Trials@uspto.gov
571-272-7822

Paper No. 8
Entered: July 2, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSL BEHRING GMBH and CSL BEHRING LLC,
Petitioner,

v.

SHIRE VIROPHARMA INC.,
Patent Owner.

Case IPR2019-00459
Patent 10,080,788 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and RICHARD J. SMITH, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

On December 21, 2018, CSL Behring GmbH and CSL Behring LLC (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–30 of U.S. Patent No. 10,080,788 B2 ("the '788 patent," Ex. 1001). Paper 3 ("Pet."). Shire ViroPharma Inc. ("Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

We have the authority and discretion to determine whether to institute an *inter partes* review. 35 U.S.C. § 314; 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . 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). Additionally, in determining whether to institute an *inter partes* review, we "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." 35 U.S.C. § 325(d). Upon considering the arguments and evidence of record, we determine it is appropriate to exercise our discretion to deny institution under § 325(d).

II. BACKGROUND

A. Related Matters

Patent Owner has asserted the '788 patent and other related patents against Petitioner in the following consolidated cases pending before the U.S. District Court for the District of Delaware: *Shire ViroPharma Inc. v. CSL Behring LLC*, Case Nos. 17-414 and 18-1476 (D. Del.). *See* Pet. 63; Paper 5, 1. Additionally, one of those related patents, U.S. Patent 9,616,111 ("the '111 patent"), was previously challenged by Petitioner in IPR2017-01512. *Id.* The Board denied institution in that proceeding. *See* IPR2017-

01512 (PTAB Dec. 7, 2017) (Paper 12). Petitioner and Patent Owner also identify as related matters certain proceedings concerning foreign counterpart patents in Europe. Pet. 63; Paper 5, 2.

B. The '788 Patent

The '788 patent, entitled "C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated with C1 Esterase Inhibitor Deficiency," issued on September 25, 2018, and claims priority to a provisional application filed March 15, 2013. Ex. 1001, (45), (54), (60). It is directed generally to compositions and methods for treating disorders associated with C1 esterase inhibitor (C1-INH) deficiency, and in particular hereditary angioedema (HAE), which is a genetic disorder in which patients can experience life-threatening inflammation of the larynx, abdomen, face, extremities, and urogenital tract. *Id.* at 1:28–44.

According to the '788 patent, the "restoration of active C1 esterase inhibitor levels in patients having a disorder associated with deficient or reduced levels of active C1 esterase inhibitor (e.g., HAE) is an effective measure for treating such disorders." *Id.* at 2:4–7. The '788 patent notes that intravenous administration of a C1 esterase inhibitor, such as that under the trade-name of Cinryze, was known in the art. *Id.* at 2:8–10. The '788 patent teaches "[s]urprisingly, the subcutaneous ['sc'] administration of the C1 esterase inhibitor is sufficient to maintain the blood levels of the C1 esterase inhibitor." *Id.* at 2:12–15. Thus, the '788 patent teaches more concentrated formulations suitable for subcutaneous administration. *Id.* at 2:24–27, 50–58. In particular, the '788 patent describes studies that "demonstrated that there is not a solubility limit to preparing C1 INH at concentrations up to 500 U/ml," and notes that while "[t]here is an increase

in viscosity once the concentrations reach the 400-500 U/ml range," those higher concentration formulations are "manageable and still allow facile delivery by injection for standard syringe systems." *Id.* at 10:35–41.

C. Illustrative Claim

Among the challenged claims, independent claim 1 is representative and reproduced below:

> 1. A method for prophylactic treatment of hereditary angioedema (HAE) comprising subcutaneously administering to a subject in need thereof a pharmaceutical composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5–8.0, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL, and wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1, and wherein the administration of the composition increases the level of the C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL.

Ex. 1001, 13:13–23.

