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Paper 113
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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 Owner.

IPR2021-00816
Patent 9,220,631 B2

Before ERICA A. FRANKLIN, ROBERT L. KINDER, and JAMIE T. WISZ, *Administrative Patent Judges*.

KINDER, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

[redacted]

I. INTRODUCTION

On April 16, 2021, Regeneron Pharmaceuticals, Inc. ("Petitioner" or "Regeneron")[1] filed a Petition to institute *inter partes* review of claims 1–26 (all claims) of U.S. Patent No. 9,220,631 B2 (Ex. 1001, "the '631 patent"). Paper 1 ("Petition" or "Pet."). On October 26, 2021, we instituted the petitioned review (Paper 13, "Institution Decision" or "Inst. Dec.").

Novartis Pharma, AG, et al., ("Patent Owner" or "Novartis")[2] filed a Patent Owner Response (Papers 35, 40[3] "PO Resp.") to oppose the Petition. Regeneron filed a Reply (Papers 72, 73 "Pet. Reply") to the Patent Owner Response. Patent Owner filed a Sur-reply (Papers 92, 93 "Sur-reply") to the Reply. We conducted an oral hearing on July 21, 2022. A transcript has been entered into the record (Paper 112, "Tr.").

We have jurisdiction under 35 U.S.C. § 6(b)(4) and § 318(a). This Decision is a final written decision under 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73 as to the patentability of claims 1–26 of the '631 patent. We determine Petitioner has shown by a preponderance of the evidence that those claims are unpatentable.

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[1] Petitioner identifies Regeneron Pharmaceuticals, Inc. as the real party in interest. Pet. 1.
[2] Patent Owner identifies the named parties (Novartis Pharma AG, Novartis Technology LLC, and Novartis Pharmaceuticals Corporation) as the real parties in interest. Paper 4, 2.
[3] Two papers listed include both the public, redacted, version and the sealed confidential version.

II. BACKGROUND

A. Related Cases and Proceedings

The '631 patent is involved in two district court cases. Pet. 1–2. On June 19, 2020, Patent Owner filed a complaint[4] in the United States District Court for the Northern District of New York (NDNY) alleging that Petitioner infringes at least claim 1 of the '631 patent. Pet. 2 ("parallel district court litigation"). On July 17, 2020, Regeneron filed a complaint[5] in the Southern District of New York (SDNY) against Novartis and Vetter Pharma International GmbH seeking judgment that (i) Novartis's and Vetter's conduct violates Section 1 of the Sherman Act, (ii) Novartis's conduct violates Section 2 of the Sherman Act, and (iii) the '631 patent be declared unenforceable. Pet. 2–3 ("antitrust litigation").

On June 19, 2020, Novartis filed a complaint at the International Trade Commission ("ITC") alleging that Regeneron infringes claims 1–6 and 11–26 of the '631 patent. Pet. 1–2 ("ITC Investigation"). On April 8, 2021, Novartis filed a motion to terminate the ITC Investigation on the basis of withdrawal of the complaint. Pet. 2; Ex. 1006. On April 8, 2021, the Administrative Law Judge issued an initial determination terminating the ITC Investigation. Ex. 1010.

On July 16, 2020, Petitioner filed petitions in IPR2020-01317 (IPR'1317) and IPR2020-01318 (IPR'1318) challenging claims 1–26 of

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[4] Novartis Pharma AG et al. v. Regeneron Pharms., Inc., No. 20-cv-690 (N.D.N.Y.) (filed Jun. 19, 2020).
[5] Regeneron Pharms., Inc. v. Novartis Pharma AG et al., No. 20-cv-5502 (S.D.N.Y.) (filed July 17, 2020).

the '631 patent. Pet. 2. On December 2, 2020, Petitioner filed a motion to terminate IPR'1318 and the Board issued an order terminating the proceeding on December 7, 2020. On January 15, 2021, the Board exercised its discretion under 35 U.S.C. § 314(a) and denied institution of IPR'1317 based on the ITC Investigation that was co-pending at that time.

B. The '631 Patent

The '631 patent is titled "Syringe." Ex. 1001, code (54). The '631 patent "relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections." *Id.* at code (57). The U.S. application resulting in the '631 patent was filed on January 25, 2013 (*id.* at code (22)), and identifies multiple purported foreign priority applications, the earliest of which was filed in July 2012[6] (*id.* at code (30)).

The Specification notes that for small volume syringes intended for eye injections, sterilization can present issues that are not necessarily associated with larger syringes. *Id.* at 1:22–30. Further, certain therapeutics are particularly sensitive to sterilization techniques, thus it is important for the syringe to remain robustly sealed but also easy to use in that the force required to depress the plunger to administer the medicament must not be too high. *Id.* at 1:31–40.

[6] Patent Owner contends that the claims are entitled to a priority date of July 3, 2012. PO Resp. 7. Whether the claims are entitled to the July 3, 2012 priority date, or to the date of October 23, 2012 (Ex. 1003 ¶ 20) alleged by Petitioner, makes no difference in our ultimate patentability determination.

Figure 2 of the '631 patent, reproduced below, illustrates a cross section through the syringe. *Id.* at 10:60–67.

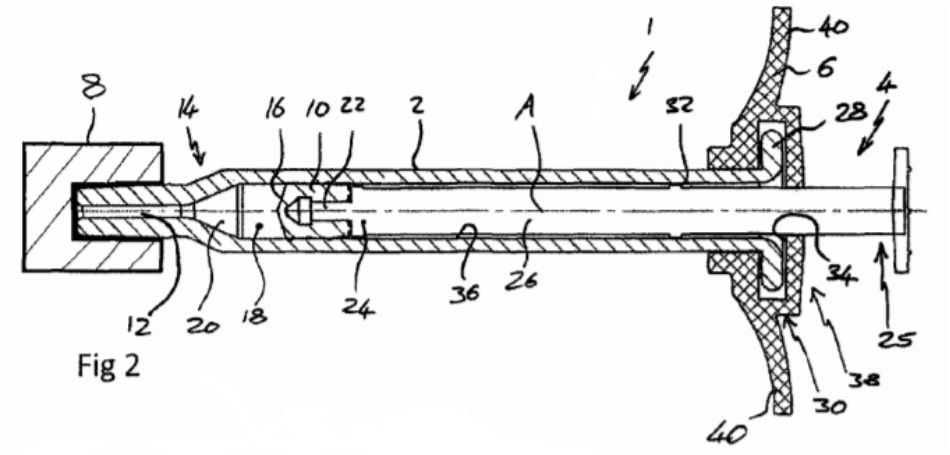

Figure 2 (above) depicts a cross section of a top down view of a syringe. *Id.* at 10:48–49.

As described, syringe 1 comprises body 2, stopper 10 and plunger 4. *Id.* at 10:61–67. Syringe 1 extends along first axis A, and body 2 comprises outlet 12 at outlet end 14. *Id.* Stopper 10 is arranged within body 2 such that front surface 16 of stopper 10 and body 2 define variable volume chamber 18. *Id.* Variable volume chamber 18 contains injectable medicament 20 comprising an ophthalmic solution comprising a VEGF antagonist. *Id.* at 10:67–11:2. Injectable fluid 20 can be expelled though outlet 12 by movement of stopper 10 towards outlet end 14 thereby reducing the volume of variable volume chamber 18. *Id.* at 11:3–5.

C. Challenged Claims

The '631 patent includes twenty-six claims, and Petitioner challenges each claim. Claim 1 is illustrative and reads as follows:

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

Ex. 1001, 19:2–13. Claim 24 is "[a] method of treating a patient . . . using a pre-filled syringe according to claim 1." *Id.* at 20:29–38.

D. Asserted Grounds of Unpatentability

Petitioner asserts several grounds of unpatentability (Pet. 21–23), which are provided in the table below:

Claim(s) Challenged	35 U.S.C. §[7]	Reference(s)/Basis
1–3, 5–9, 14–22, 24	103(a)	Sigg,[8] Boulange,[9] "and if necessary USP789"[10]
1–3, 5–9, 14–22, 24	103(a)	Lam[11] and Boulange
4, 10, 23	103(a)	Sigg, Boulange, Fries[12]
4, 10, 23	103(a)	Lam, Boulange, Fries
11–13	103(a)	Sigg, Boulange, Furfine[13]
11–13	103(a)	Lam, Boulange, Furfine

[7] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. § 103. Because the challenged claims of the '631 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA version of 35 U.S.C. § 103 in this Decision.
[8] PCT Patent Publication No. WO 2011/006877 (Ex. 1007).
[9] PCT Patent Publication No. WO 2009/030976 (Ex. 1008).
[10] U.S. Pharmacopeia, USP 789, Particulate Matter in Ophthalmic Solutions, USP 34 NF 29 (2011) ("USP789") (Ex. 1019). Petitioner contends that "USP789 demonstrates a POSITA would have known that Sigg and Lam were required to meet the claimed particle amounts. . . . Petitioner's obviousness arguments remain the same if USP789 should be explicitly listed in Grounds 1-10." Pet. 21 n.7.
[11] PCT Patent Publication No. WO 2008/077155 (Ex. 1029).
[12] Arno Fries, Drug Delivery of Sensitive Biopharmaceuticals With *Prefilled Syringes*, 9(5) DRUG DELIVERY TECH. 22 (2009) (Ex. 1012).
[13] PCT Patent Publication No. WO 2007/149334 (Ex. 1021).

Claim(s) Challenged	35 U.S.C. §[7]	Reference(s)/Basis
25	103(a)	Sigg, Boulange, 2008 Macugen Label[14]
25	103(a)	Lam, Boulange, 2008 Macugen Label
26	103(a)	Sigg, Boulange, Dixon[15]
26	103(a)	Lam, Boulange, Dixon

The parties rely on numerous declarations and exhibits relevant to our determination as we examine below.

III. ANALYSIS

A. Legal Standards of Obviousness

Section 103(a) forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art;

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[14] Internet Archive WayBack Machine, March 7, 2011 Record of Drugs.com, Macugen Prescribing Information, available at https://web.archive.org/web/20110307065238/http://www.drugs.com:80/pro/macugen.html (Ex. 1009).

[15] James A. Dixon, et al. "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration." *Expert opinion on investigational drugs* 18.10 (2009): 1573–1580 (Ex. 1030).

(2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when available, evidence such as commercial success, long-felt but unsolved needs, and failure of others. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966); *see KSR*, 550 U.S. at 407 ("While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls."). The Court in *Graham* explained that these factual inquiries promote "uniformity and definiteness," for "[w]hat is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context." *Graham*, 383 U.S. at 18.

The Supreme Court made clear that we apply "an expansive and flexible approach" to the question of obviousness. *KSR*, 550 U.S. at 415. Whether a patent claiming the combination of prior art elements would have been obvious is determined by whether the improvement is more than the predictable use of prior art elements according to their established functions. *Id*. at 417. To reach this conclusion, however, it is not enough to show merely that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc*., 655 F.3d 1352, 1360 (Fed. Cir. 2011). Rather, obviousness additionally requires that a person of ordinary skill at the time of the invention "would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id*.

A claimed invention may be obvious even when the prior art does not teach each claim limitation, so long as the record shows why one of skill in the art would have modified the prior art to obtain the claimed invention.

See Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1307 (Fed. Cir. 2006). As a factfinder, we also must be aware "of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 550 U.S. at 421. This does not deny us, however, "recourse to common sense" or to that which the prior art teaches. *Id*.

B. Level of Ordinary Skill in the Art

We are faced with the unusual situation where Petitioner advocates for two different standards for the person of ordinary skill in the art: one level of skill for the apparatus claims (1–23), and another unique level of skill for "the method of treating a patient" claims (24–26) of the '631 patent.

Petitioner first contends, with respect to claims 1–23, that

> A person having ordinary skill in the art ("POSITA") relevant to the '631 Patent as of July 3, 2012 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.

Pet. 24 (citing Ex. 1003 ¶¶ 30–32). Petitioner also contends 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." *Id.*

With respect to "method claims 24–26, a POSITA would have an M.D. with a specialty in ophthalmology." *Id.* (citing Ex. 1003 ¶¶ 30–32; Ex. 1031 ¶¶ 22–23). Petitioner's declarant, Mr. Horst Koller, explains:

> 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.

Ex. 1003 ¶ 32. Petitioner also provides the declaration of Dr. Szilard Kiss, an ophthalmologist, in support of its contentions with respect to claims 24–26. Ex. 1031 ¶¶ 4–6.

"Patent Owner disagrees with the split definition of POSA proposed by Petitioner, which presumes that a POSA would have had sufficient expertise to single-handedly develop a PFS,[16] or a method of treatment using a PFS, as claimed in the '631 patent." PO Resp. 6. Patent Owner proposes that "a POSA designing a PFS or method of treatment using a PFS would have worked *in collaboration with others* having complementary skills and experience." *Id.* (emphasis added). Similar to Petitioner, Patent Owner further proposes that the person of ordinary skill in the art would have had an advanced degree and at least 2–3 years of professional experience. *Id.* Patent Owner further advocates that "[s]uch a person would have been a member of a product development team and would have drawn upon not only his or her own skills, but also the specialized skills of team members in complementary fields including ophthalmology, microbiology and toxicology." *Id.*

[16] PFS stands for pre-filled syringe and it "is a syringe that is packaged and sold with a drug formulation already loaded into the syringe." Ex. 1003 ¶ 36.

In reply, Petitioner disagrees that a person of ordinary skill in the art would "consult someone with 'specialized skills' in toxicology." Pet. Reply 1. Petitioner further notes that "Novartis previously acknowledged that toxicology was immaterial, as its definition in the ITC investigation included no such requirement." *Id.* (citing Ex. 1253, 18–19).

As both parties recognize, the disagreement in the level of ordinary skill in the art has no bearing on the ultimate determination of obviousness. *See* PO Resp. 7 ("Under either party's proposed POSA definition, however, the challenged claims of the '631 patent would not have been obvious."); Pet. Reply 1 ("the claims would have been obvious under either definition").

Based on the final record, we adopt Petitioner's unique approach for identifying the person of ordinary skill in the art. Specifically, for claims 1–23, the person of ordinary skill in the art would have had at least an advanced degree with research experience in mechanical engineering, biomedical engineering, materials science, chemistry, or a related field, or at least 2–3 years of professional experience. Further, the person of ordinary skill in the art would have had experience with the design of pre-filled syringes and sterilization of drug delivery devices. We recognize that claims 24–26 require administering an ophthalmic solution using the pre-filled syringe described in claim 1, and agree with Petitioner that that a person of ordinary skill in the art for these claims would be an ophthalmologist with experience administering VEGF-antagonist drugs to patients via the intravitreal route.

C. Claim Construction

Petitioner proposes claim interpretations for several claim terms or phrases. Pet. 24–26. Patent Owner does not object to Petitioner's proposed constructions, or to our preliminary constructions set forth in the Institution Decision. *See* Inst. Dec. 31–34. We address those claim terms in the following discussion.

"Stopper Break Loose Force"

Claim 1 requires "the syringe has a stopper break loose force of less than about 11N." In the Petition, Petitioner proposes construing the term "stopper break loose force" to mean "the force required to make the plunger/stopper move from its resting position in the syringe barrel." Pet. 24 (citing Ex. 1003 ¶¶ 47–52, 121). As for timing, Petitioner further argues that "[t]he '631 Patent does not specify when the break loose force is measured (*i.e.*, storage time prior to testing)." *Id.*

Having reviewed the evidence of record, including the Specification of the '631 patent, we find Petitioner's proposed construction persuasive. *See* Ex. 1001, 5:15–21. Mr. Koller also persuasively shows that the term "stopper break loose force," would have been known in the art. Ex. 1003 ¶¶ 47–52; Ex. 1001, 5:34–45. Thus, based on the final record, we are persuaded by Petitioner's proposed construction. We do not find cause to limit the break loose force measurement to any specific time.

"Stopper Slide Force"

Claims 14–16 recite "a stopper slide force of less than" a specified amount. Petitioner also proposes construing the related term "stopper slide force" to mean "the force required to sustain movement of the stopper after

movement has already begun." Pet. 25 (citing Ex. 1003 ¶¶ 47–52, 121). As for timing, Petitioner further argues that "the '631 Patent does not specify when the stopper slide force is measured (*i.e.*, storage time prior to testing)." *Id.*

Mr. Koller has also persuasively shown that the term "stopper slide force," would have been known in the art. Ex. 1003 ¶¶ 47–52; Ex. 1001, 5:34–45. Based on the final record, we are persuaded by Petitioner's proposed construction. We do not find cause to limit the stopper slide force measurement to any specific time.

"Terminally Sterilized"

Petitioner proposes construing "terminally sterilized." Pet. 25. We agree with Petitioner that the term "terminally sterilized" should be construed because one issue in contention is whether or not the asserted prior art fully enables terminally sterilizing a VEGF antagonist-filled syringe for purposes of an obviousness analysis.

Petitioner first notes that "'[t]erminal sterilization' can refer to sterilizing both the drug product in the container and the surface of the container in a single process." *Id.* (citing Ex. 1003 ¶ 81). Petitioner contends that the '631 patent discloses that in its specific "terminal sterilisation" methods, "[t]he package is exposed to the sterilising gas until the outside of the syringe is sterile," but that "significant amounts of the sterilising gas should not enter the variable volume chamber of the syringe." *Id.* (quoting Ex. 1001 at 9:49–56; 10:2–4) (alteration in original). Petitioner, and Mr. Koller, conclude that "in the '631 Patent 'terminally sterilized' refers to a process whereby the outside of a pre-filled syringe is sterilized,

while contact between the sterilizing agent and the drug product within the syringe is minimized." *Id.* (citing Ex. 1003 ¶ 120).

The Specification explains that traditional "[s]terilisation can be achieved by terminal sterilisation in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas." Ex. 1001, 1:17–21. The Background section of the Specification also describes a goal "to ensure that while a suitable level of sterilisation is carried out, the syringe remains suitably sealed, such that the therapeutic is not compromised." *Id.* at 1:33–36. In the section of the Specification labeled "Sterilisation," it describes that "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 (H_2O_2) sterilisation process," and "[t]he package is exposed to the sterilising gas until the outside of the syringe is sterile." *Id.* at 9:48–56. Further, the Specification notes that significant amounts of the sterilizing gas should not enter the chamber and then defines what significant amounts encompass. *Id.* at 10:2–7.

Based on the final record, we are persuaded that a person of ordinary skill in the art would understand that the term "terminally sterilized," as used in the '631 patent, includes the sterilization of the outside of a 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. *See* Ex. 1003 ¶ 120. Notably, the '631 patent recognizes that some amounts of the sterilizing gas may interact with the ophthalmic solution so long as the amount does not "cause unacceptable

modification of the ophthalmic solution within the variable volume chamber." Ex. 1001, 10:5–7.

"About"

The claimed silicone oil ranges (claims 1, 3, 22), break loose force (claims 1, 14), stopper slide force (claims 14–16), and silicone oil thickness (claim 2) use the modifier "about." Petitioner notes that the '631 patent has provided its own definition for the term "about." Pet. 25 (quoting Ex. 1001, 10:24–29). Petitioner argues that for the term "about," it is unnecessary to determine "the outer boundaries of the claimed ranges (e.g., whether 'about 1 μg to 100 μg' encompasses 110 μg, 150 μg, etc.)." Pet. 25–26.

We disagree with Petitioner that it is unnecessary to determine the boundaries of the term "about," because the issue is before us for at least claim 14's requirement of "a stopper slide force of less than about 5N." We, however, agree with Petitioner's remaining argument that the term "about" in relation to a numerical value x is defined by the '631 patent to mean "for example, x±10%." Ex. 1001, 10:24–29.

D. Obviousness over Sigg, Boulange, and USP789

Petitioner asserts that claims 1–3, 5–9, 14–22, and 24 would have been obvious over Sigg, Boulange, and USP789. Pet. 26–54, 71–74; Pet. Reply 1–17, 21–27. Patent Owner disagrees. PO Resp. 8–39, 46–60; Sur-reply 1–27.

Based on our review of the parties' arguments and the cited evidence of record, we determine that Petitioner has met its burden of showing by a

preponderance of the evidence that claims 1–3, 5–9, 14–22, and 24 are unpatentable.

1. Sigg

Sigg is titled, "Surface Decontamination of Prefilled Containers in Secondary Packaging." Ex. 1007, code (54). Sigg is directed to "terminal-sterilization methods suitable for prefilled containers containing sensitive products, such as biotech (biological) drug solutions." *Id.* at 7:29–8:2. Sigg explains 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 1:5–7.

Sigg notes that prior art sterilization techniques like high temperature steam and gamma irradiation risked denaturing or chemically modifying biologic drug solutions. *Id.* at 2:20–29. To solve this problem, Sigg proposes "treatment of prefilled containers in secondary packaging by an application of vaporized-hydrogen peroxide, in which vapors are controllable by certain post-treatment measures." *Id.* at 8:8–13.

Sigg discloses two post-application methods for removing or inactivating the hydrogen peroxide residue and thereby preventing the hydrogen peroxide from leaching into the pre-filled syringe: application of a vacuum to reverse the direction of vapor flow, and inactivation of the hydrogen peroxide vapors. *Id.* at 3:19–30, 14:9–23. Sigg provides Example 1, which discloses vaporized H_2O_2 (VHP) sterilization of 0.5 mL syringes filled with a protein solution such as the anti-VEGF antibody ranibizumab intended for intravitreal injection. *Id.* at 20:10–21:11, 9:11–14;

Ex. 1003 ¶ 123. The results showed that with respect to byproducts and degradation products "there were no differences between the results of the untreated syringes and with hydrogen-peroxide treated syringes." Ex. 1007, 21:2–3.

2. Boulange

Boulange is titled "Medical Device and Smooth Coating Therefor." Ex. 1008, code (54). Boulange discloses several syringes, including pre-filled syringes. *Id.* at code (71), 14:19–21. Boulange also discloses a series of examples in which the break loose and glide forces of syringes internally coated with silicone oil are compared to un-siliconized syringes. *Id.* at 18:15–19:10.

Boulange relates "to a medical device, for example a syringe, comprising at least one smooth coated part, [] for example a container and/or a piston, said parts being able to move one relative to the other, for example translationally and/or rotationally, when the medical device is operated." *Id.* at 1:3–7. Boulange discloses a pre-filled syringe with decreased silicone oil to limit the risk of interaction between the silicone oil and any drug stored in the syringe. *Id.* at 6:10–32 ("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"). Boulange further discloses that the pre-filled syringe has decreased break loose (activation) and slide (sustainable) forces while preserving a tight seal between the piston and barrel. *Id*.

