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Paper 13
Date: October 26, 2021

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 KRISTI L. R. SAWERT, *Administrative Patent Judges*.

KINDER, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

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."). Novartis Pharma, AG, et al., ("Patent Owner" or "Novartis")[2] filed a Preliminary Response to the Petition. Paper 8 ("Preliminary Response" or "Prelim. Resp."). Pursuant to our authorization, Petitioner filed a Reply (Paper 11, "Reply") and Patent Owner filed a Sur-Reply (Paper 12, "Sur-Reply").

An *inter partes* review may not be instituted unless the information presented in the petition and the preliminary response shows "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). For the reasons set forth below, upon considering the Petition, Preliminary Response, Reply, Sur-Reply, and evidence of record, we are persuaded that Petitioner has demonstrated, under 35 U.S.C. § 314(a), a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims. Accordingly, we institute an *inter partes* review of the challenged claims.

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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.

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[3] 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[4] 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 infringed 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 the

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

'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 (*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.

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

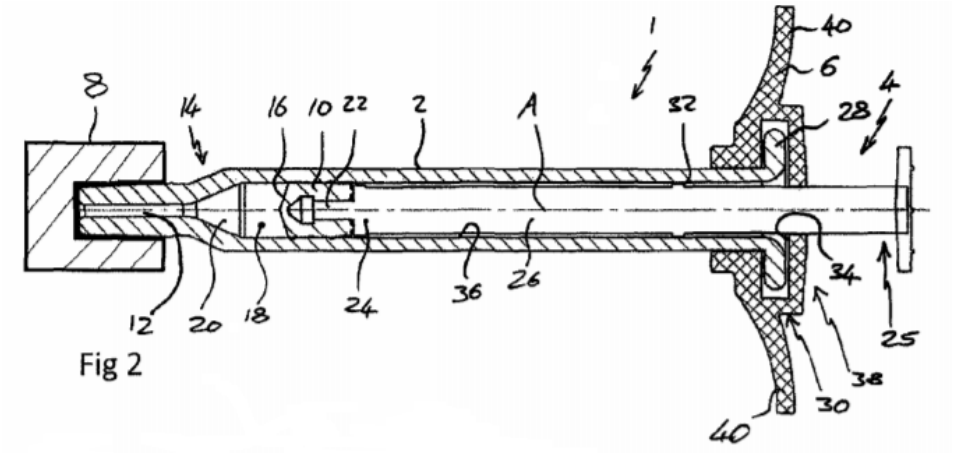

Figure 2 (above) depicts a cross section of a top down view of a syringe. *Id.* at 10:48–49.

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.

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. §	Reference(s)/Basis
1–3, 5–9, 14–22, 24	103(a)[5]	Sigg,[6] Boulange,[7] "and if necessary USP789"[8]

[5] 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.
[6] PCT Patent Publication No. WO 2011/006877 (Ex. 1007).
[7] PCT Patent Publication No. WO 2009/030976 (Ex. 1008).
[8] 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. . . .

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–3, 5–9, 14–22, 24	103(a)	Lam[9] and Boulange
4, 10, 23	103(a)	Sigg, Boulange, Fries[10]
4, 10, 23	103(a)	Lam, Boulange, Fries
11–13	103(a)	Sigg, Boulange, Furfine[11]
11–13	103(a)	Lam, Boulange, Furfine
25	103(a)	Sigg, Boulange, 2008 Macugen Label[12]
25	103(a)	Lam, Boulange, 2008 Macugen Label
26	103(a)	Sigg, Boulange, Dixon[13]
26	103(a)	Lam, Boulange, Dixon

Petitioner also relies on the declarations of Horst Koller (Ex. 1003) and Szilárd Kiss, M.D. (Ex. 1031). Patent Owner relies on the declaration of

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Petitioner's obviousness arguments remain the same if USP789 should be explicitly listed in Grounds 1-10." Pet. 21 n.7.

[9] PCT Patent Publication No. WO 2008/077155 (Ex. 1029).

[10] Arno Fries, Drug Delivery of Sensitive Biopharmaceuticals With *Prefilled Syringes*, 9(5) DRUG DELIVERY TECH. 22 (2009) (Ex. 1012).

[11] PCT Patent Publication No. WO 2007/149334 (Ex. 1021).

[12] 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).

[13] 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).

Karl R. Leinsing (Ex. 2001). The parties rely on numerous other exhibits relevant to our determination as we examine below.

III. ANALYSIS

A. Discretionary Denial of Institution Under 35 U.S.C. § 314(a)

Patent Owner argues that we should exercise discretion under 35 U.S.C. § 314 and deny institution under the Board's precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020), because the '631 patent is the subject of the parallel district court litigation involving the same parties. Prelim. Resp. 16–22. For the reasons discussed below, we decline to exercise discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review.

1. Legal Standards

Institution of *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("[T]he PTO is permitted, but never compelled, to institute an IPR proceeding."); 35 U.S.C. § 314(a). The Board has held that the advanced state of a parallel district court action is a factor that may weigh in favor of denying a petition under § 314(a). *See NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 20 (PTAB Sept. 12, 2018) (precedential); Patent Trial and Appeal Board, Consolidated Trial Practice Guide, 58 & n.2 (Nov. 2019) ("Trial Practice Guide").[14] We consider the following factors to assess "whether

[14] Available at https://www.uspto.gov/TrialPracticeGuideConsolidated.

efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding:"

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
>
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
>
> 3. investment in the parallel proceeding by the court and the parties;
>
> 4. overlap between issues raised in the petition and in the parallel proceeding;
>
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Fintiv, Paper 11 at 5–6. In evaluating these factors, we "take[] a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* at 6.

2. Facts

As noted above in Section II.A., the ITC Investigation filed on June 19, 2020, was terminated on April 8, 2021, at the request of Novartis just before the commencement of the trial for that proceeding. Ex. 1006, 1. On March 26, 2021, the ITC Staff submitted its pretrial brief arguing, *inter alia*, that "the asserted claims [of the '631 patent] are invalid," because "the claimed invention of the '631 patent would have been obvious over the asserted combinations," which included Sigg in view of Boulange and Lam in view of Boulange. Ex. 1005, 13, 25, 44–45, 57–81, 89–94.

Less than one month after Novartis filed its complaint in the ITC, Regeneron filed IPR'1317 and IPR'1318. Regeneron voluntarily dismissed IPR'1318 (December 2020) and we later exercised our discretion under 35 U.S.C. § 314(a) to deny institution in IPR'1317 (January 2021), mainly because of the ITC proceeding would proceed to a final determination before we could enter a final written decision. Ex. 1064, 2–3, 8–24. Our decision to deny institution was based largely upon Novartis's assurance that the ITC "will produce a final determination before the Board's [FWD]." Ex. 1051, 1. On February 12, 2021, Petitioner filed a request for rehearing of our January 2021 denial of institution. Petitioner later withdrew this request on April 27, 2021. Petitioner filed the instant proceeding (IPR2021-00816) on April 16, 2021.

As also noted above in Section II.A., the parallel district court litigation between Petitioner and Patent Owner also involves the '631 patent. The Complaint in the parallel district court litigation was filed by Patent Owner in June 2020. Ex. 1083. Petitioner filed its Answer on July 11, 2021. Prelim. Resp. 17. At the Rule 16 conference on August 18, 2021, the district court, consistent with local patent rules, adopted a schedule without setting a trial date. Exs. 1090, 2093, 2094. Recent data from the NDNY shows that the time to trial in civil cases is about forty months. Ex. 1078, 2 (National Judicial Caseload Profile year ending Sept. 30, 2020). At no time in the past five years has the median time from filing to trial been less than thirty-nine months in the NDNY. *Id.* Claim construction briefing has not yet begun and fact and expert discovery deadlines will not be set until after the district court issues a *Markman* Order. Ex. 2094, 19 (stating "Opening

Markman Briefs" are due "December 24, 2021," and "Initial Expert Reports" are due "60 days after claim construction decision," with "All Discovery" to be completed by "90 days after claim construction decision"); Ex. 1090 ("A Scheduling Order will be issued.").

