 190 mm/min when filled with ranibizumab, as described in the '631 Patent specification, would result in slide forces less than or equal to those disclosed in Tables 5 and 7 of Boulange.

~~163~~184. Additionally, a POSITA would not expect any incompatibility between baked-on siliconization as taught by Boulange and VHP sterilization disclosed in Sigg. Specifically, Sigg teaches a POSITA that the VHP technique is broadly applicable to pre-filled syringes. Sigg (Ex. 1007) at 8:21-25. A POSITA would understand that pre-filled syringes typically contain silicone oil lubricant and would therefore expect that the pre-filled syringes of Sigg contained some silicone oil lubricant, and thus the terminal sterilization being applied was done to a siliconized syringe. Furthermore, a POSITA would understand that the VHP terminal

sterilization processes in Sigg would not affect the siliconized interior of the syringe barrel or the break loose or slide forces because Sigg discloses that “the contents of the container are sterile and unaffected by surface decontamination methods as described herein.” Sigg (Ex. 1007) at 9:16-17. Furthermore, a POSITA would understand that the VHP would not affect the interior (or the drug) of the pre-filled syringe because Sigg discloses that during the decontamination process, VHP is prevented from diffusing into the pre-filled syringe. *Id.* at 14:~~27-15~~2715:20. Moreover, as explained above, the syringe of Boulange is gas-tight and would prevent any sterilizing gas from ingressing into the drug product. Thus, a POSITA would have understood that baked-on siliconization disclosed in Boulange is compatible with the VHP sterilization disclosed in Sigg.

~~164~~185. Boulange also discloses that the “invention allows to have decreased activation, sustainable and final forces.. .without having to add lubricant and while preserving the tightness of the contact region between two parts.” Boulange (Ex. 1008) at 6:~~10-14~~10-14. A POSITA would have understood that maintaining a tight seal provides protection during the sterilization process, which would allow terminal sterilization to be applied without allowing negative interactions with the VEGF-antagonist formulation. Sigg (Ex. 1007) at 3:27-30 (“It further has been found that among the commercially available primary packaging components, there are only very few packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gasses into the pharmaceutical liquid enclosed by the prefilled container”). And as explained above, Boulange explicitly acknowledges the need to ensure a syringe design that provides sufficient tightness to protect the drug product and endure various sterilization techniques. See VIII.A above. Moreover, Sigg and Boulange both relate to aspects of ~~pre-filled~~prefilled syringe manufacture, and are therefore

complementary to one another, which would further motivate their combination and create a more than reasonable expectation of making a pre-filled syringe as described in the claims of the ‘631 patent.

186. I understand that Novartis has argued that a POSITA would not have reasonably expected to succeed in terminally sterilizing a syringe based on the combination of Sigg and Boulange due to the potential ingress of sterilizing agent. I disagree with Novartis’s assertion. As I explained above, the syringe disclosed in Boulange was specifically designed with the understanding that “possible degradation is sometimes initiated by the processes used to sterilize the medical devices containing them” and that the “medical product potentially present in the medical device [is] to be preserved.” Boulange (Ex. 1008) at 4:3-5, 4:26-27. Thus, a POSITA would have understood that Boulange’s design was intended to protect drug products, including from the potential effect of sterilizing agents.

Moreover, as of the effective filing date of the ‘631 patent, it was well-known in the art how to design a pre-filled syringe that could be terminally sterilized. Lam, for example, describes that a glass syringe combined with a rubber stopper is suitable for preventing ingress of sterilizing gas. Lam (Ex. 1029) at 2:7-9, 2:29-33. Similarly, by February 2012 a terminally sterilized PFS comprising the VEGF-antagonist aflibercept was approved in Australia. See Ex. 1066.005, .007. Finally, the Macugen PFS was distributed in a “sterile foil pouch” by August 2008, which a POSITA would understand means that Macugen PFS was terminally sterilized.

187. For at least these reasons, a POSITA would have had a reasonable expectation of success in terminally sterilizing the combination of Sigg and Boulange.

2. Particulate Content

~~165. Sigg discloses a pre-filled syringe that includes a VEGF-antagonist, such as ranibizumab, for intravitreal injection. A POSITA would understand that the ranibizumab solution disclosed in Sigg is an ophthalmic solution. When making a pre-filled syringe including a VEGF-antagonist for intravitreal injection, such as the ophthalmic ranibizumab solution disclosed in Sigg, a POSITA would have been aware of and motivated to comply with USP789, which is prior art and sets forth particulate content requirements for ophthalmic solutions. Those particulate content requirements from USP789 were directly copied into the claims of the '631 patent. In order to achieve regulatory compliance and approval, which is ultimately the goal for most if not all pharmaceutical formulations, a POSITA would have understood that compliance with USP789 was highly desirable if not mandatory.~~

~~166. A POSITA would have had a reasonable expectation of success that the combination of Sigg and Boulange would result in a pre-filled syringe containing a VEGF-antagonist for intravitreal injection that meets the particulate matter requirements of USP789. A POSITA would understand that the ophthalmic ranibizumab solution disclosed in Sigg should meet the USP789 requirements. The '631 patent provides no information regarding how a VEGF-antagonist solution is prepared such that it complies with the USP789 requirements, thus conceding such a preparation would have been known to a POSITA. Furthermore, a POSITA would understand that ophthalmic solutions of VEGF-antagonists were already known in the art *i.e.*, Macugen, Lucentis, and Eylea and that the methods of preparing these solutions such that they meet the requirements of USP789 would be known to one of ordinary skill in the art.~~

~~167. With respect to meeting the requirements of USP789, the '631 patent states only that "the syringe has low levels of silicone oil sufficient for the syringe to meet USP789 "Ex. 1001 at 6:28-30. As explained above, Boulange discloses a syringe siliconized using baked-on siliconization that has low levels of silicone oil falling within the ranges claimed in the '631 patent. Accordingly, a POSITA would have expected that the combination of Boulange and Sigg would result in a pre-filled syringe meeting the particulate content requirements of USP789.~~

BC. Claim 1

**1. [1.a] A pre-filled, terminally sterilized syringe for
intravitreal injection**

~~168~~188. Sigg discloses terminal sterilization of pre-filled syringes containing sensitive biologic drug products for intravitreal injection:

Terminal sterilization of prefilled containers in secondary packaging is one way to provide the device to an end user.. Moreover there is a strong market need for terminally anti-microbially-treated medical devices, such as prefilled syringes used for intravitreal injections.

Described herein is a terminal sterilization and surface decontamination treatment of prefilled containers, specifically for sterilization of prefilled containers containing sensitive solutions, such as a drug product or biological therapeutic, within secondary packaging.

The method and system described herein decontaminate or, more preferably render sterile an outside surface of primary packaged drug products within a secondary pack,

thereby improving safety of products for critical administration (e.g. use in a surgical suite or for intravitreal injections).

In one embodiment, the prefilled container is **a syringe..** .filled with a drug product.. .In another embodiment, a solution is any drug product having requirements or desirability for sterility of the drug product container surface. In one particular embodiment, the drug product is a protein solution, such as ranibizumab (e.g. 6mg/ml or 10 mg/ml) solution for **intravitreal injection**.

Sigg (Ex. 1007) at 2:15-19, 3:8-13, 4:12-15, 9:1-14, 20:10-21:11.

~~+69~~189. Boulange ~~also~~ discloses glass syringes that are filled with water prior to testing. and intended for biomedical applications. Boulange (Ex. 1008) at 13:11-12 (“The container 2 is a glass syringe body accommodating a piston 3 able to move translationally. . .”); 14:19-21 (“tests were applied on containers filled with 1 mL of demineralised water and each plugged with one piston to be tested (coated or uncoated)”). 1:1-2 (“The present invention relates in general to a medical device, for example a syringe”); 1:14-15 (“[T]he container is intended to accommodate a medical product in the liquid, gaseous, fluid, pasty or lyophilized phase.”).

2. [1.b] the syringe comprising a glass body forming a barrel, a stopper and a plunger

~~+70~~190. Sigg discloses that the pre-filled syringe has a barrel, stopper, and plunger. An annotated version of Figure 1 of Sigg is reproduced below, showing the location of each of these pre-filled syringe components. :

~~171~~191. Sigg discloses glass syringes. Sigg (Ex. 1007) at 2:1-6, 22:8-11. While Sigg does not explicitly state the syringes in Example 1 were glass, as explained ~~in 113~~ above, it would have been obvious to a POSITA to utilize a glass syringe for the particular embodiment disclosed in Sigg Example 1 (*i.e.*, a pre-filled syringe containing ranibizumab that is terminally sterilized using VHP).

~~172~~192. Boulange discloses a syringe comprising a glass body forming a barrel, and a stopper (which is referred to in Boulange as a “piston”):

With reference to figures 1 and 2, the medical device 1 comprises a first and a second parts 2 and 3, one being complementary to the other, for example a piston 3 housed in a container 2, the piston 3 and the internal surface of the container 2 being in contact with one another via a contact region 10. The piston 3 and the container 2 are able to move one with respect to the other in a predetermined gliding movement 4, for example translationally and/or rotationally.

The container 2 is a glass syringe body accommodating a piston 3 able to move translationally along arrow 4 of figure 2 inside the container 2.

Boulange (Ex. 1008) at 9:21-35, 13:11-12.

~~173~~193. The “plunger” recited in the ‘631 ~~patent’s~~patent claims refers to a plunger rod. It would be obvious to a POSITA that, although not depicted in Figures 1 and 2 of Boulange, the syringe stopper would be coupled to a plunger rod in order for the syringe to be used. See ISO 11040-5 (Ex. 1028) (describing the standard plungers for pre-filled syringes).

An annotated version of Figure 2 of Boulange is reproduced below showing where a POSITA would understand the plunger rod would be coupled to the stopper.

As described in **Section V.B** above, a plunger rod is a standard component of a ~~pre-~~
~~filled~~pre-filled syringe. A POSITA would understand that the Boulange syringe would include
one ~~in order to~~to allow the user to advance the piston and expel the product contained in the
syringe. Often, the two components are used together and therefore stoppers are often referred
to as plunger stoppers. See Nema Vol. 1 at 300 (Ex. 1015.315); Sigg (Ex. 1007) at 2:1-3;
Chacornac (Ex. 1014) at [0008]; The figure below illustrates the conventional components
of a glass-prefilled syringe, including a stopper, plunger, and glass barrel:

3. [1.c] and containing an ophthalmic solution which
comprises a VEGF-antagonist, wherein:

~~174~~194. Sigg discloses an embodiment in which the pre-filled syringe contains an
ophthalmic solution comprising the VEGF-antagonist ranibizumab (Lucentis):

In another embodiment, a solution is any drug product having requirements or
desirability for sterility of the drug product container surface. In one particular
embodiment, the drug product is a protein solution, such as **ranibizumab (e.g. 6mg/ml
or 10 mg/ml) solution for intravitreal injection.**

A formulation as described in U.S. Patent No. 7,060,269²¹ was tested for protein
degradation following treatment by VHP.. ..Filling of 0.5 mL syringes was performed in
a sterile lab for hydrogen peroxide treatment.

Sigg (Ex. 1007) at 9:11-14, 20:17-21.

²¹ U.S. Patent No. 7,060,269 is a Genentech Patent directed to “anti-VEGF antibodies”
(i.e., a VEGF antagonist). Baca (Ex. 1023) at 2:14-19.

~~175~~195. While Boulange does not explicitly disclose a VEGF-antagonist, a POSITA would understand that the pre-filled syringes disclosed in Boulange with baked-on silicone oil and optionally coated stoppers would be especially preferred for use with protein formulations such as VEGF-antagonist solutions on account of the reduced incompatibility between baked-on siliconization and protein formulations, and also between coated stoppers and protein formulations intended for ophthalmic use. See Badkar at 569 (Ex. 1044.006) (“Overall data suggested that the baked-on silicone process was better suited for protein formulation development in PFS as it represented a lesser degree of risk for the formation of subvisible particulate matter as well as minimized any potential for protein precipitation on the Si-oil droplets.”); Schoenknecht at 10 (Ex. 1013.004) (explaining that baked-on siliconization reduces the silicone’s “chemical reactivity” whereby “the product’s stability is increased”); Shah at 54 (Ex. 1011.004) (baked-on silicone “is a clear benefit for silicone-sensitive drugs”).

4. [1.d] the syringe has a nominal maximum fill volume of between about 0.5 mL and about 1 mL

~~176~~196. Sigg discloses a syringe with a nominal maximum fill volume of 0.5 mL and 1 mL. Sigg (Ex. 1007) at 20:20-21 (“Filling of 0.5 mL syringes was performed in a sterile lab for hydrogen peroxide treatment.”); 22:8-10 (“Additionally, the oxidative stress exerted on a 0.5% Polysorbate 20 solution in pre-filled glass syringes (1 mL long, ISO) was investigated by measurement of peroxides according to standard protocols.”). A POSITA would have understood that the 0.5 mL and 1 mL volumes disclosed in Sigg refers to the nominal maximum fill volume. A POSITA would also have understood that a small volume syringe in the 0.5-1 mL range would be used for intravitreal injection, including for example, injection of ranibizumab, since the amount of fluid capable of being injected ~~into the eye~~intravitreally is limited. See

Nema Vol. 1 at 2 (Ex. 1015.017) (administration volume for intravitreal injection is “generally < 0.1 mL”); ~~See~~ Furfine (Ex. 1021) at [0059], [0061] (disclosing 1 mL prefilled glass syringe for VEGF-antagonist); 2004 Macugen Label at 11 (Ex. 1062.009) (disclosing that Macugen is provided in a 1 mL glass syringe). The fill volume of the syringe has to be more than the volume that is desired for injection, in order to account for priming and loss of product. As explained in **Section V.B**, 0.5 mL and 1 mL are the smallest standard syringe sizes and were known to be used for drug products for intravitreal injection.

~~177~~197. Boulange also discloses a syringe with a nominal maximum fill volume of 1 mL. Boulange (Ex. 1008) at 14:19-21 (“Activation Gliding Force (AGF) tests were applied on containers filled with 1 mL of demineralised water and each plugged with one piston to be tested (coated or uncoated).”). A POSITA would also understand that “a surface area of 10 cm²,” as ~~disclosed in Example 5 of~~ described in Boulange, corresponds to a standard 1 mL syringe. According to ISO-11040-4, a short/standard 1 mL syringe has an inner diameter of 8.65 mm (equivalent to a radius, r , of 4.325 mm and a height (or length), h , of 35.7 mm. ~~Ex. 1028.008~~ ISO-11040-4 at 4 (Table 1) (Ex. 1028.008). The surface area, S , of the syringe barrel, can be calculated using those dimensions, using the conversion of 10 mm = 1 cm, and the equation $S = 2 \pi rh$, is 9.70, or ~10 cm². For a long 1 mL syringe, the inner diameter is 6.35 mm (equivalent to a radius, r , of 3.175 mm and a height (or length), h , of 54 mm. The surface area, S , of the syringe barrel, is 10.77 cm² (also ~ 10 cm²).

~~178. Furthermore, a~~198. A POSITA would understand that the disclosure in Boulange of the amount of silicone oil applied per cm² (*i.e.*, 4 ~~µg~~µg/cm² for baked-on siliconization) is applicable regardless of the syringe fill volume (and therefore applicable to both 0.5 mL and 1.0 mL syringes), because in baked-on siliconization, thin “[m]ono-layers of the lubricant are affixed

to the glass surface,” which allows “the lubricant to spread out evenly over the glass surface and creates a thin, uniform film,” and therefore the amount of silicone oil applied is proportional to the surface area of the inside of the syringe barrel. Fries at 26 (Ex. 1012.006).

5. [1.e] the syringe barrel comprises from about 1 µg to 100 µg silicone oil

~~179~~199. Boulange, in Example 5, discloses pre-filled syringe embodiments wherein “a silicone lubricant was deposited and baked onto the internal surface of the syringe body 2, at a rate of 40 ~~µg~~µg for a surface area of 10 cm², but no silicone was used or sprayed on the pistons 3.” Boulange (Ex. 1008) at 20:15-17, 21:1-3 (Table 7 disclosing “4 ~~µg~~µg/cm²” for Scenario 1). A POSITA would understand that the reference to “a surface area of 10 cm²” refers to the approximate surface area of a 1 mL syringe, as explained above in ~~177~~197.

~~180~~200. As also explained above in ~~178~~198, the silicone oil spray rate of 4 ~~µg~~µg/cm² rate in Boulange would be expected to remain the same regardless of the syringe size, because in baked-on siliconization the amount of silicone oil used varies directly with the surface area of the surface being sprayed. Thus, at a rate of 4 ~~µg~~µg/cm², a total of 27.8, or ~28, ~~µg~~µg of silicone oil, would be applied for a 0.5 mL standard syringe as disclosed in Sigg using the method of Boulange. This calculation is based on the syringe specifications of ISO-11040-4, wherein a standard 0.5 mL syringe has an inner diameter of 4.65 mm (equivalent to a radius, r , of 2.325 mm and a height (or length), h , of 47.6 mm. The surface area, S , of the syringe barrel, calculated using those dimensions, the conversion of 10 mm = 1 cm, and the equation $S = 2\pi rh$, is 6.95 cm². Multiplying that number by 4 ~~µg~~µg/cm², gives you a total of 27.8, or ~28, ~~µg~~µg of silicone oil to be applied on the inside of the syringe barrel for a 0.5 mL standard syringe.

201. And as explicitly described in Boulange, the 1 ml syringe comprises 40 µg of silicone oil. A POSITA would understand that a 1 ml syringe, as disclosed in Boulange, would also be suitable for a VEGF-antagonist for intravitreal injection, as disclosed in Sigg. 2004 Macugen Label at 11 (Ex. 1062.009) (disclosing that Macugen is provided in a 1 mL glass syringe).