D. The Asserted Ground of Unpatentability

Petitioner asserts claims 1–30 of the '788 patent are unpatentable based on the following ground:

Claim(s) Challenged	Statutory Basis	References
1–30	§ 103	Schranz[1] (as evidenced by the Cinryze Label,[2] Levi,[3] and Block[4]) in view of Gatlin[5] and Other References

Petitioner further relies upon the declarations of Dr. Timothy Craig (Ex. 1012), Hanno Waldhauser (Ex. 1013), Dr. Hubert Metzner (Ex. 1014), and Dr. Gerhard Winter (Ex. 1015).

III. ANALYSIS: 35 U.S.C. § 325(d)

Patent Owner contends that the Board should exercise its discretion under 35 U.S.C. § 325(d) to deny institution because the same or substantially the same prior art and arguments have been considered and rejected by the Office. Prelim. Resp. 8–23. In particular, Patent Owner contends that the Office considered the same or substantially the same prior

---

[1] Schranz et al., *Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Subcutaneous (SC) CINRYZE® (C1 Esterase Inhibitor [Human])with Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Hereditary Angioedema (HAE)*, ViroPharma Incorporated, Poster L21 presented at the 2012 American Academy of Allergy, Asthma & Immunology annual meeting (Ex. 1004) ("Schranz").

[2] Cinryze® Prescribing Information, ViroPharma Incorporated, Nov. 2012 (Ex. 1010) ("Cinryze Label").

[3] Levi et al., *Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency*, 117 J. ALLERGY & CLIN. IMMUNOL. 904–08 (2006) (Ex. 1009) ("Levi").

[4] Bock et al., *Human C1 Inhibitor: Primary Structure, cDNA Cloning, and Chromosomal Localization*, 25 BIOCHEM. 4292–4301 (1986) (Ex. 1011) ("Bock").

[5] Larry A. Gatlin & Carol A. Brister Gatlin, *Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products*, Chapter 17 in INJECTABLE DRUG DEVELOPMENT: TECHNIQUES TO REDUCE PAIN AND IRRITATION 401–21 (Pramod K. Gupta & Gayle A. Brazeau, eds., Interpharm Press 1999) (Ex. 1006) ("Gatlin").

art and arguments during: (1) the prosecution of the parent application that issued as the '111 patent (Application No. 14/855,168); (2) the Board's evaluation of Petitioner's challenges in IPR2017-01512 concerning the '111 patent; and (3) the prosecution of the application that issued as the '788 patent (Application No. 15/837,677). As it is dispositive, we focus our analysis on whether the Petition should be denied under § 325(d), and do not reach the merits of Petitioner's patentability challenges or Patent Owner's other arguments for denial of institution. We provide a brief overview of the prior art and the prior Office proceedings before turning to our analysis.

A. Overview of the Prior Art

1. Schranz (Ex. 1004)

Schranz is a poster that was allegedly displayed at the 2012 annual meeting for the American Academy of Allergy, Asthma & Immunology ("AAAAI"), in which Patent Owner's predecessor, ViroPharma Inc., reported that it was concurrently developing two C1-INH formulations for subcutaneous administration: a volume-reduced formulation of Cinryze alone, and a large-volume formulation of Cinryze in combination with recombinant human hyaluronidase (rHuPH20). Ex. 1004; Ex. 1013 ¶¶ 2–5.

Schranz describes two studies: a "Prior 200 Study," in which 26 HAE patients received twice-weekly 1000U or 2000U sc doses of Cinryze as two or four 1.5mL injections (i.e., 1000U in 3mL or 2000U in 6mL); and a "Current 204 Study," in which 12 patients from the Prior 200 Study received twice-weekly 1000U or 2000U sc doses of Cinryze in combination with rHuPH20 as a single 10 mL or 20mL injection. Ex. 1004, Abstract; Fig. 1 (study design). Schranz provides data on the mean plasma C1-INH functional concentrations (with certain outliers excluded) for subjects in

whom the drug was administered intravenously and subcutaneously (both alone and in combination with rHuPH20), and concludes that the combination therapy "resulted in physiologically relevant and sustained C1 INH functional concentrations >0.4 U/mL." *Id.*, Fig. 2, Conclusion.