With respect to the SDNY antitrust ligation, the enforceability — not invalidity — of the '631 patent is at issue. Unenforceability and invalidity are separate legal defenses. *Smith Int'l, Inc. v. Hughes Tool Co.*, 759 F.2d 1572, 1578 (Fed. Cir. 1985). Accordingly, even if similar issues may be addressed in the antitrust litigation as in this proceeding, the legal defenses are distinct and not dependent on one another. Thus, we determine that it is unnecessary to address this antitrust litigation in the *Fintiv* analysis below.

3. Factor 1: Whether the court granted, or will grant, a stay

A stay of a parallel proceeding pending resolution of the PTAB trial allays concerns about inefficiency and duplication of efforts, and, as such, this fact has strongly weighed against exercising the authority to deny institution. *Fintiv*, Paper 11 at 6. Patent Owner argues that parallel district court litigation is not currently stayed and will not be stayed. Prelim. Resp. 17. There is no evidence before us to suggest whether the district court will consider a stay. We determine that this factor weighs in favor of exercising authority to deny institution.

4. Factor 2: Proximity of the Court's Trial Date to the Board's Projected Statutory Deadline

According to *Fintiv*, we must consider the "trial date" of the parallel proceeding compared to our projected statutory deadline for our final decision. *Fintiv*, Paper 11 at 9 ("If the court's trial date is earlier than the

projected statutory deadline, the Board generally has weighed this fact in favor of exercising authority to deny institution under *NHK*."). "This factor looks at the *proximity* of the district court's trial date to the expected statutory deadline for the Board's final decision." *Philip Morris Prods., S.A. v. RAI Strategic Holdings, Inc.*, IPR2020-00921, Paper 9 at 16 (PTAB Nov. 16, 2020).

No trial date has been set in the parallel district court litigation. Petitioner estimates that the earliest trial date would be up to two years after a final written decision in this proceeding because the most recent data from the NDNY shows that the time to trial in civil cases is forty months from the date a complaint is filed. Pet. 6 (citing Ex. 1078, 2).

Patent Owner contends this factor weighs in favor of denial because the parallel district court litigation could go to trial concurrently with our final written decision. Patent Owner relies on two scheduling orders issued over six years ago by the presiding district court judge that suggest a 14–18 month trial date from the initial Rule 16 scheduling order, which to our knowledge has not yet issued. *See* Exs. 2060, 2061.

Based on the record before us, we believe it very unlikely that the district court trial would begin before the Board issues its final written decision. Our final written decision should issue on or before one year from this Decision (October 2022). *See Sand Revolution II, LLC v. Continental Intermodal Grp.—Trucking LLC*, IPR2019-01393, Paper No. 24 at 9 (PTAB June 16, 2020) (informative) ("[G]enerally, barring exceptional circumstances, the Board adheres to a one-year statutory deadline prescribed by 35 U.S.C. § 316(a)(11) for entry of final decisions in instituted *inter*

partes reviews."). No date is set for the district court trial, and we decline to speculate further about when the district court trial will take place.

For the reasons set forth above, we determine that this factor weighs against our exercise of discretion to deny institution.

5. Factor 3: Investment in the Parallel Proceeding by the Court and Parties

We consider the amount and type of work already completed in the parallel litigation or proceeding by the court and the parties at the time of the institution decision. *Fintiv*, Paper 11 at 9. If, at the time of the institution decision, the district court has issued substantive orders related to the validity of the challenged patent, this fact weighs in favor of denial. *See Fintiv*, Paper 11 at 9–10. On the other hand, if the district court has not issued such orders, this fact weighs against discretionary denial. *Id.* at 10.

At this juncture, the district court has not issued any substantive orders related to the challenged patent, there is no trial date, and a Rule 16 conference was just held in August 2021. *See* Exs. 1090, 2093, 2094.

Patent Owner contends "the parties are well positioned to move the NDNY action forward because much of discovery is complete" and "[t]he parties have agreed to cross-designate discovery from the ITC Investigation (i.e., all interrogatory responses, expert reports, deposition transcripts, and filings) in the NDNY action and the SDNY Antitrust Litigation." Prelim. Resp. 18 (citing Ex. 2058, 3; Ex. 2089, 1). Thus, Patent Owner argues "Factor 3 favors denial of institution because of the parties' extensive investment in discovery that will be used in the NDNY action." *Id.* at 19. Patent Owner also contends that Petitioner was not diligent in filing its

Petition in this proceeding after withdrawing its motion for rehearing in IPR'1317, and this also weighs against institution under this factor. *Id.*

Petitioner contends that "[c]laim construction briefing will begin on December 24, 2021, while fact and expert discovery deadlines will not be set until ***after*** the Court issues a *Markman* Order," and "[a]s such, the parties will have invested little in the NDNY case by the institution deadline." Reply 5.

We weigh this factor against exercising our discretion to deny institution. We acknowledge that some of the investment by the parties in the ITC will carry over to the parallel district court litigation. However, there appears to have been very little work already completed in the parallel district court litigation, e.g., no substantive decisions on validity have been made, and claim construction briefing is not scheduled to begin until after the deadline for a decision on institution in this proceeding. Based on the record before us, we determine that the district court is not likely to expend substantial resources in the parallel district court litigation before we issue our final decision.

For the reasons set forth above, we determine that this factor weighs against our exercise of discretion to deny institution.

6. Factor 4: Overlap Between Issues Raised in the Petition and in the Parallel Proceeding

"[I]f the petition includes the same or *substantially the same* claims, grounds, arguments, and evidence as presented in the parallel proceeding, this fact has favored denial" because "concerns of inefficiency and the possibility of conflicting decisions [are] particularly strong." *Fintiv*, Paper

11 at 12 (emphasis added).

In this proceeding, Petitioner challenges at least the same independent claim (claim 1) challenged in the parallel district court litigation with substantially the same evidence and arguments. *See* Ex. 2006, 10–12, 49–50. We agree with Petitioner that the Board could reach the validity argument for '631 patent before the trial in the NDNY, and this could create estoppel under 35 U.S.C. § 315(e). Pet. 7. Although we would likely to reach the validity arguments before the district court, and such an outcome favors us not exercising our discretion to deny institution, we believe the substantial overlap of issues with this proceeding weighs more in favor of exercising our discretion to deny institution.

Accordingly, this factor weighs in favor of exercising our discretion to deny institution.

7. Factor 5: Whether the Petitioner and the Defendant in the Parallel Proceeding Are the Same Party

The parties involved in the present proceeding are also involved in the parallel district court litigation.

Accordingly, this factor weighs in favor of exercising our discretion to deny institution. *Fintiv*, Paper 11 at 6.

8. Factor 6: Other Circumstances that Impact the Board's Exercise of Discretion, Including the Merits

As detailed below, the Petition demonstrates a reasonable likelihood of prevailing in showing the unpatentability of at least one challenged claim. Patent Owner raises some viable arguments with respect to whether the prior art is properly enabled, and other issues, but at this phase of the proceedings,

based on the current record, we find Petitioner's argument and evidence sufficient for institution.

We determine that in these proceedings, "other circumstances" exist that weigh strongly against exercising our discretion to deny institution. First, as detailed above, Novartis represented in the IPR'1317 that the ITC would issue a final determination addressing the validity of the '631 patent. Relying on those representations, we exercised our discretion to deny institution in that case in favor of the ITC Investigation. Patent Owner, however, moved to withdraw the ITC Investigation after the petition was denied.

Patent Owner argues that Regeneron should have brought the termination of the ITC Investigation to our attention in its pending motion for rehearing of the IPR'1317 denial, but did not, and this weighs in favor of exercising our discretion to deny institution. Sur-Reply 1–2. Although Patent Owner is correct that the Board has entertained requests to reconsider institution denials under *Fintiv* based on post-decision developments, *see id.*, the plain language of our regulations did not require Petitioner to do so. *See* 37 C.F.R. § 42.71(e) ("The request must specifically identify all matters the party believes *the Board misapprehended or overlooked*, and *the place where each matter was previously addressed in a motion*.") (emphases added). Based on the unique circumstances before us, Petitioner's decision to essentially refile its evidence and arguments from the IPR'1317 and IPR'1318 petitions in this proceeding is understandable.