Boulange describes tests conducted to evaluate break loose and slide forces on 1 mL pre-filled glass syringes with different piston (stopper)

configurations—labeled as A, B1, B2, and C, in Table 1 ("configurations of pistons"). *Id.* at 14 ("Table 1"), 13:11–12 ("[C]ontainer 2 is a glass syringe body accommodating a piston 3"), 14:19–21 ("tests were applied on containers filled with 1 mL of demineralised water"). "Regarding the coated pistons, several surface finishes or roughnesses of the outer surface of coating were tested, as summarized in Table 1 below." *Id.* at 13:19–21.

Table 1 : configurations of pistons A, B1 and C

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 = 3.1 µm Rt = 24.0 µm
C (comparative)	Chlorobutyl rubber	No	---	Smooth Ra = 0.7 µm Rt = 11.0 µm

Table 1 from Boulange shows configurations of pistons A, B1, and C, with column headings of "Viscoelastic substrate," "Coating," "Coating thickness," and "Surface finish." Ex. 1008, 14.

Boulange discloses measurements of "friction force B," which corresponds to the claimed break loose force. *Id.* at 15:6–8 ("the force required, under static conditions, to break the contact . . . between the piston 3 and the container 2"). Boulange also discloses forces S and F, which are slide forces measured at different stopper positions. *Id.* at 15:9–11 ("S is the force . . .

for moving the piston 3 . . . measured half way of the piston travel."), 15:13–16 ("F is the force . . . to move the piston 3 when it reaches the end of its travel").

Boulange provides "Example 5," wherein the forces with silicone oil either baked on ("Scenario 1") or sprayed on ("Scenario 2") to the syringe barrel are measured. Ex. 1008, 20:13–21. Boulange discloses baked-on silicone oil was applied to the barrel at "a rate of 40 μg for a surface area of 10 cm^2," while spray-on silicone was applied "at a rate of 500 μg for a surface area of 10 cm^2." *Id.* at 20:15–21. Boulange's Table 7 discloses that Pistons A and C had certain break loose and slide forces with the baked-on syringes when tested unaged (T=0), while Piston B1 had break loose and slide forces less than 5 N for both the unaged (T=0) and aged (T=1) syringe. *Id.* at 21.

Boulange tested syringes with baked-on silicone oil, where the pistons (A, B1, and C) were also coated with silicone oil. For those syringes, Table 5 discloses break loose and slide forces for Pistons B1 and C for both unaged (T=0) and aged (T=1) syringes.

Table 5 : Activation Gliding Forces, Pistons A, B1 and C

Silicone/internal surface of container		4 µg/cm²			4 µg/cm²			4 µcm²		
Silicone/piston		5 µg/cm²			15 µg/cm²			50 µg/cm²		
Force (N)		B	S	F	B	S	F	B	S	F
Piston	$A_{T=0}$	6.6 (0.6)	5.8 (1.0)	4.7 (1.0)	7.2 (0.5)	6.9 (1.9)	4.7 (1.9)	6.6 (0.8)	6.5 (1.5)	4.0 (1.5)
	$A_{T=1}$	12.0 (2.3)	8.4 (2.0)	3.2 (1.3)	11.0 (0.8)	8.0 (1.9)	3.3 (1.0)	10.7 (1.2)	6.7 (1.5)	3.6 (1.7)
	$B1_{T=0}$	2.2 (0.2)	2.7 (0.4)	2.7 (0.4)	2.2 (0.2)	3.0 (0.6)	3.0 (0.6)	2.1 (0.1)	2.6 (0.5)	2.6 (0.5)
	$B1_{T=1}$	2.8 (0.3)	4.3 (1.2)	4.3 (1.2)	2.6 (0.6)	3.3 (0.3)	3.3 (0.3)	2.5 (0.2)	3.4 (0.3)	3.4 (0.3)
	$C_{T=0}$	4.7 (0.4)	6.5 (0.6)	4.6 (0.6)	4.2 (0.3)	6.0 (0.7)	4.2 (0.7)	3.9 (0.5)	5.2 (0.7)	4.0 (0.7)
	$C_{T=1}$	8.4 (0.6)	8.3 (1.9)	4.1 (1.6)	7.5 (0.6)	8.3 (1.4)	4.8 (2.2)	7.8 (1.1)	6.2 (1.0)	3.7 (1.5)

Petitioner's highlighted Table 5 of Boulange depicts activation and gliding forces for pistons A, B1, and C. Pet. 31; Ex. 1008, Table 5.

3. USP789

USP789 is a monograph in United States Pharmacopeia. Ex. 1019. USP789 is a well-known standard in the art for ophthalmic solutions. Pet. 36, 45, 59. Mr. Koller testifies that "[t]he applicable limits on particulate content are set forth in USP789." Ex. 1003 ¶ 90 & n.10 ("USP is a nonprofit scientific organization founded in 1820 that develops and disseminates public compendial standards for drug products."). According to Mr. Koller, although "the USP is not legally binding, it was well known in the art that USP specifications are de facto requirements for regulatory approval of a drug product." *Id.* ¶ 92 (citing Ex. 1057, 1). Further, Mr. Koller opines that "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." *Id.* USP789 is also mentioned in the '631 patent, "[i]n one embodiment, the

syringe has low levels of silicone oil sufficient to meet USP789." Ex. 1001, 2:1–4, 6:15–30.

According to USP789, ophthalmic solutions are required to contain fewer than 50 particles per mL ≥ 10 μm, fewer than 5 particles per mL ≥ 25 μm, and fewer than 2 particles per mL ≥ 50 μm. Ex. 1019, 6 (citations to added pagination). "Every ophthalmic solution . . . is subject to the particulate matter limits set forth . . . unless otherwise specified." *Id.* at 5.

Petitioner relies on USP789 to demonstrate that a POSITA would have known that Sigg and Lam were required to meet the claimed particle amounts. Pet. 21 n.7. "Petitioner does not believe that USP789 needs to be listed in Grounds 1-10," but nonetheless includes this reference in each ground, "if necessary." *Id.* For example, Petitioner alleges that "[a] POSITA would understand that ranibizumab solution disclosed in Sigg is an ophthalmic solution," and as such, "when making a pre-filled syringe as disclosed in Sigg, a POSITA would have been motivated to comply with the prior art particulate requirements for ophthalmic solutions set forth in USP789." Pet. 36.

Patent Owner notes that it "accepts Petitioner's position that it did not need to list USP 789 in its Grounds because Sigg discloses an 'ophthalmic solution' and a POSA would have understood that USP 789 is a 'de facto requirement for regulatory approval' of an ophthalmic solution." PO Resp. 19 n.3 (quoting Ex. 1003 ¶ 92).

We include USP789 in each asserted ground for clarity and because at least one argument made by Patent Owner relates to USP789.

4. Independent Claim 1

Below, we first set forth Petitioner's arguments and evidence. Next, we examine Patent Owner's arguments and evidence. In the following section, we examine each parties' evidence and argument related to the objective indicia of nonobviousness. Finally, we provide our analysis by examining the totality of the evidence and argument before us. As explained more below, Petitioner has shown by a preponderance of the evidence that claim 1 would have been obvious over Sigg, Boulange, and USP789.

a) Petitioner's Arguments

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

Petitioner contends Sigg discloses terminal sterilization of pre-filled syringes for intravitreal injection. Pet. 40–41 (citing Ex. 1007, 2:15–19 ("[T]here is a strong market need for terminally antimicrobially-treated [*i.e.* sterilized] medical devices, such as prefilled syringes used for intravitreal injections."), 3:8–19, 9:4–14, 12:15–16:21, 20:10–21:11; Ex. 1003 ¶¶ 188–189).

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

Petitioner relies on Figure 1 of Sigg as evidence of the claimed structure, whereas Figure 1 shows a barrel, stopper, and plunger. Pet. 41 (citing Ex. 1003 ¶ 190).

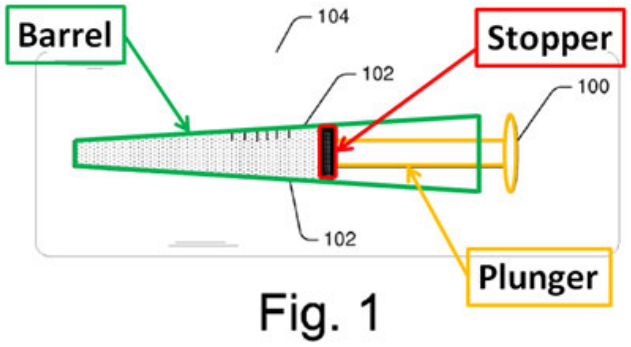

Fig. 1

Petitioner's annotated and highlighted Figure 1 of Sigg, with the barrel labeled in green, the plunger labeled in yellow, and the stopper labeled in red. Pet. 41.

For the "glass body" limitation, Petitioner argues that it would have been obvious to use a glass barrel in Sigg because it was a known design option for ranibizumab and was known to be impermeable to sterilizing gasses. Pet. 41 (citing Ex. 1003 ¶¶ 124, 191; Ex. 1002, 1274–75 (Patent Owner explaining during prosecution that "syringes which are prefilled with biologics are comprised of glass barrels.")).

Alternatively, Petitioner argues that "Boulange discloses a syringe comprising a glass barrel and a piston (*i.e.*, stopper)." Pet. 41–42 (citing Ex. 1008, 9:21–35, 13:11–12; Ex. 1003 ¶ 192). Petitioner contends that "a POSITA would understand that the stopper would be coupled to a plunger to enable the user to advance the stopper during use." Pet. 42 (citing Ex. 1003 ¶ 193). Mr. Koller provides an annotated Figure 2 of Boulange showing where the plunger would be coupled to the stopper. Ex. 1003 ¶ 193.

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

Sigg discloses a pre-filled syringe containing an ophthalmic solution

comprising ranibizumab, which is one of the three VEGF-antagonists identified in the '631 patent. Pet. 43 (citing Ex. 1007, 9:11–14 ("[T]he drug product is a protein solution, such as ranibizumab."); *see also id.* at 20:17–21, 24:21–22, 26:10–11; Ex. 1003 ¶¶ 194–195).

[1.d] (a) the syringe has a nominal maximum fill volume of between about 0.5 ml and about 1 ml

Petitioner relies on teachings from both Sigg and Boulange for this limitation. Pet. 43–44. Petitioner notes that Sigg discloses a syringe with a nominal maximum fill volume of 0.5 mL. Pet. 43 (citing Ex. 1007, 20:20–21 ("Filling of 0.5 mL syringes was performed in a sterile lab.")). Relying on the testimony of Mr. Koller, Petitioner contends that "[i]t also would have been obvious to use a 0.5 to 1 mL syringe for ranibizumab because only a small volume of fluid can be injected intravitreally." *Id.* (citing Ex. 1003 ¶¶ 196; Ex. 1031 ¶ 27; Ex. 1027, 1 (2010 Lucentis Label describing injection of 0.05 mL of solution)).

Petitioner additionally argues that "Boulange discloses a syringe with a nominal maximum fill volume of 1 mL." Pet. 43 (citing Ex. 1008, 14:19–21 ("Activation Gliding Force (AGF) tests were applied on containers filled with 1 mL of demineralised water."); Ex. 1003 ¶ 197). According to Petitioner, and Mr. Koller, "[a] POSITA would also understand that 'a surface area of 10 cm^2, disclosed in Boulange is the approximate inner surface area of a 1 mL syringe." *Id.* at 43–44 (citing Ex. 1008, 20:15–17; Ex. 1003 ¶¶ 197–198).

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

Petitioner relies on the teachings of Boulange for this limitation. Pet. 44. According to Petitioner, "Boulange discloses that for the syringes with baked-on silicone oil, 40 μg was deposited (*i.e.*, applied) to an internal surface area of 10 cm^2 (*i.e.*, 4 μg/cm2)." *Id.* (citing Ex. 1008, 20:15–17 ("[S]ilicone 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."), 21:1–3 (Table 7 disclosing "4 μg/cm^2" for Scenario 1); Ex. 1003 ¶¶ 199–202. Petitioner relies on Mr. Koller's calculations and concludes that "[a] POSITA would understand that the rate of application disclosed in Boulange (4 μg/cm^2) would apply to other syringe sizes, and would result in approximately 28 μg of silicone oil for a 0.5 mL syringe." Pet. 44 (citing Ex. 1003 ¶ 200 ("Thus, at a rate of 4 μg/cm^2, a total of 27.8, or ~28, μg of silicone oil, would be applied for a 0.5 mL standard syringe as disclosed in Sigg using the method of Boulange.")).

[1.f] (c) the VEGF-antagonist solution comprises no more than 2 particles >50 μm in diameter per ml

As noted above, this particulate content limitation relies on the industry standard set forth in USP789. Ex. 1003 ¶¶ 90–92. Petitioner contends that "[a] POSITA would understand that an ophthalmic solution, as disclosed in Sigg, should meet USP789, including comprising no more than 2 particles >50 μm in diameter per ml." Pet. 44–45 (citing Ex. 1003 ¶¶ 60–61, 66, 161, 165, 195, 203–205). Petitioner further contends that

a POSITA would have had a reasonable expectation that

> combining Sigg and Boulange would satisfy USP789 given that Boulange discloses a pre-filled syringe with less than 50 μg of silicone oil and is designed to "limit the risk of interaction between a lubricant, for example silicone oil, and the therapeutic molecules potentially stored in the container."

Pet. 45 (citing Ex. 1008, 6:26–29; Ex. 1003 ¶ 206).

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

Petitioner contends that "Boulange discloses a stopper break loose force less than 11 N." Pet. 45 (citing Ex. 1003 ¶¶ 207–209). Petitioner relies on two unique stoppers, either of which would allegedly be acceptable for the combination – stopper B1 (Parylene-C)[17] and stopper C. Pet. 37 ("Boulange discloses multiple stopper configurations that a POSITA would have been motivated to combine with Sigg."), 38–39 (examining stopper C), 45–47; *See* Tr. 10:1–19 ("Either stopper would be considered acceptable for this combination.")

Relying on the testimony of Mr. Koller, Petitioner argues that a person of ordinary skill in the art would have been motivated to utilize stopper C in Table 5 of Boulange. Pet. 38. Petitioner recognizes that "Boulange states that stopper C in Table 7 'does not appear to be acceptable for a medical device,'" but Petitioner explains that person of ordinary skill in the art "would have understood that is because stopper C in Table 7 did not

[17] Because we determine Petitioner's arguments and evidence related to stopper C of Boulange are sufficient to ultimately prove by a preponderance of the evidence that claim 1 is unpatentable, we focus on each party's arguments and evidence related to stopper C, and not stopper B1.

include any coating." *Id.* at 38–39 (citing Ex. 1003 ¶ 181). Mr. Koller relies on Table 5 of Boulange, set forth below, which "discloses break loose forces (B) of less than about 11N for stoppers that were coated with silicone oil[] and tested with baked-on syringes having 40 µg of silicone oil (*i.e.*, 4 µg/cm^2):" Ex. 1003 ¶ 208.

Table 5 : Activation Gliding Forces, Pistons A, B1 and C

Silicone/internal surface of container		4 µg/cm²			4 µg/cm²			4 µcm²		
Silicone/piston		5 µg/cm²			15 µg/cm²			50 µg/cm²		
Force (N)		B	S	F	B	S	F	B	S	F
Piston	$A_{T=0}$	6.6 (0.6)	5.8 (1.0)	4.7 (1.0)	7.2 (0.5)	6.9 (1.9)	4.7 (1.9)	6.6 (0.8)	6.5 (1.5)	4.0 (1.5)
	$A_{T=1}$	12.0 (2.3)	8.4 (2.0)	3.2 (1.3)	11.0 (0.8)	8.0 (1.9)	3.3 (1.0)	10.7 (1.2)	6.7 (1.5)	3.6 (1.7)
	$B1_{T=0}$	2.2 (0.2)	2.7 (0.4)	2.7 (0.4)	2.2 (0.2)	3.0 (0.6)	3.0 (0.6)	2.1 (0.1)	2.6 (0.5)	2.6 (0.5)
	$B1_{T=1}$	2.8 (0.3)	4.3 (1.2)	4.3 (1.2)	2.6 (0.6)	3.3 (0.3)	3.3 (0.3)	2.5 (0.2)	3.4 (0.3)	3.4 (0.3)
	$C_{T=0}$	4.7 (0.4)	6.5 (0.6)	4.6 (0.6)	4.2 (0.3)	6.0 (0.7)	4.2 (0.7)	3.9 (0.5)	5.2 (0.7)	4.0 (0.7)
	$C_{T=1}$	8.4 (0.6)	8.3 (1.9)	4.1 (1.6)	7.5 (0.6)	8.3 (1.4)	4.8 (2.2)	7.8 (1.1)	6.2 (1.0)	3.7 (1.5)

Mr. Koller provides annotated Table 5 depicting activation gliding forces for pistons A, B1, and C with added yellow highlights for certain break loose forces (B) in the 4 µg/cm^2 column. *Id.*

Mr. Koller explains that "Table 5 of Boulange discloses stoppers siliconized with 5 µg/cm2 of silicone oil." *Id.* ¶ 208 n.23. Petitioner argues that "Table 5 likewise discloses break loose forces less than 11N for the baked-on syringes with 40 µg of silicone oil (4 µg/cm2) for stoppers B1 and C at T=0 and T=1." Pet. 46.

Petitioner concludes that "[a] POSITA would understand that the break loose forces disclosed in Table 5 and 7 of Boulange would remain the same even with a ranibizumab solution contained in the syringe instead of water because the break loose force is independent of the viscosity of the

fluid." Pet. 47 (citing Ex. 1003 ¶ 209).

Reasons for Combining

> Petitioner contends that
>
> [a] POSITA would have been motivated to combine Sigg with Boulange to minimize the amount of silicone oil in Sigg's terminally sterilized pre-filled syringe, which would reduce the risk of interaction between the silicone oil and drug product, and minimize the amount of silicone oil that could be transferred to the patient's eye upon administration.

Pet. 31 (citing Ex. 1003 ¶¶ 128, 145–147, 159–167). According to Petitioner and Mr. Koller, "[a] POSITA would have understood that a lubricant is required on the syringe barrel to enable movement of the stopper, and that baked-on and spray-on siliconization were the two known application options." *Id.* (citing Ex. 1003 ¶¶ 54–71). Petitioner reasons that "the combination of Sigg with Boulange also would have been obvious as the use of a known technique (baked-on siliconization) to a known device (pre-filled syringe) that yields a predictable result (reduced amount of silicone oil)." Pet. 31–32 (citing Ex. 1003 ¶ 163).

Petitioner also relies on substantial testimony and evidence showing the known risks of silicone oil for drug products in general, and specifically for intravitreal injections. Pet. 32 (citing Ex. 1003 ¶¶ 159–162; Ex. 1015, 330; Ex. 1013, 4; Ex. 1012, 6). Petitioner contends that "it was well-known that injecting silicone oil into a patients' eye can cause complications," including persistent elevations in intraocular pressure. *Id.* (citing Ex. 1003 ¶¶ 61, 66, 161; Ex. 1025, 11). Petitioner alleges that "by 2010 that it was desirable to minimize the amount of silicone oil in syringes used for

intravitreal injection." Pet. 32–33 (citing Ex. 1067, 5; Ex. 1080, 2; Ex. 1003 ¶¶ 159–167).

Based on this evidence and reasons for minimizing the risks of silicone oil for intravitreal injections, Petitioner contends

> a POSITA would have looked to Boulange because it discloses that "it is possible to decrease the total amount of lubricant, for example silicone oil, that is necessary" and limits "the risk of interaction between . . . silicone oil, and the therapeutic molecules potentially stored in the container of the medical device."

Pet. 33 (quoting Ex. 1008, 6:23–29). For these reasons, Petitioner contends that "a POSITA would have been motivated to use the baked-on syringes in Boulange, which utilized approximately one-tenth the silicone oil quantity of sprayed-on syringes, while retaining low break loose and slide forces and a tight seal between the stopper and the barrel." *Id.* at 33–34 (citing Ex. 1003 ¶¶ 163, 185–186).

Petitioner further contends that "[a] POSITA would have had a reasonable expectation of success that the combination of Sigg and Boulange would result in a terminally sterilized pre-filled syringe having silicone oil and forces within the claimed ranges." Pet. 34 (citing Ex. 1003 ¶¶ 182–187). Petitioner provides several reasons, including "Boulange explicitly discloses a 1 mL glass syringe with 40 μg silicone oil (*i.e.*, 4 μg/cm^2) and resulting break loose and slide forces of less than 11N and 5N." *Id.* (citing Ex. 1008, 20:15–21:14). Petitioner notes that "[i]t was known that baked-on siliconization applies one-tenth the amount of silicone oil relative to spray-on siliconization (*e.g.*, 40 μg versus 500 μg for a 1.0 mL

syringe) with comparable break loose and slide forces," and as such "the claimed forces are nothing more than the quantification of the results of a known process and cannot be used to argue non-obviousness." *Id.* (citing Ex. 1003 ¶¶ 63–71, 182–183). Petitioner also argues "a POSITA would not expect incompatibility between the VHP[18] terminal sterilization disclosed in Sigg and the baked-on syringe disclosed in Boulange," because "Sigg discloses that its VHP process is broadly applicable to pre-filled syringes, and does not affect the contents of the container." *Id.* (citing Ex. 1003 ¶¶ 184–186; Ex. 1007, 9:16–17, 14:27–15:20). "Thus," Petitioner concludes that "a POSITA would have understood that Sigg's terminal sterilization would not impact the siliconization levels or the forces of Boulange because Sigg's VHP method prevents the sterilizing gas from ingressing into the syringe." Pet. 34–35 (citing Ex. 1003 ¶ 184).

Petitioner reasons that "Boulange clearly discloses a pre-filled syringe suitable for Sigg's terminal sterilization method." Pet. 35. Mr. Koller testifies that it was standard in the art to design pre-filled syringes to be gas-tight to protect the drug product from degradation during its shelf life. Ex. 1003 ¶ 172. Petitioner also relies on the teachings of Boulange to show that "a POSITA would have readily understood that Boulange's syringe is designed to be gas-tight, which would prevent any sterilizing gas from entering the syringe," because "Boulange describes 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

[18] VHP stands for vaporized hydrogen peroxide (H_2O_2).

region between said two parts.'" Pet. 35 (quoting Ex. 1008, 6:10–14) (citing Ex. 1003 ¶¶ 172, 184–186). Petitioner also notes that "Boulange explicitly discloses that its syringe can accommodate a drug product in a gaseous phase," thus demonstrating "that Boulange's syringe was sufficiently tight to prevent gas from exiting or entering the syringe." *Id.* (citing Ex. 1008, 1:14–16; Ex. 1003 ¶¶ 172, 184–186).