2. Gatlin (Ex. 1006)

Gatlin is a chapter from a textbook on injectable drug development describing formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Ex. 1006, 401. Gatlin teaches that injection pain is a potential disadvantage associated with parenteral therapy, and that "[d]ue to the location of human pain receptors, formulation approaches to reduce pain are more critical for subcutaneous (SC) and intradermal injections and less critical for intramuscular (IM) and intravenous (IV) administration." *Id.* at 405. Gatlin further teaches that injection volume is an important consideration in the formulation development of a commercial product, and that "[d]rugs recommended for SC injection include nonirritating aqueous solutions and suspensions contained in 0.5 to 2.0 mL (target 1 mL or less) of fluid." *Id.* at 417.

3. Levi (Ex. 1009)

Levi describes a study investigating the feasibility, efficacy, and safety of on-demand and prophylactic self-administration of C1-INH concentrate in patients with frequent attacks of angioedema. Ex. 1009, Abstract. Levi teaches that "for prevention of attacks, subphysiologic levels of C1-inhibitor (as low as 40% of normal levels [i.e., 0.4U/mL] are sufficient." *Id.* at 907–08.

4. Cinryze Label (Ex. 1010)

The Cinryze Label provides the prescribing information for intravenous administration of Cinryze, which received FDA approval in 2008. Ex. 1010, 673. As noted in the Label, Cinryze had been approved for routine prophylaxis against HAE attacks, at a dose of 1,000 Units intravenously every 3 or 4 days and an infusion rate of 1 mL/min (10 min). *Id*. (Table 1). The Label teaches that the specific activity of Cinryze is 4.0–9.0 units/mg protein, where one "Unit" (U) corresponds to the mean quantity of C1-INH present in 1 mL of normal fresh plasma. *Id.* § 11. The Label further teaches that, following reconstitution with 5 mL of sterile water for injection, each vial contains approximately 500 units of functionally active C1-INH with a pH 6.6–7.4. *Id.*

5. Block (Ex. 1011)

Block teaches the primary structure of human C1 inhibitor as determined by peptide and DNA sequencing. Ex. 1011, Abstract, 4294.

B. Prior Office Proceedings

1. '111 Patent Prosecution

During prosecution of the application that issued as '111 patent, the Examiner rejected similar method of treatment claims reciting a C1-INH "concentration of at least about 400 U/mL" as being unpatentable for obviousness over Jiang[6] and the "UNC" reference.[7] Ex. 2001, 3900, 4187–

[6] Haixiang Jiang et al., *Subcutaneous Infusion of Human C1 Inhibitor in Swine*, 136 CLIN. IMMUNOL. 323 (2010) (Ex. 1005) ("Jiang").
[7] The "UNC" reference relied upon by the Examiner has not been included as a separate exhibit in this proceeding, but appears to be a webpage from the Pharmaceutics and Compounding Laboratory of the University of North Carolina's Eshelman School of Pharmacy. *See* https://pharmlabs.unc.edu/labs/parenterals/subcutaneous.htm.

97. The Examiner asserted that Jiang "concludes that subcutaneous administration is a viable treatment option for patients with HAE," and although "Jiang does not teach the dosage of about 400 U/mL in a single subcutaneous dose," further asserted based on UNC that "one of skill in the art would recognize that a subcutaneous dose of any drug is limited generally to a total injection volume of approximately 2 mL." *Id.* at 4188. More particularly, the Examiner explained:

> The teachings of volume limitations of subcutaneous doses would limit the 1000 U of Cinryze to a 2 ml subcutaneous dose, which would have at least 400 U/ml, even considering that Jiang used doses of 100 U/ml (i.e. the artisan would have a motivation from the prior art to make the injection of the entire Cinryze dose limited to a 2 ml volume, resulting in at least 400 U/ml). The resulting increase in blood level would be expected to inherently occur, as the prior art provides for the same method of administration and total volume.

Id. at 4189.