202. Boulange unequivocally discloses that 40 µg was the amount of silicone oil that was applied to (i.e., deposited) onto the syringe. Boulange (Ex. 1008) at 20:15-18 (“a silicone lubricant was deposited and baked onto the internal surface of the syringe body 2, at a rate of 40 µg for a surface area of 10 cm², but no silicone was used or sprayed on the pistons 3.”). Boulange does not explicitly describe how the silicone amount was measured, but one of ordinary skill would recognize that it was done via a non-destructive method of measurement, such as measuring the spray parameters, differential weighing of the syringe barrel (i.e., measuring the mass of the barrel before and after applying the silicone oil), or by measuring the thickness of the silicone oil coating on the syringe barrel. In particular, Boulange describes that the amount of silicone oil was measured before the force testing (i.e., AGF Testing) was conducted. Boulange (Ex. 1008) at 17:11-12 (“The silicone amount was measured prior to any AGF testing.”). As such, a POSITA would have known that the silicone oil amount disclosed in Boulange could not have been measured using solvent extraction²² because that would remove all the silicone oil from the syringe barrels, making

²² I note that even if Boulange measured the silicone oil amount using solvent extraction, that would fall within the scope of the claims because the specification describes that the claimed silicone amounts can be measured by extraction using a solvent. ‘631 patent at 5:5-15 (describing measuring silicone oil on syringe barrel using “quantitation by infrared-spectroscopy of the oil diluted in a suitable solvent”).

them unsuitable for testing. DC365 FAQ at Question 15 (Ex. 1034.004) (describing that all silicone oil can be extracted from a syringe after baking). Moreover, removing the silicone oil prior to force testing using solvent extraction would not provide useful information concerning the low limit of silicone oil that would produce acceptable break loose and slide forces, which is the stated purpose of Boulange. Boulange (Ex. 1008) at 17:12-15 (“This measurement was done in order to...define the low limit for the silicone amount acceptable for functional testing (AGF test).”).

6. [1.f] the VEGF-antagonist solution comprises no more than 2 particles > 50 ~~µm~~µm in diameter per mL

~~181~~203. It would be obvious to a POSITA 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~~µm in diameter per mL.

~~182~~204. Sigg discloses a terminally sterilized pre-filled syringe containing a solution of the VEGF-antagonist ranibizumab for intravitreal injection. Sigg (Ex. 1007) at 9:11-14 (“In another embodiment, a solution is any drug product having requirements or desirability for sterility of the drug product container surface. In one particular embodiment, the drug product is a protein solution, such as ranibizumab (e.g. 6mg/ml or 10 mg/ml) solution for intravitreal injection.”); ~~20:17-21~~1721 (“A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by VHP.. ..Filling of 0.5 mL syringes was performed in a sterile lab for hydrogen peroxide treatment.”).

~~183~~205. As explained in **Section V.F and VIII.A.2**, a POSITA would understand that “no more than 2 particles >50 ~~µm~~µm in diameter per mL” is one of the USP789 standards required for ophthalmic drugs such a VEGF-antagonist solution intended for intravitreal use. *See*

Scypinski (Ex. 1017) at 10:19-22 (“United States Pharmacopoeia (USP) Chapters <788> *Particulate Matter in Injections* and <789> *Particulate Matter in Ophthalmic Solution* describe physical tests for the purpose of enumerating extraneous particles within specific size ranges.”). Specifically, a POSITA 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~~µm per mL. A POSITA would understand that ophthalmic solutions of VEGF-antagonists were already known in the art—*i.e.*, Macugen®, Lucentis®, and Eylea®—and that preparing these solutions such that they meet the requirements of USP789 would be within the level of ordinary skill in the art.

~~184~~206. A POSITA would have a reasonable expectation that the combination of Sigg (*i.e.*, a VEGF-antagonist solution in terminally sterilized a pre-filled syringe) and Boulange (pre-filled baked-on syringe with low silicone oil) would satisfy the USP789 particulate matter limitations. Badkar at 569 (Ex. 1044.006) (“Overall data suggested that the baked-on silicone process was better suited for protein formulation development in PFS as it represented a lesser degree of risk for the formation of subvisible particulate matter as well as minimized any potential for protein precipitation on the Si-oil droplets.”). A POSITA would understand that the ophthalmic solution disclosed in Sigg is required to meet USP789, as I described above. The ‘631 patent does not explain how to achieve a solution that meets USP789 (~~see Ex. 1001~~‘631 patent at 6:28-30), and thus concedes that preparation of such a solution was known to a POSITA. Moreover, Boulange discloses a syringe siliconized using baked-on siliconization that has ~~low levels~~less than 50 µg of silicone oil ~~falling~~, which falls within the ranges claimed in the ‘631 patent. Accordingly, a POSITA would have expected that the combination of Boulange and

Sigg would result in a pre-filled syringe meeting the particulate content requirements of USP789 because Boulange explicitly states that its invention limits the risk of interaction between the silicone oil and the ~~ophthalmic solution. See also~~ drug product. Boulange (Ex. 1008) at 6:26-29 (“~~the~~[T]he medical device of the invention allows to limit the risk of interaction between a lubricant, for example silicone oil, and the therapeutic molecules potentially stored in the container”).

**7. [1.g] and wherein the syringe has a stopper break loose
force of less than about 11N.**

~~+85~~207. Boulange discloses a pre-filled syringe with a stopper break loose force of ~~of~~ less than 11 N. Table 7 from Boulange is reproduced below and discloses break loose forces of 6.6, 2.1 and 3.9 for an unaged syringe (*i.e.*, T=0) for the syringes in which silicone was applied to the ~~syringe~~ barrel using baked-on siliconization. The baked-on syringe including a coated stopper (B1) also has a break loose force of 3.0 N at T=1.

208. Similarly, Table 5 of Boulange discloses break loose forces (B) of less than about 11N for stoppers that were coated with silicone oil²³ and tested with baked-on syringes having 40 µg of silicone oil (*i.e.*, 4 µg/cm²):

~~+86~~209. Boulange further discloses that “[t]he medical device of the invention allows to have decreased activation, sustainable and final forces for moving a first part relative to a second part, for example for moving a piston within the container in which it is lodged” and that “it is possible to decrease the total amount of lubricant, for example silicone oil, that is necessary in such a medical device.” Boulange (Ex. 1008) at 6:10-25. As explained above, a

²³ Table 5 of Boulange discloses stoppers siliconized with 5 µg/cm² of silicone oil.

POSITA would understand that the break loose forces disclosed in Table 5 and 7 of Boulange would remain substantially the same even if the syringe is empty or when a VEGF-antagonist such as ranibizumab is contained in the syringe rather than water, because the viscosity of the fluid does not affect the break loose force (which is the force required to overcome the friction between the stopper and barrel measured at static conditions). See Section V.C and VIII.B above. Additionally, a POSITA would understand that different needle sizes and testing speeds would also not impact the break loose force. *Id.* The break loose force recited in claim 1 of the '631 patent is nothing more than the measurement of force in a syringe produced by a process (baked-on siliconization) that was already known in the art.

CD. Claims 2, 3, 5-9, ~~14, 16-22~~ and ~~24~~14-22

~~187~~210. The limitations of claims 2, 3, 5-9, ~~14, 16-21~~ and ~~24~~14-22 are likewise disclosed and rendered obvious by Sigg in view of Boulange.

1. Claim 2

~~188~~211. Claim 2 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.”

~~189~~212. Further to the explanation provided in Section VIII.B above with respect to claim 1, Boulange discloses a pre-filled syringe with 4 ~~mg~~µg/cm² of silicone oil. Boulange (Ex. 1008) at 20:15-17 (“a silicone lubricant was deposited and baked onto the internal surface of the syringe body 2, at a rate of 40 ~~mg~~µg for a surface area of 10 cm², but no silicone was used or sprayed on the pistons 3.”); 21:1-3 (Table 7). Boulange discloses the mass of ~~sprayed-on~~ silicone per unit surface area (surface density); and a POSITA would readily be able to convert between surface density and the thickness of the silicone oil, using the known density of silicone oil

(0.97 g/cm³). Specifically, the layer thickness of silicone oil is equal to the surface density of the silicone oil being applied (e.g., 4 ~~μg~~μg/cm²), divided by the density of the silicone oil itself, which is 0.97 g/cm³.

$$\begin{aligned}\text{Layer thickness} &= (4 \text{ } \del{\mu\text{g}}\text{ } \u{\mu\text{g}}/\text{cm}^2) / (0.97 \text{ g/cm}^3) \\ &= (4 \text{ } \del{\mu\text{g}}\text{ } \u{\mu\text{g}}/\text{cm}^2) * (\text{cm}^3/0.97\text{g}) * (10^7 \text{ nm/cm}) * (\text{g}/10^6 \text{ } \del{\mu\text{g}}\text{ } \u{\mu\text{g}}) \\ &= (4 \text{ } \del{\mu\text{g}}\text{ } \u{\mu\text{g}}/\text{cm}^2) * (\text{cm}^3/0.97\text{g}) * (107 \text{ nm/cm}) * (\text{g}/10^6 \text{ } \del{\mu\text{g}}\text{ } \u{\mu\text{g}}) \\ &= (4 * 10 / 0.97) \text{ nm} \\ &= 41.2 \text{ nm}\end{aligned}$$

~~190~~213. This is significantly less than the 450 nm limit recited in claim 2 of the ‘631 patent, and it is consistent with the prior art, which shows that it was well known that the thickness of the baked-on silicone oil layer is much thinner than the thickness of oily siliconized layers. For example, the Fries reference states that the typical thickness for baked-on layer is 76.83 nm. Fries at 26 (Ex. 1012.006). Thus, Boulange ~~not only~~ discloses ~~a pre-filled syringe with silicone oil that has~~ and renders obvious an average thickness of less than 450 nm, ~~but also teaches a silicone oil layer thickness known to be~~ which was typical for baked-on silicone oil syringes.

2. Claims 3 and 22

~~191~~214. Claim 3 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 ~~μg~~μg silicone oil.” Claim 22 recites “[a] pre-filled syringe according to claim 1, wherein the syringe barrel has an internal coating of from about 1-50 ~~μg~~μg silicone oil.”

~~192~~215. As explained with regard to limitation [1.e], and further to the explanation provided in **Section VIII.BC** above with respect to claim 1, Boulange discloses that “a silicone

lubricant was deposited and baked onto the *internal* surface of the syringe body 2, at a rate of 40 μg for a surface area of 10 cm^2 , but no silicone was used or sprayed on the pistons 3.” Boulange (Ex. 1008) at 20:15-17, 21:1-3 (Table 7 disclosing “4 $\mu\text{g}/\text{cm}^2$ ” for Scenario 1). A POSITA would understand that the reference to “a surface area of 10 cm^2 ” is referring to the approximate internal surface area of a 1 mL syringe, as explained with respect to limitation [1.e]. Accordingly, Boulange discloses that the baked-on 1 mL syringe has an internal coating of 40 μg of silicone oil on the syringe barrel.

~~193~~216. Furthermore, as explained above in **Section ~~VHLB~~VIII.C.4** and **Section ~~VHLB~~VIII.C.5** for limitations [1.d] and [1.e], a POSITA would also understand that the 4 $\mu\text{g}/\text{cm}^2$ rate of silicone application of Boulange would be applicable to other syringe sizes, and would result in an internal coating of approximately 28 μg of silicone oil for a ~~standard~~ 0.5 mL syringe, as disclosed in Sigg.

3. Claims 5 and 6

~~194~~217. Claim 5 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 $>25\ \mu\text{m}$ in diameter per mL, and (ii) no more than 50 particles $>10\ \mu\text{m}$ in diameter per mL.” Claim 6 recites “[a] pre-filled syringe according to claim 1, wherein the VEGF-antagonist solution meets USP789.”

~~195~~218. As explained above in **Section V.F and VIII.A.2**, a POSITA would understand that “(i) no more than 5 particles $>25\ \mu\text{m}$ in diameter per mL, and (ii) no more than 50 particles $>10\ \mu\text{m}$ in diameter per mL” are USP789 requirements. My analysis above in **Section ~~VHLA.2~~ and ~~Section~~ VIII.BC.6** demonstrates that it would be obvious to a POSITA that the combination of Sigg and Boulange would meet the requirements of USP789.

4. Claims 7, 8, and 9

~~196~~219. Claim 7 recites “[a] pre-filled syringe according to claim 1, wherein the VEGF antagonist is an anti-VEGF antibody.” Claim 8 recites “[a] pre-filled syringe according to claim 7, wherein the anti-VEGF antibody is ranibizumab.” Claim 9 recites “[a] pre-filled syringe according to claim 8, wherein the ranibizumab is at a concentration of 10 mg/mL.”

~~197~~220. Further to the explanation provided in **Section VIII.BC** above with respect to claim 1, Sigg expressly discloses a pre-filled syringe containing ranibizumab, which the ‘631 ~~Patent~~patent describes as an anti-VEGF antibody, and discloses ranibizumab at a concentration of 10 mg/mL. Sigg (Ex. 1007) at 9:11-14 (“In another embodiment, a solution is any drug product having requirements or desirability for sterility of the drug product container surface. In one particular embodiment, the drug product is a protein solution, such as **ranibizumab (e.g. 6mg/mL or 10 mg/mL) solution for intravitreal injection.**”), 20:17-21 (“A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by VHP...Filling of 0.5 mL syringes was performed in a sterile lab for hydrogen peroxide treatment.”); ~~Ex. 1001~~‘631 patent at 6:~~30-35~~3035 (“Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and bevacizumab (Avastin®)”;

5. Claims 14 and 16

~~198~~221. Claim 14 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.” Claim 16 recites “[a] ~~prefilled~~pre-filled syringe according to claim 1, wherein the syringe has a stopper slide force of less than about 11N.”

~~199. Further to the explanation provided in Section VIII.B above with~~222. With
respect to claim ~~14~~14, Boulange discloses a pre-filled syringe with a stopper break loose force of
less than 5N and a stopper slide force of less than 5N. As shown below, the syringe with the
coated stopper (B1) has stopper break loose and slide force below 5N at T=0 and T=1 in both
Table 5 and Table 7.

With respect to stopper C in Table 5, the break loose force is less than 5N at T=0 (4.8 N),
the slide force F is less than 5 N (4.6 N), while the slide force S is 6.5 N. A POSITA would
understand, however, that it would have been a matter of routine optimization to achieve a
force of less than 5 N for Force S for Stopper C in Table 5. In particular, a POSITA would
have understood that the stopper slide force is proportional to the speed at which the
stopper is tested, as I explained above. See Section VIII.B supra. Boulange, for example,
discloses that the tests were performed at 380 mm/min. Boulange (Ex. 1008) at 16:13-15.
Thus, a POSITA would have known that the slide force of 6.5 N for Stopper C could be
reduced to less than 5 N by reducing the stopper speed, which a POSITA would have been
motivated to do to assess the forces at different speeds at which the user could operate the
syringe. See, e.g., Overcashier at 80 (Ex. 1076.005) (describing testing at 4 mm/sec (i.e., 240
mm/min), which is “representative of manual syringe delivery”).

223. With respect to claim 16, Tables 5 and 7 above disclose that all
configurations of the Boulange syringes include a stopper slide force (S and F) of less than
11 N at T=0 and T=1.

Ex. 1008 at 21:1-3 (Table 7)

~~See also Ex. 1008 at 6:10-25 (“The medical device of the invention allows to have decreased~~
~~activation, sustainable and final forces for moving a first part relative to a second part, for~~

example for moving a piston within the container in which it is lodged... Moreover, with the medical device of the invention, it is possible to decrease the total amount of lubricant, for example silicone oil, that is necessary in such a medical device.”).

~~200~~224. As explained in ~~162~~182 above, a POSITA would understand that the break loose forces disclosed in ~~Table~~Tables 5 and 7 of Boulange would remain substantially the same even when a VEGF-antagonist such as ranibizumab is contained in the syringe rather than water because break loose force is independent of viscosity. Moreover, the slide forces disclosed in Table 5 and Table 7 of Boulange for Stopper B1 would increase by approximately 1.3 when a VEGF-antagonist such as ranibizumab is contained in the syringe rather than water due to the higher viscosity of ranibizumab, and still be less than 5N. Thus, the slide forces for Stopper B1 at T=0 would remain less than 5N (i.e., 2.7 x 1.3 = 3.5N), while the slide forces for all configurations would remain less than 11N because the highest slide force in either Table 5 or Table 7 for the baked-on syringes is 8.3 N (8.3 N x 1.3 = 10.8 N). Thus, the claimed break loose and slide force is nothing more than the measurement of force resulting from the baked-on process that was already well known in the art.

6. Claim 15

~~201~~225. Claim 15 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 ~~x~~*0.5 inch needle attached to the syringe.” Claim 15 is obvious based on Sigg in view of Boulange because it would be obvious to use a 30 G x 0.5 inch needle for a pre-filled syringe containing a VEGF-antagonist for intravitreal injection, and the break loose forces disclosed in Boulange in Table 5 and Table 7 would be less than 5 N

when measured using a filled syringe with a stopper traveling speed of 190 mm/min and a 30 G x 0.5 inch needle.