As for the motivation to combine Sigg and Boulange with USP789 to arrive at the claimed particulate content, Petitioner contends "[a] POSITA would understand that ranibizumab solution disclosed in Sigg is an ophthalmic solution," and as such, "when making a pre-filled syringe as disclosed in Sigg, a POSITA would have been motivated to comply with the prior art particulate requirements for ophthalmic solutions set forth in USP789." Pet. 36 (citing Ex. 1003 ¶¶ 90–92, 122–123, 168).

Petitioner also alleges that the person of ordinary skill in the art "would have expected to succeed in combining Sigg and Boulange to meet USP789 requirements." *Id.* Petitioner states that "Boulange discloses a pre-filled syringe with silicone oil amounts within the claimed ranges," and "a POSITA would have reasonably expected that the combination of Sigg and Boulange would result in a terminally sterilized pre-filled glass syringe having the claimed silicone oil content and operational forces in conjunction with a VEGF antagonist (*i.e.*, ranibizumab) solution that meets USP789." *Id.* (citing Ex. 1003 ¶¶ 168–170).

Petitioner next argues that although "[t]he '631 Patent includes no limitations regarding the lubrication or coating for the stopper, Boulange discloses multiple stopper configurations that a POSITA would have been

motivated to combine with Sigg." Pet. 37. These include stopper C in Table 5 of Boulange. Pet. 38. Petitioner contends that "a POSITA would have been motivated to utilize stopper C in Table 5 of Boulange." Pet. 38. Petitioner acknowledges that "[a]lthough Boulange states that stopper C in Table 7 'does not appear to be acceptable for a medical device,' a POSITA would have understood that is because stopper C in Table 7 did not include any coating." Pet. 38–39 (quoting Ex. 1008, 21:4–5) (citing Ex. 1003 ¶ 181). Mr. Koller testifies that "[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." Ex. 1003 ¶ 181 n.20 (citing Ex. 1008, 21:4–14). Petitioner notes that "[i]n contrast, Table 5 discloses stopper C with a coating of silicone oil (5 μg/cm^2), which was conventional in the art." Pet. 39 (citing Ex. 1003 ¶¶ 178–180). Petitioner further recognizes that "Boulange describes that stopper C in Table 5 was 'markedly inferior' to stopper B1 (Ex. 1008 at 19:6–7)," but Petitioner contends "a POSITA would have understood that the resulting break loose and slide forces for stopper C would have been suitable for intravitreal injection." Pet. 39 (citing Ex. 1003 ¶¶ 178–180; Ex. 1001, 5:31–36 (acknowledging that known pre-filled syringes used for intravitreal injection had forces less than 20 N)). Mr. Koller testifies that "the results for Configuration C in Table 5 are consistent with typical industry expectations," and "[t]he results for Stopper C in Table 5 are substantially less than 20 N." Ex. 1003 ¶ 180.

Based on this evidence and testimony, Petitioner argues that "Boulange's statement that stopper C in Table 5 is inferior cannot constitute

teaching away of the *claimed invention* because the forces for stopper C are well within the ranges claimed." Pet. 40 (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.").

b) Patent Owner's Arguments

Patent Owner does not necessarily challenge whether the individual references in the combination teach each element of claim 1. *See* PO Resp. 8–25. Instead, Patent Owner makes several arguments directed to the combination of references. *See id.* First, Patent Owner argues a person of ordinary skill in the art (POSITA) would not have been motivated to combine Sigg and Boulange to arrive at the claimed invention because of the force profile of Boulange syringe (stopper) C and because Boulange teaches away from Syringe C. *Id.* at 13–18. Further, Patent Owner contends a POSITA would not have been motivated to use a solution having no more than two particles greater than 50 μm in diameter per mL. *Id.* at 18–20. Patent Owner argues a POSITA would not have had a reasonable expectation of success because they would not have reasonably expected Boulange's syringes to be compatible with VHP. *Id.* at 20–25. Patent Owner also argues that Petitioner has failed to show that Sigg enables a sterilization method for a PFS. *Id.* at 25–32. Patent Owner relies heavily on several declarants as discussed below. We highlight each of Patent Owner's

contentions in turn.[19]

Patent Owner notes that a POSITA would have balanced the need to minimize silicone oil "with more pressing concerns, such as ensuring that (1) the PFS had sufficiently low break loose forces that remained consistent over time; (2) the VEGF-antagonist did not degrade; and (3) potentially toxic substances were not introduced into the patient's eye." PO Resp. 9; *see also* Tr. 50:1–3 ("For intravitreal injection a person of skill in the art would want a syringe where the forces were low and consistent over time." (citing Ex. 2204 ¶¶ 67, 70, 99) (Declaration of Andrew F. Calman, M.D., Ph.D)).

i. Force Profile of Syringe (Stopper) C

Patent Owner contends that a POSITA "would not have been motivated to use Boulange Syringe C in a PFS for intravitreal administration of a VEG-F antagonist because Syringe C has inconsistent forces that increase over time." PO Resp. 8. Patent Owner notes that Boulange makes disparaging statements about stopper C and the data shows that its forces are inconsistent and increasing with time. *Id.* at 13–14. Patent Owner argues that a POSITA "would have known that a PFS for intravitreal injection must maintain consistent, low break loose forces over time to avoid injuring a patient's eye," and Boulange emphasizes the importance of maintaining forces over time, even after storage. *Id.* at 14 (citing Ex. 2204 ¶¶ 67, 70, 99; Ex. 1008, 6).

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[19] As noted above, because we do not rely on Petitioner's arguments related to Boulange stopper (syringe) B1 (containing Parylene-C), we do not address Patent Owner's arguments related to the same.

Examining Boulange Table 5, Patent Owner argues that "while the break loose force for Syringe C was initially 4.7 N, it nearly doubled to 8.4 N within just one month of accelerated storage, which simulated three months of actual storage time." PO Resp. 14 (citing Ex. 1008, 21). Patent Owner alleges that because of this force profile (4.7 to 8.4 N), "Boulange characterizes Syringe C as 'markedly inferior' and not 'acceptable for a medical device.'" *Id.* (quoting Ex. 1008, 19:7, 21:4–5).

Patent Owner contends "that the break loose forces for Syringe C in Table 7 and Table 5 were essentially identical, showing that that the statement of discouragement logically applied to both." PO Resp. 15 (citing Ex. 2001 ¶ 89–90) (Declaration of Karl Leinsing). Patent Owner argues that "[g]iven the data in Table 5 and Boulange's explicit statements, a POSA would not have been motivated to use Syringe C in combination with Sigg." *Id.* Further, Patent Owner notes "that even if the forces were 'acceptable' at T_0 and T_1, as Mr. Koller argues (Ex. 1003 ¶179), Syringe C could not be used for a PFS for intravitreal injections because the forces are inconsistent over time and may continue to rise over the shelf life of the PFS." *Id.* (citing Ex. 2204 ¶ 72; Ex. 2201 ¶¶ 43–44) (Supplemental Declaration of Karl Leinsing); *see also* Tr. 48:19–49:25 ("[T]he question about the change from 4.7 to 8.4, . . . it's not acceptable because of the one-month aging change. So the magnitude, it's not the magnitude of the numbers, it's the fact that they jump up over one month that Boulange . . . says it's markedly inferior."). For these reasons, Patent Owner argues "[c]onsidered as a whole, Boulange teaches away from Syringe C," and "Boulange would have discouraged a POSA from using Syringe C in a PFS," thus, "Petitioner's

argument that a POSA would have been motivated to combine Syringe C with Sigg must fail." PO Resp. 16, 18 (citing Ex. 2201 ¶ 38–46).

ii. 2 particles > 50 μm in diameter per ml

As noted above, Petitioner relies on the industry standard set forth in USP789 to teach the claim requirement of "2 particles > 50 μm in diameter per ml" (particulate content limitation). *See* Pet. 44–45 ("POSITA would understand that an ophthalmic solution, as disclosed in Sigg, should meet USP789, including comprising no more than 2 particles >50 μm in diameter per ml."). Patent Owner disagrees with this conclusion and argues that "even if a POSA would have been motivated to comply with USP 789, that does not mean the POSA would have been motivated to meet this claim limitation," because USP789 does not require an ophthalmic solution to meet this particulate content limitation. PO Resp. 19 (citing Ex. 2189, 205:17–20; 208:15–209:6; Ex. 1003 ¶ 205).

Patent Owner contends that "USP 789 provides a two-stage test approach," and only ophthalmic solutions that fail the first test (no more than 50 particles greater than or equal to 10 μm in diameter per mL) are required to pass the microscopic method test (the requirement of having no more than 2 particles greater than or equal to 50 μm in diameter per mL). *Id.* (citing Ex. 1019, 5–6; Ex. 2189, 204:1–205:20). Patent Owner relies on the statement in USP789 that "[i]t is expected that most articles will meet the requirements on the basis of the light obscuration test alone." *Id.* (quoting Ex. 1019, 5). Patent Owner further argues "Petitioner has provided no motivation for a POSA to have met this claim element," because Petitioner has not explained "why a POSA would have anticipated that the VEGF-

antagonist solution of Sigg would be among the minority of solutions that fail the first test and are thus subject to the second test with its additional requirement." PO Resp. 20 (citing Ex. 2201 ¶¶ 82–84). Mr. Leinsing similarly testifies that "having fewer than 2 particles greater than 50 μm in diameter per milliliter is not a requirement," and "USP789 only has a specific limit on particles greater than 50 μm in diameter for solutions that fail to satisfy the light obscuration test." Ex. 2201 ¶¶ 82–84.

iii. Reasonable Expectation of Success – Compatibility of Boulange's Syringes with VHP

Patent Owner questions whether Boulange's syringe could withstand terminal sterilization with VHP when filled with a VEGF-antagonist solution and contends Petitioner failed to establish a reasonable expectation of success. PO Resp. 20. Patent Owner relies on Mr. Koller's cross examination testimony and argues that "not every combination of barrel and stopper would work to protect a sensitive drug product." *Id.* (citing Ex. 2189, 92:4–93:8). Mr. Leinsing testifies that terminal sterilization with VHP is conducted under vacuum and extreme pressure, which can permit gas to pass between the syringe barrel and stopper in a way that does not occur under standard pressure conditions. *See* Ex. 2201 ¶ 49. He further notes that "Boulange mentions nothing about using VHP to sterilize its syringes," and "[n]othing in Boulange suggests that the authors had considered terminal sterilization of any of the syringes they used, or that the syringes would be suitable for terminal sterilization." *Id.* ¶ 65. Mr. Leinsing concludes that "[a] POSA would not assume that any syringe was compatible with VHP sterilization unless specifically designed for that

purpose." *Id.*

Patent Owner examines and challenges evidence relied on by Mr. Koller from Boulange that relates to whether a POSITA would have sterilized the syringe by a VHP method. PO Resp. 21–23. Patent Owner first argues that the statement in Boulange that "possible degradation is sometimes initiated by the processes used to sterilize the medical devices containing them," refers only to degradation of the piston, or the stopper, and not the drug product stored in the syringe. *Id.* at 22 (citing Ex. 2189, 182:8–15; Ex. 2201 ¶ 131; Ex. 1008, 4:3–5). Next, Patent Owner addresses Mr. Koller's testimony related to a statement in Boulange that "tightness in the region of contact between the piston and the container can be guaranteed to be maintained." *Id.* (quoting Ex. 1003 ¶ 172 (citing Ex. 1008, 3:20–27)). Patent Owner contends that this statement "has nothing to do with ingress of gases, but rather refers to the ability to ensure that liquid drug product 'escapes only via the distal end of the container' and does not leak out of the back during injection." *Id.* (quoting Ex. 1008, 3:20–27, 6:10–22). Thus, according to Patent Owner, "[a] POSA would have understood that a syringe must be significantly tighter to prevent gaseous ingress during terminal sterilization by VHP than merely to prevent liquid drug product from leaking out." *Id.* (citing Ex. 2201 ¶ 54). Patent Owner argues that other similar statements in Boulange convey "nothing about the syringe's ability to preserve the medical product if sterilized with VHP or other sterilizing gases." *Id.* at 23–24. Patent Owner concludes that "without any indication that Boulange's syringe was designed to permit terminal sterilization by sterilizing gases, a POSA would have had no reason to expect that it would

be among the 'very few' syringes tight enough to be amenable to such a process." *Id.* at 24–25 (citing Ex. 2201 ¶ 129).

iv. Enablement of Sigg's VHP Method

Patent Owner contends that Sigg is not self-enabled because it fails to identify any syringe designs that can withstand its VHP method, and, neither Mr. Koller's opinions nor the prior art cited by Petitioner supports enablement. PO Resp. 25. Patent Owner, and its declarant, both contend that because "VHP sterilization is performed under vacuum and subjects the PFS to extreme pressure," an enabling disclosure must teach a person of ordinary skill in the art "how to design a syringe for these circumstances." *Id.* at 26 (citing Ex. 2201 ¶¶ 51, 93; Ex. 2189, 51:14–51:13).

Patent Owner dismisses Mr. Koller's opinion that "it was conventional that a pre-filled syringe should be gas-tight to protect certain drug products from exposure to oxygen and degradation," because "[t]he issue facing the POSA was not how to prevent ingress of oxygen during *normal storage conditions*; it was how to prevent ingress of sterilizing gas under the *extreme conditions* of VHP." *Id.* Patent Owner presents additional evidence alleging [redacted] *Id.* (citing Ex. 2140, 2; Ex. 2206 ¶¶ 33, 40 (Declaration of Juergen Sigg, Ph.D)). Patent Owner makes a similar argument with respect to [redacted] *Id.* at 27 (citing Ex. 2140, 2; Ex. 2206 ¶¶ 33, 40). According to Patent Owner, the "evidence demonstrates that a POSA would have had to

engage in undue experimentation to identify a PFS that could be terminally sterilized using Sigg's VHP method without unacceptably modifying the VEGF-antagonist solution in the syringe." *Id.*

Patent Owner questions Mr. Koller's testimony related to enablement based on the 2008 Macugen Label because "that label does not show the Macugen PFS design, does not state that the product was terminally sterilized, and does not disclose the sterilization technique used." *Id.* at 28 (citing Ex. 2189, 186:18–187:3; 196:12–21; Ex. 2001 ¶ 99); *see also* Tr. 52:19–53:2. Patent Owner argues that the description of a "sterile foil pouch" does not necessarily suggest to a POSITA that Macugen PFS was terminally sterilized because a product does not have to be terminally sterilized to receive the label "sterile." PO Resp. 28 (quoting Ex. 2189, 186:18–186:22) (citing Ex. 2203 ¶ 102 (Declaration of Michael Miller, Ph.D); Ex. 2201 ¶ 115). Thus, Patent Owner concludes that "[t]he Macugen 2008 label therefore would have offered no guidance to a POSA who wanted to practice Sigg's VHP method." *Id.* at 29.

Patent Owner further notes that its syringe described in the '631 patent provides an enabling disclosure for terminal sterilization, but "[t]he fact the '631 patent does not claim the details of its syringe design that provide an enabling disclosure is not legally relevant." PO Resp. 30 n.7. Patent Owner argues that "the possibility that prior-art syringe components could have been cobbled together to permit terminal sterilization of a PFS for intravitreal injection containing a VEGF-antagonist does not satisfy Petitioner's burden." *Id.* at 31.

c) Arguments Related to Objective Evidence of Nonobviousness[20]

Patent Owner's Arguments

Patent Owner contends that "[s]everal objective indicia strongly support the nonobviousness of the challenged claims." PO Resp. 46. According to Patent Owner, "there was a need for a terminally sterilized PFS for intravitreal injection of VEGF-antagonists containing low silicone oil levels and operable with acceptable break loose forces," yet Patent Owner contends "no pharmaceutical company could put such a PFS on the market before the inventions of the '631 patent." *Id.* at 47–48. Patent Owner examines PFS products made by Genentech, Pfizer, and Becton Dickinson and argues that these products used high levels of silicone oil despite the long felt need for low silicone oil syringes. *Id.* at 49. Patent Owner alleges another company, Vetter, [redacted] *Id.* (citing Ex. 2206 ¶ 24).

Nexus

Patent Owner contends it "is entitled to a presumption of nexus because Lucentis PFS, marketed in the United States by Genentech, is an embodiment of at least Claims 1, 3, 7, 8, 14, 17, 21, 22, and 24 of the '631 patent, and is co-extensive with them." *Id.* at 50 (citing Ex. 2201

[20] We examine secondary considerations under the heading for claim 1 because the parties largely argue secondary considerations together for the claims. To the extent that unique arguments are made for other claims (*e.g.*, claims 8, 22), we note those arguments and address them.

¶ 166; Ex. 2204 ¶ 31). Patent Owner provides a claim chart and argues that claims 1, 3, 7, 8, 14, 17, 21, 22, and 24 of the '631 patent are co-extensive with the Lucentis PFS. *Id.* at 50–52 (citing Ex. 2201 ¶¶ 170–285, as well as various exhibits related to Lucentis PFS). Lucentis PFS contains ranibizumab in an ophthalmic solution, which Patent Owner equates to the claimed "VEGF-antagonist" of claim 1. *Id.* at 51. Patent Owner alleges that "the claims above cover the entirety of the Lucentis PFS, and the Lucentis PFS does not contain any unclaimed features," because "the Lucentis PFS is not a component of a larger product," and "[i]t consists only of the claimed syringe body filled with a VEGF-antagonist." *Id.* at 53 (citing Ex. 2201 ¶ 287).

Patent Owner relies on the claimed combination as a whole and contends that "[a] nexus may be presumed even if the individual limitations of a claimed invention are all in the prior art." *Id.* Patent Owner believes that "Petitioner is mistaken when it suggests that the commercial success of Lucentis 'could only plausibly be relevant to claims 8–10, which are the only claims that are limited to ranibizumab (*i.e.*, Lucentis).' (Pet. 72 n.20[])," because not every embodiment of the claims must be sold in order to rely upon evidence of commercial success. *Id.* at 54 (quoting *In re Huai-Hung Kao*, 639 F.3d 1057, 1069 (2011) ("there would never be commercial success evidence for a claim that covers more than one embodiment")). Patent Owner also contends that the evidence shows the existence of a nexus between the objective evidence and the challenged claims. *Id.*

Commercial Success

Relying on the testimony of James E. Malackowski (Ex. 2205), Patent

Owner contends that the Lucentis PFS has achieved significant commercial success since its launch in 2017. PO Resp. 55 (citing Ex. 2205 ¶¶ 36–44). Patent Owner notes that in [redacted]. *Id.* Patent Owner contends that "the commercial success of Lucentis PFS is due to the inventions claimed in the '631 patent." *Id.* Patent Owner alleges that "Genentech's ability to sell Lucentis in a PFS presentation, under a license to the '631 patent, substantially increased both the absolute sales and the market share Lucentis achieved." *Id.* Patent Owner notes that a Lucentis product was launched by Genentech in 2006 as a vial presentation. *Id.* Patent Owner notes that "Lucentis vial sales generally increased through 2014, but began to decline in 2015 due to market competition," but when the PFS presentation was launched in 2017, Lucentis PFS reversed the prior sales decline and caused sales to climb higher than they had been at any previous time. *Id.* (citing Exs. 2266, 2275, 2161, 2099, 2205 ¶ 20). Patent Owner claims that "the PFS launch turned around Lucentis's market share trajectory . . . leading to sustained share increases against other VEGF-antagonist competitors." *Id.* at 56 (citing Ex. 2205 ¶¶ 36–43, Figs. 6–9).

Long-Felt Need

Patent Owner alleges there was a long-felt need for the claimed invention, specifically "a terminally sterilized PFS for intravitreal injection of a VEGF-antagonist containing the claimed amounts of silicone oil." *Id.* at 56–57. Patent Owner contends that this "need had not been met in the marketplace prior to the launch of the Lucentis PFS." *Id.* at 57. Patent Owner argues that "as of the priority date, the only PFS for intravitreal

injection of a VEGF-antagonist on the market (Macugen) had [redacted] of silicone oil and was known to cause 'intravitreal contamination by silicone oil droplets.'" *Id.* (quoting Ex. 1003 ¶ 66) (citing Ex. 2001 ¶¶ 41, 182; Ex. 2257, 51:20–52:4). Patent Owner contends that "Pfizer, the developer and marketer of Macugen, had every incentive to meet the market need by offering Macugen with the silicone oil levels described in *Boulange*, but did not do so." *Id.* Patent Owner alleges that "[i]f it were obvious that a syringe with silicone oil amounts within the ranges claimed by the '631 patent could function properly, Genentech would likewise have been motivated to develop it," yet, Patent Owner points to evidence suggesting that "Genentech still believed that the preferred silicone oil amount for a PFS containing a biologic like a VEGF-antagonist was between 200–500 μg." *Id.* (citing Ex. 2022, 11).

Patent Owner also notes that "Becton Dickinson, the assignee of the Boulange application . . . never pursued a patent based on the Boulange application, while its Hypak for Biotech SCF syringe, which it marketed to Novartis and others as its low silicone oil prefillable syringe for sensitive biological products, had [redacted] of silicone oil." *Id.* at 58 (citing Ex. 2206 ¶ 21; Ex. 2141, 30).

Failure of Others

Patent Owner contends, "[t]he evidence shows that others had attempted, but failed, to develop a terminally sterilized PFS for intravitreal injection of a VEGF-antagonist within the claims of the '631 patent." PO Resp. 58. Patent Owner relies on the "[redacted]

[redacted]." *Id.* ("[T]he current record contains substantial additional support, including internal Genentech documents, the testimony of Genentech witness Mr. Overcashier, and the first-hand knowledge and contemporaneous documents of Dr. Juergen Sigg." *Id.* (citing Ex. 2206 ¶¶ 5–18; Exs. 2099–2115, Ex. 2194, 37:1–13).

Skepticism

Patent Owner relies on evidence related to communications between [redacted] and Novartis. PO Resp. 59. Specifically, "[redacted]" *Id.* (citing Ex. 2206 ¶¶ 24–26, 28; Exs. 2142, 2143). Patent Owner asserts that "[redacted] skepticism is particularly relevant to claim 22, which requires 'from about 1 to 50 μg silicone oil.'" *Id.*

Licensing

Patent Owner contends that "Genentech's licensing of the '631 patent is likewise strong evidence of nonobviousness." PO Resp. 60. According to Patent Owner, "[redacted]," and [redacted] *Id.* (citing Ex. 2121). Patent Owner notes that "[redacted]" *Id.* Further, "Genentech used the license to the '631 patent by commercializing Lucentis PFS in the U.S. with a syringe that practices the '631 patent." *Id.*

Petitioner's Arguments

In its Petition, "Petitioner provides a preliminary statement explaining why there is no evidence of secondary considerations that could overcome the clear evidence of obviousness set forth herein." Pet. 71.