To overcome this rejection, the applicant submitted the Declaration of Dr. Jennifer Schranz under 37 C.F.R. § 1.132 ("the Schranz Declaration"), in which Dr. Schranz asserted, *inter alia*, that (1) there was a consensus in the field that C1-INH could not be formulated at a high-concentration in view of its large size, high glycosylation, high viscosity, and propensity to aggregate; (2) the claimed high-concentration formulations exhibited unexpected bioavailability; and (3) there was a long-felt need for an sc C1-INH formulation that others had tried and failed to satisfy. Ex. 2001, 4654–65; Ex. 1003 ¶¶ 9–24. The Examiner did not initially consider the Schranz Declaration persuasive to overcome the pending rejection (Ex. 2001, 4194–97), but after considering additional arguments and supporting evidence

submitted by the applicant (*id.* at 4272–79), the Examiner allowed the claims with the following statement of reasons for allowance:

> The closest prior art (Jiang as previously cited) teaches administration of C1-INH subcutaneously at a dose of 100 U/ml. However, the instant claims require a dose of at least 400 U/ml, which is not provided by the prior art. The declaration and evidence as submitted by the Applicants as of 11 November 2016 has been found sufficient by the Examiner to establish secondary considerations in the form of long felt need and failure of others (MPEP 716.04) to rebut the prima facie case of obviousness. As no obviousness rejection can be made in light of the secondary consideration and nothing in the prior art suggests the dosages as instantly claimed for subcutaneous administration, the claims are found to be novel and unobvious.

Id. at 4918. During prosecution of the '111 patent, the Examiner also considered Petitioner's third party observations from foreign proceedings (involving corresponding GB and EP patent applications) addressing Schranz and other prior art. *Id.* at 4639–46, 4956–67, 5115. The '111 patent issued on April 11, 2017.

2. IPR2017-01512

On May 31, 2017, Petitioner filed a petition for *inter partes* review challenging the issued claims of the '111 patent. *See* IPR2017-01512, Paper 1. Petitioner challenged the patentability of claims 1–18 of the '111 patent on the following grounds:

References	Basis	Claims Challenged
Schranz (as evidenced by Cinryze Label and Bock), Gatlin, Pharming,[8] and Levi	§ 103(a)	1–18
Jiang (as evidenced by Cinryze Label and Bock), Gatlin, Pharming, Zuraw,[9] and Levi	§ 103(a)	1–18

On December 7, 2017, the Board denied institution in IPR2017-01512. *See* IPR2017-01512, Paper 12. With respect to the grounds relying upon Schranz, the Board determined that the joint declaration submitted in that proceeding was insufficient to establish that Schranz is prior art. *Id.* at 6–9. Additionally, the Board determined that Petitioner was making essentially the same arguments as to obviousness over Jiang that the Examiner already considered, and thus denied institution as to the second ground under § 325(d). *Id.* at 10–15. With respect to the Schranz Declaration, the Board noted that "[t]he prosecution history demonstrates that the Examiner considered many of the same issues with respect to the Schranz Declaration as Petitioner is arguing here," and "[a]lthough the Examiner noted in allowing the claims that Applicant Shire had established the secondary consideration of long-felt need and failure of others, the Examiner also stated that the art did not suggest the claimed dosage." *Id.* at 14.

[8] Mannesse et al., WO 2007/073186 A2, published June 28, 2007 (Ex. 1007) ("Pharming").
[9] Zuraw et al., *Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema*, 363(6) N. ENGL. J. MED. 513–22 (2010) (Ex. 1008 in IPR2017-01512) ("Zuraw").

3. '788 Patent Prosecution

The '788 patent issued from an application filed December 11, 2017, and claims priority as a continuation of the '111 patent. Ex. 1001, (22), (63).

At the outset of the '788 patent prosecution, the applicant, in an Information Disclosure Statement (IDS), cited Petitioner's GB, EP, and Canadian Observations and Protests (designated C10, C11, C141), Schranz (C131, C160, C161, including enlarged sections), Gatlin (C69), the Cinryze Label (C9), the Schranz Declaration from the '111 patent prosecution (C157, C158), and the petition from IPR2017-01512 (C50), and submitted copies of those documents. Ex. 1002, 112–23; Ex. 2004, 79–157, 217–20, 223–35, 295–305, 509– 77, 614–24, 625–702, 823–26.