~~202~~226. The tests summarized in Table 7 of Boulange were conducted using a 1 mL syringe filled with water and a 380 mm/min stopper speed. Boulange (Ex. 1008) at 14:19-21; 16:13-15; 17:17-18; 20:13-14 ~~Further to the explanation provided in Section VIII.B above with respect to claim 1.~~ As explained above, the break loose force is the force required to overcome the friction between the stopper and barrel and is measured at static conditions. See Boulange (Ex. 1008) at 15:6-8 (“the friction force B is the force required, under static conditions, to break the contact at the contact region 10 between the piston 3 and the container 2”). As such, the viscosity of the solution, needle type, and stopper traveling speed do not impact the break loose force, and instead only affect the slide force. Accordingly, a POSITA would understand ~~from that~~ the disclosure break loose forces in Boulange that ~~the tests were likely conducted using a standard long 1 mL syringe or a standard short 1 mL syringe with a 27 G or 30 G needle. The calculations allowing a POSITA to reach this conclusion are shown in Appendix A at Section I.A.~~ are less than 5 N (Stopper B1 in Table 5 and 7, and Stopper C in Table 5) would remain less than 5N if tested filled at 190 mm/min with a 30G x 0.5 inch needle attached.

~~203. The viscosity of the solution, needle type, and stopper traveling speed are irrelevant to break loose force, and only impact the slide force. As explained above in Section V.C, the break loose force is largely attributable to the ageing of the stopper within the syringe, which becomes sticky with age and forms a tight seal against the barrel. The tighter seal results in a higher force required to initially displace the stopper, which is the break loose force. Because the break loose force is between the stopper and the inside of the barrel, and is the force required~~

~~to get the stopper to just about begin moving, the break loose force is largely unaffected by the viscosity of the fluid in the pre-filled syringe or other factors that impact the slide force, such as needle size and stopper traveling speed.~~

~~204~~227. Because VEGF antagonists such as ranibizumab are intended for intravitreal injection into the eye, it would have been obvious to a POSITA to use a thin needle of higher gauge, such as a 30 G needle, for such an application. A needle length of 0.5 inches would also have been obvious to use because of the shallow depth of intravitreal injection,~~to avoid damaging the optic nerve. See Ex. 1015.036 (“Care must be taken not to inject the optic nerve directly. A 1 to 0.5 inch long, 25-gauge stainless steel needle is generally employed.”).~~ Thus, ~~for.~~ For example, the Macugen ~~pre-filled syringe~~PFS used a 30 G x 0.5” needle.~~See Ex. 1009.007. A POSITA~~ for intravitreal injection. See Macugen 2008 Label at 11 (Ex. 1009.009). Similarly, the Lucentis label as of 2010 described using a 30 G x 0.5” needle for intravitreal injection. Lucentis Label at 6 (Ex. 1027.002). A POSITA would also understand that the selection of an appropriate needle size for administration would have been routine optimization well within ordinary skill.

Thus, it would be obvious to a POSITA to utilize a 30 G x 0.5 inch needle with a pre-filled syringe containing a VEGF-antagonist for intravitreal injection~~as a matter of routine optimization based on the use of a 30-gauge needle for the Macugen pre-filled syringe and the knowledge that a 25-gauge or smaller needle would have been preferred for intravitreal administration.~~

~~205. As noted above, because the break loose force is a measure of force required for initial movement only, it is unaffected by the stopper traveling speed, needle type, or viscosity. Thus, the “friction force B” (i.e., break loose force) in Table 7 of Boulange will remain the same~~

~~if measured at a stopper speed of 190 mm/min, with a 30 G x 0.5 inch needle, and the syringe filled with a VEGF antagonist (such as ranibizumab), as required by claim 15. Thus, it would be obvious to a POSITA that the break loose forces disclosed in Boulange would be maintained at less than 5 N when measured using a stopper traveling speed of 190 mm/min, a 30 G x 0.5 inch needle and the syringe filled with a VEGF antagonist (such as ranibizumab).~~

~~206. Likewise, given the results reported in Table 7 from the conditions used in Boulange, the slide force resulting from the conditions in claim 15 can be obtained from the Hagen-Poiseuille formula, as shown in **Appendix A at Section I.B.** As the calculations in the Appendix show, the slide forces listed in Table 7 of Boulange would *also* still be less than 5 N if the syringe is filled with ranibizumab instead of water, used 190 mm/min instead of 380 mm/min, and has a 30 G x 0.5 inch needle. Although the calculations show that the disclosure of Boulange renders claim 15 obvious with regard to value of the slide force, such proof is unneeded, since claim 15 would still be obvious to a POSITA based only on the break loose force. Claim 15 recites “the stopper break loose force *or* stopper slide force,” is measured under the specified conditions, and, as explained above, a POSITA would understand that the break loose force would not be affected by those conditions.~~

7. Claim 17

~~207~~228. Claim 17 recites “[a] blister pack comprising a pre-filled syringe according to claim 1, wherein the syringe has been sterilised using H₂O₂ or EtO.”

~~208~~229. Further to the explanation provided in **Section VIII.BC** above with respect to claim 1, Sigg discloses a pre-filled syringe packaged in a blister pack that is terminally sterilized by VHP—(i.e., vaporized H₂O₂). Sigg (Ex. 1007) at 6:26-28 (“‘Secondary packaging’ refers to packaging enclosing the pre-filled container, such as plastic wrapping, foil wrapping,

paper wrapping or other suitable wrapping, *such as blister packs.*” (emphasis added)), 8:21-24 (“Referring to Fig. 1, *a prefilled container 100* previously filled under aseptic conditions is decontaminated on surfaces 102 following encasement or packaging *in a secondary package 104 by vaporized-hydrogen peroxide or tunable-beta radiation as described herein.*”), 9:1-4 (“In one embodiment, the prefilled container is a syringe.. filled with a drug product”); Sigg Declaration at 4 (Ex. 1070.004) (“The present application disclosed for the first time, and contrary to conventional thinking, that it is possible to obtain sufficient sterilization of the outer surface of a syringe in secondary packaging at ambient pressure.”).

8. Claims 18 and 19

~~209~~230. Claim 18 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.” Claim 19 recites “[a] blister pack comprising a pre-filled syringe according to claim 17, wherein the syringe has been sterilised using EtO or H₂O₂ and the total EtO or H₂O₂ residue found on the outside of the syringe and inside of the blister pack is 0.1 mg.”

~~240~~231. Further to the explanation provided in **Section VIII.BC** above with respect to claim 1, and above with respect to claim 17, Sigg teaches a method by which the concentration of the sterilizing gas can be reduced or eliminated after VHP sterilization.

~~Post-treatment~~Sigg teaches that post-treatment measures are used to reverse the direction of vapor diffusion by application of a vacuum and to destroy any residual peroxide traces, for example by eliminating radicals formed by action of VHP and inactivating VHP action such as oxidative action by ultraviolet rays, chemical agents, or gas plasma. Sigg (Ex. 1007) at 10:17-28; 14:2-26; 15:21-28. Specifically, Sigg discloses a method of VHP terminal sterilization that degrades all potentially remaining hydrogen peroxide residue. Sigg (Ex. 1007) at 3:22-27

(“Further, inclusion of a gas plasma treatment after completion of the vaporized hydrogen peroxide cycle will further degrade *all potentially remaining* hydrogen peroxide residues.”)

(emphasis added). A POSITA would understand that degrading “all potentially remaining” hydrogen peroxide residues would result in a syringe with no residue, and thus 1 ppm on the outer surface of the syringe as well as 0.1 mg on the outside of the syringe and inside the blister pack.

232. Sigg also provides a specific teaching to motivate a POSITA to reduce or eliminate the H₂O₂ residues, stating that the “[p]revention prevention or reduction of leaching of detrimental concentrations of hydrogen peroxide into the protein solution in the syringe, either by removal of vapors or inactivation of vapors, ensures that the long-term stability of the protein is not compromised.” *Id.* A POSITA would understand that removal of all potentially remaining hydrogen peroxide residue, which would leave no residue, would result in having less than 1 ppm H₂O₂ residue on the outer surface (and less than 0.1 mg outside the syringe and inside the blister pack), and that to achieve that level would be a matter of routine optimization. For example, Sigg discloses that the method can be optimized by testing various conditions. Sigg (Ex. 1007) at 3:17-19 (“It 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.”). Inclusion of the gas plasma treatment to degrade VHP residues is provided as an example of one of the parameters that can be varied. Sigg (Ex. 1007) at 3:19-24 (“*As an example*, the application of a vacuum at the end of the treatment will inverse the diffusion direction and reduce, if not stop, leaching of hydrogen peroxide through the rubbers. *Further*, inclusion of a gas plasma treatment after completion of the vaporized hydrogen peroxide cycle will further degrade all potentially

remaining hydrogen peroxide residues.”). A POSITA would have understood that such optimization of the methods disclosed in Sigg for removal or inactivation of vapors could be used to achieve the removal of H₂O₂ to the desired level. As explained in Sigg, a POSITA would have been motivated to eliminate all residue to protect the drug product from potential ingress of residue. That a POSITA would have known how to achieve this is confirmed by the ‘631 patent specification, which only describes terminally sterilizing syringes using known processes, and otherwise provides no information regarding how to achieve these claimed parameters. See ‘631 patent at 9:49-54 (“As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide (EtO) or a hydrogen peroxide (H₂O₂) sterilisation process.”).

~~211. A POSITA would also understand that removal of all potentially remaining hydrogen peroxide residue, which would leave no residue, would result in having less than 0.1 mg of total H₂O₂ residue on outside of the syringe and inside of the blister pack. As explained above, Sigg discloses that the method can be optimized by testing various conditions. A POSITA would know that such optimization of the methods disclosed in Sigg for removal or inactivation of vapors could be used to achieve the removal of H₂O₂ to the desired level.~~

9. Claim 20

~~212~~233. Claim 20 recites “[a] blister pack comprising a pre-filled syringe according to claim 18, wherein 5% of the VEGF-antagonist is alkylated.”

~~213~~234. Further to the explanation provided in **Section VIII.BC** above with respect to claim 1, and above with respect to claims 17-19, Sigg discloses in Example 1 that the pre-filled syringes containing a VEGF-antagonist were treated with VHP sterilization treatment. Sigg (Ex. 1007) at 20:11-21 (“In the following experiment, prefilled syringes were treated with a

vaporized-hydrogen peroxide sterilization treatment A formulation as described in U.S.

Patent No.

7,060,269 was tested for protein degradation following treatment by VHP.”). The process of terminal sterilization disclosed in Sigg was further shown to not substantially affect the stability of the VEGF-antagonist protein. *Id.* at 20:22-21:3 (“Analysis after the treatment with VHP revealed the following protein contents.. there were ***no differences*** between the results of the untreated syringes and with hydrogen-peroxide treated syringes.”).

Table 1: Protein Stability Following Treatment with VHP

Batch	IEC (% main peak)	IEC (% basic peak)	SEC (% monomer)
Control			
9823.01 CSi	98	2	100
9823.02 CSi	98	2	100
1 x treatment			
9823.04 CSi	98	2	100
9823.05 CSi	98	2	100
2 x treatment			
9823.07	98	2	100
9823.08	98	2	100

Sigg (Ex. 1007) at 20:25-21:1 (Table 1)

~~214~~235. A POSITA would understand that alkylation is a proxy for assessing how much the protein has been affected by the sterilization gas. Accordingly, a POSITA would understand that because Sigg discloses “no differences” between the treated and untreated syringes, the protein contained in the treated syringes would be less than 5% alkylated. The HPLC (high performance liquid chromatography) method used in Sigg, which separates chemical entities based on particular properties, would have been able to detect alkylation of the protein, as well as other modifications. IEC, or ion exchange chromatography, separates molecules by charge, whereas SEC, or size exclusion chromatography, separates molecules by size. Ex.

1053.010. The “basic peak” of the IEC readout would contain the alkylated product, since alkylation increases the basicity of the protein. Thus, since no change in the IEC basic peak between the control and experimental conditions is seen in the experiment disclosed using the terminal sterilization techniques of Sigg, a POSITA would understand that this indicates that ~~no~~ ~~substantial increase in the level of~~ there was no alkylation with the disclosed VHP treatment. This is consistent with the fact that VHP was not known to cause alkylation, but instead was known as an oxidizing agent. McDonnell at 156 (Ex. 1024.010) (“H₂O₂ acts as an oxidant by producing hydroxyl free radicals (•OH) which attack essential cell components, including lipids, proteins, and DNA.”).

10. Claim 21

~~215~~236. Claim 21 recites “[a] blister pack comprising a pre-filled syringe according to claim 17, wherein the syringe has been sterilised using EtO or H₂O₂ with a Sterility Assurance Level of at least 10⁻⁶.”

~~216~~237. Further to the explanation provided in **Section VIII.BC** above with respect to claim 1, and above with respect to claim 17, Sigg discloses a method of terminal sterilization using VHP that provides for a sterile packaging of a pre-filled syringe. Sigg (Ex. 1007) at 10:3-6 (“In one embodiment, terminal sterilization and surface decontamination of prefilled containers within secondary packaging is carried out by treating surfaces of the prefilled container within secondary packaging with vaporized-hydrogen peroxide and applying post-treatment measures, within a decontamination chamber.”).

~~217~~. Sigg further defines sterile to mean the complete absence of microbial life, and notes that a standard sterility assurance level (SAL) is at least 10⁻⁶. *Id.* at 7:8-13 (“‘Sterility’ as used herein is meant to refer to complete absence of microbial life as defined by a probability of

nonsterility or a sterility assurance level (SAL). The required SAL for a given product is based on regulatory requirements. For example, required SALs for health care products are defined to be at least 10^{-6} , i.e. a chance of less than 1:1 million of a non-sterile product for aseptically manufactured and terminally sterilized products, respectively.”). Thus, a POSITA would understand Sigg’s terminal “sterilization” method achieves a sterility assurance level of at least 10^{-6} .

~~218~~238. Based on the teachings of Sigg and the knowledge of a ~~POSIT~~POSITA, it also would have been a matter of routine optimization for a POSITA to ensure that the sterility assurance level of 10^{-6} is achieved. *Id.* at 15:29-16:10 (“Reference is made to treatment times that are sufficient to terminally sterilize the prefilled container. In one embodiment, a sufficient treatment time or the duration of the presence of vaporized-hydrogen peroxide within the chamber to sufficiently decontaminate the container surface is determined by routine validation.. .By plotting treatment time against presence of bacterial growth, the treatment time to achieve decontamination, thus the absence of bacterial growth, can easily be determined. Validation techniques apply whether terminal sterilization is carried out by vaporized-hydrogen peroxide as described above or carried out by exposure to beta radiation as described below.”).

IX. ~~Petition 1~~, Ground ~~23~~: Sigg in View of Boulange and Fries Renders Obvious Claims 4, 10, and 23

~~219~~239. Dependent claims 4 and 23 depend from claim 1, and require that the silicone oil is DC365 emulsion or that the silicone oil has a viscosity of about 350 cP. Dependent claim 10, depends from claim 8 and requires silicone oil with a viscosity of about 350 cP and further recites particulate content requirements from USP789.

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

10. 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~~µm in diameter per mL, and (ii) no more than 50 particles >10 ~~µm~~µm in diameter per mL.

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

~~220~~240. Further to the explanation provided in **Section VIII.V.BD.2** above ~~with respect to claim 1~~, it was well known in the art prior to 2012 that DC365 ~~could be~~was used as a silicone oil emulsion in the baked-on process, and was a preferred commercially-available emulsion for baking silicone, ~~as shown for example~~ onto syringe barrels. This is confirmed by Fries, which teaches that DC365 is used for baked-on siliconization in pre-filled syringes. Fries at 26 (Ex. 1012.006) (“The baked siliconization method uses emulsions of silicone oil (e.g., Dow Corning 365, 35% Dimethicone NF Emulsion, diluted in HPW) sprayed into syringe barrels followed by heat treatment in a tunnel.”). The ‘631 ~~Patent discloses~~patent admits that DC365, which contains DC360 oil with a viscosity of 350 cP, was typically used for syringe siliconization. ~~Ex. 1001~~ before the 631 Patent. ‘631 patent at 5:9-14914 (“Various types of silicone oil are available, but *typically* either DC360 (Dow Corning®; with a viscosity of 1000 cP) or DC365 emulsion (Dow Coming®; DC360 oil with a viscosity of 350 cP) are used for syringe siliconisation.”); ~~see also~~. Moreover, an FAQ published by Dow Corning—the manufacturer of DC365—explains that DC365 can be used for syringes and has a viscosity of 350 cSt, which is “about 350 cP.”²⁴ DC365 FAQ at Question 1 (Ex. 1034.002). centiStokes (cSt) can be converted to centipoise (cP) by multiplying the cSt by the specific gravity of the fluid. cP = cSt * specific gravity. The specific gravity of DC 360 is

~~221~~241. A POSITA would have been motivated to ~~combine Fries with~~ use DC365 silicone oil emulsion in the syringe resulting from the combination of Sigg and Boulange. Boulange, in Example 3 and 5, discloses a syringe with silicone oil applied to the barrel using baked-on siliconization, but it does not specify the type of ~~the silicone that is used or the viscosity of that~~ silicone oil or its viscosity. Fries is a publication regarding the manufacture of pre-filled syringes, and like Boulange discusses the benefits of ~~lowering the amount of silicone oil used and~~ baked-on siliconization. Fries at 25 (Ex. 1012.005) (“Even though silicone oil is inert toward most drug products, interactions with sensitive biopharmaceuticals have been observed.... Advanced siliconization technology has been developed to lower the level of free (non-bound) silicone oil in prefilled syringes.”). As explained above, Fries discloses that DC365, which has a viscosity of 350 cP, is used for baked-on siliconization in pre-filled syringes. *Id.* at ~~006~~; 26 (Ex. ~~1001~~1012.006); ‘631 patent at 5:9-14. A POSITA would therefore have been motivated to combine the design option disclosed in Fries regarding the type of silicone oil with the siliconized syringe disclosed in Boulange given that both publications pertain to lowering the amount of silicone oil and using baked-on siliconization. The results of siliconization using this widely available silicone oil emulsion from Dow ~~Coming~~Corning with a viscosity of about 350 cP would have been predictable, and would have led to a ~~prefilled~~pre-filled syringe as recited in claims 4, 10 and 23 of the ‘631 patent.