Petitioner first notes that

> the unsupported assertion of unexpected results in the '631 Patent (Ex. 1001 at 5:15-25) with respect to reducing silicone oil amounts while maintaining acceptable break loose and slide forces is clearly contradicted by Boulange, which discloses the claimed silicone oil amounts in conjunction with the claimed break loose and slide forces.

Pet. 71–72 (citing Ex. 1003 ¶¶ 305–314).

Petitioner next argues that "long-felt need cannot demonstrate non-obviousness because all claim elements were already described in the prior art (e.g., Sigg, Lam, Boulange)," and "Macugen® PFS was a VEGF antagonist sold in a 1 mL glass pre-filled syringe and sold in a sterile blister pack by August 2008." Pet. 72 (Ex. 1003 ¶¶ 295–304, 148–153).

As for the commercial success of Lucentis PFS,[21] Petitioner alleges that Novartis cannot demonstrate non-obviousness because it cannot demonstrate that Lucentis PFS is co-extensive with the challenged claims. *Id.* Additionally, Petitioner contends that "because all the claimed features were already known in the art, any success of Lucentis PFS is not relevant." Pet. 72–73. Petitioner also alleges that "Patent Owner's licenses for the '631 Patent cannot demonstrate nonobviousness," because "Patent Owner

[21] Genentech brought Lucentis PFS to market in 2016 (Ex. 2015) and licensed the '631 patent from Patent Owner as discussed more below.

will be unable to show that there is a nexus between its license agreement with Genentech and the '631 Patent." Pet. 73.

Petitioner contends that Patent Owner will not be able to show failure of others "because the evidence will show that others succeeded before Patent Owner." *Id.* For example, "[b]y June 2010, Petitioner had reduced to practice a 1 mL Eylea pre-filled syringe that was (i) terminally sterilized, (ii) used a baked-on syringe with less than 100 μg of silicone oil on the syringe barrel, and (iii) met the requirements of the USP789." *Id.* (citing Ex. 1005, 109–110, 114–125). Petitioner notes that its "Eylea PFS was subsequently used in clinical studies and approved by regulatory authorities in Australia in 2012." *Id.* (citing Ex. 1066).

In its Reply, Petitioner addresses Patent Owner's evidence of objective indicia of nonobviousness as follows and argues "Novartis's secondary considerations evidence, which lack nexus and is otherwise irrelevant, cannot overcome the compelling evidence of obviousness." Pet. Reply 21.

Nexus and Commercial Success

Petitioner first argues that there is no nexus between any commercial success of Lucentis PFS and the '631 patent because "non-patented features and features known in the prior art underlay the commercial success." Pet. Reply 21 (quoting *Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016)). Petitioner relies on Patent Owner's evidence and testimony to support its position "that numerous unclaimed features contribute to the success of Lucentis PFS:"

- [redacted] critical to

terminal sterilization and commercialization. Ex. 2206 ¶¶ 46–48; Ex. 2201 ¶¶ 105–106.

- A "baked silicone" application process critical to preventing silicone oil being injected into the eye. Ex. 2209 ¶ 36 (Declaration of Jeremy Wolfe, M.D.).
- A [redacted] critical to terminal sterilization. Ex. 2141, 51.
- [redacted] critical to achieving low break loose and slide forces. Ex. 2141, 33; Ex. 2064, 30.

Pet. Reply 22 (also citing Ex. 1105 ¶¶ 100–106 (Reply Declaration of Mr. Koller)).

Petitioner next relies on admissions of Patent Owner and its witnesses to argue "that the success of Lucentis PFS is due to features that were known in the art." Pet. Reply 22. For example, "Dr. Wolfe and [redacted]—testified that physicians use Lucentis PFS due to its convenience, which was a known PFS feature and not attributable to the '631 Patent claims." *Id.* (citing Ex. 2209 ¶ 31; Ex. 1161, 115:8–14, 115:22–116:18; Ex. 1106 ¶¶ 30–34)

Petitioner next contends that "[t]here is also no nexus because Lucentis PFS is not coextensive with the claims," and "there must be some evidence that other embodiments within the claim would produce the same results." *Id.* at 23 (citations omitted). Petitioner first notes that "Lucentis PFS contains a single VEGF-antagonist—ranibizumab—but the '631 Patent functionally claims any VEGF-antagonist." *Id.* (citing Ex. 1105 ¶ 99). Petitioner alleges that "there is no evidence that a PFS comprising other VEGF-antagonists within the claim scope would be successful," but "there is evidence that the Beovu PFS, which Novartis contends practices

multiple claims, ***would not*** be successful." *Id.* at 23–24 (citing Ex. 1005, 42; Ex. 1106 ¶ 35; Ex. 1208, 58:5–15).

Petitioner next argues that because Lucentis PFS contains between [redacted] but the claims cover up to about 100 µg (claims 1–21, 23–26) or about 50 µg (claim 22), the claims actually cover embodiments that would not be suitable for a commercial product. *Id.* at 24. Petitioner relies on the cross-examination testimony of Dr. Sigg, "[redacted] (Ex. 1158, 110:2–17), meaning the claims cover embodiments unsuitable for a commercial product." *Id.*

As for commercial success regardless of presumed nexus, Petitioner argues that "Novartis has not set forth evidence linking any commercial success to the specific claimed features, and instead has only shown a correlation between increased sales and introduction of Lucentis PFS." *Id.* at 24 (Ex. 1107 ¶¶ 39–51). Petitioner contends that "Novartis ignores that Lucentis was also approved for new indications when the PFS launched," and "Novartis's Global Head of Ophthalmology did not believe '[redacted]'" Ex. 1161, 100:22–101:11; Ex. 1107 ¶ 48.

Long-Felt Need

Petitioner first responds that the need for a terminally sterilized PFS for intravitreal injection of a VEGF-antagonist containing the claimed amounts of silicone oil was a need that was met by the prior art. Pet. Reply 24–25. Petitioner contends that "Macugen PFS was a terminally sterilized PFS containing a VEGF-antagonist with sufficiently low operational forces by 2008," and "Becton Dickinson had disclosed in

Boulange [redacted] 1 mL glass syringes comprising less than 50 µg silicone oil by May 2011." *Id.* (citing Ex. 1105 ¶¶ 107–109, 113; Ex. 1106 ¶¶ 19–20; Ex. 1215 ¶¶ 3–5; Ex. 1162, 1–6).

Petitioner next alleges that the claims do not satisfy the need identified by Novartis. *Id.* at 25. Petitioner notes that "Novartis characterized the need as including a 'syringe with low levels of silicone oil' to prevent silicone oil injection into the eye." *Id.* (citing Ex. 2204 ¶¶ 80, 91). According to Petitioner, however, the '631 patent only claims silicone oil applied to the syringe barrel, yet, silicone oil also can be introduced into a PFS via the stopper and filling process, neither of which are claimed. *Id.* (citing Ex. 1105 ¶ 111; Ex. 1207, 35:20–36:6). Petitioner also contends the process used to apply the oil is important as to whether the silicone oil migrates from the syringe barrel and into the patient's eye, but yet again, the process is not claimed. *Id.* (citing Ex. 1105 ¶ 111; Ex. 1207, 35:20–36:6). "Thus," according to Petitioner, "the claims do not satisfy the need for a 'syringe with low levels of silicone oil' that avoids silicone oil injection into the eye," and "[t]o the extent Lucentis PFS does, it is due to unclaimed features." *Id.* (citing Ex. 1105 ¶¶ 110–112).

Petitioner next argues that "there is no evidence that others actually made efforts to meet the need as characterized by Novartis," because "Macugen PFS already met every need expressed by Novartis, except for the claimed silicone oil amount." *Id.* at 26 (citing Ex. 1105 ¶¶ 108–116). Petitioner further asserts that "the silicone oil amounts were met by [Becton Dickinson's (BD's)] baked-on syringes," yet, "while it was clearly obvious as of 2011 to use a baked-on syringe for a VEGF-antagonist PFS, sales of

Macugen PFS had declined by that time due to more effective drug products (e.g., Lucentis, EYLEA)." *Id.* (citing Ex. 1105 ¶¶ 113–116). "Thus," according to Petitioner, "there is no evidence that the makers of Macugen PFS made efforts to incorporate BD's baked-on syringe." *Id.*

Failure of Others

Petitioner addresses each of Patent Owner's alleged failures by others. Pet. Reply 26. Petitioner contends "[redacted]" *Id.* (citing Ex. 1100 ¶¶ 58–59) (Declaration of James Agalloco). Petitioner next argues that "Macugen PFS successfully terminally sterilized a PFS by 2008," and "Regeneron successfully manufactured commercial-scale batches of a terminally sterilized Eylea PFS in 2010, which were used in clinical trials from 2011–2014 and approved in Europe and Australia in 2012." *Id.* at 26–27 (Ex. 1102 ¶¶ 14–29, 36, 40–41).

Skepticism

Petitioner contends that "Novartis's argument that Vetter was allegedly skeptical about applying less than 100 μg of silicone oil is unsupported," because "[t]he challenged claims cover up to 'about 100μg,' meaning [redacted]" Pet. Reply 27 (citing Ex. 1105 ¶¶ 117–120). Petitioner further relies on correspondence between Novartis and Vetter to contradict Novartis's position that Vetter was [redacted]. *Id.* (citing Ex. 1213, 101:9–103:3; Ex. 1168, 2–4; Ex. 2143, 2 ([redacted])).

Licensing

Petitioner contends that "Genentech's license has no nexus to the '631 Patent," because it "is clearly directed to [redacted] that are not disclosed in the '631 Patent." Pet. Reply 27 (citing Ex. 2121, 1; Ex. 1105 ¶¶ 124–132; Ex. 1107 ¶¶ 54–58). Petitioner argues "[t]hat the license also provided rights to the '631 Patent is insufficient to demonstrate a nexus." *Id.*

d) Analysis

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record, Petitioner has demonstrated by a preponderance of the evidence that claim 1 of the '631 patent would have been obvious to the person of ordinary skill in the art based on the combination of Sigg, Boulange, and USP789. Petitioner persuasively shows how each element of claim 1 is taught by the combination of references and provides sound reasoning for the combination of references. Pet. 31–47; Pet. Reply 21–27. Patent Owner has not shown that the combined evidence of secondary considerations of nonobviousness is persuasive enough to overcome Petitioner's strong case of obviousness.

The combination of Sigg and Boulange teaches that pre-filled syringes may be made of glass because Boulange discloses a syringe comprising a glass barrel and a piston (*i.e.*, stopper) that would work in Sigg's device. *See* Pet. 41–42 (citing Ex. 1008, 9:21–35, 13:11–12; Ex. 1003 ¶ 192). Sigg also teaches a pre-filled terminally sterilized syringe containing a VEGF-antagonist for intravitreal injection with a nominal maximum fill volume of between 0.5 mL and 1 mL. Ex. 1003 ¶ 159. The current record establishes

that the claim limitation "2 particles >50 μm" comes from the USP-789 standard, which is an accepted standard for ophthalmic drugs such a VEGF-antagonist solution intended for intravitreal use. Ex. 1019; Ex. 1003 ¶¶ 90–92. We are persuaded by Mr. Koller that, because Sigg discloses a PFS with ranibizumab, a known VEGF-antagonist solution intended for intravitreal use, Petitioner has established that it would have obvious to a POSITA that the VEGF-antagonist solution in Sigg must comply with the USP-789 standard. Ex. 1003 ¶ 92.

As for the limitation requiring about 1 μg to 100 ug silicone oil and a specific break loose force (less than about 11 N), Sigg does not disclose any particular break loose force, but Boulange discloses several tests of "friction force B" of various syringes. Ex. 1008, 15:6–8. We find persuasive Petitioner's evidence that Table 5 of Boulange discloses break loose forces (B) of less than about 11 N for stoppers that were coated with silicone oil[] and tested with baked-on syringes having 40 μg of silicone oil (*i.e.*, 4 μg/cm2). Ex. 1003 ¶ 208; Pet. 46 ("Table 5 likewise discloses break loose forces less than 11 N for the baked-on syringes with 40 μg of silicone oil (4 μg/cm2) for stoppers B1 and C at T=0 and T=1.").

Based on the final record, we also find Petitioner's reasoning and evidentiary underpinnings show by a preponderance of the evidence that a POSITA would have been motivated to combine Sigg's terminally sterilized PFS comprising a VEGF-antagonist with Boulange's low-silicone and low break loose/gliding force syringe and the combination would have had a reasonable expectation of success. *See* Ex. 1003 ¶¶ 159–187. 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. *Id.* ¶ 159. We determine that it was known in the art that pre-filled syringes are typically siliconized to achieve desired break loose and gliding forces. *See, e.g.*, Ex. 1001, 4:48–50. The evidence of record establishes that the person of ordinary skill in the art was aware that reducing the amount of silicone oil in intravitreal injections was desirable to avoid potential "incompatibilities includ[ing] aggregation, deformation, and inactivation of native protein structures of the delivered drug." *See* Ex. 1003 ¶¶ 159–160 (quoting Ex. 1012, 6).

Further, the advantages of using baked-on siliconization as disclosed in Boulange would help reduce the amount of "residual" or "free" silicone oil that can enter the protein formulation and cause negative effects because the baking attaches the silicone oil to the inner surface of the syringe barrel. *Id.* ¶ 165. Accordingly, and based on the final record, we determine that Petitioner has provided sufficient articulated reasons and evidentiary underpinnings for its reasons for combining Sigg's terminally sterilized PFS comprising a VEGF-antagonist with Boulange's low-silicone and low break loose/gliding force syringe.

We address each of Patent Owner's arguments in more detail below.

i. Force Profile of Syringe (Stopper) C

As noted above, Patent Owner contends that a POSITA "would not have been motivated to use Boulange Syringe C in a PFS for intravitreal

administration of a VEG-F antagonist because Syringe C has inconsistent forces that increase over time." PO Resp. 8; Sur-reply 5 ("Even though the forces remain under 11N, they almost double over that period. A POSA would be concerned those inconsistent forces would continue to rise, making the syringe unsuitable for intravitreal use.").

We first note that claim 1 does not require any particular break loose force at a particular time. *See* Tr. 15:17–16:5. Patent Owner's contentions are not challenging whether the prior art teaches any particular limitation, but instead whether the POSITA would have been motivated to use Boulange Stopper C in a PFS for intravitreal administration of a VEGF-antagonist. We determine that the combined evidence demonstrates the POSITA would have been motivated to use Boulange Stopper C as proposed by Petitioner.

Stopper C is lubricated with silicone oil, which was a typical stopper configuration and used in a prior art terminally sterilized PFS comprising a VEGF-antagonist. *See* Ex. 1105 ¶¶ 30–33; Ex. 1207, 41:9–12, 46:4–10 (Deposition of Karl Leinsing). More specifically, a POSITA would have known that siliconized Stopper C was suitable for a terminally sterilized PFS comprising a VEGF-antagonist because siliconized rubber stoppers had already been used for that purpose in the Macugen PFS. *See* Pet. Reply 3; Ex. 1008, 13:11–15, Table 1 and 5; Ex. 1220, 97, 229 ([redacted]); Ex. 1105 ¶¶ 30–33.

The final record establishes that stopper C in Boulange has acceptable break loose forces and side forces both at time zero and after accelerated aging. Ex. 1008, 13:11–15, Tables 1, 5. As seen in Table 5 of Boulange

below, the siliconized Stopper C maintained break loose forces less than 11 N (8.4 N, 7.5 N, 7.8 N) after accelerated aging. *Id.*

Table 5 : Activation Gliding Forces, Pistons A, B1 and C

Silicone/internal surface of container		4 µg/cm²			4 µg/cm²			4 µcm²		
Silicone/piston		5 µg/cm²			15 µg/cm²			50 µg/cm²		
Force (N)		B	S	F	B	S	F	B	S	F
Piston	$A_{T=0}$	6.6 (0.6)	5.8 (1.0)	4.7 (1.0)	7.2 (0.5)	6.9 (1.9)	4.7 (1.9)	6.6 (0.8)	6.5 (1.5)	4.0 (1.5)
	$A_{T=1}$	12.0 (2.3)	8.4 (2.0)	3.2 (1.3)	11.0 (0.8)	8.0 (1.9)	3.3 (1.0)	10.7 (1.2)	6.7 (1.5)	3.6 (1.7)
	$B1_{T=0}$	2.2 (0.2)	2.7 (0.4)	2.7 (0.4)	2.2 (0.2)	3.0 (0.6)	3.0 (0.6)	2.1 (0.1)	2.6 (0.5)	2.6 (0.5)
	$B1_{T=1}$	2.8 (0.3)	4.3 (1.2)	4.3 (1.2)	2.6 (0.6)	3.3 (0.3)	3.3 (0.3)	2.5 (0.2)	3.4 (0.3)	3.4 (0.3)
	$C_{T=0}$	4.7 (0.4)	6.5 (0.6)	4.6 (0.6)	4.2 (0.3)	6.0 (0.7)	4.2 (0.7)	3.9 (0.5)	5.2 (0.7)	4.0 (0.7)
	$C_{T=1}$	8.4 (0.6)	8.3 (1.9)	4.1 (1.6)	7.5 (0.6)	8.3 (1.4)	4.8 (2.2)	7.8 (1.1)	6.2 (1.0)	3.7 (1.5)

Petitioner's highlighted Table 5 of Boulange depicts activation and gliding forces for pistons A, B1, and C. Pet. 31; Ex. 1008, Table 5.

We have considered the testimony from Patent Owner's experts but determine that a POSITA would not have been deterred from using Stopper C because the break loose force increases from 4.7 N to 8.4 N (Δ 3.7 N) after accelerated aging. *See* PO Resp. 14–15; Ex. 2201 ¶ 88; Ex. 2204 ¶¶ 67–73; Sur-reply 5–6. We find Petitioner's position more persuasive—because Stopper C's forces after aging are within the claimed range and suitable for intravitreal injection, the POSITA would not be deterred from using Stopper C. Pet. Reply 4; Ex. 1105 ¶¶ 38–42; Ex. 1208, 17:1–7, 27:10–17 (Dr. Calman acknowledging his preferred PFS for intravitreal injection requires up to 10 N force). As Mr. Koller explains, "[a] POSITA would have understood that most pre-filled syringes are expected to experience

some level of force increase over the shelf-life of the syringe," and such an entirely expected increase would not deter the POSITA. Ex. 1105 ¶ 39.

We also agree with Mr. Koller that Stopper C's increase in force from 4.7 N to 8.4 N would not be an inconsistent "force profile" that would affect an ophthalmologist's use of the syringe. *Id.* ¶ 41. Mr. Koller persuasively shows how a force increase of less than 4 N after aging would have been expected and acceptable "based on tolerances and variations in manufacturing processes," as evidenced by data from Regeneron demonstrating that the break loose force for Eylea PFS can vary from approximately [redacted]. *Id.* ¶ 42 (citing Ex. 1154, 15). Further, even Patent Owner's declarants agreed that they found the Eylea PFS to have consistent forces from syringe to syringe despite this stated variance. Ex. 1105 ¶ 42 (citing Ex. 1212 (Wolfe Dep. Tr.), 28:7–9; Ex. 1208 (Calman Dep. Tr.), 22:3–9).

Patent Owner contends that Boulange describes all configurations of Stopper C as "unacceptable," however, based on the final record, we disagree. *See* PO Resp. 14; Sur-reply 5–6; Ex. 2001 ¶¶ 89–90. Boulange only states that Stopper C *in Table 7* "does not appear to be acceptable for a medical device." Ex. 1008, 21:5. As Mr. Koller explains, Stopper C in Table 7 is distinct from other embodiments because it is not siliconized. Ex. 1105 ¶¶ 34–37. In contrast, Stopper C in Table 5 is siliconized and had much lower break loose forces after accelerated aging (8.4 N, 7.5 N, 7.8 N) than Stopper C in Table 7 (14.4 N). *Id.* ¶ 35 ("the statement in Boulange . . . comes directly after Table 7 of Boulange and is clearly referring to the configuration of Stopper C that has no lubrication on it at all"). We agree

with Mr. Koller that this "statement would not be understood to apply to the results in Table 5 of Boulange because that is an entirely different configuration of Stopper C (*i.e.*, it includes a silicone oil lubricant)." *Id.*; *see also* Tr. 18:4–14, 41:18–42:8.

Even though Boulange describes siliconized Stopper C as "markedly inferior" to Stopper B1 (coated with Parylene C), we do not see this as a teaching away as argued by Patent Owner. *See* Sur-reply 5. Although Stopper C's 8 N (after accelerated aging) is inferior to the values for Stopper B1 (less than 3 N), the values for Stopper C are still within the claimed "about 11N," but more importantly, well under the 20 N that the '631 patent acknowledges was "known in the art" to be acceptable for intravitreal injection. Ex. 1105 ¶ 37; Ex. 1001, 5:31–38 ("Break loose and slide forces for prefilled syringes *known in the art* are typically in the region of less than 20N.") (emphasis added).

We find persuasive Mr. Koller's testimony that a POSITA would recognize Boulange's aging conditions correspond to the intended storage life for a VEGF-antagonist. Further, because the results from Stopper C are low even after 12 months of shelf life, a POSITA would understand Stopper C is an acceptable alternative to Stopper B1 (Parylene C), even though it is categorized as "markedly inferior" to Stopper B1. *Id.* A POSITA would have understood that Stopper C's low force profile would indeed work, but also that Stopper B1 has an extremely low force profile making it the superior alternative for that one condition. Further, as Mr. Koller explains, a POSITA would have been motivated to use Stopper C as opposed to Stopper B1, because Stopper C was "comprised of rubber and coated with silicone

oil, which was a common stopper design in the prior art." Ex. 1105 ¶ 33 ("[A] POSITA would have known that rubber stoppers coated with silicone oil had been used in a PFS comprising a VEGF-antagonist for intravitreal injection before the '631 Patent.").

Thus, we determine the descriptions in Boulange are distinct from those set forth in *AstraZeneca AB v. Mylan Pharm. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021), relied on by Patent Owner. *See* PO Resp. 16. In *AstraZeneca*, the Federal Circuit determined that a reference teaches away when a POSITA "would be discouraged from following the path set out in the reference." *AstraZeneca AB*, 19 F.4th at 1337 (Fed. Cir. 2021) ("reference that properly teaches away can preclude a determination that the reference renders a claim obvious").

The prior art in *AstraZeneca* taught a control formulation and a novel formulation (similar to Boulange Stoppers C and B1 (novel Parylene C)) and the Federal Circuit affirmed that the prior art taught away from the control formulation (Rogueda). *Id.* The district court, and Federal Circuit, relied on "AstraZeneca's expert . . . testify[ing] that a skilled artisan looking at the adhesion test results in Rogueda would conclude that the control formulations 'were not suitable' and 'clearly don't work,'" and the "control formulations" had "poor adhesion." *Id.* at 1336. Further, "the particle size reported by Rogueda was significantly larger, indicating that there were 'huge agglomerates . . . floating around' in the formulations, rendering them 'completely unsuitable.'" *Id.* at 1337.