The Examiner rejected the claims as obvious over the combination of Jiang and UNC using the same rationale as the rejection made during the '111 patent prosecution. Ex. 1002, 96–98. In response, the applicant distinguished Jiang and relied on the Schranz Declaration and other evidence of objective indicia of nonobviousness, including long-felt need. *Id.* at 146–52. The Examiner once again found this evidence persuasive to overcome the rejection, and allowed the claims, noting:

> The Examiner has previously allowed methods of treatment utilizing highly similar products in parent USP 9,616,111. In the instant claims, the methods of treatment of HAE use an identical product (a C1-INH composition) and an identical method of administration (subcutaneous dosage at 500 U/mL) that were previously found to be novel and unobvious in the '111 patent. In the instant application, the Declaration of Dr. Schranz has similarly been found persuasive to establish a secondary consideration of long felt but unmet need that rebuts a conclusion of obviousness. The art does not recognize

> formulations of C1-INH of 500 U/mL or higher as now claimed.

Id. at 317.

C. Discussion

Section 325(d) gives us express discretion to deny a petition when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In evaluating whether to exercise our discretion under § 325(d), we weigh the following non-exclusive factors: (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 prior art or arguments. *NHK Spring Co. v. Intri-Plex Techs., Inc.*, Case IPR2018-00752, slip op. at 11–12 (PTAB Sept. 12, 2018) (Paper 8) ("*NHK*") (precedential).[10]

[10] These factors were adopted from the Board's previously designated informative decision in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) ("*Becton Dickinson*") (informative). For ease of reference and consistency with the arguments presented by Patent Owner, we continue to refer to the factors as the "*Becton Dickinson* factors."

Having considered the parties' respective arguments and evidence, we determine that exercising our discretion is appropriate under the facts and circumstances of this case.

1. Factors (a)–(d)

Becton Dickinson factors (a)–(d) relate to whether and to what extent the prior art asserted in the Petition was considered and relied on by the Examiner during prosecution, as well as the extent of overlap between arguments made during examination and the manner in which Petitioners rely on the prior art. We find that these factors weigh in favor of denial.

As noted by Patent Owner, the two main references relied upon by Petitioner—Schranz and Gatlin—were cited to the Examiner, indicated as considered during both the '788 patent and '111 patent prosecution, and were also evaluated by the Board in IPR2017-01512. Prelim. Resp. 17. Petitioner also acknowledges that "the documents from IPR2017-01512 were submitted during prosecution of the '788 patent in an Information Disclosure Statement containing nearly 250 total references," but asserts that "the Examiner did not cite *Schranz* or *Gatlin*, and there is no indication that he substantively relied on those references or the related arguments in the prior petition and accompanying declarations." Pet. 61; *see also id.* at 1 ("The Examiner failed to appreciate and did not rely on the closest prior art, *Schranz*, which is Patent Owner's own work.").[11]

[11] Petitioner further asserts that the alleged insufficiency with respect to the joint declaration submitted in IPR2017-01512 has been addressed in the current Petition, which presents new evidence to establish the prior art status of Schranz. Pet. 60–61. Although the Board previously determined that Petitioner had not made a threshold showing that Schranz is prior art (*see* IPR2017-01512, Paper 12, 6–9), and Patent Owner continues to contest the