On balance, and based on the merits of the Petition being sufficient, we determine that the facts underlying the sixth factor do not weigh in favor of exercising discretion to deny institution under § 314.

9. Holistic assessment of factors.

We have considered the circumstances and facts before us in view of the *Fintiv* factors. Our analysis is fact driven and no single factor is determinative of whether we exercise our discretion to deny institution under § 314(a). In our holistic review of all the *Fintiv* factors, the weight of the evidence sufficiently tips the balance in favor of not exercising our discretion to deny institution under § 314(a).

B. Discretionary Denial Under General Plastic

1. Legal Standards

When determining whether to exercise our discretion under § 314(a) in a "serial petition" situation, we may consider the following non-exhaustive factors:

1. whether the same petitioner previously filed a petition directed to the same claims of the same patent;
2. whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
3. whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;

4. the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
5. whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;
6. the finite resources of the Board; and
7. the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha, IPR2016-01357, Paper19 at 15–16 (PTAB Sept. 6, 2017) (precedential). The *General Plastic factors* are not dispositive, but part of a balanced assessment of the relevant circumstances in a proceeding, including the merits. *See* Trial Practice Guide, 58.

2. Analysis

The present proceeding is virtually the same petition challenging the same claims based on the same prior art except for a modified combination of references — Lam/Boulange instead of Lam/Reuter, with Reuter being dropped. *See* Reply 3–4 ("[T]he Lam/Boulange ground is not a shift in prior art arguments because both references and the corresponding motivation to combine were already presented in the original IPRs, but never addressed on the merits."). The current situation is distinct from the typical serial petition circumstance. First, the grounds asserted in the instant proceeding are essentially the same as those in IPR'1317 and IPR'1318, with the exception of one reference. *Id.* Second, we never reached the merits of unpatentability

in IPR'1317 and IPR'1318. *See id.* at 2 ("Regeneron is asserting the same prior art references from the original IPRs, which were never addressed on the merits."). Accordingly, many of the *General Plastic* factors are not directly applicable to the situation before us.

Patent Owner argues that the current petition could have been avoided if Petitioner would have brought the ITC dismissal to our attention in Petitioner's then-pending request for rehearing. Prelim. Resp. 8; Sur-Reply 2. As noted above, however, the plain language of 37 C.F.R. § 42.71(d) states that a request for rehearing should argue issues that were "previously addressed in a motion." Further, a party may "file a single request for rehearing," but only within "30 days of the entry of a final decision." 37 C.F.R. § 42.71(d). Thus, although the Board has allowed additional evidence and briefing during other unrelated rehearing proceedings (*see* Sur-Reply 2), our rules do not mandate such a course of action. In this instance, Petitioner was still within the one-year statutory deadline for filing another petition for *inter partes* review. As such, we do not find anything inherently wrong with the course of action taken by Petitioner.

We are aware that Petitioner has the advantage of receiving two preliminary responses (Prelim. Resp. 11–12), but we never commented upon the merits of patentability addressed in those preliminary responses. As such, Petitioner has not gained any advantage by using our decisions as a roadmap, as we have not issued a decision. Petitioner has also modified some of its arguments. For one example, Petitioner addresses secondary considerations for the first time after this evidence was produced during the

ITC Investigation. *See id.* at 7, 11–13, 15 ("Petitioner's course of action can only be explained by its attempts to leverage what it learned about Patent Owner's position from the earlier IPR responses and the ITC proceeding."). We recognize Petitioner does gain a few advantages, but from our observations the petitions have not changed remarkably and the underlying theories are substantially the same. *See id.* at 13 (pointing out changes between petitions). We are also cognizant that Petitioner's advantages were precipitated by Patent Owner's motion to terminate the ITC Investigation after we denied institution in the prior IPR'1317.

According to Petitioner, it filed the current petition for *inter partes* review because Patent Owner dismissed its ITC Investigation on the eve of trial:

> Novartis avoided institution of Regeneron's original IPR by representing that the ITC would decide the validity of the 631 Patent before a FWD. Novartis, however, abandoned the ITC Investigation days after learning that the ITC Staff concluded there was ***clear and convincing evidence*** that the 631 Patent is invalid as obvious. Regeneron subsequently filed this Petition to obtain an expeditious invalidity determination and stop Novartis's attempt to forum shop the determination of invalidity to the NDNY. This unique situation, created solely by Novartis's gamesmanship, would make denial under *General Plastic* unjust.

Reply 1 (citations omitted). Although we will not speculate on Novartis's reasons for withdrawing the ITC Investigation on the eve of trial, we agree with Petitioner that this is a unique situation created solely by Novartis's actions. Thus, we find that denying the Petition under these circumstances is not warranted.

C. Discretionary Denial Under Section 325(d)

1. Legal Standards

Section 325(d) of Title 35 of the United States Code provides, in relevant part: "In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." The Board uses a two-part framework for evaluating arguments under § 325(d):

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

In applying the two-part framework, we consider several non-exclusive factors from *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("*Becton, Dickinson*"), which provide "useful insight into how to apply the framework." *Advanced Bionics*, Paper 6 at 9. The *Becton, Dickinson* factors are:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;

(e) whether Petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18. If, after review of factors (a), (b), and (d), we determine that the same or substantially the same art or arguments previously were presented to the Office, we then review factors (c), (e), and (f), which relate to whether the petitioner demonstrates that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 10.

Below, we discuss the parties' arguments and then apply the *Advanced Bionics* framework.

2. Analysis

There is no dispute that Sigg, Lam, and Boulange were not before the Examiner during prosecution. The fact that not one of the asserted prior art references to this proceeding was previously before the Office supports the

Board not exercising its discretion (on behalf of the Director) to deny institution. The first two *Becton, Dickinson*, factors also consider the similarities and material differences between the asserted art and the prior art involved during examination and also whether the asserted art is simply cumulative to the prior art evaluated during examination. *Becton, Dickinson*, Paper 8 at 17–18. We examine these factors in more detail below.

a) Part One of the Advanced Bionics Framework

Petitioner argues that we should not exercise our discretion to deny institution under § 325(d) because the Petition presents new art and arguments. Pet. 9–11. In particular, Petitioner argues that "there was no art before the Examiner that disclosed terminal sterilization of a pre-filled syringe with a VEGF-antagonist—the very subject matter that Sigg and Lam disclose." Pet. 10 (citing Ex. 1003 ¶¶ 116–117 (Koller Declaration)). Further, Petitioner points out that "[t]he '631 Patent discloses that existing techniques – ethylene oxide and hydrogen peroxide – may be used, but fails to acknowledge that they had been used on pre-filled syringes containing a VEGF-antagonist." *Id.* (citing Ex. 1001 at 9:49–54). Mr. Koller, Petitioner's declarant, testifies that none of the prior art "references[15] disclose terminal sterilization of a pre-filled syringe comprising a VEGF-

[15] Petitioner and Mr. Koller specifically address WO 2007/084765 and WO 97/44068, the references that Novartis alleged disclosed terminal sterilization that is pertinent to the claims of the '631 patent. *See* Prelim. Resp. 23. These references "were disclosed on IDSs initialed by the Examiner." *Id.*

antagonist," and "[t]here was nothing disclosed during the prosecution of the '631 Patent with respect to terminal sterilization which was cumulative of the disclosures provided in Sigg and Lam." Ex. 1003 ¶ 116. He supports this position by detailing the differences in each reference and shows that none "describe sterilizing a syringe after it is filled with the claimed drug product (i.e., terminal sterilization as claimed in the '631 Patent)." *Id.* ¶ 117 (stating that the references were "silent as to the type of drug product in the syringe" and did not "disclose terminal sterilization of a pre-filled syringe comprising a VEGF-antagonist").

Petitioner additionally argues that Boulange discloses a baked-on syringe with the claimed silicone oil ranges, and break loose and slide forces, yet "[t]here was no single reference before the Examiner that disclosed a syringe that met both the silicone oil and force limitations of the challenged claims." Pet. 10 (citing Ex. 1003 ¶ 118 ("The examiner did not have the benefit of one reference which contained all of the key silicone oil limitations. For example, Hioki only disclosed a wide range of silicone oil amounts, and did not disclose the break loose or glide forces. *See* Hioki (Ex. 1020).")).