The force profiles set forth in Boulange for Stopper C would not have discouraged the skilled artisan from following the path set out in Boulange

because Stopper C's force profiles were markedly low, even though Stopper B1 was superior in comparison. *See* Ex. 1105 ¶ 37 ("Although 8N is inferior to the values for Stopper B1 (less than 3N), the values for Stopper C are within the claimed 'about 11N' and" below those "known to be acceptable for intravitreal injection."). The control formulation examined in *AstraZeneca* is distinct from Stopper C in Boulange because a skilled artisan at the time of invention would have viewed Stopper C as having acceptable break loose forces and slide forces both at time zero and after accelerated aging. Further, a variance of 4.7 N to 8.4 N (Δ 3.7 N) after accelerated aging is within accepted industry standards and would have been a viable option for the POSITA. *See* Ex. 1154, 15 (break loose force for Eylea PFS varying from approximately [redacted]); Tr. 16:7–20; Ex. 1212, 28:7–9; Ex. 1208, 22:3–9.

ii. 2 particles > 50 μm in diameter per ml

The parties agree that Sigg discloses an ophthalmic solution and a POSITA would have understood that USP789 is a de facto requirement for regulatory approval of an ophthalmic solution. *See* PO Resp. 19 n.3; Ex. 1003 ¶ 92. As noted above, however, Patent Owner contends that USP789 does not require an ophthalmic solution to meet the particulate content limitation (2 particles > 50 μm in diameter per ml). PO Resp. 19.

Even accepting Patent Owner's contention as true – that USP789 does not dictate that the particulate content limitation be met in every situation – USP789 nonetheless teaches use of the particulate content limitation. The limitation comes directly from the microscopic test of USP789, which explains that it "may be necessary to test . . . by the light obscuration test

followed by the microscopic test." Ex. 1019, 5; *see also id.* ("[M]icroscopic testing may be used exclusively" where "the ophthalmic solution cannot be tested by light obscuration."). Accordingly, USP789 provides clear motivation for a POSITA to design an ophthalmic solution to pass the light obscuration *and* microscopic tests to ensure compliance, including having no more than 2 particles > 50 μm. Ex. 1105 ¶¶ 43–45; Ex. 2002, 10 (Declaration of Marie Picci asserting that "USP<789> standard requires no more than 2 particles > 50 μm").

iii. Reasonable Expectation of Success

As noted above, Patent Owner questions whether Boulange's syringe could withstand terminal sterilization with VHP when filled with a VEGF-antagonist solution and Patent Owner contends that not every combination of barrel and stopper would work to protect a sensitive drug product. PO Resp. 20–25; Ex. 2201 ¶ 135. Based on the final record, Petitioner has persuasively shown that Boulange's pre-filled syringe would have been compatible with Sigg's terminal sterilization method (VHP) and a POSITA would have reasonably expected the combination to work as proposed by Petitioner.

First, it is important to reiterate our claim construction for "terminally sterilized," as the sterilization of the outside of a 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. *See* Ex. 1003 ¶ 120. As we previously emphasized, the '631 patent recognizes that some amounts of the sterilizing gas may interact with the ophthalmic solution so long as the amount does not "cause unacceptable

modification of the ophthalmic solution within the variable volume chamber." Ex. 1001, 10:5–7. Thus, some amount of contact between the drug product within the pre-filled syringe and the sterilizing agent is contemplated within the scope of the claims.

We find persuasive Mr. Koller's testimony that it was standard in the art to design pre-filled syringes like those in Boulange to be gas-tight to protect the drug product from degradation during its shelf life. Ex. 1003 ¶ 172 (quoting Ex. 1008, 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, 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")). Petitioner's position that a POSITA would have readily understood that Boulange's syringe to be gas-tight, preventing sterilizing gas from entering the syringe, is more persuasive because "Boulange describes 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 said two parts.'" Pet. 35 (quoting Ex. 1008, 6:10–14) (citing Ex. 1003 ¶¶ 172, 184–186); *see also* Ex. 1008, 1:14–16 (Boulange describing that its syringe can accommodate a drug product in a gaseous phase).

Patent Owner posits that a syringe would not be able to withstand sterilization conditions unless specially designed to do so. PO Resp. 21; Ex. 2201 ¶ 65 (explaining also that Boulange does not discuss terminal sterilization). Regardless of Boulange's lack of discussion of terminal

sterilization, a POSITA would have still had an expectation of success. Boulange discloses use of structure for achieving gas tightness, similar to the '631 patent, and notes that it preserves the tightness, such that a POSITA would reasonably expect compatibility with VHP sterilization. *See* Pet. Reply 8; Pet. 34–35. The evidence does not support Patent Owner's contention that Boulange's discussion of gas tightness was just "aspirational." Sur-reply 8. Boulange instead describes a functional siliconized rubber stopper (Stopper C), similar to that which had already been used in the [redacted] terminally sterilized Macugen PFS approved by the FDA. Ex. 1105 ¶¶ 48–52, 264.

Patent Owner contends that Boulange discloses that the syringe components are sterilized before the syringe is filled with the active (aseptic filling), whereas terminal sterilization takes place after the syringe is filled. Sur-reply 6–7. Thus, according to Patent Owner, a POSITA would not have been motivated to combine Boulange with a reference that teaches terminal sterilization (Sigg). *Id.* First, Boulange makes no reference to aseptic filling and the evidence cited by Patent Owner does not support such a conclusion. Regardless, we are not persuaded that a POSITA would have been dissuaded from combining the syringe structure taught by Boulange with the terminal sterilization technique taught by Sigg because all PFSs are designed to be gas-tight during normal storage to prevent air from negatively interacting with the drug product – Boulange's relied upon structure remains consistent. Ex. 1105 ¶ 48; Ex. 1003 ¶ 172; Ex. 1008, 4:21–32.

Patent Owner further argues that terminal sterilization requires special tightness beyond the tightness described in Boulange because of pressure

variations that may cause stopper movement. PO Resp. 22–23; Ex. 2201 ¶ 54. Petitioner demonstrates, however, that "[t]his argument is not applicable to the VHP method disclosed in Sigg, which can be done at ambient pressure." Pet. Reply 9 (citing Ex. 1213, 71:3–8; Ex. 1252, 222 (¶ 9); Ex. 1105 ¶¶ 59–61); *see also* Ex. 1207, 120:17–22 ("Q. Now, with respect to terminal sterilization using ethylene oxide or vaporized hydrogen peroxide, is your understanding that the pressure changes associated with those sterilization cycles would cause the stopper to move? A. Not necessarily, no."). As Mr. Koller persuasively explains, "a POSITA would understand that Sigg teaches a VHP method that attempts to minimize the use of pressure changes" during the VHP process such that terminal sterilization process could be achieved without causing the stopper to move. Ex. 1105 ¶ 61 (citing Ex. 1007, 14:3–6, 14:9–11, 14:18–20). The evidence in the final record does not demonstrate that any special tightness or specific stopper material, coating, or dimensions, would have been required to achieve terminal sterilization within the scope of the claims of the '631 patent. *See* Ex. 1207, 109:1–13, 113:10–17; Ex. 1105 ¶ 49. Further, the '631 patent does not claim any specific structure for achieving the same result. Accordingly, we determine that a POSITA would have determined that the stoppers disclosed in Boulange would result in an acceptably tight seal for terminal sterilization (even with pressure changes), and thus, Boulange discloses a stopper compatible with VHP sterilization.

iv. Enablement of Sigg's VHP Method

For the reasons previously examined, and as set forth below, we determine that Petitioner demonstrates that Sigg is enabled for the portions

of its disclosure that are cited. Further, we determine that evidence in the final record establishes that a skilled artisan would have been able to make and use the claimed invention as set forth in Petitioner's proposed combination of reference without undue experimentation.

In a § 103 analysis, we need not consider a prior art reference in a vacuum. Instead, as the Federal Circuit stated in *Raytheon*:

> We have explained that there is no absolute requirement for a relied-upon reference to be self-enabling in the § 103 context, so long as the overall evidence of what was known at the time of invention establishes that a skilled artisan could have made and used the claimed invention. We have also previously expounded the principle that if an obviousness case is based on a non-self-enabled reference, and no other prior art reference or evidence would have enabled a skilled artisan to make the claimed invention, then the invention cannot be said to have been obvious.

Raytheon Techs. Corp. v. Gen. Elec. Co., 993 F.3d 1374, 1376–77 (Fed. Cir. 2021). Based on the final record, we do not find this to be a case where no other prior art reference or evidence would have enabled a skilled artisan to make the claimed invention. The final record, including Sigg, contains persuasive teachings demonstrating that a POSITA would have known how to use a VHP method to terminally sterilize a PFS containing sensitive biological solutions. *See* Ex. 1003 ¶¶ 78–89.

We again note our claim construction for "terminally sterilized," which Patent Owner has not challenged. The '631 patent recognizes that some amounts of the sterilizing gas may interact with the ophthalmic solution. Ex. 1001, 10:5–7.

Next, we consider that the '631 patent discloses, but does not claim, any specific structure that enables terminal sterilization of a PFS. The claims of the '631 patent are not directed to a particular stopper or plunger rod design, and instead appear to encompass any stopper and plunger rod that allow terminal sterilization in the manner claimed. *See* Ex. 1003 ¶ 108. Typically, unclaimed features cannot be used to distinguish a patent over the prior art.

Patent Owner contends that Sigg is not self-enabled because it fails to identify any syringe designs that can withstand its VHP method, and, neither Mr. Koller's opinions nor the prior art cited by Petitioner supports enablement. PO Resp. 25–26. Many of Patent Owner's arguments are similar to those we have already considered, but found unpersuasive. Our reasoning carries over to the issue here and we add the following analysis.

Weighing the testimony in the final record, and examining all of the evidence before us, we recognize that terminally sterilizing a PFS with VHP was technically challenging at the time of invention. Even still, we are more persuaded by Mr. Koller's testimony that conducting terminal sterilization of a PFS with VHP in light of the prior art of record would not require undue experimentation. *See* Ex. 1003 ¶¶ 83–88; Ex. 1105 ¶¶ 66–71. Mr. Koller provides persuasive testimony as to how Sigg's disclosure of "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)." Ex. 1003 ¶ 83. Mr. Koller relies on a quotation from Sigg that describes its VHP sterilization method of

> 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. ¶ 84 (quoting Ex. 1007, 3:11–16). Mr. Koller then provides testimony about cold sterilization using EtO (*id.* ¶¶ 85–87) but then notes that:

> 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.

Id. ¶ 87.

Mr. Koller further testifies that the POSITA would be aware of certain regulations that seek to minimize the amount of sterilizing agent residue that is permissible for exposure. *Id.* ¶ 88. With that awareness, the person of ordinary skill in the art would understand that "the gas or vapor must be allowed to sufficiently exit the secondary packaging of pre-filled syringe after the sterilization process is over" and would thus be able to effectively carry out Sigg's step in the VHP sterilization process "to remove VHP by 'applying post-treatment measures, within a decontamination chamber.'" *Id.* (citing Ex. 1007, 10:5–6).

Patent Owner bases many of its arguments on the disclosure in Sigg that "very few" (Ex. 1007, 4) syringe components are capable of making the

tight seal required for terminal sterilization. *See* Ex. 1007, 3:27–30 ("[T]here are only very few packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gasses"); PO Resp. 25–26, 28. The final record, including Sigg, contains persuasive evidence showing that a POSITA would have been capable of making and using the invention without undue experimentation, and would have understood which of the "very few" components described by Sigg would have worked in a PFS that was terminally sterilized with VHP.

Patent Owner's contentions that Sigg is not enabling are also contradicted by its prior representations to the USPTO. *See* Pet. Reply 11. As Petitioner points out, "Sigg is a Novartis patent publication, which it prosecuted extensively as Application No. 13/382,380 ('380 Application'). Ex. 1252." *Id.* As explained by Petitioner, "[f]rom January 2012 to April 2014, across six office actions and five responses, Novartis repeatedly attempted to obtain claims directed to a PFS terminally sterilized with VHP comprising a VEGF-antagonist—the ***exact*** subject matter that Novartis presently alleges that Sigg does not enable," but the claims were rejected as obvious. Pet. Reply 11–12 (citing Ex. 1252, 170–177, 192–201, 223–230, 249–255, 277–284, 302–310).

Thus, even if "very few" syringe components are capable of making the tight seal and development of the Lucentis PFS with VHP was "technically very challenging" (PO Resp. 26), the Sigg '380 Application provides further evidence that a POSITA would have read Sigg as providing sufficient support to enable VHP sterilization as claimed. For example, Dr. Sigg submitted a declaration with the '380 Application testifying, "[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." Ex. 1252, 222 (declaration dated May 2, 2013); *see also* Tr. 22:21–23:17. This statement, filed as a declaration, provides further evidence demonstrating that a POSITA would not have had to engage in undue experimentation to make and use a PFS that could be terminally sterilized using Sigg's VHP method. We have considered Dr. Sigg's new testimony that he knew by 2011 that the VHP sterilization method in Sigg did not work. Ex. 2206; Ex. 1213, 79:15–80:17; PO Resp. 26. In light of his prior declaration and the totality of the evidence, we find that the inventor's new testimony is not credible.

Patent Owner contends that Sigg is not enabled because VHP sterilization is "performed under vacuum and subjects the PFS to extreme pressure." PO Resp. 26. We do not find this position persuasive. First, Dr. Sigg previously represented to the USPTO that Sigg's VHP method does not require a vacuum, contradicting Patent Owner's current position. *See* Ex. 1252, 222 (¶ 9) ("[I]t is possible to obtain sufficient sterilization . . . *at ambient pressure*." (emphasis added)). Next, as previously examined, even if Sigg's VHP sterilization does require a vacuum, Mr. Leinsing admitted that a vacuum may not cause the stopper to move at all (Ex. 1207, 120:17–22, 145:17–20); *see also* Ex. 1105 ¶¶ 59–60 ("Mr. Leinsing's assertion that pressure changes could cause movement of the stopper during Sigg's terminal sterilization process is unsupported," because "[a] POSITA would understand that Sigg's VHP process would not necessarily cause a stopper to

move, and Mr. Leinsing has not demonstrated why using Sigg's VHP method on the Boulange syringe specifically would cause such movement."). Finally, even if stopper movement would occur due to pressure variations, Mr. Koller presents persuasive testimony explaining prior art mechanisms that can be used to prevent stopper movement due to these pressure changes. Ex. 1105 ¶¶ 65–71. We examine this testimony more below.

Mr. Koller persuasively explains that "[a] POSITA would have thus readily understood that stopper movement could occur during terminal sterilization, and would have known how to incorporate one of many features known in the art to prevent such movement." *Id.* ¶ 55. Mr. Koller relies on one such feature found in the Macugen PFS, and explains that the device uses "a clip that locked the plunger rod and stopper in place to inhibit stopper movement during terminal sterilization." *Id.* The Macugen PFS was a sterilized PFS containing a VEGF-antagonist with sufficiently low operational forces that was known by 2008. Ex. 1105 ¶¶ 107–109; Ex. 1106 ¶¶ 19–20 (Reply Declaration of Dr. Kiss). The parties dispute whether the Macugen PFS is prior art and whether it was terminally sterilized. PO Resp. 28; Ex. 2201 ¶¶ 113–117; Pet. Reply 14. Regardless of its status as prior art, the evidence surrounding its development and launch is still relevant to the knowledge base of the POSITA. *See Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018) ("[N]on-prior art evidence of what was known . . . can be relied on for their proper supporting roles, e.g., indicating the level of ordinary skill in the art."). Accordingly, the terminally sterilized Macugen PFS, which was FDA approved and

on-sale in the United States before the filing date of the '631 patent, further supports that [redacted] terminal sterilization was within the level of ordinary skill in the art upon based on the teachings of Sigg. Pet. Reply 14; Ex. 1254, 9.

The evidence in the final record before us also suggests that the inventors of the '631 patent pursued VHP sterilization at least in part because they knew it was [redacted] *Id.* (quoting Ex. 1254, 9 ("[redacted]")) (citing Ex. 2063, 92). Petitioner also relies on the Eylea PFS, and Mr. Koller persuasively explains how this device was terminally sterilized with VHP and approved in Australia by February 2012. Ex. 1003 ¶ 124 n.15.

Based on the totality of the evidence presented, we find persuasive Mr. Koller's testimony that "Sigg teaches a VHP method that attempts to minimize the use of pressure changes," and "features for minimizing stopper movement during a terminal sterilization process . . . were likewise well-known in the art." *Id.* ¶ 61 (citing Ex. 1007, 14:3–6, 14:9–11, 14:18–20); Ex. 1105 ¶ 66. Further, we agree with Mr. Koller that "prior art pre-filled syringe designs were known in the art for preventing gas from ingressing into the drug product, as reflected in Boulange." Ex. 1105 ¶ 66. Based on the background knowledge examined above, and Mr. Koller's testimony, we determine a POSITA would have found Sigg's VHP method enabled.

Patent Owner submits additional evidence and testimony related to [redacted], and relies on the statement that VHP was "[redacted]." PO Resp. 27 (quoting Ex. 2206 ¶ 17). Petitioner presents contradictory evidence showing that

[redacted] Pet. Reply 13 (citing Ex. 2148, 2 [redacted]); Ex. 1100 ¶ 51. We have considered both parties' arguments and evidence related to [redacted] work and find it unpersuasive for either party.

The evidence in the final record demonstrates persuasively how a POSITA would know to use the teachings of Sigg and Boulange to achieve the tight seal required for terminal sterilization using a VHP method. A POSITA would need only perform routine optimization to perform the VHP terminal sterilization process described in Sigg in the manner claimed by the '631 patent.

v. Objective Indicia of Nonobviousness

Before any final obviousness determination, we must consider the evidence of obviousness in light of any objective evidence of nonobviousness presented by Patent Owner. *See Graham*, 383 U.S. at 17–18 ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) ("This objective evidence must be 'considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.'" (quoting

Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538–39 (Fed. Cir. 1983))).

Objective evidence of nonobviousness is relevant only if there is a nexus between the evidence and the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). A presumption of nexus applies if the asserted objective evidence "is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" *Id.* (quoting *Polaris Indus., Inc. v. Artic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018)). To the extent that a presumption of nexus does not apply, Patent Owner may still prove nexus "by showing that the evidence of secondary considerations is the 'direct result of the unique characteristics of the claimed invention.'" *Id.* (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). The stronger the showing of nexus, the greater the weight accorded the objective evidence of nonobviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

As set forth above, Patent Owner presents arguments and evidence directed to objective indicia of non-obviousness, including nexus, commercial success, satisfaction of a long-felt but unmet need, failure of others, skepticism, and licensing. PO Resp. 46–60. Petitioner challenges each indicium. Pet. Reply 21–27. We address each of these below.

Nexus

As noted above, Patent Owner contends that the Lucentis PFS, marketed in the United States by Genentech (licensee of the '631 patent), is an embodiment of certain claims of the '631 patent, and is co-extensive with them. PO Resp. 50 (citing Ex. 2201 ¶ 166; Ex. 2204 ¶ 31). Patent Owner

provides a claim chart showing how Lucentis PFS meets all the limitations of these claims. *Id.* at 50–52. Patent Owner argues that the Federal Circuit has "never held that the existence of one or more unclaimed features, standing alone, means nexus may not be presumed." *Id.* at 53 (quoting *Fox Factory,* 944 F.3d at 1374). All that is required for a presumption of nexus is that "the patentee demonstrate that the product is essentially the claimed invention." *Id.* Patent Owner alleges that Lucentis PFS does not contain any unclaimed features and it is not a component of a larger product. Ex. 2201 ¶ 287.

Based on the final record before us, Patent Owner has not established that the Lucentis PFS is coextensive with the claims and essentially the claimed invention. The claims of the '631 patent are broader than the Lucentis PFS, and cover embodiments well beyond Lucentis PFS that may not be successful. Ex. 1105 ¶ 98. Petitioner has presented persuasive evidence demonstrating that several unclaimed features are significant to the structure and function of the Lucentis PFS and these unclaimed features also contribute to the success of the Lucentis PFS. *See* Pet. Reply 22. We find Petitioner's reasoning persuasive and address these features below.

Significant Unclaimed Features

The Lucentis PFS utilizes [redacted] that Patent Owner, and its declarants, have touted [redacted]. Ex. 2206 ¶¶ 42, 46–48; Ex. 2201 ¶¶ 104 ([redacted]

[redacted]), 105–106.

In his declaration, Dr. Sigg discusses a report submitted to a regulatory authority describing "[redacted]" Ex. 2206 ¶ 46. In a section of the report related to "[redacted]" Dr. Sigg discusses "[redacted]" and explains that these "[redacted]"" *Id.* (quoting Ex. 2141, 49). Dr. Sigg testifies that "[redacted]" was addressed by "[redacted]" *Id.* ¶ 47. Further, the [redacted] *Id.* ¶ 48.

Patent Owner's expert, Mr. Leinsing, testifies that "the inventors of the '631 patent also redesigned the stopper to increase the distance between the first and last circumferential ribs of the stopper," which addressed the risk of sterility breach during sterilization of the outer surface of the syringe." Ex. 2201 ¶ 104; *see also* Ex. 2064, 4 ("Change of plunger stopper design to reduce risk of sterility breach."). "This modification increased the size of the 'sterility zone,' which improved the syringe's tolerance for stopper movement during sterilization without breaching the sterility (and

thus the integrity of the drug product)." Ex. 2201 ¶ 104 (quoting Ex. 2141, 54–55). According to Mr. Leinsing, "[t]hese new design elements work together to reduce the risk of sterility breach and enable sterilization to acceptable sterility assurance levels by ensuring that any stopper movement that occurs during sterilization (or at other times) does not result in a sterility breach." *Id.* ¶ 105 ("The inventors' syringe design thus allowed them to develop [redacted]"). As explained by Mr. Leinsing, "[t]he '631 patent also describes these innovations and their significance for terminal sterilization." Ex. 2201 ¶ 106.

Mr. Koller testifies that "the Lucentis PFS includes a stopper coated with silicone oil, which Novartis documents describe as [redacted] Ex. 1105 ¶ 104 (quoting Ex. 2064, 30 ([redacted]") (citing Ex. 2141, 33 [redacted]

Mr. Koller further explains that "the stopper used in the Lucentis PFS is coated with [redacted] on the product contacting side," and "Mr. Leinsing opined that polymer coatings are critical to a PFS because they can 'reduc[e] the degree to which leachables from the rubber closure may enter into the drug formulation.'" *Id.* at 102 (citing Ex. 2224, 9; Ex. 2001 ¶ 52).