~~222~~242. As explained in **Section V.F** and VIII.A.2, a POSITA would understand that “(i) no more than 5 particles \geq 25 ~~µm~~µm in diameter per mL, and (ii) no more than 50

specific gravity of the fluid. cP = cSt * specific gravity. The specific gravity of DC 360 is 0.97. Based on this specific gravity: 350 cSt = 339.5 cP, which is about 350 cP.

particles >10 ~~µm~~um in diameter per mL” are requirements set forth in USP789. My analysis above in ~~Section~~Sections ~~VIII.A.2 and Section VIII.B.C.6~~ demonstrates that it would be obvious to a POSITA that the combination of Sigg and Boulange would meet ~~the~~these requirements of USP789.

X. ~~Petition 1~~, Ground 35: Sigg in view of Boulange and Furfine Renders Obvious Claims

11-13

~~223~~243. Dependent claims 11, 12 and 13 further require that the VEGF-antagonist is a non-antibody VEGF-antagonist, the non-antibody VEGF-antagonist is aflibercept or conbercept, and the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL, respectively. Sigg discloses in one embodiment that the pre-filled syringe includes a VEGF-antagonist (ranibizumab), ~~and it.~~ It would have been obvious to a POSITA to use a different VEGF-antagonist, such as aflibercept ~~or conbercept~~, which ~~were both~~was well-known prior to 2012, in the pre-filled syringe for intravitreal administration. For example, Furfine discloses aflibercept, which is a ~~biologic therapeutic~~non-antibody VEGF-antagonist approved for treatment of wet AMD that is administered by intravitreal injection. Furfine also discloses a non-antibody VEGF-antagonist in a pre-filled glass syringe. Furfine (Ex. 1021) at [0059], [0061]; The ‘631 patent likewise admits that aflibercept, a non-antibody VEGF-antagonist, was already an approved drug before the ‘631 patent was filed. See ‘631 patent at 6:38-44. A POSITA would have understood that aflibercept was a non-antibody VEGF-antagonist drug invented by employees of Regeneron.

~~224~~244. A POSITA would have been motivated to use aflibercept in a terminally sterilized pre-filled syringe ~~as disclosed in Sigg, for all the reasons discussed above in Section VIII with respect to the VEGF-antagonist solution ranibizumab~~(i.e., Sigg) comprising less than

50 µg of silicone oil (i.e., Boulange), given all the benefits of administering drugs via a pre-filled syringe with minimized levels of silicone oil. See Section V.B and V.D.2 above. Indeed, Sigg makes clear that the disclosed terminal sterilization is applicable to a broad range of solutions, including those that are temperature, oxidation, or radiation sensitive. Sigg (Ex. 1007) at 6:21-25, 7:20-8:7. Sigg specifically notes that “the prefilled container itself is not drug specific.” *Id.* at 8:6-767. Likewise, Boulange is directed towards improvements for pre-filled syringes used to dispense therapeutic molecules, but is not limited in its use to any particular molecule. Boulange (Ex. 1008) at 6:~~2629~~26-29. A POSITA would have recognized that aflibercept, marketed as Eylea®, is a sensitive biologic that would be suited for use in the terminally sterilized pre-filled syringe for intravitreal injection disclosed in Sigg. For example, it was known that Australian health authorities had approved by February 17, 2012 a pre-filled syringe comprising aflibercept that was terminally sterilized with vaporized hydrogen peroxide. See Ex. 1066.005, .007.

A. Claims 11 and 12

~~225~~245. Claim 11 recites “[a] pre-filled syringe according to claim 1 wherein the VEGF antagonist is a non-antibody VEGF antagonist.” Claim 12 recites “[a] ~~pre-filled~~prefilled syringe according to claim 11, wherein the non-antibody VEGF antagonist is aflibercept or conbercept.”

The ~~226.~~ ~~Furfine discloses a non-antibody VEGF-antagonist known as~~VEGF antagonist aflibercept- was known in the art before the ‘631 patent, as demonstrated by Furfine. Furfine (Ex. 1021) at [0005] (“Stable formulations of a VEGF-specific fusion protein antagonist are provided. Pharmaceutically acceptable formulations are provided that comprise a VEGF ‘trap’ antagonist with a pharmaceutically acceptable carrier. In specific embodiments,

liquid and lyophilized formulations are provided.”), [0006] (“In a first aspect, a stable liquid ophthalmic formulation of a VEGF-specific fusion protein antagonist is provided, comprising a fusion protein that comprises a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a ‘VEGF trap’).”). The ‘631 patent states that aflibercept is a non-antibody VEGF-antagonist.~~Ex. 1001,~~ and acknowledges that aflibercept is also known as “VEGF trap.” ‘631 patent at 6:~~3640~~36-40.

~~B. Claim 13~~

~~227. Claim 13 recites “[a] pre-filled syringe according to claim 12, wherein the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL.”~~

~~228. Furfine discloses a VEGF-antagonist~~246. It was also known in the art that aflibercept was supplied at a concentration of 40 mg/mL~~., as described in Furfine. Furfine~~ (Ex. 1021) at [0013] (“In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about **40 mg/mL** of the VEGF-antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 40mM sodium chloride, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.”); [0059] (“Stability of **40 mg/mL VEGF Trap** Liquid Formulation Stored at 5°C in Pre-Filled Glass Syringe”). It would have been obvious to a POSITA to use aflibercept at a concentration of 40 mg/mL as disclosed in Furfine, which was the dosage concentration for EYLEA (i.e., aflibercept) as of its FDA approval in 2011. See Eylea Label at 6 (Ex. 1040.006) (disclosing approved 40 mg/mL Eylea formulation in vial form).

~~XL-Petition~~XI. Ground 2,~~Ground 1:~~ **Lam in View of ~~Reuter~~Boulange Renders**

Obvious Claims ~~1-10~~1-3, 5-9, and ~~14-23~~14-22

~~229~~247. As set forth in detail below, claims ~~1-10~~1-3, 5-9, and ~~14-23~~14-22 of the '631 patent are separately rendered obvious by Lam in view of ~~Reuter~~Boulange. The discussion below specifies where each element of the aforementioned claims is found in the applied references, and includes a detailed explanation of the significance of the quotations and citations from the applied references.

**A. Motivation to Combine Lam and ~~Reuter~~Boulange With a Reasonable
Expectation of Success**

1. Silicone Oil and Break Loose / Slide Forces

248. In the paragraphs above, I explained why a POSITA would have been motivated to combine the teachings of Sigg and Boulange with a reasonable expectation of success. The motivations set forth above are also applicable to the combination of Lam and Boulange because Lam, like Sigg, discloses a terminally sterilized pre-filled syringe comprising the VEGF-antagonist ranibizumab. Thus, a POSITA would have been motivated to use a pre-filled syringe comprising the silicone amounts disclosed in Boulange in conjunction with the teachings of Lam. See V.D and VIII.A-B above.

249. Similarly, a POSITA would have reasonably expected to succeed in combining Lam and Boulange in achieving the claimed invention, for the reasons set forth above. See VIII.B above. As previously explained, syringe designs, including stoppers and plunger rods, suitable for terminal sterilization were well-known in the art, including the design disclosed in Boulange. See Section VIII.A-B above. Thus, a POSITA would have expected to succeed in combining Lam and Boulange to achieve a terminally sterilized syringe that resulted in the '631 Patent claims.

230. As detailed in ~~Section VII.B~~, Lam teaches a pre-filled terminally sterilized glass syringe for intravitreal injection. Because the pre-filled syringe of Lam contained a VEGF-antagonist solution, which is a protein formulation (also loosely referred to in the art as biologics, biotechnology products, etc.), a POSITA would have been motivated to minimize the amount of silicone oil used in the syringe barrel in order to reduce or avoid the negative interactions that were known to occur between silicone oil and protein formulations. See Ex. 1013.004 (“One particularly common problem has been that [biotechnology formulations] can react with the oily form of silicone, which is used as a lubricant to coat the sliding components of the syringe.”).

231. A POSITA would be further motivated to lower the amount of silicone oil, because pre-filled syringes are both “containers and drug delivery systems at the same time,” Ex. 1012.006, and therefore the silicone oil in the syringe would be in contact with the protein formulation for an extended period of time, which would heighten the stability concerns. As such, a POSITA would look to avoid higher levels of silicone oil in pre-filled syringes containing sensitive protein formulations such as VEGF antagonists, because of potential “incompatibilities includ[ing] aggregation, deformation, and inactivation of native protein structures.” Ex. 1012.006.

232. Moreover, it was known that silicone oil “can flow away from the inner surface [of a syringe barrel] and pass into the container’s content,” Ex. 1014 at [0024], and such “[d]etachment of silicone oil in water-filled syringes is possible and can result in particulate matter and clouding phenomenon.” Ex. 1015.330. Thus, a POSITA would be especially motivated to lower the amount of silicone oil used in pre-filled syringes for intravitreal injection to avoid injecting silicone oil into the eye, which could cause floaters and/or an increase in

~~intra-ocular pressure. See, e.g., Ex. 1025.011 (“silicone contaminants, when injected into the vitreous cavity at the time of anti-VEGF injections, could cause persistent elevations in [intraocular pressure]”); Ex. 1001 at 4:50-55 (“However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including ‘floaters’ and an increase in intra-ocular pressure.”); Ex. 1015.036 (explaining the precautions necessary for intravitreal administration). Thus, a POSITA would have looked to reduce or minimize the amount of silicone oil used in the pre-filled syringe of Lam by using the teachings of Reuter, which disclose baked-on siliconization of a pre-filled syringe, resulting in syringes comprising lower silicone levels.~~

~~233. Reuter teaches that it was generally known in the art that “the main objective in siliconization is to achieve the most homogenous possible coating with the minimum possible quantity of silicone oil.” Ex. 1010.004. “Sub-visual silicone oil particles are thought to promote protein aggregation which can increase the severity of immune responses and reduce the drug’s tolerability.” *Id.* Thus, a POSITA would have looked to Reuter because it discloses that “[b]aked-on siliconization reduces the measurable quantity of free silicone oil to approx. 10 % of the normal value. As a result, there are fewer sub-visual and visual silicone oil particles in the solution. This siliconization process is therefore recommended for use with sensitive protein formulations. It is also advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.” *Id.* at .005.~~

~~234. Moreover, a POSITA would have been motivated to employ the baked-on syringes disclosed in Reuter because those syringes retain their lubricating effect while using approximately one-tenth the amount of silicone oil in comparison to the sprayed-on syringes. Ex.~~

~~1014 at [0026] (baked-on siliconization, “(i) is more precise and more homogenous than [sic] a simple standard siliconizing operation; and (ii) makes it possible to reduce the amount of silicone that is used...by about a factor of 10 without any loss of lubricating effect”); Ex. 1012.006-007 (reporting that baked-on siliconized syringes having “low levels” of silicone oil that reduce “[t]he amount of extractable silicone oil... below the detection limit (0.03 mg [*i.e.*, 30 mg])”) while maintaining syringe functionality, with “plunger gliding forces in the range of 5 to 10 N”).~~

235. ~~Baked-on siliconization as disclosed in Reuter 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 interactions. See Ex. 1011.004 (“Baked Silicone: Binding the silicone to the glass barrel through a proprietary technology reduces the level of free silicone. This is a clear benefit for silicone-sensitive drugs.”); Ex. 1010.005 (“Baked-on siliconization reduces the measurable quantity of free silicone oil to approx. 10% of the normal value.”); Ex. 1015.330 (“Recent 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”). Thus, it was known that “the baked-on silicone process was better suited for protein formulation development in PFS as it represented a lesser degree of risk for the formation of subvisible particulate matter as well as minimized any potential for protein precipitation on the Si-oil droplets.” Ex. 1044.006.~~

236. ~~Additionally, it was known that the baked-on process could reduce the incidence of the break-loose effect, as described in Section V.D.2 above, because the baked-on process results in a more homogeneous coating of silicone oil on the inside of the barrel. Ex. 1012.006 (in baked on siliconization the “[r]emoval of water enables the lubricant to spread out evenly over the glass~~

surface and creates a thin, uniform film”); Ex. 1013.004 (“The second benefit of baked-on silicone is that it reduces the frequency of the ‘break loose’ effect”). Thus, with baked-on siliconization, “[l]ubrication is maintained so that the initial force required to inject using prefilled syringes with baked-on silicone remains consistently low before and after storage.” *Id.* As would have been readily understood by a POSITA, 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. *See, e.g.*, Ex. 1015.358 (“Moreover gliding forces must be continuous, or without increases and decreases. Should the movement be ‘interrupted,’ then one speaks of shattering of the syringe.”).

237. A POSITA would have a reasonable expectation that the combination of Lam with Reuter would result in a terminally sterilized, low volume, pre-filled glass syringe having an amount of silicone oil and break loose and slide forces falling within the ranges claimed in the ‘631 patent. As explained below with respect to limitations [1.e] and [1.g], a POSITA would understand that the baked-on syringe disclosed in Reuter would have low amounts of silicone oil falling within the claimed ranges and break loose and slide forces that also fall within the claimed ranges. This is consistent with other prior art that discloses that baked-on siliconization results in 40 to 100 μ g of silicone oil for a 0.5–1 mL syringe without any loss in lubricating effect. Ex. 1014 at [0026] (discloses that baked-on siliconization “makes it possible to reduce the amount of silicone that is used (that is, loaded on the inner surface of the container) by about a factor of 10 without any loss in lubricating effect” and that a “0.5–1 mL syringe reservoir” includes “from 40 to 100 μ g of silicone.”).

238. A POSITA would understand that the syringe stopper forces in Reuter would remain substantially the same even when a VEGF-antagonist such as ranibizumab is contained in

~~the syringe rather than, for example, the empty syringe of Reuter, because the viscosity of the fluid does not affect the break loose force.~~

239. ~~While the viscosity of the solution does affect the slide force, the viscosity of a VEGF-antagonist solution such as ranibizumab (1.3 cp) will not add a significant amount to the slide force. As explained further below, a POSITA would be able to calculate the additional slide force required to expel a VEGF-antagonist solution based on its viscosity, the size of the needle, and the injection speed. Such a calculation would show that the additional force required to expel, for example, a ranibizumab solution (1.3 cp), would be at most approximately 2 N, resulting in a total slide force of 3.7 N or 2.5 N, which is still below 5 N.~~

~~240~~250. Additionally, a POSITA would not expect any incompatibility between baked-on siliconization as taught by ~~Reuter~~Boulangue and EtO terminal sterilization disclosed in Lam. ~~In fact,~~ for the reasons described above. See Section V.E, VII.B, VIII.A-B above. Lam teaches a POSITA that the EtO technique is broadly applicable to pre-filled syringes. Lam (Ex. 1029) at 2:~~7-9, 27-9, 2~~:29 (“In one aspect, the invention provides a method for surface-sterilizing an object having an ~~ethylene-oxide~~ethyleneoxide (EtO)-impermeable interior space containing a compound with a temperature-sensitive and EtO-sensitive activity In some embodiments, the object is a syringe.”). It would be expected that the pre-filled syringes of Lam contained some silicone oil lubricant, and thus the terminal sterilization being applied was done to a siliconized syringe. ~~Reuter discloses using baked-on siliconization, which creates “a permanent hydrophobic layer” such that “part of the silicone oil cannot be removed [from the syringe barrel surface] with solvent.” Ex. 1010.005. Maintaining such a layer of silicone oil within the barrel ensures the maintenance of a tight seal between the barrel and the stopper during sterilization. See Ex. 1015.330 (silicone oil in syringes provides “sealability”).~~ U.S. Patent

No. 7,404,278 to Wittland et al. (~~Ex. 1026~~) describes the process of applying a silicone emulsion to a pre-fillable syringe body, followed by fixing the silicone oil via heat (baking on the silicone oil), wherein the syringe body is then sterilized “in particular with gas, for example ethylene oxide (ETO).” Wittland (Ex. 1026) at 3:52-65, 4:16-19. Wittland clearly demonstrates that EtO sterilization was used to sterilize syringes with baked-on silicone oil, which is further evidence that sterilization with EtO would not impact the functionality and operational forces of a syringe comprising baked-on silicone. Thus, a POSITA would have understood that baked-on siliconization disclosed in ~~Reuter~~Boulange is compatible with the EtO sterilization disclosed in Lam. In particular, a POSITA would have understood that the sterilization method taught in Lam would not impact the silicone levels or operation forces of ~~Reuter’s~~Boulange’s syringe because the interior of the syringe would be sealed from the sterilizing agent, as described in Lam and as is understood in the art. See Lam (Ex. ~~1029.003~~1029) at 3 (“In one aspect, the invention provides a method for surface-sterilizing an object having an ethylene-oxide (EtO)-impermeable interior space....”).

251. Lam and Boulange both relate to aspects of pre-filled syringe manufacture, and are therefore complementary to one another, which would further motivate their combination and create a more than reasonable expectation of making a pre-filled syringe as described in the claims of the ‘631 patent.

2. Particulate Content

~~241~~252. Lam discloses a pre-filled syringe that includes a VEGF-antagonist, such as ranibizumab, for intravitreal injection. When making a pre-filled syringe including a VEGF-antagonist for intravitreal injection, a POSITA would have been aware of and motivated to comply with USP789, which is prior art and sets forth particulate content requirements for

ophthalmic solutions. Those particulate content requirements from USP789 were directly copied into the claims of the ‘631 patent. In order to achieve regulatory compliance and approval, which is ultimately the goal for most if not all pharmaceutical formulations, a POSITA would have understood that compliance with USP789 was highly desirable if not mandatory.