Patent Owner asserts that "the references are substantially the same as art and information that was disclosed in prosecution and considered extensively by the Examiner." Prelim. Resp. 22. Specifically, Patent Owner contends that "the teachings from Sigg and Lam on terminal sterilization are cumulative of art before the Examiner: the patent itself acknowledges that techniques for terminal sterilization were known as of the invention date, including sterilization with either hydrogen peroxide or ethylene oxide—the

methods disclosed by Sigg and Lam." *Id.* at 22–23. Patent Owner recognizes, however, that Sigg and Lam both disclose more than what the record prior art disclosed: "Contrary to Petitioner's assertion (Pet. at 10), neither Sigg nor Lam adds materially to this art. Those references simply noted an ***aspiration*** to terminally sterilize a VEGF antagonist-filled syringe, but, as discussed below (pp. 31–37, 53–55, *infra*), neither reference explains how this step could be accomplished." *Id.* at 24. Thus, Patent Owner concedes that both of these references describe at least an aspirational goal to terminally sterilize a VEGF antagonist-filled syringe, which the prior art before the Office did not address.

Patent Owner contends that Sigg and Lam do not provide sufficient detail to enable a person of ordinary skill in the art to terminally sterilize a VEGF antagonist-filled syringe (*id.* at 31–32) based on just the aspirational disclosure, but these so-called aspirational teachings in Sigg and Lam are still materially different from the prior art of record before the Examiner. Likewise, because Sigg and Lam describe the goal of terminally sterilizing a VEGF antagonist-filled syringe, both Sigg and Lam are not cumulative of the prior art evaluated during examination. Notably, the requirement to terminally sterilize a VEGF antagonist-filled syringe was the limitation added during prosecution to overcome the prior art of record. *See* Ex. 1003 ¶¶ 113–115; Ex. 1002, 1458–49, 1370 (claim amended to add "pre-filled, terminally sterilized syringe," which resulted in the application being allowed). Whether Sigg and Lam have a sufficient enabling disclosure is a different issue, but both disclosures are admittedly different from the prior

art presented to the Office during examination and not cumulative for purposes of § 325(d).

Further, although the art previously presented to the Office taught the baked-on siliconization method (Prelim. Resp. 24), we agree with Petitioner that Boulange is distinct and not cumulative because it discloses both a baked-on syringe with the claimed silicone oil ranges and the claimed break loose and slide forces. Because there was no single reference before the Examiner that disclosed a syringe that met both the silicone oil and force limitations of the challenged claims, Boulange is materially different and not cumulative.

Accordingly, we determine that Sigg, Lam, and Boulange are materially different and not cumulative under *Becton, Dickinson* factors (a) and (b).

Regarding *Becton, Dickinson* factor (d), which is "the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art," we determine the primary arguments before us do not overlap. A main issue before us is whether the distinct disclosures in Sigg and Lam are sufficiently enabling to teach terminally sterilizing a VEGF antagonist-filled syringe. No such issue was before the Examiner. Accordingly, we determine that there is little or no overlap between the manner in which Petitioner relies on the prior art and the positions taken by the Examiner during examination.

For the above reasons, we determine that Sigg, Lam, and Boulange are not the same or substantially the same as the prior art previously

presented to the Office under *Becton, Dickinson* factors (a), (b), and (d). In view of the above, we determine that Petitioner's art and arguments are not the same or substantially the same as the art and arguments previously presented to the Office.

b) Part Two of the Advanced Bionics Framework

Because we determine, under *Advanced Bionics* part 1 that the Examiner did not consider the same or substantially the same prior art and arguments as Petitioner presents, we need not determine whether the Examiner erred under *Advanced Bionics* part 2.

c) Conclusion

For the above reasons, we find that the same or substantially the same art or arguments were not previously presented, and we do not exercise our discretion under § 325(d) to deny institution in this proceeding.

D. 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; (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*.

E. 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 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. 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. Kiss, an ophthalmologist, in support of its contentions with respect to claims 24–26. Ex. 1031 ¶¶ 4–6.

Patent Owner does not respond to these positions or independently address the person of ordinary skill in the art. Patent Owner's declarant, Mr. Leinsing, recognizes Petitioner's proposed definition and applies it for the purposes of analysis and opinions. *See* Ex. 2001 ¶¶ 61–62.

It is not common to see two distinct standards for the level of ordinary skill in the art within the same patent. At this stage in the proceeding, Petitioner's declarant has sufficiently explained why administering the ophthalmic solution using the pre-filled syringe required by claims 24–26 would require the expertise and understanding of a medical doctor with a specialty in ophthalmology. We note, however, that a person of ordinary skill should also "have the training or knowledge to develop the claimed [method]." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007). It is unclear to us whether a medical doctor with a specialty in ophthalmology would necessarily fit that description absent "additional specialty training" in creating a pre-filled syringe used in the method. *Id.* Thus, although we adopt Petitioner's understanding of the person of ordinary skill in the art for purposes of this decision, our determination is preliminary and Petitioner may consider addressing this standard again in Reply.

Moreover, to the extent Patent Owner has any objection to this split standard, the objection should be discussed in Patent Owner's Response, or be deemed waived.

F. Claim Construction

Petitioner proposes claim interpretations for four claim terms or phrases. Pet. 24–26. Patent Owner contends that "there are no claim construction disputes bearing on institution and thus does not address the issue here." Prelim. Resp. 30, n.10.[16]

First, we note that the '631 patent has provided its own definitions for the terms "comprising" and "about." Ex. 1001, 10:24–29. Petitioner also addresses the term "about" but concludes that 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.)," and based on a review of the prior art before us, we agree. Pet. 25–26. Petitioner proposes claim interpretations for three more terms that we address below.

"Stopper Break Loose Force"

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

[16] Patent Owner makes the following assertion: "Petitioner states (at 26) that its grounds do not turn on any claim construction dispute." Prelim. Resp. 30, n.10 (citing Pet. 26). We see no such concession stated in the Petition at page 26. Petitioner only addressed the term "about" and its belief that the outer boundaries of ranges for "about" were unnecessary to determine. Patent Owner should take better care to not misrepresent positions in this proceeding.

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.*

On the current record, we are persuaded by Petitioner's proposed construction. Absent some meaningful evidence to the contrary (such as an industry standard), we do not find cause to limit the break loose force measurement to any specific time.

"Stopper Slide Force"

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.*

On the current record, we are persuaded by Petitioner's proposed construction. Further, absent some meaningful evidence to the contrary (such as an industry standard), 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 currently before us 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, 55–56; 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 record currently before us, 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.

G. Alleged 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, if necessary, USP789. On this record, Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one of claims 1–3, 5–9, 14–22, and 24 would have been obvious over Sigg, Boulange, and USP789 for the reasons explained below.

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 7:29–8:1. 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 or "Parylene C" are compared to un-siliconized syringes. *Id.* at 18:15–19:10. Parylene C is "polymer material" described in Boulange. *Id.* at 2:7–20.

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 5N for both the unaged (T=0) and aged (T=1) syringe. *Id.* at 21.

3. USP789

USP789 is a monograph in United States Pharmacopeia. Ex. 1019. Petitioner suggests that 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.

For purposes of this decision, we treat USP789 as part of Petitioner's grounds to provide adequate notice to Patent Owner. Upon the final record, however, if Petitioner's contentions remain uncontested that USP789 is a widely known and accepted industry standard, we may adopt Petitioner's position that a POSITA would have known that Sigg and Lam were required to meet the claimed particle amounts (that fall within USP789) without having USP789 in the combination of references.

4. Independent Claim 1

Below, we first set forth Petitioner's arguments and evidence, then Patent Owner's arguments and evidence, and then we analyze the totality of

the evidence and argument before us with a focus on those issues currently contested. As explained more below, Petitioner has shown a reasonable likelihood that it would prevail in showing 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).