We are not persuaded that the Examiner failed to appreciate the significance of Schranz and Gatlin during prosecution. To the contrary, Petitioner's prior arguments relying upon Schranz's study involving sc administration of C1-INH at a concentration of 333 U/mL were repeatedly cited to the Examiner. *See, e.g.*, Ex. 2001, 4639 (GB observation in which Petitioner argued that Schranz "report[ed] a study in which C1-INH was subcutaneously administered at a concentration of 333 U/ml, with no suggestion of any formulation or stability problems at that concentration"); *id.* at 4963 (EP observation in which Petitioner described Schranz's "previous 200 study" as "corresponding to a concentration of **333 U/mL** of C1-INH" in which "[n]o solubility or viscosity problems are reported"); Ex. 2004, 109–111 (petition in IPR2017-01512 in which Petitioner asserted that Schranz achieved plasma levels of 0.4 U/mL by sc administration of 200U of Cinryze at a concentration of 333 U/mL (Prior 200 Study) or 100 U/mL (Current 204 Study)). Likewise, Petitioner's prior arguments relying upon Gatlin as providing a motivation to increase the concentration of Schranz's formulations were also presented to the Examiner. Ex. 2004, 111–115. Indeed, the unpatentability ground set forth in the current Petition is nearly identical to the unpatentability ground relying upon Schranz and Gatlin set forth in the petition for IPR2017-01512. *Id.* at 106–28.

Furthermore, the Schranz Declaration, which highlighted ViroPharma's efforts at developing an sc formulation of Cinryze, played a prominent role during prosecution of both the '111 patent and '788 patent.

---

prior art status of Schranz in this proceeding (Prelim. Resp. 24–27), we assume *arguendo* for purposes of our § 325(d) analysis herein that Schranz qualifies as a prior art printed publication.

Contrary to Petitioner's contention that Dr. Schranz failed to mention in her declaration her own studies using a concentrated C1-INH formulation (Pet. 11 n.10), the Schranz Declaration referred specifically to "ViroPharma's 2012 AAAAI poster (attached as Exhibit D)." Ex. 1003, 7 n.1. This appears to be the same Schranz poster relied upon as prior art in the Petition as there is no evidence that ViroPharma presented any other poster at the 2012 AAAAI conference.

Additionally, even though the Examiner did not reject any of the claims based on Schranz and Gatlin during prosecution, we find that the Examiner's rejection based on Jiang and UNC relied on prior art teachings and a rationale which, although not entirely cumulative, are very similar to those presented in the current Petition. Petitioner acknowledges that Schranz, like Jiang, teaches a C1-INH concentration below the "about 500 U/mL" concentration recited in the challenged claims. Pet. 20–21. Although Petitioner highlights the higher concentration of 333 U/mL disclosed in Schranz's Prior 200 study, Schranz nonetheless used a formulation with a 100 U/mL concentration (the same concentration the Examiner found to be disclosed in Jiang) as the basis for further study. Ex. 1004, Fig. 1. Moreover, Petitioner's reliance on Gatlin's teaching as providing a motivation to limit the total injection volume for sc administration is analogous to the Examiner's reliance on UNC. *Compare* Pet. 22 ("But *Gatlin* teaches that low volumes (between 0.5 to 2.0 mL) are preferred for sc administration."), *with* Ex. 1002, 98 ("With respect to concentration levels and sc dosing, one of ordinary skill in the art is aware that sc administration is limited by volume ~2 mL.").

We also do not find that the additional references relied upon in the Petition present any new teachings that were not already considered by the Examiner. For instance, the Petition cites the Cinryze Label as evidence that Cinryze has the same buffer and pH as recited in the claims, and that Cinryze was manufactured in a manner that did not alter its amino acid sequence. Pet. 30, 33–34 (citing Ex. 1010 § 11). The Petition further cites Block for its teaching of the amino acid sequence of C1-INH. *Id.* at 33 (citing Ex. 1011, 7–8). The Examiner, however, cited other prior art teachings that "[t]he Cinryze composition is known to be presented as a vial containing 500 U of C1 esterase inhibitor (identical to residues 23–500 of SEQ ID NO:1), sodium citrate at pH 6.6–7.4 after reconstitution in water, and that the active ingredient is nanofiltered, pasteurized (sterile),and lyophilized." Ex. 1002, 97. The Petition also relies upon Levi as evidence establishing that plasma levels of 0.4U/mL are physiologically relevant to prevent HAE attacks. Pet. 19 (citing Ex. 1009, 15–16). But the Examiner relied upon Jiang's Figure 4 as showing that sc administration of a lower dosage of Cinryze (50 U/mL) still results in C1 esterase levels in plasma of > 0.4 U/mL. Ex. 1002, 97. These prior art teachings were not disputed during prosecution, and we fail to see how the new prior art cited in the current Petition would have materially affected the Examiner's conclusions.