~~242~~253. A POSITA would have had a reasonable expectation of success that the combination of Lam with ~~Reuter~~Boulange would result in a pre-filled syringe containing a VEGF-antagonist for intravitreal injection that meets the particulate matter requirements of USP789. A POSITA would understand that the ophthalmic ranibizumab solution disclosed in Lam should meet the USP789 requirements. The ‘631 ~~Patent~~patent provides no information regarding how a VEGF-antagonist solution is prepared, such that it complies with the USP789 requirements, thus conceding such a preparation would have been known to a POSITA. Furthermore, a POSITA would understand that ophthalmic solutions of VEGF-antagonists were already known in the art— *i.e.*, Macugen, Lucentis, and Eylea—and that the methods of preparing these solutions such that they meet the requirements of USP789 would be known to one of ordinary skill in the art.

~~243~~254. With respect to meeting the requirements of USP789, the ‘631 patent states only that “the syringe has low levels of silicone oil sufficient for the syringe to meet USP789.” ~~Ex. 1001~~‘631 patent at 6:28-30. As explained above, ~~Reuter~~Boulange discloses a syringe siliconized using baked-on siliconization that has ~~low~~ levels of silicone oil falling within the ranges claimed in the ‘631 patent. ~~In addition, Reuter discloses that baked-on siliconization is “advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.” Ex. 1010.005. A POSITA would have understood this reference to particle contamination requirements in Reuter to include USP789.~~

Accordingly, a POSITA would have expected that the combination of Lam with ~~Reuter~~Boulange would result in a pre-filled syringe meeting the particulate content requirements of USP789.

B. Claim 1

1. [1.a] A pre-filled, terminally sterilized syringe for intravitreal injection

~~244~~255. Lam discloses terminal sterilization of pre-filled syringes containing sensitive biologic drug products for intravitreal injection:

The invention is based, in part, on the surprising discovery of **ethylene-oxide-based sterilization** conditions that will effectively sterilize the surface of an object but which do not significantly damage ethylene-oxide-sensitive, temperature-sensitive compounds contained inside.

In some embodiments, the object is **a syringe**.

In some embodiments, the compound is present in an aqueous pharmaceutical composition.

In some embodiments, the pharmaceutical composition is designed for **intraocular injection**.

In some embodiments, the compound is a polypeptide, *e.g.* an antibody, ~~----~~ In some embodiments, the antibody is an antigen-binding fragment, *e.g.* a Fab fragment. In some embodiments, the Fab fragment binds VEGF, *e.g.* **ranibizumab (LUCENTIS®)**.

Lam (Ex. 1029) at 2:4-6, 2:29, 11:30-31, 2:18-24. A syringe filled with ranibizumab is tested in the Example of Lam. ~~Ex~~Id. 1029 at 13:14-15 (“We performed EtO sterilization runs on syringes containing a ranibizumab solution.”).

~~245. Reuter discloses the siliconization of pre-filled syringes. Ex. 1010.002 (“The siliconization of the syringe barrel is an extremely important aspect of the production of sterile, prefillable glass syringes because the functional interaction of the glass barrel siliconization and the plunger stopper siliconization is crucial to the efficiency of the entire system”) Reuter also describes the baked-on siliconization methods as relevant to ophthalmological preparations, which a POSITA would understand to include intravitreal injections. Id. at 005 (“It is also advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.”).~~

256. Boulange also discloses glass pre-filled syringes intended for biomedical applications. Boulange (Ex. 1008) at 13:11-12 (“The container 2 is a glass syringe body accommodating a piston 3 able to move translationally...”); 14:19-21 (“tests were applied on containers filled with 1 mL of demineralised water and each plugged with one piston to be tested (coated or uncoated)”); id. at 1:1-2 (“The present invention relates in general to a medical device, for example a syringe”); id. 1:14-15 (“[T]he container is intended to accommodate a medical product in the liquid, gaseous, fluid, pasty or lyophilized phase.”).

2. [1.b] the syringe comprising a glass body forming a barrel,
a stopper and a plunger

~~246~~257. Lam discloses that the pre-filled syringe has a glass barrel, and stopper, ~~and plunger.~~ Lam (Ex. 1029) at 2:29-33 (“In some embodiments, the object is a syringe. In some embodiments the syringe comprises glass and comprises a stopper comprising D777-7

laminated with FluroTec®; and a tip cap comprising D777-7 laminated with FluroTec® or D21-7H laminated with FluroTec®.”); *id.* at 15:12-14 (“We also tested several different syringe components: where the stopper on the plunger comprised D777-7 laminated with a 125 ~~µm~~um coating of FluroTec® barrier film. . .”).

~~247~~258. In addition, as explained above in ~~121~~Sections V.D and VIII.C.2, it would have been obvious to a POSITA to use glass barrels where the syringe contains ranibizumab, as disclosed in the Example in Lam.

~~248. Reuter likewise describes~~259. Boulange discloses a syringe comprising a glass body forming a barrel, and a ~~plunger-stopper. Ex. 1010.002 (“The siliconization of the syringe barrel is an extremely important aspect of the production of sterile, prefillable glass syringes because the functional interaction of the glass barrel siliconization and the plunger stopper siliconization is crucial to the efficiency of the entire system”). Reuter illustrates such a syringe, for example, in Figure 3:~~stopper (which is referred to in Boulange as a “piston”). See VII.C above. As explained above, it would have been obvious to a POSITA that the stopper in Lam and Boulange would be coupled to a plunger to enable the user to advance the stopper, as was conventional in the art. See VIII.C.2 above.

~~Ex. 1010.004 (Fig. 3)~~

3. [1.c] and containing an ophthalmic solution which comprises a VEGF-antagonist, wherein:

~~249~~260. Lam discloses an embodiment in which the pre-filled syringe contains an ophthalmic solution comprising the VEGF-antagonist ranibizumab:

We performed EtO sterilization runs on syringes containing a ranibizumab solution . . .

In some embodiments, the compound is a polypeptide, *e.g.* an antibody, In some embodiments, the antibody is an ~~antigen-binding~~antigenbinding fragment, *e.g.* a Fab fragment. In some embodiments, the Fab fragment binds VEGF, *e.g.* ranibizumab (LUCENTIS®).

Lam (Ex. 1029) at 13:~~14-15,2~~14-15, 2:18-24.

~~250. As explained in Section VII.D, above, Reuter also discloses that the baked-on siliconization methods disclosed therein are advantageous for ophthalmological preparations. Ex. 1010.005 (“It is also advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.”).~~

261. While Boulange does not explicitly disclose a VEGF-antagonist, a POSITA would understand that the pre-filled syringes disclosed in Boulange with baked-on silicone oil and optionally coated stoppers would be especially preferred for use with protein formulations such as VEGF-antagonist solutions on account of the reduced incompatibility between baked-on siliconization and protein formulations, and also between coated stoppers and protein formulations intended for ophthalmic use, as explained above. See VIII.C.3 above.

4. [1.d] the syringe has a nominal maximum fill volume of between about 0.5 mL and about 1 mL

~~251~~262. Although Lam does not specify the maximum fill volume of the syringe containing ranibizumab, it would have been obvious to a POSITA that a small volume syringe in the 0.5-1 mL range would be used for intravitreal injection, including for example, injection of ranibizumab, since the amount of fluid capable of being injected ~~into the eye~~intravitreally is limited. See Nema Vol. 1 at 2 (Ex. 1015.017) (administration volume for intravitreal injection is

“generally < 0.1 mL”); see Furfine (Ex. 1021) at [0059], [0061] (disclosing 1 mL prefilled glass syringe for VEGF-antagonist); 2004 Macugen Label at 11 (Ex. 1062.009) (disclosing that Macugen is provided in a 1 mL glass syringe); Ex. 1027.002 (describing intravitreal injection of 0.05 mL of ranibizumab).

~~252. Reuter~~263. Boulange also discloses a ~~1 mL long syringe. Ex. 1010.004~~ (“Studies on ~~1 mL long syringes have revealed considerable potential for reducing the amount of silicone oil required~~”).syringe with a nominal maximum fill volume of 1 mL. Boulange (Ex. 1008) at 14:19-21 (“Activation Gliding Force (AGF) tests were applied on containers filled with 1 mL of demineralised water and each plugged with one piston to be tested (coated or uncoated).”); see also VIII.C.4 above (explaining how Boulange discloses a 1 ml syringe).

5. [1.e] the syringe barrel comprises from about 1 µg to 100 µg silicone oil

~~253. Reuter discloses two force curves for a “standard 1 mL long syringe” using 800 µg and 500 µg of silicone oil, respectively, where the respective mean (i.e., average) break loose forces were reported to be 2.5 N and 1.7 N, and the respective mean glide forces were 1.7 N and 0.5 N. Ex. 1010.004-005. The forces curves from that Reuter study are reproduced below:~~

~~Ex. 1010.005 (Fig. 5)~~

~~254. Reuter teaches that baked-on siliconization can be used to greatly reduce the amount of silicone oil in the syringe barrel. Specifically, Reuter teaches that baked-on siliconization could be used to achieve an “extremely thin layer of silicone,” which “in conjunction with the low quantity of silicone oil used in the emulsion minimizes free silicone in the syringe and ensures that the required quality of finish is achieved.” Id. at 005. Reuter discloses that the amount of silicone oil used in baked-on siliconization in terms of the silicone layer thickness: “The layer~~

thickness measures 15-50 nm. By comparison, the average layer thickness with oily siliconeization is 500-1,000 nm.” *Id.* Based on the thickness, a POSIT A would readily be able to obtain the amount of silicone oil per unit area of syringe barrel inner surface (i.e., the surface density), using the known density of the silicone oil within the DC 365 emulsion.¹⁰ The surface density of the silicone oil being applied is equal to the layer thickness of silicone oil times the density of the silicone oil itself, which is 0.97 g/cm³:

$$\begin{aligned}
 \text{Surface density} &= (50 \text{ nm}) * (0.97 \text{ g/cm}^3) \\
 &= (50 \text{ nm}) * (0.97 \text{ g/cm}^3) * (1 \text{ cm}/10^7 \text{ nm}) * (10^6 \text{ } \mu\text{g/g}) \\
 &= (50 \text{ nm}) * (0.97 \text{ g/cm}^3 \cdot \text{cm}^2) * (1 \text{ cm}/10^7 \text{ nm}) * (10^6 \text{ } \mu\text{g/g}) \\
 &= (50 * 0.97 / 10) \text{ } \mu\text{g/cm}^2 \\
 &= 4.85 \text{ } \mu\text{g/cm}^2
 \end{aligned}$$

255264. As explained above in ~~Section VIII.B.4~~, the surface area of a 1 mL standard syringe barrel is 9.70 cm² and the surface area of a 1 mL long syringe barrel is 10.77 cm², such that the total amounts of silicone oil are 47.0 μ g and 52.2 μ g, respectively. Thus, at the high end of the 15-50 nm thickness range recited in Reuter, the syringe barrel comprises between 47.0 μ g and 52.2 μ g (i.e., around 50 μ g) which is well less than the 100 μ g of silicone oil recited in claim 1 of the ‘631 patent for a 1 mL syringe. Boulange discloses 1 ml syringes comprising 40 μ g of silicone oil. Boulange (Ex. 1008) at 20:15-17 (“a silicone lubricant was deposited and baked onto the internal surface of the syringe body 2, at a rate of 40 μ g for a surface

¹⁰ This calculation assumes that substantially all the water from the emulsion is vaporized during the baking process, and what remains coating the syringe barrel is only the silicone oil from the emulsion, which is *Dow Corning 360 Medical Fluid*, 350 cSt, having a density of 0.971 g/cm³. The density of the DC 365 emulsion itself is 0.99 g/cm³, which would therefore lead to a substantially similar calculation and result even if the water from the emulsion is not vaporized.

area of 10 cm².’); see also Boulange (Ex. 1008) at 20:15-17, 21:13 (Table 7 disclosing “4 µg/cm²” for Scenario 1); Table 5 (disclosing “4 µg/cm²”). A POSITA would understand that the reference to “a surface area of 10 cm²” refers to the approximate surface area of a 1 mL syringe. See Section VIII.C.4 above.

~~256. Thus, it would have been obvious to a POSITA to apply the baked-on siliconization process disclosed in Reuter to the 1 mL glass syringe tested in Reuter to achieve lower levels of silicone oil in the barrel while maintaining similar low operable syringe stopper forces. Because Reuter teaches that for the 1 mL syringe tested, 500 µg of silicone oil provided break loose forces of 1.7 N, and a glide force of about 0.5 N, a POSITA would understand that applying the baked-on siliconization process of Reuter would result in similarly operable low forces, which are far below the level claimed in the ‘631 patent, while using about 10% of the 500 µg of silicone oil, which is about 50 µg silicone oil, consistent with the calculation in the previous paragraphs. Ex. 1010.004-005; see also Ex. 1014 at [0026]. The analysis would be the same if a POSITA were to use the 1 mL syringe tested in Reuter which had 800 µg of silicone oil, which would result in similar low operable forces with low silicone oil levels (~80 µg) within the claimed range.~~

6. [1.f] the VEGF-antagonist solution comprises no more than 2 particles >50 µm in diameter per mL

~~257~~265. It would be obvious to a POSITA that the combination of Lam and ~~Reuter~~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.

~~258~~266. Lam discloses a pre-filled syringe containing a solution of ranibizumab intended for intravitreal injection. Lam (Ex. 1029) at 13:14-15 (“We performed EtO sterilization runs on

syringes containing a ranibizumab solution.”), 2:4-6 (“The invention is based, in part, on the surprising discovery of ethylene-oxide -based sterilization conditions that will effectively sterilize the surface of an object but which do not significantly damage ethylene-oxide-sensitive, temperature-sensitive compounds contained inside.”). ~~Reuter discloses that the baked-on siliconization method disclosed is “advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.” Ex. 1010.005. A POSITA would understand this reference to particle contamination requirements in Reuter to include USP789.~~

~~259~~267. As explained in **Section V.F and VIII.A.2** above, a POSITA would understand that “no more than 2 particles >50 ~~µm~~µm in diameter per mL” is one of the USP789 standards required for ophthalmic drugs such a VEGF-antagonist solution intended for intravitreal use. See Scypinski (Ex. 1017) at 10:19-22 (“United States Pharmacopoeia (USP) Chapters <788> *Particulate Matter in Injections* and <789> *Particulate Matter in Ophthalmic Solution* describe physical tests for the purpose of enumerating extraneous particles within specific size ranges.”). Specifically, a POSITA 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:~~ Therefore, a POSITA would have been motivated to have no more than 2 particles of diameter > 50 ~~µm per~~µg per mL in the ophthalmic solution disclosed in Lam. Meeting that requirement would be a matter of routine optimization. A POSITA would understand that ophthalmic solutions of VEGF-antagonists were already known in the art— *i.e.*, Macugen[®], Lucentis[®], and Eylea[®]—and that preparing these solutions such that they meet the requirements of USP789 would be within the level of ordinary skill in the art.

~~260~~268. A POSITA would have a reasonable expectation that the combination of Lam (VEGF-antagonist in pre-filled syringe) ~~with Reuter~~and Boulange (pre-filled baked-on syringe with low silicone oil) would satisfy the USP789 particulate matter limitations. ~~A POSITA would understand that the ophthalmic solution disclosed in Lam is required to meet USP789, as I described above. The ‘631 patent does not explain how to achieve a solution that meets USP789 (see Ex. 1001 at 6:28-30), and thus concedes that preparation of such a solution was known to a POSITA. Moreover, Reuter discloses a syringe siliconized using baked-on siliconization that has low levels of silicone oil falling within the ranges claimed in the ‘631 patent. Accordingly, a POSITA would have expected that the combination of Reuter and Lam would result in a pre-filled syringe meeting the particulate content requirements of USP789, given that baked-on siliconization reduces the risk for the formulation of particulate matter. Ex. 1010.005 (“As a result, there are fewer subvisual and visual silicone oil particles in the solution. The [baked-on] siliconization process is therefore recommended for use with sensitive protein formulations. It is also advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.”); Badkar at 569 (Ex. 1044.006) (“Overall data suggested that the baked-on silicone process was better suited for protein formulation development in PFS as it represented a lesser degree of risk for the formation of subvisible particulate matter as well as minimized any potential for protein precipitation on the Si-oil droplets.”).~~ A POSITA would understand that the ophthalmic solution disclosed in Lam is required to meet USP789, as I described above. The ‘631 patent does not explain how to achieve a solution that meets USP789 (see ‘631 patent at 6:28-30), and thus concedes that preparation of such a solution was known to a POSITA. Moreover, Boulange discloses a syringe siliconized using baked-on siliconization that has levels of silicone oil falling within the ranges claimed in the

'631 patent. Accordingly, a POSITA would have expected that the combination of Boulange and Lam would result in a pre-filled syringe meeting the particulate content requirements of USP789 because Boulange explicitly states that its invention limits the risk of interaction between the silicone oil and the drug product. See also Boulange (Ex. 1008) at 6:26-29 ("the medical device of the invention allows to limit the risk of interaction between a lubricant, for example silicone oil, and the therapeutic molecules potentially stored in the container").

7. [1.g] and wherein the syringe has a stopper break loose force of less than about 11N.