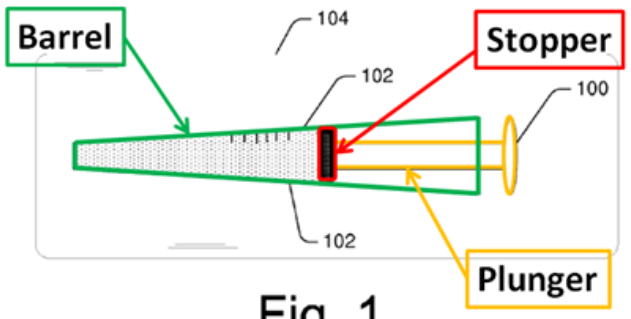

Fig. 1

Petitioner's annotated 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 alleged 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). Relying on the testimony of Mr. Koller, Petitioner argues that "[t]he baked-on syringes comprising 40 μg of silicone oil (4 μg/cm^2) have a break loose force (B) less

than 11N for all stopper configurations in Table 7 at T=0," and "[s]topper B1 also had a break loose force of 3.0 N after one month of accelerated storage (T=1)." Pet. 45 (citing Ex. 1003 ¶ 207). Petitioner relies on the following annotated and modified Table 7 from Boulange.

Table 7

Baked-On

		Scenario 1			Scenario 2		
Silicone/internal surface of syringe		4 µg/cm²	4 µg/cm²	4 µg/cm²	50 µg/cm²	50 µg/cm²	50 µg/cm²
Silicone/piston		---	---	---	---	---	---
Force (N)		B	S	F	B	S	F
Piston	$A_{T=0}$	6.6 (0.3)	6.9 (1.4)	4.0 (1.4)	5.5 (0.5)	1.2 (0.3)	4.0 (2.0)
	$A_{T=1}$	15.7 (2.9)	5.3 (2.6)	6.1 (4.2)	8.6 (1.1)	1.6 (0.7)	5.6 (4.1)
	$B1_{T=0}$	2.1 (0.1)	2.5 (0.3)	2.6 (0.3)	1.9 (0.2)	1.3 (0.3)	2.1 (0.7)
	$B1_{T=1}$	3.0 (0.4)	3.4 (0.5)	2.8 (0.6)	2.2 (0.2)	1.4 (0.3)	2.4 (0.6)
	$C_{T=0}$	3.9 (0.6)	6.6 (2.5)	3.9 (2.5)	4.2 (0.6)	1.0 (0.4)	4.7 (2.9)
	$C_{T=1}$	14.4 (2.2)	4.8 (2.1)	3.6 (1.1)	5.4 (1.2)	1.3 (0.5)	4.3 (2.8)
	$A_{T=3}$	17.2 (6.1)	4.3 (2.4)	2.9 (1.2)	10.0 (1.0)	1.5 (0.3)	4.0 (3.0)
	$A_{T=6}$	20.5 (4.0)	6.1 (3.0)	3.0 (1.0)	15.1 (1.4)	2.5 (1.5)	3.0 (2.0)

Petitioner presents annotated Table 7 from Exhibit 1008 highlighting certain break loose forces from Scenario 1 (baked on). Pet. 46. As explained by Mr. Koller, "Table 7 from Boulange . . . discloses break loose forces of 6.6, 2.1 and 3.9 for an unaged syringe (i.e., T=0) for the syringes in which silicone was applied to the barrel using baked-on siliconization," and "[t]he baked on syringe including a coated stopper (B1) also has a break loose force of 3.0 N at T=1." Ex. 1003 ¶ 207.

Next, Mr. Koller relies on Table 5 of Boulange, 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/cm²):" *Id.* ¶ 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 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).

Motivation to Combine and Reasonable Expectation of Success

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). Petitioner notes that the assignee of Boulange is "a world leader in pre-filled syringe design and manufacturing, including for intravitreal injection," and a skilled artisan would have looked to Boulange for that reason. *Id.* 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." Pet. 33–34 (citing Ex. 1003 ¶¶ 163, 185–186).

Petitioner contends "[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, and Mr. Koller, point to 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 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 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 references 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 B1 in Table 7 of Boulange, which had break loose and slide forces less than 5 N for the baked-on syringes." *Id.* Petitioner contends that "Boulange explains that stopper B1 includes a coating of Parylene C, but no silicone oil coating," and "[a] POSITA would have expected that Parylene C would have been suitable for use in a pre-filled syringe comprising a VEGF-

antagonist." *Id.* (citing Ex. 1008, 19:4–5, 20:15–17; Ex. 1003 ¶ 141, 171–177). Petitioner notes that "Boulange describes that a stopper comprising Parylene C would prevent 'possible degradation [that] is sometimes initiated by the processes used to sterilize the medical devices containing them.'" Pet. 37–38 (quoting Ex. 1008, 4:3–8). Petitioner further relies on Boulange's teaching "that its prefilled syringe design avoids negative interactions between lubricants and drug products." Pet. 38 (citing Ex. 1008, 6:26–29). Relying on Mr. Koller's testimony, Petitioner concludes that "[b]ased on these disclosures," that "a POSITA would have expected that Parylene C would not interact negatively with drug products (*e.g.*, VEGF-antagonists) and would be compatible with known sterilization processes (*e.g.*, terminal sterilization using VHP or EtO)." *Id.* (citing Ex. 1003 ¶¶ 171–177; Ex. 1074, 10 (describing that Parylene C has "been demonstrated in a wide range of medical coating applications over the past three decades"); Ex. 1072, 1 (describing that Parylene C is widely used in pre-filled syringes)).

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.").

Objective Indicia of Nonobviousness

"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[17] 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,[18] 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 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

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[17] 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.

[18] Genentech brought Lucentis® PFS to market in 2016 (Ex. 2015) and licensed the '631 patent from Patent Owner. Prelim. Resp. 57–58.

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).

Although "Petitioner believes that secondary considerations are more appropriately addressed after institution," it argues that "none of the secondary considerations that Patent Owner may raise can demonstrate that the '631 Patent claims are non-obvious." Pet. 71, 73.

b) Patent Owner's Arguments

Patent Owner makes several arguments directed to the combination of references, but Patent Owner first argues that Petitioner has failed to show that Sigg enables a sterilization method for a PFS. Prelim. Resp. 31. Patent Owner relies heavily on the testimony of Mr. Leinsing (Ex. 2001).

Whether Sigg enables a sterilization method for a PFS

Patent Owner contends "[b]ecause Sigg is the only reference on which Petitioner relies to argue that a POSA would have known how to use the VHP method to terminally sterilize a PFS containing sensitive biological solutions, Petitioner must show that Sigg enables this method." Prelim. Resp. 32. Patent Owner alleges that "Petitioner fails to make any such showing," "which is fatal to its obviousness argument." *Id.* at 33.

Patent Owner's arguments focus on the tightness of the seals in Sigg

and the unknown difficulty of achieving the required tightness to avoid ingress of sterilizing gases in the pharmaceutical liquid. *Id.* "Critically, Sigg does not identify the 'very few' syringe/stopper combinations that provide a sufficiently tight seal to permit terminal sterilization of a biological solution, leaving a POSA to guess whether any particular PFS design would be compatible with Sigg's method." *Id.* (citing Ex. 2001 ¶¶ 70– 75, 108, 176–178). Patent Owner believes the details in Sigg are simply too sparse, or in invitation for further research, including the "exemplary" syringe (Figure 1 of Sigg), which lacks any specificity. *Id.* at 34 (citing Ex. 2001 ¶¶ 71, 181). Patent Owner next notes that "Sigg does not disclose the material used for this syringe," and "a POSA would have had no way to know if a glass syringe would have ensured the requisite tightness for the VHP sterilization process or if only plastic syringes would have been suitable." *Id.* at 35. Patent Owner, and Mr. Leinsing, suggest that Sigg does not disclose whether glass barrels would be suitable for VHP sterilization. *Id.* (citing Ex. 2001 ¶¶ 48–50).