Although these new design features to the plunger rod and stopper may be described, in part, in the '631 patent (Ex. 2201 ¶ 106), none of these

features were claimed. *See* Tr. 31:13–34:21. The claims require a "stopper and plunger," but as Mr. Leinsing recognizes, the important design innovations for the Lucentis PFS plunger and stopper, [redacted], are not claimed. *See* Ex. 2201 ¶ 104; *see also* Ex. 1105 ¶¶ 102, 104. Based on the final record, each of these plunger rod and stopper features contribute to the commercial success of Lucentis PFS, but these features are not captured in the claims of the '631 patent. For example, according to Dr. Sigg, [redacted]. Ex. 2206 ¶ 48. Indeed, the [redacted]." Ex. 2201 ¶ 105.

Next, although the claims recite a specific amount of silicone oil as part of the syringe barrel, the claims are not limited to syringes using the baked silicone process used in the Lucentis PFS. *See* '631 patent, claim 1 ("about 1 μg to 100 ug silicone oil"). Each party agrees that two features of the Lucentis PFS were critical to reducing residual silicone oil that could be injected into the eye: a reduction in the amount of silicone oil used (claimed) and the "baked silicone" application technique (not claimed). Ex. 1105 ¶ 103; Ex. 2209 ¶ 36 (Declaration of Jeremy Wolfe, M.D.).

Dr. Wolfe (Patent Owner's declarant) explains the dangers of silicone oil mixing with medication, and further details that the Lucentis PFS carries "a very low risk of silicone oil being injected into the eye," because of "the

use of an optimized application process of the silicone oil to the syringe wall in pre-filled syringes, and to a reduction in the amount of silicone oil used in this new application process." Ex. 2209 ¶ 36 (citing Ex. 2018, 3) (describing the baked silicone process as reducing the incidence of silicone-related complications). Dr. Wolfe opines that "[t]his is an important consideration in light of the large number of repeating anti VEGF intravitreal injections performed on a particular patient, and given that treatment of retinal pathologies can require years of repeated injections." *Id.* (citing Ex. 2215, 1, 8).

Mr. Koller, testifying for Petitioner, agrees. Ex. 1105 ¶ 103. He testifies that "the method of siliconization (spray-on or baked-on) impacts the way silicone oil interact with drug products," and "baked-on siliconization creates a thin layer of silicone oil to the inner surface of glass syringe barrels, thereby reducing the amount of 'residue' or 'free' silicone oil." *Id.*; Ex. 1003 ¶¶ 65, 66. Mr. Koller opines that "[u]sing baked-on siliconization is therefore important for a PFS containing a protein drug formulation because excessive silicone oil can cause protein aggregation and drug degradation." Ex. 1105 ¶ 103. Even though this optimized application process is an important feature of the Lucentis PFS, the '631 patent claims do not require a specific siliconization process, and thus cover both baked-on and spray-on siliconization. *Id.*

Another product feature important to the Lucentis PFS, but unclaimed, is the [redacted] *Id.* ¶ 105. Mr. Koller persuasively explains that "[redacted]," because [redacted]

[redacted]." *Id.* (citing Ex. 2194 (Overcashier Dep. Tr.)), 142:17–143:2. Mr. Koller relies on [redacted] *Id.* (quoting Ex. 2141, 51). As Mr. Koller notes, "the '631 Patent does not claim a tip cap." *Id.*

The Claims of the '631 Patent Are Broader than the Lucentis PFS

Petitioner has also produced persuasive evidence showing that other embodiments within the claim scope would not necessarily produce the same results as Lucentis PFS and be commercially successful. *See* Pet. Reply at 23. We find persuasive Mr. Koller's testimony that nearly all of the claims (except claims 8–10) do not require the PFS to contain an ophthalmic solution comprising the drug Lucentis, but encompass a PFS that contains an ophthalmic solution that comprises any VEGF-antagonist, regardless of the effectiveness of such drug product. Ex. 1105 ¶¶ 98–99. Specifically, Lucentis PFS[22] contains a single VEGF-antagonist—ranibizumab—but claim 1, for example, recites that the ophthalmic solution comprises "a VEGF-antagonist," without limiting it to any particular VEGF-antagonist. Yet, Patent Owner offers no evidence that a PFS comprising other VEGF-antagonists within the claim scope would be commercially successful. *Id.*

[22] "The Lucentis® drug formulation and the Lucentis® active ingredient molecule (ranibizumab) are the same in the vial presentation as in the PFS presentation. In the PFS presentation, the Lucentis® drug formulation is stored in the PFS for the entirety of its shelf life." Ex. 2204 ¶ 57.

Mr. Koller also testifies persuasively that the Lucentis PFS contains only [redacted] of silicone oil on the syringe barrel, but the claims broadly cover silicone oil amounts as high as 100 µg (claims 1–21, 23–26) or about 50 µg (claim 22). Ex. 1105 ¶ 98. There is evidence showing that Novartis deemed that a syringe comprising [redacted]. *Id.* (citing Ex. 1158, 112:13–113-4; Ex. 1159, 81:1–82:8). For example, as explained by Juergen Roettele, Ph.D (a Novartis technical project lead for Lucentis PFS), a process using 100 micrograms of silicone oil for a prefilled syringe, "[redacted]" Ex. 1159, 81:1–82:8, 18:21–19:5. Because the upper bounds of the claimed silicone oil range were purportedly not commercially feasible, the nexus and coextensiveness become more of a challenge for Patent Owner to establish.

Summary

Considering the totality of the unclaimed features and components of the Lucentis PFS, and the evidence that demonstrates these features and components were deemed important to the function and success of the product, Patent Owner has not met its burden to establish that the Lucentis PFS embodies the claimed features and is coextensive with them. We are cognizant of *Fox Factory*'s caution that the existence of one or more unclaimed features, standing alone, does not necessarily mean that nexus cannot be presumed. *Fox Factory, Inc.*, *944 F.*3d at 1374. Considering the evidence as a whole, including Patent Owner's lack of persuasive rebuttal as to the importance of each feature examined above, we cannot reach a

determination that the Lucentis PFS "is the invention disclosed and claimed." *Id.*

The features of the Lucentis PFS examined above, even according to Patent Owner's own declarants, are not "additional insignificant features," or merely "standard components of any PFS." *Id.*; Sur-reply 21. To the contrary, these features are described by Patent Owner's own documents and witnesses as: [redacted] *See supra.*

Commercial Success

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). "Demonstrating that an invention has commercial value, that it is commercially successful, weighs in favor of its non-obviousness." *WBIP*, 829 F.3d at 1337. Further, "non-patented features and features known in the prior art underlay the commercial success." *Ethicon Endo-Surgery, Inc.*, 812 F.3d at 1034.

There is little dispute that Lucentis PFS practices certain claims of the '631 patent and that Lucentis PFS was commercially successful. For reasons set forth below, however, Patent Owner has not persuasively shown that the commercial success of Lucentis PFS was due to a claimed feature that was not already known in the art prior to the '631 patent. Based on the full record developed during trial, we determine that the success of Lucentis PFS was driven by a number of unclaimed product design features and the efficacy of the Lucentis drug (ranibizumab).[23] Further, we find that there is no persuasive evidence in the final record that Lucentis PFS was commercially successful primarily because of the claimed features, *i.e.*, a terminal sterilization and 1–100 μg of silicone oil with break loose forces less than 11 N.

Patent Owner claims that "Lucentis PFS is a '[redacted] and [redacted] product that enjoys '[redacted]' which doctors [redacted]" Sur-reply 20 (emphasis added) (citing Ex. 2348, 24:6–8, 37:21–38:6, 40:10–18). As examined above, however, many of the features that make the Lucentis PFS '[redacted] are not claimed in the '631 patent. Some of the reasons that it was [redacted] are due to unclaimed features such as the [redacted]. Ex. 2201 ¶¶ 104–105; Ex. 2206 ¶¶ 46–48.

[23] These arguments related to the efficacy of the drug (ranibizumab) are relevant to claim 1 and to all claims that do not require ranibizumab.

Petitioner persuasively argues, "Dr. Wolfe and [redacted] testified that physicians use Lucentis PFS due to its convenience, which was a known PFS feature and not attributable to the '631 Patent claims." Pet. Reply 22 (citing Ex. 2209 ¶ 31; Ex. 1161, 115:8–14, 115:22–116:18; Ex. 1106 ¶¶ 30–34). As for convenience, this is also a feature not directly attributable to the claims of the '631 patent as we examine below.

As Petitioner's testifying ophthalmologist, Dr. Kiss, persuasively explains, "physicians overwhelmingly prefer a PFS over vial," and they do

> so for reasons that were already known in the prior art (e.g., Macugen PFS). A PFS requires fewer steps and less time to administer. For example, using a vial requires two needles while using a PFS requires only one. *See* Ex. 2209, ¶ 32. Because administering a PFS requires fewer steps and less time than a vial and syringe, using a PFS allows an ophthalmologist to treat more patients. Moreover, fewer steps with PFS translates to a clinically meaningful reduction in the rate of endophthalmitis. *See* Ex. 2215.003; *see also* Ex. 2209, ¶ 35 . . . . Therefore, ophthalmologists strongly prefer using the Lucentis PFS over the vial presentation of Lucentis because the PFS provides efficiency, convenience, and reduced risk of infection due to fewer administration steps.

Ex. 1106 ¶ 30.

Dr. Kiss and Dr. Wolfe (Patent Owner's testifying ophthalmologist) seem to agree that certain factors make a PFS much more preferable to use over a vial. Ex. 1106 ¶ 31; Ex. 2209 ¶ 31. These factors include that "PFS are 'significantly more convenient, save physician time, minimize risk of physician error, and decrease the risk of infection,'" and, a "reduced risk of infection from using a PFS" due "to the elimination of several steps in the

process required to transfer the medication from the vial to the syringe." Ex. 1106 ¶ 31 (citing Ex. 2209 ¶ 35). Dr. Kiss relies on [redacted] *Id.* ¶ 32 (citing Ex. 2171, 2). Dr. Kiss testifies, and we find persuasive, that "[redacted]." *Id.*

Thus, many of the attributes identified above that drive ophthalmologists' use of the Lucentis PFS existed in prior art PFSs for intravitreal injection. *See id.* "For example," Dr. Kiss points to the "Macugen PFS and Trivaris PFS, both commercially available as pre-filled syringes prior to 2012," as "provid[ing] ophthalmologists with efficiency, convenience, reduced risk of infection due to fewer administration steps, and more accurate dosing." *Id.* ¶ 33. For these reasons, Dr. Kiss testifies persuasively that "an ophthalmologist would very much prefer to use the Lucentis PFS over a Lucentis vial format." *Id.* ¶ 34.

Testimony and evidence produced by both parties attributes a significant portion of the success of the Lucent PFS to the drug used in the product—ranibizumab. For example, a Novartis employee overseeing all of Novartis's development activities in ophthalmology testified that [redacted]. Ex. 1161,

17:19–20, 115:22–116:18 [redacted]). As Petitioner shows, however, "Lucentis PFS contains a single VEGF-antagonist—ranibizumab—but the '631 Patent functionally claims any VEGF-antagonist." Pet. Reply 23 (citing Ex. 1105 ¶ 99) (also noting claims 8–10 are limited to ranibizumab). Patent Owner has not persuasively shown that a PFS comprising other VEGF-antagonists within the claim scope of claim 1 would be successful.[24] For instance, Petitioner produces persuasive evidence showing that Beovu PFS, also developed by Novartis, and allegedly within the scope of the claims, would not be successful. *See* Ex. 1005, 42; Ex. 1106 ¶ 35 (noting "reports of Beovu causing 'severe vision loss, retinal artery occlusion and/or vasculitis' (Ex. 1250)"; Ex. 1208, 58:5–15. Even though the PFS version of this drug has apparently "not yet been launched" (Sur-reply 23) we find this presents additional evidence showing the importance of ranibizumab to the success of the Lucentis PFS. Because claim 1 encompasses any PFS that comprises any VEGF-antagonist, regardless of how effective the drug product is, this presents

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[24] As noted above, claim 8 specifically requires "ranibizumab." The burden is on Patent Owner to establish the significance of ranibizumab to the secondary considerations asserted. Although a Novartis witnesses testifies that the [redacted]" Patent Owner has not persuasively argued or explained how embodiments of the invention requiring ranibizumab (claims 8–10) would have been uniquely commercially successful or how the drug relates to other secondary considerations. Ex. 1161, 17:19–20.

further evidence that a nexus is lacking between the alleged commercial success of the Lucentis PFS and claim 1. Ex. 1105 ¶ 99; Ex. 1106 ¶ 34.

The low silicone oil content of Lucentis PFS presents a safer delivery system (as examined above) and this is achieved because Lucentis PFS "[redacted]" (PO Resp. 51). The claims, however, cover up to about 100 µg of silicone oil (claims 1–21, 23–26) or about 50 µg (claim 22). Pet. Reply 24 (citing Ex. 1105 ¶ 98). There is evidence in the final record which suggests that 100 µg would have been unsuitable for Lucentis PFS. For example, "Dr. Sigg testified [redacted] (Ex. 1158, 110:2–17), meaning the claims cover embodiments unsuitable for a commercial product." Pet. Reply 24. In essence, the breadth of claim scope up to about 100 µg of silicone oil encompasses successful ranges (Lucentis PFS) as well as the upper bounds that may be [redacted] We do not give this 100 µg testimony considerable weight, however, because other evidence suggests that a "silicone oil level (*i.e.*, 100 µg) was low enough to avoid unwanted interactions with sensitive drugs." Ex. 1105 ¶ 119. Regardless, the upper bounds of claim 1 (up to 100 µg of silicone oil), would most likely "[redacted]," as testified by Dr. Sigg. Ex. 1158, 110:2–17.

We have considered Patent Owner's evidence related to the significant commercial success of the Lucentis PFS, including the declaration of Mr. Malackowski. PO Resp. 55–56; Ex. 2205. The data presented by Patent Owner shows that the launch of the Lucentis PFS

presentation in January 2017 helped to slow declining sales of the vial presentation and sales eventually climbed higher than they had been at any previous time. PO Resp. 55 (citing Ex. 2099). We disagree, however, with Patent Owner's conclusion that "these data confirm nexus because they show that it was the PFS presentation, embodying the '631 patent, that enabled Genentech to reverse the downward trend for Lucentis and to capture incremental sales and market share." *Id.* at 56. Patent Owner and Mr. Malackowski wrongly focus on the purported nexus between commercial success and the Lucentis PFS, instead of the nexus between commercial success and the claimed inventions of the '631 patent. *See* Ex. 1107 ¶¶ 32–38 (Declaration of Lisa J. Cameron, Ph.D). We agree with Dr. Cameron that "Mr. Malackowski assumes that the Lucentis PFS is coextensive with the claimed inventions of the '631 Patent," and thus, "makes no attempt to establish a nexus between the claimed inventions of the '631 Patent and the alleged commercial success of the PFS form of Lucentis." *Id.* ¶ 34 (emphasis omitted).

Although the Lucentis PFS earned significant sales, "Mr. Malackowski fails to provide a systematic analysis of Lucentis PFS revenues relative to those of other anti-VEGF treatments." *Id.* ¶ 33. As one example, Eylea, a leading FDA-approved, anti-VEGF treatment, was used to treat more eyes than Lucentis both before and after the launch of the Lucentis PFS and appears to have gained considerable market share over Lucentis both before and after launch of the Lucentis PFS. Ex. 1107 ¶ 23; Ex. 2205 ¶ 42.

Further, we agree with Dr. Cameron that "Mr. Malackowski never addresses the critical issue of whether the PFS form of Lucentis has generated substantial incremental profits over and above those associated with the vial form of Lucentis." *Id.* For example, Mr. Malackowski relies on data showing that "Lucentis vial sales had generally increased from 2010 through 2014," and the sales of the Lucentis vial in the 12-month period before launch of the Lucentis PFS [redacted]. Ex. 2205 ¶¶ 38–39. For the 12-month period after the launch of Lucentis PFS in 2017, however, sales remained fairly flat at [redacted] showing almost no growth due to the PFS launch. *Id.* Mr. Malackowski presents evidence showing how Lucentis was losing market share to Eylea, but with the launch of Lucentis PFS the market [redacted]. *Id.* ¶¶ 39–42 ("Beginning in 2015 Lucentis vial sales began to decline," but "in 2017, Lucentis sales 'increased by 1% in the US, mainly driven by the launch of prefilled syringes' and growth in new indications."). Thus, although market share data is not required to show commercial success, Patent Owner's analysis of Lucentis PFS revenues relative to those of other anti-VEGF treatments is not persuasive to demonstrate the patented invention was a noticeable driver of commercial success. As a result, we find Mr. Malackowski's testimony less persuasive as to commercial success.

Based on the final record, the commercial success of Lucentis PFS was inadequately linked to the claimed invention. We determine that there is no nexus between any commercial success of Lucentis PFS and the '631 patent because "non-patented features and features known in the prior art underlay the commercial success." *Ethicon Endo-Surgery, Inc.*, 812 F.3d at

1034. As set forth in our analysis above, all the claimed features were already known in the art as demonstrated by Boulange and Sigg, and Patent Owner has not persuasively established how claim 1 as a whole would have driven the commercial success of Lucentis PFS apart from the non-patented features. Finally, although Patent Owner need not produce evidence of commercial success for every potential embodiment of the claims, in this instance, Novartis has not provided an adequate basis to support the conclusion that other embodiments falling within the claims will behave in the same manner.

Claim 8 of the '631 patent recites "the anti-VEGF antibody is ranibizumab." Apart from pointing out that Lucentis PFS contains ranibizumab, Patent Owner has not persuasively explained why the subject matter of this claim, apart from other claims, would have been commercially successful. *See* PO Resp. 51, 54 ("Claim 1 includes, but is not limited to, ranibizumab."). Similarly, claim 22 requires up to about 50 μg of silicone oil, yet the Lucentis PFS uses "[redacted]" *Id.* Patent Owner has not shown whether a product with more than [redacted] of silicone oil would have been viable, no less commercially successful.

Long-felt Need, Failure of Others

Because the evidence between long-felt need and failure of others is so intertwined, we examine these indicia together. "The existence of a long-felt but unsolved need that is met by the claimed invention is further objective evidence of non-obviousness." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). Establishing long-felt need first requires objective evidence that a recognized problem existed in

the art for a long period without solution. *See Orthopedic Equip. Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376 (Fed. Cir. 1983). Second, another must not have satisfied the long-felt need before the invention of the challenged patent. *Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Third, the invention of the challenged patent must satisfy the long-felt need. *In re Cavanagh*, 436 F.2d 491, 496 (CCPA 1971); *see also Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332–33 (Fed. Cir. 2009) (articulating all three factors).

As noted above, Patent Owner makes arguments related to others attempting to solve the problem of high levels of silicone oil known to cause intravitreal contamination but ultimately failing. The evidence in the final record establishes that others had PFS products that were terminally sterilized with VHP by at least 2010. Ex. 1102 ¶¶ 14–21; Ex. 1105 ¶¶ 63–64. Patent Owner has, however, shown how certain of these products had shortcomings as compared to the claimed invention. Below, we consider each of these products, and how their development and commercialization impact long-felt need, failure of others, and skepticism.

Macugen PFS

Patent Owner alleges there was a long-felt need for the claimed invention, specifically "a terminally sterilized PFS for intravitreal injection of a VEGF-antagonist containing the claimed amounts of silicone oil," and "the only PFS for intravitreal injection of a VEGF-antagonist on the market (Macugen) had [redacted] of silicone oil and was known to cause 'intravitreal contamination by silicone oil droplets.'" PO Resp. 56–57. Petitioner counters that Macugen PFS successfully terminally sterilized a PFS by 2008.

Pet. Reply 26. Further, Becton Dickson had already made public syringes with less than 100 µg of silicone oil and break loose force less than 11 N, i.e., Boulange. Ex. 1003 ¶¶ 163–164.

Based upon our review of the final record, Becton Dickinson successfully manufactured Macugen PFS, a terminally sterilized 1 mL syringe. Ex. 1105 ¶ 62. This product, however, never integrated the teachings set forth in Becton Dickinson's Boulange application of reducing the amount of silicone oil used in the pre-filled syringe. *Id.* As such, Patent Owner has shown that the problems solved by reduced silicone oil in the claimed invention were encountered by Macugen PFS and not solved. Specifically, because Macugen PFS had up to [redacted] of silicone oil, the excessive silicone oil caused some degree of intravitreal contamination. PO Resp. 56–57; Ex. 2189, 44:19–21; Ex. 2001 ¶ 42 ("known to be associated with accumulation of silicone oil droplets in patients' eyes") (citing Ex. 1080, 1; Ex. 2023, 11–12). Patent Owner's evidence of problems attributable to silicone oil causing intravitreal contamination in Macugen PFS is scant, thus, it does not appear to be a substantial recognized problem. Although Becton Dickinson had disclosed (Boulange) [redacted] 1 mL glass "[redacted]" syringes comprising less than 50 µg silicone oil by May 2011 (Ex. 1105 ¶ 138), Becton Dickinson never integrated its low silicone oil know-how into the commercialized Macugen PFS to address any issues with silicone oil causing intravitreal contamination. Ex. 1105 ¶ 113; Ex. 1215 ¶¶ 3–5; Ex. 1162, 1–6.

The evidence and argument related to Macugen PFS is mixed, but slightly in favor of Patent Owner. The development of Macugen PFS does

not necessarily evince a failure of others because the problems purportedly addressed by the claims of the '631 patent were either already met by Macugen PFS, or not a concern based on the evidence before us. We agree with Petitioner that "Macugen PFS already met every need expressed by Novartis, except for the claimed silicone oil amount." Pet. Reply 26 (citing Ex. 1105 ¶¶ 108–116). Where we diverge from Petitioner's position is the argument that "[i]n turn, the silicone oil amounts were met by BD's baked-on syringes." *Id.* The evidence shows that Macugen PFS never integrated the teachings related to low silicone oil in a commercialized product. Thus, there was a need to reduce silicone oil contamination that was not necessarily met by Macugen PFS.

Eylea PFS (2010)

As noted above, in an attempt to demonstrate that others succeeded before Patent Owner, Petitioner relies on the Eylea PFS, and alleges that "[b]y June 2010, Petitioner had reduced to practice a 1 mL Eylea pre-filled syringe that (i) was terminally sterilized, (ii) used a baked-on syringe with less than 100 μg of silicone oil on the syringe barrel, and (iii) met the requirements of the USP789," and thereafter "used in clinical studies and approved by regulatory authorities in Australia in 2012." Pet. 73 (citing 14 pages of an ITC Brief – Ex. 1005, 109–110, 114–125; Ex. 1066); Pet. Reply 26–27 (citing 19 paragraphs of Dr. Graham's expert report – Ex. 1102 ¶¶ 14–29, 36, 40–41).