269. As explained above, Boulange discloses this limitation. See VIII.C.7 above.

~~261. As explained above, Reuter discloses low break loose and slide forces using oily siliconization in a 1 mL long syringe with 800 µg and 500 µg of silicone oil, respectively, where the respective break loose forces were reported to be 2.5 N and 1.7 N, and the respective glide forces were 1.7 N and 0.5 N. Ex. 1010.004-005 (Fig. 5).~~

~~262. A POSITA at the time would have been well aware that the application of baked-on siliconization uses about 10% or less of the amount of silicone oil as used in oily siliconization, while still maintaining similarly low operable forces. See, e.g., Ex. 1014 at [0026] (baked-on siliconization "makes it possible to reduce the amount of silicone that is used ... by about a factor of 10 without any loss of lubricating effect."). Thus, because Reuter discloses the specific break loose and slide forces achieved with the oily siliconized 1 mL glass syringe tested, a POSITA would know that the baked-on process would produce the same or similarly low syringe stopper forces in the same syringe, that fall within the claimed ranges. Figure 7 of Reuter confirms that the break loose and slide forces for the baked-on syringe are essentially the same as the oily syringe (except that the break loose force of the baked-on syringe is better after storage).~~

Accordingly, a POSITA would understand that the break loose force for the baked-on syringe is less than 11 N.

Ex. 1010.006 (Fig. 7) (annotations in orange)

263. Additionally, as explained in 238 above, a POSITA would understand that the break loose forces disclosed in Figure 5 of Reuter would remain substantially the same even when a VEGF-antagonist such as ranibizumab is contained in the syringe because the viscosity of the fluid in the syringe does not affect the break loose force. Specifically, as explained in **Section V.C** above, because the break loose force is the force required to get the stopper to just about begin moving, and because the force is between the stopper and barrel and therefore a function of siliconization, and stopper material and coating, the measured break loose force is largely independent of the viscosity of the fluid within the pre-filled syringe.

C. Claims ~~2-10~~2, 3, 5-9, and ~~14-24~~14-22

~~264~~270. The limitations of claims ~~2-10~~2, 3, 5-9, and ~~14-24~~14-22 are likewise disclosed and or rendered obvious by Lam in view of ~~Reuter~~Boulange.

1. Claim 2

~~265~~271. Claim 2 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.”

266. Reuter discloses that the layer thickness for a syringe with baked-on siliconization is 15-50 nm. Ex. 1010.005 (“The layer thickness measures 15-50 nm. By comparison, the average layer thickness with oily siliconization is 500-1,000 nm. Baked-on siliconization reduces the measurable quantity of free silicone oil to approx. 10% of the normal value.”). According to Reuter, the typical thickness of a baked-on silicone oil layer is 15-50 nm (as opposed to the

~~average layer thickness with oily siliconization is 500-1,000 nm) and another prior art source gives an estimate of 76.83 nm (as opposed to 232.67 nm). See *Id.* at .005; Ex. 1012.006. Reuter not only discloses a pre-filled syringe with silicone oil that has an average thickness of less than 450nm, but also teaches a silicone oil layer thickness known to be typical for baked-on silicone oil syringes.~~

272. As explained above, Boulange discloses this limitation. See VIII.D.1 above.

2. Claims 3 and 22

~~267~~273. Claim 3 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 ~~μg~~ μg silicone oil.” Claim 22 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.” As explained above, Boulange discloses an internal coating of silicone oil of 40 μg for a 1 ml syringe. See VIII.D.2 above.

~~268. As explained above with regard to limitation [1.c], it would have been obvious for a POSITA to apply the baked-on siliconization process of Reuter to achieve a pre-filled glass syringe containing about 10% of silicone oil as compared to oily siliconization, which is about 50 μg or less for a 1 mL long syringe. Ex. 1010.005. A value of 50 μg or less silicone oil is consistent with other prior art, which discloses values from 40 to 100 μg silicone oil for a 0.5-1 mL baked-on syringe with an inner surface area of approximately 8 cm^2 . Ex. 1014 at [0026] (“40 to 100 μg of silicone are sufficient for the same [0.5-1 mL] syringe (about 5 to 12 $\mu\text{g}/\text{cm}^2$) if silicone is deposited on the inner surfaces of the container and then polymerized, for example by heating”).~~

3. Claims 4, 10, and 23

~~269. Dependent claims 4 and 23 depend from claim 1, and require that the silicone oil is DC365 emulsion or that the silicone oil has a viscosity of about 350 cP. Dependent claim 10, depends from claim 8 and requires silicone oil with a viscosity of about 350 cP and further recites particulate content requirements from USP789.~~

~~4. A pre-filled syringe according to claim 1, wherein the silicone oil is DC365 emulsion.~~

~~10. 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.~~

~~23. A pre-filled syringe according to claim 1, wherein the silicone oil has a viscosity of about 350 cP.~~

~~270. Reuter specifically discloses that DC365 silicone oil emulsion was known to be used in the baked-on siliconization process. Ex. 1010.003 (“The DOW CORNING® 365 siliconization emulsion is often used in the baked-on siliconization process”). The viscosity of DC365 is 350 cP. Ex. 1034.002.~~

~~271. As explained in **Section V.F**, a POSITA would understand that “(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” are requirements set forth in USP789. My analysis above in **Section XI.A.2** and **Section XI.B.6** demonstrates that it would be obvious to a POSITA that the combination of Lam and Reuter would meet the requirements of USP789.~~

43. Claims 5 and 6

~~272~~274. Claim 5 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~~µm in diameter per ml, and (ii) no more than 50 particles >10 ~~µm~~µm in diameter per ml.” Claim 6 recites “[a] pre-filled syringe according to claim 1, wherein the VEGF-antagonist solution meets USP789.”

~~273: As explained above in Section V.F, a POSITA would understand that “(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” are USP789 requirements.~~ My analysis above in ~~Section XI~~Sections VIII.A.2, VIII.C.6 and ~~Section XI.B.6~~ demonstrates that it would be obvious to a POSITA that the combination of Lam and ~~Reuter~~Boulange would meet the requirements of USP789, including the limitations of claims 5 and 6.

54. Claims 7, 8, and 9

~~274~~275. Claim 7 recites “[a] pre-filled syringe according to claim 1, wherein the VEGF antagonist is an anti-VEGF antibody.” Claim 8 recites “[a] pre-filled syringe according to claim 7, wherein the anti-VEGF antibody is ranibizumab.” Claim 9 recites “[a] pre-filled syringe according to claim 8, wherein the ranibizumab is at a concentration of 10 mg/ml.”

~~275~~276. Lam discloses a pre-filled syringe containing ranibizumab, which the ‘631 patent characterizes as an antibody VEGF antagonist. Lam (Ex. 1029) at 13:~~14-15~~1415 (“We performed EtO sterilization runs on syringes containing a ranibizumab solution.”); ~~Ex. 1001~~‘631 patent at 6:30-35 (“Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and bevacizumab (Avastin®).”). Lam also discloses that the ranibizumab protein concentration is 10.0 mg/mL for the additional conditions tested and

summarized in Table 3. Lam (Ex. 1029) at 15:2-3 (“We performed EtO sterilization runs on syringes containing a **ranibizumab solution (at 10.0 mg/mL . . .)**”).

65. Claims 14 and 16

~~276~~277. Claim 14 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.” Claim 16 recites “[a] prefilled syringe according to claim 1, wherein the syringe has a stopper slide force of less than about 11N.”

~~277. My analysis above in Section XI.B.7 with respect to limitation [1.g] explains how the break loose and slide forces for a baked-on syringe would be less than 5 N.~~

278. As explained above, ~~Reuter measures the slide force in empty, needleless syringes at 100 mm/min, a relatively slow speed, and finds a mean slide force of 0.5 N for 1 mL long syringes with 500 µg of silicone oil applied via oily siliconization methods. Ex. 1010.005 at Figure 5. This slide force would be almost entirely comprised of the frictional force between the stopper and the barrel, with little contribution from the forces required to expel fluid (air) from the syringe through the luer tip, which is considerably wider than a needle. The additional force needed to push a ranibizumab formula, with a viscosity of 1.3 cP, even if done through a half inch 30G needle at 190 mm/s, for example, can be calculated using the Hagen-Poiseuille formula, introduced above in Section VIII.C.6, as approximately 2 N. This, added to the friction force of 0.5 N in Figure 5 of Reuter, is 2.5 N. Given that Reuter explains that baked-on siliconization allows for the same forces at a tenth of the amount of silicone oil, it would be obvious to a POSITA that a pre-filled syringe meeting the limitations of claim 14 and 16 would have a slide force of less than 5 N.~~Boulangé discloses these limitations. See VIII.D.5 above.

76. Claim 15

279. Claim 15 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 ~~x~~_±0.5 inch needle attached to the syringe.”

280. As explained above, Boulange discloses these limitations. See VIII.D.6 above.

~~280. Figure 5 of Reuter shows force curves for a “standard 1 ml long syringe” where the respective break loose forces using oily siliconization were reported to be 2.5 N and 1.7 N, and the respective glide forces were 1.7 N and 0.5 N. Ex. 1010.005. As explained above in Section XI.B.7, Figure 7 of Reuter confirms that the break loose and slide forces for the lower silicone baked-on syringe are essentially the same as the oily syringe (except that the break loose force of the baked-on syringe is better after storage).~~

~~281. The viscosity of the solution, needle type, and stopper traveling speed are irrelevant to break loose force, and only impact the slide force. As explained above in Section V.C, the magnitude of the break loose force is largely attributable to the ageing of the stopper within the syringe, which becomes sticky with age and forms a tight seal against the barrel. The tighter seal results in a higher force required to initially displace the stopper, which is the break loose force. Because the break loose force is between the stopper and the inside of the barrel, and is the force required to get the stopper to just about begin moving, the break loose force is largely unaffected by the viscosity of the fluid in the pre-filled syringe or other factors that impact the slide force, such as needle size and stopper traveling speed.~~

~~282. Because VEGF antagonists such as ranibizumab are intended for intravitreal injection into the eye, it would have been obvious to a POSITA to use a thin needle of higher gauge, such as a 30 G needle, for such an application. A needle length of 0.5 inches would also have been obvious to use because of the shallow depth of intravitreal injection. For example, the~~

~~Maeugen pre-filled syringe used a 30 G, 0.5 inch needle. See Ex. 1009.007. A POSITA would understand that the selection of needle size would have been routine optimization well within ordinary skill.~~

~~283. Because the break loose force is a measure of force required for initial movement only, it is unaffected by the stopper traveling speed or needle type, as explained above. As such, break loose force in Reuter will remain the same if measured at a stopper speed of 190 mm/min, and with a 30 G x 0.5 inch needle, as required by claim 15. Thus, claim 15 is rendered obvious by Lam in view of Reuter because: (i) it would be obvious to a POSITA to utilize a 30 G x 0.5 inch needle with a pre-filled syringe containing a VEGF-antagonist for intravitreal injection; and (ii) it would be obvious to a POSITA that the break loose forces disclosed in Reuter would be maintained at less than 5 N when using the baked on siliconization technique, when measured using a stopper traveling speed of 190 mm/min and a 30 G x 0.5 inch needle.~~

~~284. As explained above, Reuter measures the slide force in empty, needleless syringes at 100 mm/min, at relatively slow speed, and finds a mean slide force of 0.5 N for 1 mL long syringes with 500 mg of silicone oil applied via oily siliconization methods. Ex. 1010.005 at Figure 5. This slide force would be almost entirely comprised of the frictional force between the stopper and the barrel, with little contribution from the forces required to expel fluid (air) from the syringe through the luer tip, which is considerably wider than a needle. The additional force needed to push a ranibizumab formula, with a viscosity of 1.3 cP, through a half inch 30G needle at 190 mm/s, can be calculated using the Hagen-Poiseuille formula, introduced above in **Section VIII.C.6** and **Appendix A at Section I.B**, as approximately 2 N. This, added to the friction force of 0.5 N in Figure 5 of Reuter, is 2.5 N. Given that Reuter explains that baked on siliconization allows for the same function at a tenth of the amount of silicone oil, it would be~~

~~obvious to a POSITA that a syringe meeting the limitations of claim 15 and tested using the claimed parameters would have a slide force of less than 5 N. Although the slide force of less than 5 N would be obvious, this showing of obviousness based on the slide force is unnecessary, since claim 15 would still be obvious to a POSITA based only on the break loose force. Claim 15 recites “the stopper break loose force or stopper slide force,” is measured under the specified conditions, and, as explained above, a POSITA would understand that the break loose force would not be affected by those conditions.~~

87. Claim 17

~~285~~**281.** Claim 17 recites “[a] blister pack comprising a pre-filled syringe according to claim 1, wherein the syringe has been sterilised using H₂O₂ or EtO.”

~~286~~**282.** Lam discloses a pre-filled syringe packaged in a blister pack that is terminally sterilized by EtO. Lam (Ex. 1029) at 2:29-33 (“In some embodiments, **the object is a syringe.** In some embodiments, the syringe comprises glass and comprises a stopper comprising D777-7 laminated with FluroTec®; and a tip cap comprising D777-7 laminated with FluroTec® or D21-7H laminated FluroTec®. In some embodiments, **the object is contained within a package comprising an EtO-permeable material, e.g. TYVEK®.**”); id. at 15:2-3 (“We performed EtO sterilization runs on syringes containing a ranibizumab solution (at 10.0 mg/mL....”). A POSITA would have understood that the reference to TYVEK® is a reference to the material of a blister pack. It also would have been obvious that the syringe of Lam would be supplied in a blister pack comprising TYVEK, which was a commonly used means of packaging a pre-filled syringe. See, e.g., Ex. 1061.003 (“DuPont™ Tyvek® spunbonded olefin is intended for packaging of terminally sterilized medical devices The sterile barrier systems using Tyvek® are commonly sterilized using ethylene oxide (EO) gas

Emerging low-temperature sterilization methods such as: gas plasma with hydrogen peroxide, vapor phase hydrogen peroxide with peracetic acid, ozone and chlorine dioxide, require Tyvek® packaging because cellulosic porous materials are adversely affected by these strong oxidizing environments.”). Providing a medical device such as a pre-filled syringe in a blister pack or other form of pouch was a well-known and effective way of packaging such devices. See, e.g., Sigg (Ex. 1007) at 6:26-28; 2008 Macugen Label at 8-9 (Ex. 1009.008-009) (Macugen supplied in sterile foil pouch); Metzner (Ex. 1018) at [0012], [0024] (describing use of blister packs to fix movable components of syringe and prevent displacement).

98. Claims 18 and 19

~~287~~283. Claim 18 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.” Claim 19 recites “[a] blister pack comprising a pre-filled syringe according to claim 17, wherein the syringe has been sterilised using EtO or H₂O₂ and the total EtO or H₂O₂ residue found on the outside of the syringe and inside of the blister pack is 0.1 mg.”

284. Lam describes that its sterilization process includes an evacuation and nitrogen wash step. Lam (Ex. 1029) at 13:20-21 (“[E]ach run had the following standard EtO sterilization steps:... (7) evacuate chamber to about 5.0” HgA and (8) wash four times with nitrogen (each wash cycle is about 15-20 min).”). A POSITA would have known that the evacuation and wash steps described in Lam are intended to remove EtO residue from the sterilization chamber, including the syringe surface and blister pack. Gillis at 242 (Ex. 1052.004) (“Unreacted residual gas is rapidly removed through evacuation, heated nitrogen or air exchanges.”). Achieving less than 1 ppm or 0.1 mg residue on the outer

surface of the syringe and inside the blister pack would have been a matter of routine optimization by varying the evacuation and wash steps described in Lam (e.g., increasing the number of wash steps). A POSITA would be motivated to minimize the EtO residue to reduce the risk of exposing the drug product and user of the syringe to EtO residue. See e.g., Lambert at 260 (Ex. 1052.022) (explaining that EtO exposure should not exceed 1 ppm). Lam, for example, tested for residue EtO within the syringe to ensure that minimal amounts of EtO residue ingressed into the drug product. See Lam (Ex. 1029) at 15:17-18 (“We measured the residual EtO in the syringe....”).

285. It would have been obvious to a POSITA to design the terminal sterilization process for a pre-filled syringe such that the residual EtO on the outer surface of the syringe has 1 ppm EtO and the residual EtO outside the syringe and inside the blister pack is 0.1 mg. It was well-known in the art that it was desirable to minimize the residual sterilizing agent on the outer surface of a medical product to reduce the risk of exposure to the patient and clinician. See V.E above. In fact, since 2001 OSHA has recommended that medical products have less than 1 ppm of EtO residue. See V.E above. A POSITA would have expected to succeed in achieving such a level of residual EtO based on routine optimization of the sterilization cycle. See also VIII.D.8 above. This is confirmed by the disclosure in the ‘631 patent, which provides virtually no information regarding how to design a sterilization cycle to achieve the residual levels of VHP or H₂O₂ required by claims 18-19.

~~288. Lam discloses a method of terminal sterilization that results in 1 ppm EtO residue.~~

~~289. A POSITA would understand that such a level of EtO residuals would also be obtainable within a blister pack, which is disclosed in Lam as being EtO permeable. Ex. 1029 at 2:29-33.~~

~~290. A POSITA would understand that 1 ppm EtO residue would be 0.1 mg EtO residue within the area of a blister pack. The value of 0.5 ppm EtO found in Table 3 of Lam is equivalent of 0.9 mg EtO per cubic meter. Ex. 1048.002. Assuming that the volume inside the blister pack for a single syringe is less than 1/9 of a cubic meter, Lam discloses this limitation. For example, if the blister pack were even as large as a cube with sides of 20 cm (0.2 m) each, the total volume of the blister pack would be .008 cubic meters, which, at a rate of 0.9 mg per cubic meter, would result in .072 mg of EtO residue, which is less than 0.1 mg.~~

~~109.~~ **Claim 20**

~~291~~286. Claim 20 recites “[a] blister pack comprising a pre-filled syringe according to claim 18, wherein 5% of the VEGF-antagonist is alkylated.”