Next, Patent Owner alleges that "Sigg likewise fails to provide critical details about the stopper design, including its size, shape, material, or how it fits in the barrel," and Sigg also does not "disclose whether the stopper or syringe barrel was lubricated, and, if so, the name of the lubricant." *Id.* (citing Ex. 2001 ¶¶ 73–74, 178). Relying on the testimony of Mr. Leinsing, Patent Owner alleges that "a POSA reading Sigg would have had no guidance on how to elect syringe components suitable for use with Sigg's VHP sterilization method, forcing a POSA to resort to trial and error with combinations of different barrels, stoppers, and lubricants, among other

parts." *Id.* at 37 (citing Ex. 2001 ¶¶ 175–185). "Petitioner has thus failed to show that Sigg is enabled, given the 'undue experimentation' required to find suitable components for its method." *Id.*

Whether a POSA would not have been motivated to use Boulange

Patent Owner contends that "Boulange never suggests that its Parylene C invention is compatible with intravitreal administration or would be appropriate for syringes intended for such use." Prelim. Resp. 38 (citing Ex. 1008, 16; Ex. 2001 ¶¶ 92–96). Patent Owner alleges "that only a small subset of syringes are suitable for the highly specialized use of intravitreal injection of an ophthalmologic solution," and "a POSA would have understood that a PFS used for intravitreal injection must have more than just acceptably low break loose and slide forces; those forces also must be consistent and reliably allow for a smooth injection motion into the eye." *Id.* (citing Ex. 2001 ¶¶ 40, 45, 113–115, 151–152). Patent Owner concludes that "[g]iven the strict parameters, a POSA would not have expected that a PFS would be suitable for intravitreal injection absent an express teaching of that use." *Id.*

Patent Owner points to the testing of stoppers coated with Parylene C (stoppers B1 or B2), which Boulange characterizes as the "invention," and argues that testing of other stoppers (stoppers A and C) was only for comparison. *Id.* at 39. According to Patent Owner, "[b]ased on the results of these experiments, Boulange expressly teaches away from the non-Parylene coating options, as Boulange reports that these options yielded 'relatively high' friction forces and describes the comparator syringes as 'not . . . acceptable for a medical device' and 'markedly inferior' to the Parylene

C-coated option." *Id.* (citing Ex. 1008, 15–24; Ex. 2001 ¶¶ 109–111, 142–144) (alteration in original). Patent Owner notes the significant risks involved with designing the claimed invention and argues that Petitioner must show that the PFS stopper is suitable for its intended use, and "a POSA would have avoided using components without a track record, since doing would have required more extensive testing than using well established components, whose interactions with drug solutions are more predictable." *Id.* at 41 (citing Ex. 2001 ¶¶ 112, 116–117, 119–121). Patent Owner concludes that "the uncertainty associated with using this unproven material, and the time and cost required to address that uncertainty and ensure the safety and efficacy of the PFS, would have dissuaded a POSA from considering Boulange's stopper B1." *Id.* at 42.

Patent Owner further argues that the evidence supports "Boulange's reason for rejecting the uncoated stopper C in Table 7 applies equally to the Table 5 version" because the forces measured for the stopper C configurations in Table 5 were even higher. *Id.* at 45. Patent Owner asserts that "stopper C does not make sense as an option to pursue Petitioner's asserted motivation of minimizing the amount of silicone oil used on a syringe," and its choice must have been driven by impermissible hindsight for various reasons. *Id.* at 48–49.

Whether a POSA would have had a reasonable expectation of success in combining Sigg and Boulange

Patent Owner next alleges that Petitioner has failed to show that a POSA would have expected that Sigg's VHP terminal sterilization method would be compatible with Boulange's syringe. Prelim. Resp. 49. Patent

Owner contends "a POSA would not have expected to successfully combine Boulange and Sigg absent a reasonable basis to believe that Sigg's VHP method would not adversely impact Boulange's Parylene C coating and that the Parylene C coating would not adversely impact the biologic drug in the syringe." *Id.* (citing Ex. 2001 ¶¶ 161–162). Patent Owner argues that "Boulange nowhere suggests that its Parylene C-coated stopper would be unaffected by gaseous terminal sterilization," and to the contrary, "Parylene C was known to react upon exposure to hydrogen peroxide, causing a significant increase in its coefficient of friction, which would increase the forces needed to inject the syringe." *Id.* at 49–50 (citing Ex. 2001 ¶¶ 132, 162–164).

Patent Owner similarly argues that "Petitioner has not shown that Boulange's syringes are sufficiently air-tight to be compatible with the VHP sterilization process described in Sigg," especially considering Sigg's statement that "there are only ***very few*** packaging material combinations that provide the required tightness of the system such as to avoid ingress of sterilizing gasses into the pharmaceutical liquid enclosed by the prefilled container." *Id.* at 50 (quoting Ex. 1007, 3:28–30). Mr. Leinsing testifies as to the Boulange's reference to "tightness" referring to the syringe's ability to keep the solution from leaking out when being injected—not its ability to keep gas from entering the syringe. *See* Ex. 2001 ¶¶ 157–158. Further, "even if Boulange's Parylene C syringe were 'gas-tight,' as Petitioner insists," Patent Owner argues that "a POSA still would have had no basis to conclude that the syringe would be compatible with Sigg's sterilization method." Prelim. Resp. 51 (also noting "Boulange's syringe has low

injection forces, which a POSA would have understood to convey a relatively ***loose*** fit between the piston and the glass barrel"). Patent Owner concludes by arguing that "Boulange does not indicate that Parylene C would be appropriate in a terminally-sterilized syringe for intravitreal injection of a VEGF antagonist." *Id.* at 52.

Objective Indicia of Nonobviousness

Patent Owner contends that Petitioner's arguments related to secondary considerations are conclusory and unsupported. Prelim. Resp. 55–56.

Patent Owner alleges there as a long-felt for the claimed invention because "there was no prior art product that combined all of the features needed to satisfy the long-felt needs in this area—i.e., providing a highly sterile syringe with low injection forces and low silicone oil that would be suitable for intravitreal injection of a sensitive biologic product." *Id.* at 57 (citing Ex. 2001 ¶ 187). Patent Owner notes that "the only PFS on the market at the time (Macugen) had high levels of silicone oil and was known to cause 'intravitreal contamination by silicone oil droplets.'" *Id.* (citing Ex. 1003 ¶ 66; Ex. 2001 ¶¶ 42, 188). Patent Owner alleges that for "many years sophisticated companies tried and failed to solve this problem." *Id.* Patent Owner alleges

> Genentech then spent years trying to develop a PFS without success, directly refuting Petitioner's assertion that it would have been obvious to develop the patented invention using Lam and underscoring that Lam is not enabled. Genentech was only able to bring Lucentis® PFS to market in 2016 (Ex. 2015), after licensing the '631 patent from Patent Owner and adopting the Patent Owner's technology.

Id. at 57–58. Patent Owner also suggests that Petitioner aspired to produce a PFS containing a VEGF antagonist at least as far back as June 2006. *Id.* at 58 (citing Ex. 1021, 11–12).

Patent Owner next relies on the commercial success of Genetech's Lucentis® PFS product that purportedly uses the patented technology. *Id.* According to Patent Owner, "Genentech's agreement to license the '631 patent is strong evidence of non-obviousness." *Id.* at 58–59. Patent Owner contends that the Lucentis® PFS is a commercial success and it "embodies the claims of the '631 patent by providing a terminally-sterilized PFS configuration of a VEGF antagonist for intravitreal injection." *Id.* at 59. Next, Patent Owner makes an important statement but fails to provide any supporting evidence in support. Specifically, Patent Owner alleges that "the Lucentis® PFS embodies the claims of the '631 patent, and is coextensive with them insofar as the Lucentis® PFS is a terminally-sterilized PFS for intravitreal injection of a VEGF antagonist that meets the limitations of the claims and does not include significant unclaimed features." *Id.*

Patent Owner next contends that the inventors of the '631 patent achieved unexpected results based on a statement made in the '631 patent. *Id.* at 60. Patent Owner alleges that "Boulange thus fails to show that the result described by the '631 patent—i.e., that silicone oil levels could be reduced to the claimed levels without substantially affecting force levels—was known or expected." *Id.* at 60–61.

c) Analysis

On the current record, Petitioner has shown by a reasonable likelihood 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. Further, the current objective evidence of nonobviousness related to secondary considerations have not been shown to have a nexus to the claims.