Petitioner's attempt to rely on Eylea PFS by making three bullet points with no supporting explanation as to how the arguments relate to the claims, and then incorporating dozens of pages of supporting material, is a

classic example of improper incorporation by reference, which we forbid. 37 CFR § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Further, significant portions of Ex. 1005 are redacted. We decline to dig through excess, redacted, material to discovery Petitioner's case. Accordingly, Petitioner has not shown that Eylea PFS is a proper example of others succeeding before Patent Owner.

Patent Owner does not persuasively argue or point to evidence showing that the Eylea PFS is an example of others striving to satisfy a long-felt need, or that the Eylea PFS otherwise evinces a failure of others. Instead, Patent Owner points out that "there is no evidence that the Australian syringe that Mr. Koller points to was ever launched or that the makers were actually successful in making a syringe that could be marketed to physicians to treat patients." Ex. 2201 ¶ 122. Accordingly, the evidence related to Eylea PFS does not support either party for this indicium.

Lucentis PFS – Genentech

Petitioner contends that "Novartis has not established that others failed at developing a terminally sterilized PFS," because "[redacted]." Pet. Reply 26 (citing Ex. 1100 ¶¶ 58–59); *see* Ex. 1100 ¶ 59 ("[redacted]").

Patent Owner contends that "[t]he evidence does not support Petitioner's claim that Genentech '[redacted]'" Sur-reply 18. Patent Owner argues, and we agree, that "[redacted]" *Id.* (citing Ex. 2203 ¶¶ 51–55, 83–88, 94). Petitioner's claim that [redacted] is not supported. [redacted] Sur-reply 18 (citing Ex. 2339, 18:18–20:11). Thus, Patent Owner's position that [redacted] is supported. *Id.*

We find persuasive Patent Owner's explanation as to how [redacted] *Id.* at 19 (citing Ex. 1210, 132:16–135:3, 150:6–154:2; Ex. 2115, 8). Further, we agree with Patent Owner's conclusion that [redacted] Ex. 2100, 164. Patent Owner persuasively shows that "[e]ven as of 2012, Genentech still believed that the preferred silicone oil amount for a

PFS containing a biologic like a VEGF-antagonist was between 200–500 μg." PO Resp. 57 (citing Ex. 2022, 11). However, the fact that [redacted] does not necessarily translate to a failure to reduce silicone oil levels, as Patent Owner recognizes it was not a concern. The evidence related to [redacted] weighs slightly favorable to Patent Owner. Ex. 2206 ¶¶ 5–18; Ex. 2194, 37:1–13.

Overall, we give Patent's Owner's evidence of long-felt need and failure of others some weight in favor of patentability, but for the reasons set forth below the weight is not significant when evaluating all evidence of obviousness and non-obviousness. Novartis characterizes the need that was not met as including a "syringe with low levels of silicone oil" to prevent silicone oil injection into the eye. Ex. 2204 ¶¶ 80, 91 ("the problem of silicone oil in the eye"). As Petitioner persuasively argues, "[t]he '631 Patent, however, only claims silicone oil applied to the syringe barrel," whereas "[s]ilicone oil can also be introduced into a PFS via the stopper and filling process, neither of which are claimed." Pet. Reply 25 (citing Ex. 1105 ¶¶ 110–112; Ex. 1207, 22:2–23:14; Ex. 1211, 32:18–35:16). Further, "whether the silicone oil migrates from the syringe barrel and into the patient's eye depends on the process used to apply the oil, which also is not claimed." *Id.* (citing Ex. 1105 ¶ 111; Ex. 1207, 35:20–36:6). As we have previously determined, the application of silicone oil through a baked-on process is more precise and more homogenous, using approximately one-tenth the silicone oil quantity of sprayed-on syringes. *See* Ex. 1003 ¶¶ 63–

65, 165 ("baking attaches the silicone oil to the inner surface of the syringe barrel, which reduces the amount of 'residual' or 'free' silicone oil that can enter the protein formulation and cause negative effects").

This evidence shows that producing a syringe that avoided silicone oil contamination was achieved not just by reducing the volume of oil coating the syringe, but also by the baked-on application process. Thus, for these reasons, the claims do not necessarily satisfy the need for a "syringe with low levels of silicone oil" that avoids silicone oil release into the eye. These other factors, including the oil on the stopper and filling process, are also important to satisfying that need, yet they are not claimed. As noted above, the invention of the challenged patent must satisfy the long-felt need.

Skepticism

As far as skepticism, we have considered both parties' contentions and find the evidence does not persuasively support either position, except for claim 22. Patent Owner's position is focused on communications between Vetter and Novartis. PO Resp. 59. Specifically, Patent Owner cites a statement that a syringe with [redacted]" Ex. 2206 ¶¶ 24–26, 28; Exs. 2142, 2143.

We find no skepticism because the challenged claims cover up to about 100 µg, meaning [redacted]. Ex. 1105 ¶¶ 117–120. Other evidence cited by Petitioner suggests that Vetter was [redacted]. *See*

Ex. 1213, 101:9–103:3; Ex. 1168, 2–4; Ex. 2143, 2 ([redacted]).

For claim 22, however, Patent Owner separately asserts that "[redacted] skepticism is particularly relevant to claim 22, which requires 'from about 1 to 50 μg silicone oil.'" PO Resp. 59. With regard to claim 22, we find the [redacted] communications show some skepticism by industry experts in achieving the invention claimed, which requires a maximum of 50 μg silicone oil. However, Petitioner has produced evidence showing that Becton Dickinson was offering 1 mL syringes (but not PFS) with as low as [redacted] of silicone oil on the barrel, consistent with Boulange, which likewise discloses less than 50 μg of silicone oil for a 1 mL syringe barrel. Ex. 1105 ¶ 120. Accordingly, the evidence in favor of patentability for claim 22 is only slightly in Patent Owner's favor related to skepticism.

Licensing

Novartis asserts that licenses show the non-obviousness of the '631 patent claims, specifically noting its license with Genentech [redacted]. Sur-reply 26 (citing Ex. 2346, 54:1–13). Patent Owner does not, however, provide details as to how the patent license shows a nexus to the claims at issue in the '631 patent.

Petitioner contends, and we agree, that Genentech's license has a weak nexus to the '631 patent claims, because it is directed to [redacted] that are not disclosed in the '631 patent. Pet. Reply 27 (citing Ex. 2121, 1; Ex. 1105 ¶¶ 124–132; Ex. 1107 ¶¶ 54–58). The conveyed rights encompassed the [redacted] related to a pre-filled syringe. Ex. 1105

¶ 125 (citing Ex. 2121, 10–14). Notably, the '631 patent was licensed [redacted] *Id.* (citing Ex. 2121, 22); Ex. 2206, 19–20 [redacted]

In considering the Genentech license, "the relevant inquiry is whether there is a nexus between the patent and the licensing activity itself, such that the factfinder can infer that the licensing 'arose out of recognition and acceptance of the subject matter claimed' in the patent." *GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)). Novartis does not persuasively establish that the licensing arose out of recognition and acceptance of the subject matter claimed in the '631 patent claims. [redacted] Yet, these things do not demonstrate a nexus between the '631 patent and the licensing activity itself. Novartis has not cited to evidence showing that the value of the license was driven by the '631 patent specifically, as opposed to the value of the other [redacted]. The licensing evidence provides, at most, a scant basis for assessing the value of the '631 patent. The Genentech license provides little or no evidence of non-obviousness.

vi. Overall Determination of Obviousness Based on all *Graham* Factors

In sum, having considered the complete record developed during trial, we conclude that Petitioner has demonstrated by a preponderance of the

evidence that the subject matter of claim 1 would have been obvious over the combined disclosures of Boulange, Sigg, and USP789.

Petitioner presents a strong case of obviousness and provides articulated reasons with sound support in the record for combining the references. Patent Owner's reasons why the person of skill in the art would not have made the combination run contrary to the teachings of the references and to the knowledge base of the skilled artisan at the time of invention. Patent Owner has not established a nexus between the commercial success of the Lucentis PFS and the subject matter of claim 1, in part because of "patentee's own assertions about the significance of the unclaimed features," and also because each claimed element was already known in the art and commercialized. *Fox Factory, Inc.*, 944 F.3d at 1375. The stronger evidence of obviousness cannot be overcome with the weaker evidence of long-felt need and failure of others tending to show nonobviousness. The evidence of licensing is weak at best because the '631 patent is but a minor piece of a larger agreement and the license provides a scant basis for assessing the value of the '631 patent.

Considering the totality of the evidence before us, Petitioner has established by a preponderance of the evidence that claim 1 would have been obvious for the reasons set forth above.

5. Claim 14

We next consider five dependent claims that Patent Owner alleges are separately patentable over the combination of Sigg, Boulange, and USP789. *See* PO Resp. 32–41. We address each claim in turn.

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."

Petitioner persuasively shows that the Table 5 of Boulange teaches a break loose force of 4.7 N for Stopper C, meeting claim 14's requirement of a stopper break loose force of less than about 5 N. Pet. 49–50.

Next, we examine the limitation requiring that "the syringe has a stopper slide force of less than about 5N." According to Mr. Koller, Boulange "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." Ex. 1003 ¶ 142. The disclosed slide force "F" for Stopper C in Table 5 of Boulange is less than 5 N (4.6 N), while the slide force "S" is 6.5 N. Mr. Koller testifies that "[b]ecause 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." Ex. 1003 ¶ 146.

Mr. Koller also testifies 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," because "a POSITA would have understood that the stopper slide force is proportional to the speed at which the stopper is tested." *Id.* Mr. Koller notes that "Boulange, for example, discloses that the tests were performed at 380 mm/min," and then testifies that "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." *Id.* (citing Ex. 1008, 16:13–15; Ex. 1076, 5) (describing testing at 4 mm/sec (*i.e.*, 240 mm/min), which is "representative of manual syringe delivery").

Patent Owner contends that Petitioner's assertion of "routine optimization" to achieve a slide force less than 5 N is a conclusory assertion that is insufficient for Petitioner to meet its burden. PO Resp. 32. Patent Owner argues that Petitioner failed to set forth some rational underpinning for a routine optimization argument. *Id.* Patent Owner also believes that Petitioner improperly incorporated by reference arguments from Mr. Koller's declaration. *Id.*

According to Patent Owner and its expert, Mr. Leinsing, "Mr. Koller's 'routine optimization' opinion is flawed," because "completely changing the test used to assess a syringe's slide force in order to get a more favorable result is not 'optimization,' particularly since the most obvious way for a POSA to optimize a syringe to achieve lower forces would have been to add more silicone oil." *Id.* at 33 (citing Ex. 2201 ¶ 144). Mr. Leinsing directs us to a test in Boulange using 500 μg of silicone and testifies that "the most straightforward way for a POSA to optimize the syringe to address excessive slide force would have been to increase the lubrication of the syringe by increasing the amount of silicone oil." Ex. 2201 ¶ 144. Without doing so, Mr. Leinsing explains, a POSITA would not have expected to be able to achieve lower slide forces. *Id.*

We first consider that the break loose and slide forces are a measure of the force that would in practice be asserted by a clinician to depress the plunger. Ex. 1001, 1:36–39. Such a force, as pointed out by Mr. Koller, will be dependent on several factors, including the speed of depression, and also upon the type and volume of syringe coating, as discussed above and examined by Mr. Leinsing. *See* Ex. 2201 ¶ 144. Despite the fact that the speed of depressing the plunger will alter the force required to slide the plunger, it is unclear on the current record if there is an industry standard of the appropriate speed to conduct such tests. For example, the '631 patent states that "[t]he forces are typically measured at a stopper travelling speed of 190 mm/min." Ex. 1001, 5:44–45.

With that background in mind, Mr. Koller suggests that the speed of pressing the plunger is a variable that impacts force and testifies that changing the speed would have been routine optimization. Specifically, changing Boulange's "380 mm/min" speed to "240 mm/min" as taught in an article from "Pharmaceutical Review – Technical Considerations in the Development of Pre-filled Syringes for Protein Products" (Ex. 1076) would have been simple optimization. The speed (240 mm/min) is described in the article as "representative of manual syringe delivery." Ex. 1076, 5.

Mr. Leinsing does not contest that the "240 mm/min" speed is an accurate "representative of manual syringe delivery," but instead he suggests that the most straightforward way to optimize slide forces would have been to increase the lubrication. Even if true, we find Mr. Koller's optimization approach and explanations credible and more persuasive because the impetus for combining Sigg with Boulange was to minimize the volume of

silicone oil on the syringe body, which would be defeated by Mr. Leinsing's optimization approach. *See* Ex. 1003 ¶ 159.

Next, we also are cognizant that the claim limitation requires "less than *about* 5N," which creates a degree of variance. The '631 patent states that "[t]he term 'about' in relation to a numerical value x means, *for example*, x±10%." Ex. 1001, 10:28–29 (emphasis added). Further, when the term "about" is used, it avoids a strict numerical boundary to the specified parameter. *See Cohesive Techs. v. Water Corp*., 543 F.3d 1351 (Fed. Cir. 2008).

Within this context, we determine that Petitioner has persuasively established that it would have been a matter of routine optimization for a POSITA to achieve a slide force of "less than about 5N," for Force S for Stopper C in Table 5 (disclosed as 6.5 N with a speed of 380 mm/min). A POSITA would have understood that the stopper slide force is proportional to the speed at which the stopper is tested and that a speed of "240 mm/min" would have been representative of manual syringe delivery[25] such that the slide force of Stopper C in Table 5 of Boulange would have been less than about 5 N in optimized conditions that were more representative of manual syringe delivery. Ex. 1003 ¶¶ 183, 222. As persuasively explained by Mr. Koller, physicians typically inject at lower speeds. *Id.*

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[25] Although we do not rely on the teachings of the '631 patent, had Boulange's tests been conducted at the testing speed disclosed in the '631 patent, the resulting forces in Table 5 of Boulange would have been much less because of the decrease from 380 mm/min to 190 mm/min. *See* Ex. 1003 ¶¶ 183, 222 (explaining relationship of speed to force).

In addition, we credit Mr. Koller's testimony that the friction force S and friction force F disclosed in Boulange represent slide forces. Ex. 1003 ¶ 142. Based on that testimony, we agree with Mr. Koller that friction force "F"[26] for Stopper C in Table 5 of Boulange, which is less than 5 N (4.6 N), satisfies the slide force limitation in claim 14. Ex. 1003 ¶ 222. As Mr. Koller explained, claim 14 does not limit when or where along the syringe barrel the glide force is measured, thus, slide force "F" (4.6 N) alone would also satisfy claim 14. *Id.* ¶ 144.

Because the POSITA was already attempting to minimize the silicone content in the Boulange and Sigg combination (as detailed above) we disagree that a POSITA would have been more inclined to just add more silicone oil as proposed by Mr. Leinsing. Finally, we do not see Petitioner's citation to one supporting paragraph in Mr. Koller's declaration as improper incorporation by reference.

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record, Petitioner has demonstrated by a preponderance of the evidence that claim 14 would have been obvious over Sigg, Boulange, and USP789.

[26] "[T]he 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." Ex. 1008, 15:13–15.

6. Claim 17

Claims 17 depends from claim 1 and further requires "[a] blister pack comprising a pre-filled syringe according to claim 1, wherein the syringe has been sterilized using H_2O_2 or EtO."

Petitioner asserts that "Sigg discloses a pre-filled syringe in a blister pack that is terminally sterilized by vaporized hydrogen peroxide (H_2O_2)." Pet. 51 (citing Ex. 1007, 6:26–28, 9:1–4; Ex. 1003 ¶¶ 228–229). Petitioner relies on Sigg's disclosure that "a prefilled container 100 previously filled . . . is decontaminated on surfaces 102 following encasement or packaging in a secondary package 104 by vaporized-hydrogen peroxide. Ex. 1007, 8:21–24.

Patent Owner challenges Petitioner's assertion as lacking both motivation and reasonable expectation of success. PO Resp. 33–34. Patent Owner asserts that a POSITA would have preferred Sigg's beta irradiation method, which is outside the scope of claim 17. Novartis examines "Example 1 of Sigg, which uses VHP," but allegedly "provides no information about experiment conditions and no data demonstrating whether, or how well, the method worked to sterilize the syringes." *Id.* at 34 (citing Ex. 2021 ¶ 64; Ex. 1007, 20:10–21:11). Patent Owner argues that "there is no indication that sterility testing was even done." *Id.* (citing Ex. 2001 ¶ 64; Ex. 1007, 20:10–21:11); Ex. 2203 ¶ 59. Patent Owner contends that "Example 2, which uses beta irradiation, contains far more useful information" about specific performance "under the test conditions." *Id.* Novartis reasons that picking "Sigg's VHP method while ignoring its beta irradiation method is based purely on the hindsight knowledge." *Id.*

Further, Patent Owner alleges that a POSITA "would not have reasonably expected to combine Boulange with Sigg's VHP method," because "[t]here is no example in Sigg of successful use of VHP to terminally sterilize a PFS." *Id.*

We have already considered, and found unpersuasive, Patent Owner's related arguments – Sigg's enablement and reasonable expectation of success of a VHP method to terminally sterilize a PFS. We incorporate that analysis from above. Further, we add that a disclosed motivation does not necessarily have to be the best option, only that it be a suitable option. *See Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021) ("It's not necessary to show that a combination is 'the best option, only that it be a suitable option.'" (quoting *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014)). Sigg encourages the use of VHP as "ideal for surface decontamination of prefilled containers," and, as such, it is a suitable option. Pet. Reply 15 (quoting Ex. 1007, 8:8–13). As examined above, we find the disclosures in Sigg persuasive.

Further, a POSITA would have had a reasonable expectation of success with Sigg's VHP method, even in light of Example 1, which Patent Owner alleges contains insufficient details. Sigg discloses that syringes were "treated with a vaporized hydrogen peroxide sterilization treatment" without affecting protein stability. Ex. 1007, 20:11–21:3. Further, Sigg describes that VHP is "*ideal* for surface decontamination of prefilled containers, yet not harmful to the stability or integrity of the contents of the prefilled container." *Id.* at 8:8–13 (emphasis added). As Mr. Koller persuasively testifies, "Sigg teaches using VHP to sterilize prefilled syringes

without impacting the drug product, which provides further motivation for its use." Ex. 1105 ¶ 78; *see also* Ex. 1100 ¶¶ 40–42.

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record, Petitioner has demonstrated by a preponderance of the evidence that claim 17 would have been obvious over Sigg, Boulange, and USP789.

7. Claim 21

Claim 21, depending from Claim 17, further requires "a pre-filled syringe . . . wherein the syringe has been sterilized using EtO or H_2O_2 with a Sterility Assurance Level of at least 10^{-6}."

Petitioner relies on Sigg and its disclosure of sterilizing the syringe with H_2O_2. Pet. 53. According to Petitioner, "Sigg defines sterile to mean the complete absence of microbial life, and discloses that the desired sterility assurance level (SAL) is at least 10^{-6}." *Id.* (citing Ex. 1007, 7:8–13 ("'Sterility' as used herein is meant to refer to complete absence of microbial life as defined by . . . a sterility assurance level (SAL) . . . . SALs for health care products are defined to be at least 10^{-6}."")). Petitioner relies on the testimony of Mr. Koller, who reasons that because Sigg discloses a SAL of at least 10^{-6}, "[i]t would also be routine optimization for a POSITA to achieve a sterility assurance level of 10^{-6} for the syringe." Ex. 1003 ¶¶ 236–238. Petitioner further contends that "Novartis's assertion that Sigg's disclosure of an SAL of 10^{-6} does not apply to VHP is contradicted by Sigg, and also by Novartis's prior representations to the USPTO." Pet. Reply 15–16.

Patent Owner argues that "Mr. Koller's opinions contain fundamental mistakes about sterility assurance levels." PO Resp. 35. Specifically, "Mr. Koller[] opines that a log reduction and an SAL are the same thing, and that a 6-log reduction equates to an SAL of 10^{-6}," is "incorrect, as is confirmed by Patent Owner's expert, Dr. Miller, who, unlike Mr. Koller, is a microbiologist and expert in sterilization." *Id.* at 36 (citing Ex. 2209 ¶ 90) (Declaration of Michael J. Miller, Ph.D). As counsel for Patent Owner elaborated at oral hearing, "an SAL of 10^{-6}, as is explained by our expert Dr. Miller, is a stringent sterility requirement," and [i]t requires longer treatment often, harsher treatment conditions, and it can lead to additional exposure of the drug to the sterilizing gases and to damage to the drug and it would lower the reasonable expectation of success." Tr. 52:12–16.

Patent Owner contends that "Petitioner's general statement that 'Sigg discloses a SAL of at least 10^{-6}' (Pet. 53) is insufficient to meet its burden on claim 21, as the claim specifically requires an SAL of at least 10^{-6} *using VHP or ETO*." PO Resp. 37. Patent Owner argues that because Sigg identifies two methods of terminal sterilization, beta irradiation and VHP, but only links its beta irradiation method with achieving a SAL of 10^{-6}, Petitioner has failed to meet its burden. *Id.* (citing Ex. 2189, 64:15–65:1, 58:9–13, 59:11–14). Patent Owner notes that "claim 15 of Sigg recites achieving an SAL of 10^{-6} using beta irradiation," yet, "[t]here is no similar claim for VHP." *Id.* Patent Owner argues that Example 1, which uses VHP, provides no information on SAL. *Id.* at 34. Patent Owner contends that "Petitioner has not even attempted to provide a specific motivation for a POSA to use Sigg's VHP method to achieve an SAL of 10^{-6}," and "Mr.

Koller fails to explain how this 'routine optimization' would have been achieved." *Id.* at 38. Patent Owner relies on the real-world example of the difficulty using sterilizing gases to terminally sterilize the Lucentis PFS to an SAL of 10^{-6}. *Id.*

We find Petitioner's contentions more persuasive. Sigg defines "sterility" for a health care product as 10^{-6} and describes VHP as a "sterilization" treatment. Ex. 1007, 7:6–13, 20:11–16; Ex. 1003 ¶ 237. Mr. Koller and Dr. Agalloco persuasively explain that Sigg discloses that VHP achieves an SAL of 10^{-6}, because Sigg describes that the "*required SALs* for health care products are defined to be at least 10^{-6}," which includes syringes. Ex. 1007, 7:8–13 (emphasis added); Ex. 1105 ¶ 81; Ex. 1100 ¶¶ 43–48. Establishing an SAL of 10^{-6} is based on regulatory requirements and a requirement for all PFS syringes. Ex. 1100 ¶ 43 ("a person knowledgeable in microbiology and sterilization techniques would understand that Sigg's VHP method is expected to achieve an SAL of 10^{-6} for the disclosed syringes because that was the required SAL for syringes"). Mr. Koller testifies that "Sigg repeatedly refers to VHP as a terminal sterilization method," and "a POSITA would interpret Sigg as disclosing that VHP is a method of achieving sterility for syringes, which Sigg defines as an SAL of 10^{-6}." Ex. 1105 ¶ 81.