~~292~~287. Lam discloses in the ~~Examples~~examples that the pre-filled syringes containing ranibizumab were treated with EtO sterilization treatment. Lam further discloses that stability of the protein is demonstrated by IEC data. Lam (Ex. 1029) at 15:~~17-19~~1719. (“We measured the residual EtO in the syringe and the stability of ranibizumab by IEC the same day as the treatment and at various monthly time points thereafter.”). Lam also explains how to determine the percent alkylation by IEC. *Id.* at 3:25-27 (“As used herein, “percent alkylation” in the context of a polypeptide is the percentage of polypeptide that is in the basic peak relative to polypeptide that is in the acidic or main peaks as measured by IEC.”) Table 3 shows the percent acidic peaks, main peak and basic peaks. Thus, an exemplary alkylation can be calculated using the peak data

from Row E after two months time. This calculates out to $1.80 / (96.95 + 1.24) \times 100\% = 1.83\%$. IEC is explained further in **Section VIII.CD.9**, above.

1110. Claim 21

293288. Claim 21 recites [a] blister pack comprising a pre-filled syringe according to claim 17, wherein the syringe has been sterilised using EtO or H₂O₂ with a Sterility Assurance Level of at least 10⁻⁶.

294289. Lam discloses a method of terminal sterilization using EtO that provides for a sterile packaging of a pre-filled syringe. *Id.* at 13:12-26 (“We performed 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. . . . In addition to the syringe, each run also included a paper strip with approximately 1.9×10^6 *Bacillus subtilis* spores, which was used to monitor the sterilization as follows: the strip was soaked in media, vortexed vigorously and then serial dilutions were plated and grown for one week. We then varied the following sterilization-critical factors as indicated in Table 1: temperature, relative humidity, time of exposure (gas dwell), and EtO concentration.”).

295290. Lam further defines that an object is “sterilized” when “the amount of at least one biological contaminant present on the surface of the object being treated according to the present invention is reduced following the treatment.” *Id.* at 4:3-5. Lam adds that “[t]ypically, the amount is reduced by at least one log (i.e. by at least 10-fold). In some embodiments of the invention, the amount is reduced by 2 logs, 3 logs, 4 logs, 5 logs, or 6 logs.” *Id.* at 4:5-7. [A POSITA would understand that Lam’s disclosure of reducing the biological contaminants by at least “6 logs” means that the sterilization cycle has achieved a sterility assurance level of at least 10⁻⁶.](#)

296291. A POSITA would understand that measuring the log reduction in *Bacillus subtilis* spores (that is, the killing of *Bacillus subtilis* spores in a typical logarithmic fashion over time or by dose) during sterilization would be used to optimize the level of sterility assurance by measuring the sterilization conditions needed to reduce the *Bacillus subtilis* spores, such that the desired sterility is achieved. See, e.g., Lambert at 1118 (Ex. 1049.003) (Fig. 2). It would be a matter of routine optimization for a POSITA to ensure that ~~the~~a sterility assurance level of 10^{-6} is achieved, as explained above. See Section VIII.D.10 above. This is clear from Table 1 of Lam, which discloses that the use of different gas dwell times (i.e., the amount of time the syringe was exposed to the sterilizing gas), different concentrations of EtO, and different temperatures resulted in different log reductions of spores. Lam (Ex. 1029) at 13:25-26 (“We then varied the following sterilization-critical factors....”). That achieving a desired sterility assurance level is a matter of routine optimization is confirmed by the specification of the ‘631 patent, which describes that a sterility assurance level of 10^{-6} can be achieved using known EtO sterilization methods, and otherwise provides no information regarding how to achieve such a sterility assurance level. See ‘631 patent at 9:49-54 (“As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide (EtO) or a hydrogen peroxide (H₂O₂) sterilisation process.”).

XII. Ground 4: Lam in View of Boulange and Fries Renders Obvious Claims 4, 10, and 23

292. As I explained above, claims 4, 10, and 23 are rendered obvious by Sigg in view of Boulange and Fries. In particular, Fries discloses the use of DC365 emulsion for baked-on siliconization, which includes a silicone oil component having a viscosity of about

350 cP. For the reasons set forth above, claims 4, 10, and 23 are likewise rendered obvious by Lam in view of Boulange and Fries. See Section IX above.

~~XII. Petition 2, XIII.~~ Ground 26: Lam in view of ~~Reuter~~Boulange and Furfine Renders

Obvious Claims 11-13

~~297. Dependent claims 11, 12 and 13 further require that the VEGF-antagonist is a non-antibody VEGF-antagonist, the non-antibody VEGF-antagonist is aflibercept or conberecept, or the non-antibody VEGF-antagonist is aflibercept at a concentration of 40 mg/mL. Lam discloses in one embodiment that the pre-filled syringe includes a VEGF-antagonist (ranibizumab), and it would have been obvious to a POSITA to use a different VEGF-antagonist, such as aflibercept or conberecept, which were both well-known prior to 2012, in the pre-filled syringe for intravitreal administration. Furfine discloses aflibercept, which is a biologic therapeutic approved for treatment of wet AMD that is administered by intravitreal injection. Furfine also discloses a VEGF-antagonist in a pre-filled glass syringe. Ex. 1021 at [0059], [0061];~~

~~298. A POSITA would have been motivated to use aflibercept in a terminally sterilized pre-filled syringe as disclosed in Lam, for all the reasons discussed above in Section XI with respect to the VEGF-antagonist solution ranibizumab. Indeed, Lam makes it clear that the disclosed terminal sterilization is applicable to a broad range of solutions, including those that are temperature, oxidation, or radiation sensitive. Ex. 1029 at 2:4-6 (“The invention is based, in part, on the surprising discovery of ethylene-oxide-based sterilization conditions that will effectively sterilize the surface of an object but which do not significantly damage ethylene-oxide-sensitive, temperature-sensitive compounds contained inside.”); *see also id.* at 2:7-12 (providing exemplary compositions within the sterile container). Reuter is directed towards improvements for pre-filled~~

~~syringes used to dispense therapeutic molecules, but is not limited in its use to any particular molecule. Ex. 1010.005. Reuter recommends baked-on siliconization for sensitive protein formulations and states that it is advantageous for ophthalmological preparations.. Ex. 1010.005. A POSITA would have recognized that aflibercept, marketed as EYLEA®, is a sensitive biologic that would be suited for use in the terminally sterilized pre-filled syringe for intravitreal injection disclosed in Lam.~~

293. As I explained above, claims 11-13 are rendered obvious by Sigg in view of Boulange and Furfine. In particular, Furfine discloses the non-antibody VEGF antagonist aflibercept at a concentration of 40 mg/ml. See Section X above. For the reasons set forth above, Claims 11-13 are likewise rendered obvious by Lam in view of Boulange and Furfine. *Id.* Indeed, Lam makes clear that its invention is generally applicable to biological molecules. Lam (Ex. 1029) at 2:1-2 (“The invention relates to methods for surface-sterilizing objects containing ethylene oxide-sensitive, temperature-sensitive compounds, such as biological molecules.”). Moreover, a POSITA would have expected to succeed in using aflibercept in a pre-filled syringe terminally sterilized with ethylene oxide. For example, it was known in the art that Australian health authorities had approved by February 17, 2012 a pre-filled syringe comprising aflibercept that was terminally sterilized with ethylene oxide. See Ex. 1066.005, .007.

XIV. SECONDARY CONSIDERATIONS

294. For the reasons set forth below, I disagree that any secondary considerations identified by Novartis in the ITC Investigation could support the non-obviousness of the claims in this IPR Proceeding.

A. ~~Claims 11 and 12~~ Long-Felt Need

299. ~~Claim 11 recites “[a] pre-filled syringe according to claim 1 wherein the VEGF antagonist is a non-antibody VEGF antagonist.” Claim 12 recites “[a] pre-filled syringe according to claim 11, wherein the non-antibody VEGF antagonist is aflibercept or conberecept.”~~

300. ~~Furfine discloses a non-antibody VEGF antagonist known as aflibercept. Ex. 1021 at [0005] (“Stable formulations of a VEGF-specific fusion protein antagonist are provided. Pharmaceutically acceptable formulations are provided that comprise a VEGF ‘trap’ antagonist with a pharmaceutically acceptable carrier. In specific embodiments, liquid and lyophilized formulations are provided.”), [0006] (“In a first aspect, a stable liquid ophthalmic formulation of a VEGF-specific fusion protein antagonist is provided, comprising a fusion protein that comprises a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a ‘VEGF trap’).”). The ‘631 patent states that aflibercept is a non-antibody VEGF antagonist. Ex. 1001 at 6:36-40.~~

295. I have reviewed the evidence cited by Novartis as supporting its argument that there was a “long-felt need” for the invention as claimed in the ‘631 patent. I disagree that the evidence supports Novartis’s position.

296. Novartis alleges that prior to the ‘631 patent, most VEGF antagonists approved for intravitreal administration were supplied in vials. Novartis argues that vial presentations presented several downsides, and that there were advantages to using a PFS presentation. According to Novartis, based on this, POSITAs had recognized the need to develop a PFS as claimed in the ‘631 patent long before the patent’s priority date.

297. Certainly, the advantages of administering an injection using a PFS were well-known for many years before the filing date of the ‘631 patent application. For

example, Shah was published in 2009 and identifies the many known benefits of using a PFS. Shah at 54 (Ex. 1011.004). These advantages included more accurate dosage, less overfill of the prescribed drug, a lower risk of contamination, more efficient administration, and more convenience to the medical staff. Shah at 56 (Ex. 1011.002). Similarly, Badkar confirms that these benefits were known, and explains that the “development of biotechnology products such as therapeutic proteins or vaccines in pre-filled syringes (PFS) has attracted considerable interest from pharmaceutical and biotechnology companies in the past 5 to 7 years.” Badkar at 564 (Ex. 1044.001). Badkar continues that this interest “can be attributed mainly to several benefits that PFS provide including reduction of medical dosing errors, minimized risk for microbial contamination by limiting manipulations prior to dosing, and enhanced convenience and ease of use.” *Id.* (citing Overcashier (Ex. 1076)). Badkar thus stated that pre-filled syringes “represent a win-win scenario for end-users....” Badkar at 564 (Ex. 1044.001).

298. These documents and the others confirm that the industry already knew of the advantages associated with PFS over vial administration years before the filing date of the ‘631 patent application. Novartis, however, did not invent the PFS, and the ‘631 patent does not claim only a PFS, or only a PFS filled with a VEGF antagonist. Nor could it, as the Macugen PFS was a VEGF-antagonist PFS that was FDA-approved in 2004, nearly a decade before the filing date of the ‘631 patent application. Novartis therefore cannot attribute the well-known advantages associated with a PFS filled with a VEGF antagonist to the invention claimed in the ‘631 patent, because the claimed invention was not the solution that resulted in the advantages described in the cited documents.

299. Novartis also argues that there was a long-felt need for a functional, terminally sterilized PFS having low levels of silicone oil, and asserts that the inventors of the ‘631 patent were the first to solve this problem. I do not agree that this is evidence of a long-felt need for the invention claimed in the ‘631 patent. The claims of the ‘631 patent are not merely directed to a PFS having “low levels of silicone oil.” Well before the ‘631 patent application was filed, the industry was fully aware of both the issues associated with silicone oil in the syringe barrel and the solution thereto -using syringe siliconization methods that minimized the amount of silicone. One of the documents that Novartis has relied on, which was published in 2011, confirms this, stating that “[o]ngoing developments in syringe siliconization to optimize and control the level and distribution of silicone oil to maximize functionality while minimizing the level (and excess) of silicone oil by syringe manufacturers may lead to syringes with minimal excess droplet detachment from the syringe walls during transportation or over time.” Bee (Ex. 1068).

300. Bee’s disclosure of minimizing silicone oil in syringes is with reference to a PFS. See Bee at 4165 (Ex. 1068.009) (“Silicone oil is used to lubricate the barrel of glass PFSs for smooth plunger motion with a lower injection force.”). Other evidence confirms that the industry already knew that the solution to the issue of silicone oil contaminating the therapeutic was to use siliconization techniques that minimized the amount of silicone oil required for the PFS glass barrel. For example, Badkar states, with reference to a PFS, that “the syringe is further processed for siliconization (followed by baking if required) and washing.... The overall system is then sterilized....” Badkar at 565 (Ex. 1044.002). Badkar also confirms that a baked-on siliconization technique resulted in PFSs with “approximately contain ten-fold less free silicone oil” from those that used a sprayed-on

silicone oil method, and that the baked-on silicone oil PFSs “showed no deleterious impact on product quality and no increase in subvisible particles.” Badkar at 571 (Ex. 1044.008).²⁵

301. Similarly, in 2009 Shah disclosed a number of terminally sterilized PFSs, including one having baked-on silicone oil that “reduces the level of free silicone.” Shah at 54 (Ex. 1011.004). Shah states that one of the “most important innovations” in the industry was the advent of the baked-on silicone oil approach, whereby “the concentration of silicone in the syringe and its chemical reactivity are both reduced and the product’s stability is increased.” Shah at 56 (Ex. 1011.006). Shah further noted that an additional benefit of the baked-on silicone oil approach was that it resulted in low “break loose” forces, such that the “initial force required to inject using prefilled syringes with baked-on silicone remains consistently low....” *Id.* Further, Boulange was published in 2009 and discloses glass syringes with a baked-on siliconization process, resulting in approximately 40 µg of silicone oil for a 1 mL syringe, compared to the typical sprayed-on silicone oil technique (having approximately 500 µg of silicone oil for a 1 mL syringe). Boulange (Ex. 1008) at 6:10-29, 13:8-15, 14:14-15:21, 21:1-22:8; Table 5; Table 7.

302. Therefore, to the extent that Novartis attempts to rely on evidence of a “long-felt need” for a terminally-sterilized PFS having “low levels of silicone oil,” the industry already knew of this solution, as disclosed in, for example, Bee, Badkar, Fries,

²⁵ Badkar notes that a “survey of leading PFS manufactures resulted in our finding that the typical levels” of silicone oil used on the glass barrel varied between 0.5 and 1 mg silicone per syringe. Badkar at 570 (Ex.1044.007). This converts to 500 to 1000 µg of silicone oil. Badkar’s disclosure of a “ten-fold” reduction in silicone oil using a baked-on siliconization method equates to 50 to 100 µg of silicone oil, which falls within the range claimed in the ‘631 patent.

Shah, and Boulange well before the ‘631 patent application was filed. Moreover, even if Novartis alleges that there was a long-felt need for a PFS with 100 µg or less of silicone oil on the glass barrel, the evidence also does not support that assertion either. Novartis cites Badkar for disclosing that in 2011 the “typical levels of silicone oil were between 500 and 1,000 µg per syringe.” Novartis ignores, however, that Babkar discloses that a baked-on silicone oil approach resulted in PFSs with approximately ten-fold less silicone oil, equating to silicone oil in the 50 to 100 µg range. Badkar at 571 (Ex. 1044.008). This assertion would also be refuted Boulange, which disclosed PFSs having baked-on silicone oil of approximately 40 µg. Boulange (Ex. 1008) at 6:10-29, 13:8-15, 14:14-15:21, 21:1-22:8. Even with respect to the range of silicone oil claimed in the ‘631 patent then, the solution to this alleged “long felt need” was already known in the art before the ‘631 patent application was filed.

303. Novartis has also argued that a long-felt need existed for the ‘631 patent claimed invention because a complication of developing a PFS as claimed in the ‘631 patent was that some terminal sterilization methods were considered incompatible with syringes filled with a VEGF antagonist because those methods could damage the sensitive protein molecules in the drug product. The evidence cited by Novartis does not support the proposition. Novartis cited a page from Nema that merely notes that sterilization processes may have “potentially adverse effects on the materials being processed, and the development of sterilization treatments must always consider that effect.” Nema Vol. 2 at 244 (Ex. 1016.259). This does not support Novartis’s assertion that it was known in the art that specific sterilization methods were actually “considered incompatible with VEGF antagonists.” Moreover, this evidence confirms that a POSITA would have known of the

possibility of issues associated with a particular terminal sterilization process adversely affecting the underlying drug formulation, and would have been able to account for it in selecting an appropriate process. For example, Macugen was a VEGF antagonist administered via intravitreal injection, which was provided to the market in a sterile pre-filled syringe since 2008. See 2008 Macugen Label at 8 (Ex. 1009.008) (describing that Macugen is supplied in a “sterile foil pouch”). Moreover, Bayer had received approval for a pre-filled syringe comprising aflibercept that was terminally sterilized with either ethylene oxide or vaporized hydrogen peroxide by February 2012. See Ex. 1066.005, 007.

304. For these reasons, it is my opinion that Novartis has not shown there was any long-felt need in the industry for the specific invention claimed in the ‘631 patent. Further, the evidence establishes that the industry was already aware of the alleged solutions identified by Novartis to this so-called long-felt need, well before the filing date of the ‘631 patent application.

B. ~~Claim 13~~Unexpected Results

~~301. Claim 13 recites “[a] pre-filled syringe according to claim 12, wherein the non-antibody VEGF antagonist is aflibercept at a concentration of 40 mg/mL.”~~

~~302. Furfine discloses a VEGF antagonist at a concentration of 40 mg/mL. Ex. 1021 at [0013] (“In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/mL of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 40mM sodium chloride, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.”); [0059] (“Stability of 40 mg/mL VEGF Trap Liquid Formulation Stored at 5°C in Pre-Filled Glass Syringe”). It would have been obvious to a POSITA to use aflibercept at a concentration of 40 mg/mL. See Ex. 1040.006 (disclosing approved 40 mg/mL Eylea formulation in vial form).~~

305. Novartis also has argued that the prosecution history of the ‘631 patent contains evidence of “unexpected results” achieved by the claimed invention. Specifically, Novartis has cited to statements and arguments the applicants made during prosecution of the application leading to the ‘631 patent. These statements concern the alleged “surprising” results by the inventors that lower levels of silicone oil could successfully be used in PFSs without increasing the break loose and glide forces. However, it is my understanding that in order to show unexpected results, the results of the invention must be compared to the closest prior art. To the extent that Novartis’s assertion of unexpected results is based on comparing the claims of the ‘631 patent to the Schoenknecht publication described in the specification (see ‘631 patent at 5:22-27), I disagree that this represents the closest prior art. As discussed in detail above, the prior art (e.g., Boulange) discloses baked-on siliconization achieving less than 50 µg of silicone oil on the syringe in combination with forces less than 11N.