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 a reasonable likelihood 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. Further, Table 7 in

Boulange discloses the break loose force test results for syringes A and C, which comprised 40 µg of silicone oil on the internal surface and with pistons that were not coated with Parylene C. *Id.* at 20:15–17, Table 7. We find persuasive on this record and for institution the Table 7 disclosure of the results of syringe B1, which was also siliconized with 40 µg of silicone oil on the internal surface but (unlike A and C) also has a coating of Parylene C on the piston. *Id.* Notably, in each case, Table 7 shows that the break loose force at time zero was below the claimed 11 N. *Id.* On this record, we find sufficient for institution Petitioner's arguments that Boulange discloses multiple stopper configurations that a POSITA would have been motivated to combine with Sigg. *See* Pet. 37–40. Notably, the claims of the '631 patent are silent as to any potential stopper coating.

On this record, we also find Petitioner's reasoning and evidentiary underpinnings show a reasonable likelihood 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. Further, the evidence of record establishes a reasonable likelihood 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, we determine that Petitioner has provided sufficient articulated reasons and evidentiary underpinnings on this record 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 to warrant institution.

Novartis argues that a POSITA would not look to Sigg because Sigg does not enable a syringe that can be terminally sterilized. Prelim Resp. 31. More specifically, Patent Owner argues that a POSITA would not have known how to use the VHP method to terminally sterilize a PFS containing sensitive biological solutions, and further identifies a number of reasons why Sigg would allegedly not have enabled a POSITA to terminally sterilize this syringe. *Id.* at 31–32. Patent Owner cites *Raytheon Techs. Corp. v. General Elec. Co.*, 993 F.3d 1374, 1381 (Fed. Cir. 2021), for the proposition that "[i]n the absence of [] other supporting evidence to enable a skilled artisan to make the claimed invention, a standalone § 103 reference must enable the portions of its disclosure being relied upon."

For the reasons set forth below, and on the current record, we determine that Petitioner demonstrates a reasonable likelihood that Sigg is enabled for the portions of its disclosure relied on and also that other supporting evidence provides additional enabling support as permitted in a § 103 analysis. 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.

Id. at 1376–77. First, we are not required to only look to Sigg, whereas the current record before us is more extensive and we are allowed to consider "the overall evidence of what was known at the time of invention" in order to determine whether "a skilled artisan could have made and used the claimed invention." *Id.*; *see, e.g.*, Ex. 1003 ¶¶ 78–89 (testimony and supporting cited evidence of what was known at the time of the invention). On this current 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 current record contains sufficient evidence as to how a POSITA would have known how to use the VHP method to terminally sterilize a PFS containing sensitive biological solutions. Ex. 1003 ¶¶ 78–89.

Mr. Koller provides extensive 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 several 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 testifies that the person of ordinary skill 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).

Mr. Koller further testifies that "[t]he measure of the probability that an individual article may not be sterile is referred to as the sterility assurance level, or SAL, and would have been routine for a POSITA to determine prior to July 2012." *Id.* ¶ 89 (citing Ex. 1007, 7:8–13). Mr. Koller notes that "Sigg defines both the SAL and the term 'sterility,' and recommends a SAL of 10^{-6} for health care products." *Id.* This provides additional support sufficient for institution that one of ordinary skill in the art relying on Sigg could have made and used the claimed invention.

As to Patent Owner's arguments that Sigg states that "very few" syringe components are capable of making the tight seal required for terminal sterilization, we find sufficient on this record for institution Mr. Koller's testimony to the contrary that "such components were well-known and readily available to those of ordinary skill in the art before the '631 patent. As described below, a POSITA would understand that Macugen PFS was terminally sterilized by 2008, while an EYLEA PFS terminally sterilized with VHP was approved in Australia by February 2012." Ex. 1003 ¶ 124 n.15. Petitioner produces additional evidence related to how the Macugen PFS was a syringe design for a terminally sterilized and siliconized pre-filled syringe for intravitreal injection with the tight seal required for terminal sterilization. *See id.* ¶¶ 111, 149. This evidence shows sufficiently for institution how a person of ordinary skill in the art would know to use the

teachings of Sigg and Boulange to achieve the same tight seal required for terminal sterilization.

The August 2008 Macugen PFS label provides additional enabling background because it describes that Macugen PFS was supplied in a sterile foil pouch as a single use glass syringe pre-filled with 0.3 mg of Macugen in a nominal 90 uL deliverable volume pack. *Id.* ¶ 149 (citing Ex. 1009, 8–9 (2008 Macugen Label)). Further, a sterile packaged BD single use 30G x 1/2 Precision Glide Luer Lok need is supplied in a separate pouch. *Id.* Mr. Koller explains that the August 2008 Macugen PFS label reflects the design of Macugen PFS administered in the United States and it includes the "sterile foil pouch" resulting from the terminal sterilization process, and a glass syringe using a 30 G x 1/2" needle. *Id.* ¶ 153.

Novartis suggests that the design of the plunger/stopper and plunger rod described in the '631 patent specification are features that enable a pre-filled syringe comprising a VEGF-antagonist to be terminally sterilized. *See* Prelim. Resp. 33. We first note that the '631 patent discloses, but does not appear to claim, any structure that allegedly 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. Additionally, we find sufficient for institution Mr. Koller's testimony that "the stopper and plunger rod design disclosed in the '631 patent specification were already known in the art by 2011," such

as with the pre-filled syringe design described in U.S. Patent Publication No. 2005/0182370 ('Hato' Ex. 1047)." *Id.* ¶¶ 109–110.

The evidence and testimony that Petitioner provides addressing how Sigg, Boulange, and USP789 teach the limitations of several dependent claims of the '631 patent also provide additional support, sufficient for institution, for how Sigg would have enabled a skilled artisan to make and use the claimed invention. *See* Pet. 51 (claim 17 requiring "the syringe has been sterilized using H^2O^2 or EtO"), 52 (claim 19 requiring "sterilized using EtO or H^2O^2 and the total EtO or H^2O^2 residue found on the outside of the syringe and inside of the blister pack is ≤0.1 mg"), 53 (claim 21 requiring "sterilized using EtO or H^2O^2 with a Sterility Assurance Level of at least 10^{-6}"). Based on the record before us, it appears that a POSITA would need only perform routine optimization to terminally sterilize the Sigg PFS in a syringe in the manner claimed.

Patent Owner contends that Boulange never suggests that its Parylene C invention is compatible with intravitreal administration or would be appropriate for syringes intended for such use. Prelim. Resp. 38. Based on the current record, Petitioner has sufficiently shown that a POSITA would have understood that Parylene C would be compatible with a terminally sterilized syringe comprising a VEGF-antagonist, and that it would provide sufficient tightness for terminal sterilization, as disclosed in Sigg and Lam. *See* Ex. 1003 ¶¶ 171–181. As Mr. Koller testifies, "Boulange explicitly acknowledges that Parylene C coating is impervious to gases and thus attractive for use in medical applications." *Id.* ¶ 172 (citing Ex. 1008, 2:21–24). "Boulange further acknowledges the need for a stopper design to

maintain sufficient tightness to seal the portion of the syringe comprising the drug product while maintaining acceptable operational forces." *Id.* (citing Ex. 1008, 1:18–21, 3:20–27, 4:21–32). We find persuasive Mr. Koller's testimony that

> a POSITA would understand from the disclosure in Boulange that stoppers coated with Parylene C would provide low operational forces while ensuring that the drug product in the syringe is properly sealed by the interface between the glass barrel and stopper. And a POSITA would certainly recognize that such a design with a tight seal and a coating such as Parylene C that is impervious to gases would be suitable for terminal sterilization.

Id. Mr. Koller notes that "Boulange explicitly describes that its syringe is suitable for storing a drug product in a gaseous phase, which means that it must have sufficient tightness to prevent gas from exiting or entering the syringe." *Id.* Mr. Koller cites several passages in Boulange and from this evidence opines that "Boulange encourages the use of Parylene C with the understanding that the coating must not negatively impact the drug product, must withstand the sterilization process that pre-filled syringes were known to undergo . . . and must ensure a tight seal to protect the drug product." *Id.* ¶ 173. We find this collective testimony persuasive on the current record.