We find persuasive Mr. Koller's explanation of the difference between the terms "sterilization" and "sanitization." *Id.* ¶ 82. As explained by Mr. Koller, "Dr. Sigg explained that an SAL of 10^{-6} is understood to mean 'sterilization,' while an SAL of 10^{-3} is understood to mean 'sanitization,'" and thus, "[b]y using the term 'sterilization' in the Sigg

application, Dr. Sigg intended to communicate that the method he developed was able to achieve an SAL of 10^{-6}." *Id.* (citing Ex. 2206 ¶ 14; Ex. 1213, 63:8–64:5).

Our analysis is further confirmed by examining the prosecution history of the Sigg '380 Application (previously discussed above). Ex. 1252. In the '380 Application, Novartis submitted claims during prosecution directed to an SAL of 10^{-6} using VHP. Specifically, Novartis represented to the Office that the following was encompassed within the scope of the Sigg '380 Application:

> applying vaporized-hydrogen peroxide to the surface of the prefilled syringe in secondary packaging;
>
> allowing vaporized-hydrogen peroxide to remain in contact with the prefilled syringe surface for a sufficient time to decontaminate the prefilled syringe <u>to a sterility assurance level of at least 10^{-6}</u>;

Id. at 292. Thus, Novartis previously represented to the USPTO that Sigg includes such a disclosure to enable VHP to achieve a sterility assurance level of at least 10^{-6}. *See* Tr. 28:21–24 ("That's an admission that the Sigg references discloses VHP sterilization to an SAL of 10^{-6}."). We find the about-face in this proceeding unpersuasive.

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record, Petitioner has demonstrated by a preponderance of the evidence that claim 21 would have been obvious over Sigg, Boulange, and USP789.

8. Claim 22

Claim 22 depends from claim 1 and further requires, "wherein the syringe barrel has an internal coating of from about 1-50 μg silicone oil."

Petitioner argues "Boulange discloses an internal coating of silicone oil on the syringe barrel of 40 μg." Pet. 48 (citing Ex. 1008, 20:15–17 ("a silicone lubricant was deposited . . . onto the internal surface of the syringe body 2, at a rate of 40 μg for a surface area of 10 cm^2"); Ex. 1003 ¶¶ 214–216).

Patent Owner contends that "Claim 22 further limits the amount of silicone oil on the syringe barrel to 'from about 1-50 μg,'" and "Petitioner's arguments fail for the same reasons discussed above for claim 1, and based on the objective indicia of nonobviousness discussed below." PO Resp. 39. As we previously mentioned, the commercial Lucentis PFS uses [redacted], yet, Patent Owner has not shown whether a product with more than [redacted] of silicone oil would have been viable, no less commercially successful. Further, Patent Owner argues "[redacted] skepticism is particularly relevant to claim 22." *Id.* at 59.

We previously determined that the evidence in favor of patentability for claim 22 is only slightly in Patent Owner's favor related to skepticism. Similarly, although claim 22 is closer to being coextensive with the Lucentis PFS than claim 1, claim 22 still covers a larger range of silicone oil. Weighing all the evidence of record before us, including Boulange's disclosure of an internal coating of silicone oil on the syringe barrel of 40 μg, the evidence of nonobviousness does not overcome Petitioner's stronger case of obviousness for claim 22.

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record, Petitioner has demonstrated by a preponderance of the evidence that claim 22 would have been obvious over Sigg, Boulange, and USP789.

9. Claim 24

Claim 24 is "[a] method treating a patient suffering from of an ocular disease," requiring, *inter alia*, "administering an ophthalmic solution to the patient using a pre-filled syringe according to claim 1."

Petitioner relies on Sigg's disclosure of "ranibizumab (e.g. 6mg/ml or 10 mg/ml) solution for intravitreal injection," as teaching the requirement of claim 24 of treating wet AMD or macular edema. Pet. 54 (quoting Ex. 1007, 9:11–14). Petitioner notes that "[b]y 2010, ranibizumab was approved for at least the treatment of wet AMD and macular edema following RVO." *Id.* (citing Ex. 1031 ¶¶ 33–37; Ex. 1027, 1 (Lucentis Label)).

Petitioner further relies on the testimony of Dr. Kiss as to how "ophthalmologists were well aware that the listed diseases were caused by or related to abnormal VEGF expression and therefore could be treated by a VEGF-antagonist." Ex. 1031 ¶ 34. Dr. Kiss testifies that based on Sigg disclosing a sterilized, pre-filled syringe including Lucentis, an ophthalmologist would have understood that the very purpose of a pre-filled syringe including Lucentis is to treat a patient suffering from ocular diseases listed in claim 24. *Id.* ¶ 36. Dr. Kiss opines that if "the pre-filled syringe of claim 1 is obvious, then the step of using an ophthalmic solution in a prefilled syringe to treat the recited list of diseases would also have been

obvious and well within the ordinary skill and routine practice of an ophthalmologist." *Id.* ¶ 37.

Patent Owner contends that Petitioner's showing how ranibizumab was approved for treatment of two of the specified ocular diseases is "insufficient for Petitioner to meet its burden of proving motivation and reasonable expectation of success for Claims 24–26." PO Resp. 39–40. Patent Owner argues the appropriate "questions are whether a POSA would have been motivated to combine Sigg and Boulange to make a PFS within claim 1 that could be used by a doctor to treat a patient with those ocular diseases, and whether the POSA would have reasonably expected success in doing so." *Id.* at 40. Patent Owner contends that a POSITA would need a reasonable expectation of success of using a PFS up until its expiration date. *Id.* at 41.

Patent Owner further argues "[a]n ophthalmologist would similarly not be motivated to use a PFS that had inconsistent forces because it could damage a patient's eye." Sur-reply 17.

We begin by addressing Patent Owner's last contention – an ophthalmologist would be dissuaded from using the proposed combination if it had an inconsistent or high force profile. *See* Ex. 2204 ¶¶ 67–73. We have fully examined this argument above and found it unpersuasive. Stopper C was tested at a speed of 380 mm/min (Ex. 1008, 16:13–15) and it displayed an increase in force from 4.7 N to 8.4 N (after accelerated aging), which we determine would not be an inconsistent "force profile" that would affect an ophthalmologist's use of the syringe. *Id.*; Ex. 1105 ¶¶ 37, 41. The values for Stopper C are within the claimed "about 11N," but more importantly,

well under the 20 N that the '631 patent acknowledges was known to be acceptable for intravitreal injection. *Id.* Mr. Koller persuasively shows how a force increase of less than 4 N after aging would have been expected and acceptable "based on tolerances and variations in manufacturing processes," as evidenced by data from Regeneron demonstrating that the break loose force for Eylea PFS can vary from approximately [redacted]. *Id.* Ex. 1105 ¶ 41 (citing Ex. 1154, 15). Further, Dr. Calman, on behalf of Patent Owner, fails to identify what constitutes a "high" force, or what amount of variation would make the forces "unpredictable" for an ophthalmologist. *See* Ex. 2204 ¶¶ 67–73; Ex. 1106 ¶ 13.

Next, Patent Owner improperly injects FDA expiration dates into the scope of the claimed subject matter. The '631 patent does not claim any efficacy over any time period. Petitioner must prove only that a POSITA would have had a motivation to combine accompanied by a reasonable expectation of achieving what is actually claimed. Petitioner has met its burden of showing a reasonable expectation of achieving what is claimed. Petitioner demonstrated that combining Sigg, Boulange and USP789 would result in a sterile syringe comprising reduced silicone oil and forces suitable for intravitreal injection. Pet. 32 (silicone oil), 35 (USP789 compliance), 38–39 (break loose and slide forces). Petitioner further demonstrated that an ophthalmologist would have administered the resulting syringe, as required by claims 24–26, because ranibizumab was a known treatment for wet-AMD. *Id.* at 54, 68–71; *see also* Ex. 1105 ¶¶ 89–94.

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record,

Petitioner has demonstrated by a preponderance of the evidence that claim 24 would have been obvious over Sigg, Boulange, and USP789.

10. Remaining Claims Not Separately Challenged

Petitioner asserts that Claims 2, 3, 5–9, 15, 16, and 18–20 would have been obviousness based on the combination of Sigg, Boulange, and USP789. Pet. 31–40, 47–53. Petitioner identifies disclosures in the prior art references that teach the limitations of these claims, and provides persuasive reasoning as to why the claimed subject matter would have been obvious to one of ordinary skill in the art. *Id.* Petitioner also supports its contentions for these claims with expert testimony, including from Mr. Koller. Ex. 1003 ¶¶ 211–235. For the same reasons discussed above, and for the additional reasons set forth by Petitioner, we determine that Petitioner has met its burden of demonstrating by a preponderance of the evidence that claims 2, 3, 5–9, 15, 16, and 18–20 are unpatentable. *See id.*

Patent Owner does not present any arguments for these claims other than those we have already considered and, more specifically, Patent Owner has not made any argument that these remaining dependent claims are separately patentable. Accordingly, we determine that Patent Owner has waived that right. *See* Paper 14, 8 (Scheduling Order) ("Patent Owner is cautioned that any arguments not raised in the response may be deemed waived.").

Having now considered the evidence in the complete record established during trial, we are persuaded that, based on this record, Petitioner has demonstrated by a preponderance of the evidence that claims

2, 3, 5–9, 15, 16, and 18–20 would have been obvious over Sigg, Boulange, and USP789.

E. Obviousness over Sigg, Boulange, USP789, and Fries

Petitioner contends that claims 4, 10, and 23 of the '631 patent would have been obvious over the combined teachings of Sigg, Boulange, USP789, and Fries. Pet. 65–66.

Based on our review of the parties' arguments and the cited evidence of record, we determine that Petitioner has met its burden of showing by a preponderance of the evidence that claims 4, 10, and 23 are unpatentable.

1. Fries

Fries is a 2009 article titled "Drug Delivery of Sensitive Biopharmaceuticals With Prefilled Syringes." Ex. 1012. Fries details that silicone oil has displayed incompatibilities with "sensitive biopharmaceuticals" including "aggregation, deformation, and inactivation of native protein structures," and likewise recommends baked-on siliconization as a preferred method. *Id.* at 6. Fries further describes the benefits of baked-on siliconization for pre-filled syringes. *Id.* ("[I]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."). Fries discloses that Dow Corning 365 (*i.e.*, DC365) is used for baked-on siliconization in pre-filled syringes. *Id.*

2. Claims 4, 10, and 23

Dependent claims 4, 10, and 23 require that the silicone oil is DC365 and has a viscosity of about 350 cP and claim 10 further recites particulate content requirements from USP789. Petitioner contends, and we agree, that these limitations would have been obvious based on Sigg, Boulange, USP789, and Fries. Pet. 65–66; Ex. 1003 ¶¶ 239–242.

We find persuasive Mr. Koller's testimony that "it was well known in the art prior to 2012 that DC365 was used as a silicone oil emulsion in the baked-on process, and was a preferred commercially-available emulsion for baking silicone onto syringe barrels." Ex. 1003 ¶ 240. Further, Mr. Koller persuasively testifies that Fries teaches that DC365 is used for baked-on siliconization in pre-filled syringes and that DC365, which contains DC360 oil, was typically used for syringe siliconization. *Id.* (citing Ex. 1012, 6). Finally, we also agree with Mr. Koller that "[a] POSITA would [] 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." *Id.* ¶ 241.

Patent Owner does not present any arguments for these claims other than those we have already considered and, more specifically, Patent Owner has not made any argument that these dependent claims are separately patentable. Accordingly, we determine that Patent Owner has waived that right.

We have considered the evidence and arguments of record, including those directed to claim 1 addressed above, and we determine that Petitioner

has demonstrated by a preponderance of the evidence that claims 4, 10, and 23 would have been obvious over the combined teachings of Sigg, Boulange, USP789, and Fries for the reasons discussed in the Petition and as supported by the testimony of Mr. Koller. *See, e.g.*, Pet. 65–66; Ex. 1003 ¶¶ 239–242.

F. Obviousness over Sigg, Boulange, USP789, and Furfine

Petitioner contends that claims 11–13 of the '631 patent would have been obvious over the combined teachings of Sigg, Boulange, USP789, and Furfine. Pet. 67–68.

Based on our review of the parties' arguments and the cited evidence of record, we determine that Petitioner has met its burden of showing by a preponderance of the evidence that claims 11–13 are unpatentable.

1. Furfine

Furfine is a patent publication titled "VEFG Antagonist Formulations Suitable for Intravitreal Administration," and assigned to Regeneron Pharmaceuticals, Inc. (Petitioner). Ex. 1021, codes (54), (71). Furfine "is directed to pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations." *Id.* ¶ 1. Further, "[t]he invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilize and reconstituted for intravitreal administration." *Id.* According to Mr. Koller, "Furfine discloses aflibercept,

which is a non-antibody VEGF-antagonist for intravitreal injection." Ex. 1003 ¶¶ 156–157, 243–246, 293.

2. Claims 11–13

Dependent claims 11–13 require that the VEGF-antagonist is a non-antibody VEGF antagonist, which can be aflibercept at a concentration of 40 mg/ml.

Petitioner persuasively shows how "Furfine discloses the non-antibody VEGF-antagonist aflibercept in a 1 ml pre-filled glass syringe." Pet. 68 (citing Ex. 1021 ¶¶ 5, 6, 36, 45, 59, 61; Ex. 1003 ¶¶ 239–242. Specifically, Furfine discloses "VEGF Trap," which the '631 patent acknowledges is aflibercept. Ex. 1021 ¶ 59; Ex. 1001, 6:37–41. Petitioner argues, and we agree, that "[a] POSITA would have been motivated to use aflibercept in a terminally sterilized pre-filled syringe, as disclosed in Sigg," because of the advantages of prefilled containers described by Sigg and because "Sigg further discloses that its terminal sterilization method is applicable to 'all drug products' and 'provide[s] the device to an end user with a low bioburden and low risk of contaminants.'" Pet. 67; Ex. 1003 ¶¶ 243–246, 293. "Thus," Petitioner persuasively shows that "a POSITA would have recognized that it would be desirable to administer aflibercept . . . via a terminally sterilized pre-filled syringe (Sigg []) using a baked-on syringe (Boulange) to achieve the resulting benefits described above." Pet. 67; Ex. 1003 ¶¶ 243–246, 293.

Patent Owner does not present any arguments for these claims other than those we have already considered and, more specifically, Patent Owner has not made any argument that these dependent claims are separately

patentable. Accordingly, we determine that Patent Owner has waived that right.

We have considered the evidence and arguments of record, including those directed to claim 1 addressed above, and we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 11–13 would have been obvious over the combined teachings of Sigg, Boulange, USP789, and Furfine for the reasons discussed in the Petition and as supported by the testimony of Mr. Koller. *See, e.g.*, Pet. 67–68; Ex. 1003 ¶¶ 243–246, 293.

G. Obviousness over Sigg, Boulange, USP789, and 2008 Macugen Label

Petitioner contends that claim 25 of the '631 patent would have been obvious over the combined teachings of Sigg, Boulange, USP789, and 2008 Macugen Label. Pet. 68–70.

Based on our review of the parties' arguments and the cited evidence of record, we determine that Petitioner has met its burden of showing by a preponderance of the evidence that claim 25 is unpatentable.

1. 2008 Macugen Label

We have previously discussed Macugen and its delivery system as a PFS. *See* Ex. 1009, 11. The 2008 Macugen Label is the prescribing information from the "Drugs.com" website (available March 7, 2011), which "presents product monographs approved by the US Food and Drug Administration (FDA) and compiled by drug manufacturers." Ex. 1039, 1; Ex. 1009.

The 2008 Macugen Label describes using a pre-filled syringe to treat wet AMD with the VEGF-antagonist Macugen. Ex. 1009, 7–8. The 2008 Macugen Label describes a priming step in which the physician depresses the plunger "to eliminate all the bubbles and to expel the excess drug so that the top edge of the 3rd rib on the plunger stopper aligns with the preprinted black dosing line." *Id.* at 7.

2. Claim 25

Dependent claim 25, which depends from claim 24, comprises an initial priming step in which a physician depresses the plunger of the pre-filled syringe to align the predetermined part of the stopper with the priming mark. Petitioner contends, and we agree, that these limitations would have been obvious based on Sigg, Boulange, USP789, and 2008 Macugen Label as explained by the testimony of Dr. Kiss. Pet. 68–70; Ex. 1031 ¶¶ 32, 38–39.

We find persuasive Petitioner's contention that "[a] priming step to align a plunger with a dosing line (*i.e.*, priming mark) was a known design that is broadly applicable to pre-filled syringes containing a drug product." Pet. 69–70 (citing Ex. 1031 ¶¶ 32, 38–39). The '631 patent describes the priming mark as "allow[ing] the physician to align a pre-determined part of the stopper . . . with the mark, thus expelling excess ophthalmic solution and any air bubbles from the syringe." Ex. 1001, 2:25–32. "Thus," as Petitioner contends, "the 'priming mark' of the '631 Patent is synonymous with the 'dosing line' of the 2008 Macugen Label." *Id.* at 69. Dr. Kiss persuasively explains that this priming step was a known technique, and a POSITA would have been motivated to include this feature in the pre-filled syringe disclosed

in Sigg to remove air bubbles and expel excess drug product to ensure accurate dosing, as described in the 2008 Macugen Label. Ex. 1031 ¶¶ 32, 38–39.

Patent Owner does not present any arguments for this claim other than those we have already considered and, more specifically, Patent Owner has not made any argument that this dependent claim is separately patentable. Accordingly, we determine that Patent Owner has waived that right.

We have considered the evidence and arguments of record, including those directed to claim 1 addressed above, and we determine that Petitioner has demonstrated by a preponderance of the evidence that claim 25 would have been obvious over the combined teachings of Sigg, Boulange, USP789, and 2008 Macugen Label for the reasons discussed in the Petition and as supported by the testimony of Dr. Kiss. *See, e.g.*, Pet. 68–70; Ex. 1031 ¶¶ 32, 38–39.

H. Obviousness over Sigg, Boulange, USP789, and Dixon

Petitioner contends that claim 26 of the '631 patent would have been obvious over the combined teachings of Sigg, Boulange, USP789, and Dixon. Pet. 70–71.

Based on our review of the parties' arguments and the cited evidence of record, we determine that Petitioner has met its burden of showing by a preponderance of the evidence that claim 26 is unpatentable.

1. Dixon

Dixon is an article from *Expert Opinion on Investigational Drugs* (Volume 18, October 2009), which is a recurring publication. Ex. 1030, 1. Dixon describes advantages associated with using aflibercept, including less frequent injections that would provide "the opportunity to significantly reduce treatment burden on patients and physicians." Ex. 1030, 8. Dixon further describes that "[i]n contrast to current anti-VEGF antibodies, which are rapidly cleared, [aflibercept] is relatively inert, and is degraded more slowly." *Id*. Before aflibercept was approved, "[b]y far the most commonly used anti-VEGF drugs currently in use for neovascular AMD are ranibizumab and bevacizumab," which are both antibody VEGF-antagonists. *Id.* at 5.

2. Claim 26

Dependent claim 26 further requires that the VEGF-antagonist to be administered is a non-antibody VEGF-antagonist where the patient has previously received treatment with an antibody VEGF-antagonist.

Petitioner, supported by the testimony of Dr. Kiss, persuasively argues that because "[a]flibercept was ultimately approved by the FDA in 2011 and viewed as a superior option for the treatment of neovascular AMD . . . it would have been obvious to treat a patient with aflibercept (a non-antibody VEGF-antagonist), wherein the patient has previously received treatment with ranibizumab (an antibody VEGFantagonist)." Pet. 70–71; Ex. 1031 ¶¶ 40–42.

Patent Owner does not present any arguments for this claim other than those we have already considered and, more specifically, Patent Owner has

not made any argument that claim 26 is separately patentable. Accordingly, we determine that Patent Owner has waived that right.

We have considered the evidence and arguments of record, including those directed to claim 1 addressed above, and we determine that Petitioner has demonstrated by a preponderance of the evidence that claim 26 would have been obvious over the combined teachings of Sigg, Boulange, USP789, and Dixon for the reasons discussed in the Petition and as supported by the testimony of Dr. Kiss. *See, e.g.*, Pet. 70–71; Ex. 1031 ¶¶ 40–42.

I. Obviousness Grounds with Lam

Petitioner relies upon Lam as being interchangeable with Sigg in each ground. *See* Pet. 1, 21, 55 ("For the reasons set forth above with respect to Sigg, a POSITA would have been motivated to combine the terminally sterilized pre-filled syringe comprising ranibizumab disclosed in Lam."), 65, 67, 68, 70.

As discussed in detail above, Petitioner has demonstrated by a preponderance of the evidence that each challenged claim would have been obvious over Sigg, Boulange, USP789, and an additional reference for certain dependent claims. Because we have already determined that each challenged claim is unpatentable based on the Sigg, Boulange and USP789 combinations, we need not reach these additional grounds where Lam is substituted for Sigg in each ground. *See Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. 2020) ("[T]he Board need not address issues that are not necessary to the resolution of the proceeding.").

IV. CONCLUSION

In summary:[27]

Claims	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–3, 5–9, 14–22, 24	103	Sigg, Boulange, USP789	1–3, 5–9, 14–22, 24	
4, 10, 23	103	Sigg, Boulange, USP789, Fries	4, 10, 23	
11–13	103	Sigg, Boulange, USP789, Furfine	11–13	
25	103	Sigg, Boulange, USP789, 2008 Macugen Label	25	
26	103	Sigg, Boulange, USP789, Dixon	26	
1–3, 5–9, 14–22, 24		Lam,[28] Boulange, USP789		
4, 10, 23		Lam, Boulange, USP789, Fries		
11–13		Lam, Boulange, USP789, Furfine		

[27] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

[28] As noted above, because we have already determined that each challenged claim is unpatentable based on the combinations containing Sigg, we need not reach grounds where Lam is substituted for Sigg.

25		Lam, Boulange, USP789, 2008 Macugen Label		
26		Lam, Boulange, USP789, Dixon		
Overall Outcome			1–26	

V. ORDER

Upon consideration of the record before us, it is:

ORDERED that claims 1–26 of the '631 patent have been shown to be unpatentable; and,

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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