306. Therefore, in my opinion, these statements and arguments do not constitute evidence that the invention claimed in the ‘631 patent achieved unexpected results. The Examiner overseeing the prosecution of the ‘631 patent did not agree with Novartis, as the claims were still rejected even after the applicants submitted the arguments cited by Novartis. After Novartis submitted the March 11, 2015 Response to Office Action, the Examiner promptly rejected the claims again, and stated that the applicants’ arguments “have been fully considered but they are not persuasive.... The Examiner finds that the prior art meets the claims as currently presented as set forth in the previous Office Action.” Ex. 1002.1358-1359.

307. The Examiner similarly rejected the arguments the applicants made in the August 13, 2014 and November 24, 2014 Responses. See Ex. 1002.1286-1287 (“Applicant’s arguments filed 8/13/2014 have been fully considered but they are not persuasive.. It is well known to use silicone oil in glass barrels, therefore it would have been within the level of ordinary skill in the art at the time the invention was made to use the silicone oil levels as generally described by Hioki with the glass barrel syringe of Scrypinski, and further within the level of ordinary skill to optimize the amount of silicone.”); Ex. 1002.1310-1311 (“Applicant’s arguments filed 11/24/2014 have been fully considered but they are not persuasive.. The Applicant claims the unexpected result of using less silicone actually leads to usable syringes, however, the Examiner finds that it would have been obvious to one having ordinary skill in the art to try and use less silicone, since it was common sense to use as little as possible to achieve the desired effect.”).

308. Accordingly, rather than agree with Novartis’s arguments regarding the unexpected results associated with using less silicone oil, the Examiner refuted them, pointing out that the results were not unexpected but were instead “common sense.”

309. The Examiner’s refusal to accept Novartis’s unexpected results argument is fully supported by the evidence. The claims of the ‘631 patent encompass glass barrels with up to about 100 µg of silicone oil, and break loose and glide forces up to about 11 N each (see claims 1 and 16). The prior art fully discloses these ranges, demonstrating that there was nothing “unexpected” about them.

310. For example, the evidence shows that years before the filing date of the ‘631 patent application a POSITA knew to avoid higher levels of silicone oil in pre-filled syringes containing sensitive protein formulations such as VEGF antagonists, because of potential

“incompatibilities includ[ing] aggregation, deformation, and inactivation of native protein structures.” Fries at 26 (Ex. 1012.006). It was also well known in the art prior to 2012 that siliconization could be performed to achieve a more homogeneous and thinner coating of silicone oil, while reducing the amount of silicone oil, via “baked-on” siliconization, which “involves heating the silicone-coated syringe to a specific temperature for an appropriate time.” Schoenknecht at 10 (Ex. 1013.004); Nema Vol. 1 at 315 (Ex. 1015.330) (describing siliconization achieved by “baking silicone at high heat onto the glass barrels”); Nema Vol. 1 at 50 (Ex. 1015.065) (“Silicone oil coating is commonly used on stoppers and on the inside of syringes or cartridges as a lubricant to enable movement of the plunger. . . . Current [baked-on] processes for siliconization of prefilled syringes or cartridges apply well controlled amounts and involves baking of the silicone emulsion.”); Shah at 54 (Ex. 1011.004) (same); Fries at 26 (Ex. 1012.006) (same).

311. It was also well known prior to 2012 that the baked-on siliconization process requires only about one-tenth the amount of silicone oil as the sprayed-on siliconization technique to achieve the same break loose and glide force. For example, Chacornac explains, with respect to baked-on siliconization, that “the siliconizing operation comprising a polymerization step (i) is more precise and more homogenous than [sic] a simple standard siliconizing operation; and (ii) makes it possible to reduce the amount of silicone that is used ... by about a factor of 10 without any loss of lubricating effect.” Chacornac (Ex. 1014) at [0026]. Similarly, Boulange at Table 7 shows the low break loose and glide forces for a pre-filled syringe including 4 µg/cm² silicone on the syringe barrel (prepared using the baked-on method), whereas 50 µg/cm² is used in Example 5 for the spray-on method.

312. It was similarly known well before the ‘631 patent application filing date that baked-on siliconization can reduce the incidence of the “break loose effect.” Schoenknecht at 10 (Ex. 1013.004) (“The second benefit of baked-on silicone is that it reduces the frequency of the ‘break loose’ effect.”). Schoenknecht discloses that, compared to sprayed-on silicone, “baked-on silicone provides a more consistent coating of the syringe walls, which prevents the expanding rubber closure from touching the glass wall. Lubrication is maintained so that the initial force required to inject using prefilled syringes with baked-on silicone remains consistently low before and after storage.” *Id.*

313. With respect to the claimed break loose and glide forces, syringes commercially available before the critical date of the ‘631 patent were commonly sold as “10 and 5” syringes, meaning that they would have a maximum break loose force of 10 N and a slide force of 5 N, squarely within the ranges claimed. See, e.g., Fries at 26-27 (Ex. 1012.006-007) (explaining that “plunger gliding forces in the range of 5 to 10” were sufficient to satisfy “syringe functionality” requirements). Further, Boulange specifically discloses a 1 mL syringe with 40 µg of baked-on silicone that has break loose and slide forces of less than 11 N and less than 5 N. Boulange (Ex. 1008) at 20:15-21 (40 µg of baked-on silicone); Table 7 (showing the baked-on silicone method resulted in break loose and glide forces of less than 7 N, and for some syringes break loose and glide forces below 5 N).

314. Accordingly, the evidence does not support Novartis’s contention that the claimed ‘631 patent invention achieved unexpected results. Instead, the prior art confirms that the claimed ranges of silicone oil and break loose/glide forces were known and entirely expected.

~~XHC~~. Declaration Industry Praise

315. Novartis has also asserted that there is evidence of “industry praise” for the invention claimed in the ‘631 patent, thereby demonstrating its nonobviousness. The evidence Novartis has cited does not support this contention.

316. As noted above, I have been informed that for evidence of secondary considerations to carry weight, there must be a nexus between the *claimed* invention and the secondary considerations evidence. I have reviewed the documents cited by Novartis and in my opinion none of them establish the required nexus. Those documents instead merely confirm the known advantages of using PFSs generally -not the specific invention claimed in the ‘631 patent.

317. The 2019 article, M. Colucciello, *Prefilled Syringe Delivery of Intravitreal Anti-VEGF Medications*, (Ex. 1069), merely states that PFSs are advantageous because of the “decreased endophthalmitis risk, dose accuracy, and improved clinic efficiency they can provide.” This article does not attribute these advantages to the claimed features (*e.g.*, silicone oil of below about 100 µg, or break loose forces of below about 11 N), or even identify these claimed requirements in the article. Furthermore, the advantages identified in Colucciello (dose accuracy; decreased endophthalmitis risk (which is caused by contamination); and improved clinic efficiency) were advantages of using a PFS known in the industry at least a decade earlier, as shown by Shah, published in 2009 (listing the advantages of using PFSs as, *inter alia*, “accurate measurement of dosage,” “low risk of contamination,” “shorter preparation time,” and “convenient to medical staff”). Shah at 56 (Ex. 1011.002).

318. The 2019 article, T. Sassalos *et al.*, *Prefilled Syringes for Intravitreal Drug Delivery*, (Ex. 1073), also fails to demonstrate industry praise for the claimed invention.

Similar to Colucciello, it lists the “advantages of the PFS, including reduced injection time, possible reduced risk of endophthalmitis, reduction in intraocular air bubbles and silicone oil droplets, and improved precision in the volume and dose” administered. As described above, Shaw discloses these same advantages a decade earlier. Also, as with Colucciello, there is no reference to the specific claimed features of the ‘631 patent (e.g., silicone oil of below about 100 µg, or break loose forces of below about 11 N). While Sassalos does refer to baked-on siliconization and “minimal[]” silicone, the claims do not require only “minimal” silicone oil, but a specific range, and the claims further do not require baked-on siliconization. At any rate, the advantages of baked-on siliconization and the use of silicone oil that falls within the range claimed was well-known before the ‘631 patent application was filed, as I explained in detail above.

D. Commercial Success

319. I understand that Novartis asserts that the Lucentis PFS has been commercially successful, which it claims demonstrates the nonobviousness of the claimed invention in the ‘631 patent. For the following reasons, I disagree that the evidence supports Novartis’s commercial success contention.

320. First, I understand that there must be a nexus between the claimed invention in the ‘631 patent and the evidence of commercial success. I understand a nexus exists only if a Lucentis PFS both embodies the claimed features and is coextensive with the claims. That is not the case here, because the claims are broader than the Lucentis PFS. For example, only claims 8-10 even specifically require ranibizumab, which is the drug substance in Lucentis. As such, even if Lucentis PFS was commercially successful, that could only be relevant to those claims.

321. Second, I am not aware of any evidence that the commercial success of Lucentis PFS was due to the claimed features (e.g., specific values of silicone oil content, break loose, and slide forces). I reserve the right to address any such evidence if Novartis introduces it in this proceeding.

322. For these reasons, the evidence does not show a nexus between the alleged commercial success of Lucentis PFS and the claims in the '631 patent. Accordingly, this evidence cannot support the nonobviousness of the claims.

E. Failure of Others

323. Finally, Novartis will be unable to demonstrate that others tried and failed at achieving the claims of the 631 Patent. To the contrary, Macugen was a VEGF antagonist administered via intravitreal injection, which was provided to the market in a sterile pre-filled 1 mL glass syringe by 2008. See 2008 Macugen Label at 8 (Ex. 1009.008) (describing that Macugen is supplied in a "sterile foil pouch"). Moreover, Bayer had received approval for a 1 mL glass pre-filled syringe comprising the VEGF antagonist aflibercept that was terminally sterilized with either ethylene oxide or vaporized hydrogen peroxide by February 2012. See Ex. 1066.005, 007. Finally, others had clearly succeeded at achieving syringes with levels of silicone oil and break loose and slide forces within the claimed ranges, as reflected in the test results disclosed by Becton Dickinson in Boulange.

XV. Declaration

~~303~~324. I 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: By:

Horst Koller

APPENDIX A

1. Calculations from Section VIII C.6

A. Calculations of the syringe barrel and needle size used to obtain the results in Boulange Table 7

1. The dimensions of the syringe barrel used in the testing in Boulange's Example 5 are known, and a POSITA would be able to use those barrel dimensions to readily calculate the flow rate of fluid out of the syringe barrel. The flow rate can be used in the Hagen-Poiseuille equation to determine whether a needle was used in Example 5. *Id.* As needle sizes are standardized, a POSITA would then determine and confirm that needle and syringe size.

2. Below is the Hagen-Poiseuille formula to calculate the possible inner diameter of attached needle gauge size, solved for the inner radius, r (v is the mean flow velocity, P is the pressure (*i.e.*, the measured force), p is the dynamic viscosity, and L is the length of the needle): Given from Boulange are the following first set of syringe characteristics and testing conditions for a 1 mL long syringe:

- Fill Volume = 1 mL
- Fill Media = WFI = 0.001 Pa*s
- Syringe Size = 1 mL long = 6.35 mm inner diameter = $r = 3.175$ mm
- Speed of Glide force testing = 380 mm/min
- Measured Glide force: Table 7; piston Type B1 = 2.5 N

- Assumption for injection into eye: Needle length = 1/2" (12.7mm)

I used the following conversion factors in my calculation:

- $1\text{N}=10^5\text{Pa}$
- $1\text{mL}=1000\text{mm}^3$
- $1\text{min}=60\text{s}$

3. Step 1 is the calculation of mean flow velocity, v [mL/min], based on existing information:

$$h = 31.6\text{mm (height for 1mL long fill volume / water column)}$$

If the syringe glide force is tested at a speed of 380 mm per 60 s, the stopper must travel 31.6 mm (height, above) along the barrel in 5 seconds. Thus, it takes 5 seconds for one mL of fluid to travel through the barrel. Given 60 seconds in a minute, 12 mL of fluid will travel through the barrel in one minute, giving a mean flow velocity, v , of 12 mL/min.

4. Step 2 is the calculation of the inner needle diameter using the Hagen-Poiseuille formula and the known parameters above:

Thus, the inner diameter, D_i , is 0.142 mm, which is twice the inner radius, r .

5. According to ISO 9626 specifications for Stainless Steel Needle Tubing, an inner diameter of 0.142 mm corresponds to a needle gauge size that falls between 27 G (0.184 mm) and 28 G (0.133 mm) for a regular-walled needle. Ex. 1043 at 6. If this were a thin-walled needle, the inner diameter of 0.142 mm falls between 30 G (0.165 mm) and 31 G (0.125 mm). *Id.* Given the calculations above, a POSITA would understand that a needle gauge of between 27 G and 30 G was used, and most likely a 27 G normal-walled needle. This is consistent with what a POSITA would have expected to have been used for intravitreal applications. See Ex. 1015 at 36 (intravitreal application generally involve "a 25-gauge stainless steel needle" or smaller). The

same calculation may be performed for a standard (also known as “short”) 1 mL syringe. Given from Boulange are the following syringe characteristics and testing conditions, assuming this size of syringe:

- Fill Volume = 1 mL
- Fill Media = WFI = 0.001 Pa*s
- Syringe Size = 1 mL standard = 8.65 mm inner diameter = $r = 4.325$ mm
- Speed of Glide force testing = 380 mm/min
- Measured Glide force: Table 7; piston Type B1 = 2.5 N
- Assumption for injection into eye: Needle length = 1/2” (12.7 mm)

I used the following conversion factors in my calculation:

- 1 N = 10^5 Pa
- 1 mL = 1000 mm³
- 1 min = 60 s

6. Step 1 is the calculation of mean flow velocity, v [mL/min], based on existing information:

$$h = 17.0 \text{ mm (height for 1 mL long fill volume / water column)}$$

If the syringe glide force is tested at a speed of 380 mm per 60 s, the stopper must travel 17.0 mm (height, above) along the barrel in 2.7 seconds. Thus, it takes 2.7 seconds for one mL of fluid to travel through the barrel. Given 60 seconds in a minute, 22 mL of fluid will travel through the barrel in one minute, giving a mean flow velocity, v , of 22 mL/min.

7. Step 2 is the calculation of the inner needle diameter using the Hagen-Poiseuille formula and the known parameters above:

Thus, the inner diameter, D_i , is 0.166 mm, which is twice the inner radius, r .

8. According to ISO 9626 specifications for Stainless Steel Needle Tubing, an inner diameter of 0.166 mm corresponds to a needle gauge size that falls between 27 G (0.184 mm) and 28 G (0.133 mm) for a regular-walled needle. Ex. 1043 at 6. If this were a thin-walled needle, the inner diameter of 0.166 mm falls almost exactly at 30 G (0.165 mm). *Id.* Even if a standard 1 mL syringe was used, a POSITA would understand that a needle gauge of between 27 G and 30 G was used. This is consistent with what a POSITA would have expected to have been used for intravitreal applications. See Ex. 1015 at 36 (intravitreal application generally involve “a 25-gauge stainless steel needle” or smaller).

8. **Calculations of the slide force for claim 15 based on the results in Boulange Table 7**

9. Claim 15 necessitates that the speed used to measure force is 190 mm/min and that the needles is a 30 G 1/2 inch needle. The calculations above estimate that a 30 G needle may be used in Boulange, and a 1/2 inch needle is assumed. Thus, the change in the glide force, which measures 2.5 N in Boulange, would change according to the change in measurement speed. 190 mm/min is one half of the 380 mm/min testing speed used in Boulange, and speed is proportion to force. Thus, if the speed is halved, the force should also be halved, resulting in an estimated glide force of 1.25 N, all else being equal.

10. If Boulange is assumed to be performed using a 27 G needle, the change in force using a 30 G needles changes inversely proportionally with the radius of the needle raised to the fourth power, such that:

11. The radius of the needle is either 0.0713 mm (1 mL long) or 0.0830 mm (1 mL standard), as calculated above, and the radius of the 30 G needle is 0.0665 mm. Thus, if the above-calculated needle has a force of 1.25 N when measured at 190 mm/min, the 30 G needle

measured at 190 mm/min will have a glide force of 3.03 N (1 mL standard) or 1.65 N (1 mL long), if all other conditions in Boulange stay the same.

12. Although claim 15 does not specify what the syringe is filled with when tested, assuming that the syringe is filled with a VEGF antagonist and not the water of Boulange, the viscosity of a VEGF-antagonist solution such as ranibizumab (1.3 cp) is close to the viscosity of water (1 cp). In the Hagen-Poiseuille formula, the dynamic viscosity of the fluid, η , varies proportionally with force, so the forces would be only 1.3 times greater, for example, if a ranibizumab solution is used in place of water in Example 5 of Boulange. Using the forces calculated for the 30 G syringe at 190 mm/min, the glide forces for a syringe filled with ranibizumab solution would be 3.94 N (1 mL standard) or 2.15 N (1 mL long). Thus, the glide forces remain under 5 N.

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Table Delete	0
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Table moves from	0
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