We have considered Mr. Leinsing's testimony to the contrary, specifically the testimony related to "the 'tightness' referenced in Boulange is different from the 'tightness' required by Sigg," and as related to the gaseous versus liquid compatibility. Ex. 2001 ¶¶ 157–159, 161–162. Further, Mr. Leinsing testifies that "[t]erminal sterilization by VHP treatment according to Sigg requires 'tightness' that protects the contents of

a syringe from ingress of gasses," and "a POSA would have understood Sigg's method to require tightness over and above any 'conventional' gas-tightness." *Id.* ¶¶ 157, 159. These arguments suggesting a "tightness over and above" are difficult to comprehend considering this same stringent level of tightness is not required by the disclosure and claims of the '631 patent — we would like for these disparities to be addressed. *See, e.g.*, Ex. 1001, 10:2–7 (allowing for some minor amounts of sterilizing gas to enter the variable volume chamber). At this phase of the proceeding, and considering the claim scope, we are not clear as to the significance of Patent Owner's plunger/stopper and tightness arguments and whether they would matter to Boulange's stoppers, whether coated with Parylene C on the piston (B1) or not (C). The evidence before us is sufficient to proceed to trial.

Likewise, on the current record we do not find compelling Patent Owner's contention that a POSITA would not have reasonably expected to succeed in terminally sterilizing a syringe based on the combination of Sigg and Boulange due to the potential ingress of sterilizing agent. Prelim. Resp. 50. These arguments seem contradictory to Boulange's teaching that its syringe is designed with the understanding that "possible degradation is sometimes initiated by the processes used to sterilize the medical devices containing them" and that the "medical product potentially present in the medical device [is] to be preserved." Ex. 1008, 4:3–5, 4:26–27. We are persuaded by Mr. Koller on this record, that "a POSITA would have understood that Boulange's design was intended to protect drug products, including from the potential effect of sterilizing agents." Ex. 1003 ¶ 186.

At this stage of the proceedings, we find that Petitioner's evidence and testimony is sufficient to show a reasonable likelihood of success as to these issues. We will carefully consider the final record and how each declarant responds to the initial evidence.

On the current record, Patent Owner's arguments related to the objective indicia of nonobviousness fail to develop a sufficient nexus between the claimed invention and the secondary considerations evidence. Many of Patent Owner's arguments related to secondary considerations focus on Petitioner's lack of evidentiary support but Patent Owner ignores its own burden. *See* Prelim. Resp. 55–61. Patent Owner "bear[s] the burden of proving [] evidence of secondary considerations." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1378 (Fed. Cir. 2019). Further, "[t]he patentee bears the burden of showing that a nexus exists. To determine whether the patentee has met that burden, we consider the correspondence between the objective evidence and the claim scope." *Id.* at 1373 (citations omitted). On the record currently before us, Patent Owner has not met its burden of establishing that the evidence of secondary considerations has a sufficient nexus to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention. *See id*.

Patent Owner alleges that the Lucentis® PFS is a terminally-sterilized PFS for intravitreal injection of a VEGF antagonist that meets the limitations of the claims and does not include significant unclaimed features. Prelim. Resp. 59. Patent Owner, however, fails to provide any persuasive evidence supporting these contentions. Patent Owner must meet its burden with more than just attorney argument. Specifically, during the trial it is Patent

Owner's burden to establish that the asserted secondary considerations (like commercial success) are tied to the Lucentis® PFS and that this product embodies the claimed features, is coextensive with them, and does not include significant unclaimed features. We are not persuaded that the current record is sufficient for us to determine the composition and function of the Lucentis® PFS and how it relates to any particular claim. Further, Patent Owner does not allege which claim or claims are related to Lucentis® PFS, and we note that the claims vary in scope.

We do not find either parties' evidence persuasive on this record as to the "long-felt need" and "failure of others." We have considered Patent Owner's allegations regarding the "failure of others," and specifically Mr. Leinsing's testimony (Ex. 2001 ¶ 189). Prelim. Resp. 56–58. Mr. Leinsing testifies as to the perceived failure of Genentech without any first-hand knowledge of these endeavors and based upon his reading of the Lam application. Ex. 2001 ¶ 189. We do not find his testimony on this matter persuasive as it is not adequately supported on the current record. Petitioner argues that, by June 2020, it succeeded in reducing 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, but Petitioner offers scant detail as to this device and its relation to any particular claim. Pet. 73 (citing Ex. 1005, 109–110, 114–125) (ITC Staff Pre-Hearing Brief). Petitioner is also not permitted under our rules to incorporate argument and evidence from another brief into this proceeding. *See* 37 C.F.R. § 42.6(a)(3).

Patent Owner alleges "unexpected results," but fails to back up its allegations with persuasive supporting evidence. Prelim. Resp. 60. Mr. Koller counters that Boulange previously taught the claimed silicone oil amounts in conjunction with the claimed break loose and slide forces and this shows that the results were not unexpected. Ex. 1003 ¶¶ 305–314. Mr. Leinsing disagrees, and testifies that "Boulange shows only that the use of Parylene C-coated stoppers allowed maintenance of low injection forces with lower amounts of silicone oil," but "Boulange's data overall, though, is consistent with the conventional thinking that decreasing silicone oil leads to increased forces." Ex. 2001 ¶ 192. Based on the current record, the claims of the '631 patent encompass glass barrels with up to about 100 μg of silicone oil, and break loose and glide forces up to about 11 N, but the prior art discloses these ranges as we determine above. Thus, this finding provides some evidence that there was nothing "unexpected" about these particular claim limitations and any product embodying them. *See* Ex. 1003 ¶ 309. Again, it is Patent Owner's burden to establish these objective indicia of nonobviousness and we will weigh the record developed during trial in reaching a final decision.

Based on the current record, we do not find the evidence of secondary considerations supports nonobviousness. To the extent the parties further develop the record, the objective indicia of nonobviousness could be important in our final determination.

On the record before us, based on the arguments and evidence above and considering the level of ordinary skill in the art, Petitioner has established a reasonable likelihood of prevailing on its assertion that claim 1

would have been unpatentable over the combination of Sigg, Boulange, and USP789. Nonetheless, the ultimate burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

H. Additional Claims and Grounds

At this stage in the proceeding, Patent Owner does not address separately Petitioner's arguments and evidence with respect to the dependent claims and additional grounds challenging such dependent claims. *See generally* Prelim. Resp. We have reviewed Petitioner's arguments and evidence regarding these claims, and, on the current record, we find them sufficient for purposes of institution.

Patent Owner does, however, challenge the combination of Lam and Boulange, noting that these grounds substitute Lam for Sigg. Prelim. Resp. 53–55. Relying on Mr. Leinsing's testimony, Patent Owner argues that "like Sigg, Lam does not provide sufficient detail concerning the syringe design to enable a POSA to practice its method successfully." *Id.* at 53 (citing Ex. 2001 ¶¶ 168–169, 175–182). Patent Owner argues that Lam discloses that the syringe must have a gas impermeable interior space to prevent EtO from coming into contact with the drug, but Lam does not explain how to design a syringe to meet that criterion. *Id.* at 53–54. Patent Owner recognizes that "Lam includes an example referencing the sterilization of syringes filled with ranibizumab that appears to leave the active ingredient largely intact," (*id.* at 54), and we determine that this teaching, along with Petitioner's supporting evidence and testimony, is

sufficient to create a reasonable likelihood that claim 1 would have been obvious over Lam, Boulange, and USP789. *See* Pet. 55–59.

We will further consider Patent Owner's contentions related to Lam's alleged lack of details about the syringe's design based on the final record. *See* Prelim. Resp. 54–55. We note that the issues generally noted above appear to apply also to the combination of Lam and Boulange.

IV. CONCLUSION

For the foregoing reasons, we determine that the information presented establishes a reasonable likelihood that Petitioner would prevail in showing that at least one of claims 1–26 of the '631 patent is unpatentable. At this preliminary stage, we have not made a final determination with respect to the patentability of the challenged claims or any underlying factual and legal issues. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that "there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial").

Accordingly, *inter partes* review is instituted as to all claims. *See SAS*, 138 S. Ct. at 1359–60; *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges).

Any discussions of facts in this Decision are made only for the purposes of institution and are not dispositive of any issue related to any ground on which we institute review. We have not made a final

determination with respect to the patentability of any challenged claim. Our final determination will be based on the record as fully developed during trial, including any evidence or argument timely presented by Patent Owner in a response to the Petition.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of the '631 patent is instituted on all of the challenged claims and all grounds asserted in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial commences on the entry date of this Decision.

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