Although the sole unpatentability ground set forth in the current Petition states that Schranz in view of Gatlin and "other references" render claims 1–30 obvious (Pet. 13), it is not entirely clear what those other

references are, and how they are being relied upon in the Petition.[12] Given this lack of particularity, we decline to speculate whether these other unnamed references present any new teachings that were not already considered by the Examiner. *See* 35 U.S.C. § 312(a)(3) (requiring that "the petition identifies, in writing and *with particularity*, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim") (emphasis added).

2. Factors (e) and (f)

Becton Dickinson factors (e) and (f) look to whether Petitioner has made a case for reconsidering the application of the asserted prior art in light of new evidence. Petitioner asserts generally that "this Petition highlights factual and legal flaws in Patent Owner's arguments presented in its Preliminary Response in the prior IPR, and addresses other issues, including new developments in the law, that are not contained in the documents from IPR2017-01512." Pet. 61. We find that Petitioner has not made a sufficient case under these factors to proceed with institution notwithstanding the overlap in prior art and similar arguments previously considered by the Office.

[12] For instance, Petitioner contends that "given its higher specific activity, if a POSA had simply substituted the Cinryze® used in *Schranz*'s 333U/mL formulation for an equivalent mass of Berinert® [Petitioner's FDA approved C1-INH drug], he would have obtained a C1-INH formulation having an activity-based concentration of about 500U/mL or more." Pet. 25–26 (citing Ex. 1015 ¶ 118). However, none of the other references named in the ground of unpatentability set forth in the Petition discuss Berinert, and Petitioner does not explain why the skilled artisan would have been motivated to use Berinert at 500 U/mL in place of Cinryze in Schranz's 333U/mL formulation.

In essence, Petitioner in its current Petition, asks the Board to reevaluate the Schranz Declaration considered during prosecution and in IPR2017-01512. For instance, Petitioner contends that there was no support provided in the Schranz Declaration to substantiate the claims made therein. Pet. 11, 26–27. But, as noted by Patent Owner, the Examiner only found the Schranz Declaration to be persuasive after the applicant submitted additional documentary evidence, including articles by Haller, Shire, and Kling supporting the assertions made by Dr. Schranz. Prelim. Resp. 10; Ex. 2001, 4272–79. The applicant also pointed to data included in the specification as demonstrating that when the C1-INH concentration exceeds about 400 U/mL (a concentration required for subcutaneous injection), the viscosity increases dramatically. *Id.* at 4275–76; *see also* Ex. 1001, 8:7–22 (Table 1). Petitioner fails to address how the Examiner's reliance on this evidence submitted in support of the Schranz Declaration was erroneous.

We recognize that Petitioner has presented its own experts, Dr. Craig and Dr. Winter, who call into question certain assertions made in the Schranz Declaration. Ex. 1012; Ex. 1015. But the mere fact that Petitioner has presented expert declaration evidence in support of its unpatentability challenge is not in itself a basis to proceed with institution. Otherwise, the Board's discretion under § 325(d) would be inapplicable for the vast majority of *inter partes* reviews in which petitioners rely upon new expert testimony to support their challenges. Rather, consistent with *Becton Dickinson* factors (e) and (f), we consider whether the new expert testimony demonstrates a clear error made by the Examiner or a materially false or incomplete statement made by the applicant during prosecution in order to obtain allowance of the patent.

In order for Petitioner to prevail on its challenge, we would need to credit the statements of Petitioner's declarants over the contrary statements in the Schranz Declaration that were previously considered and found persuasive by the Examiner. We are not persuaded, however, that the expert declarations submitted with the Petition demonstrate sufficiently that the Examiner committed a clear factual error in evaluating the Schranz Declaration and the prior art during prosecution. For instance, Dr. Schranz asserts in her declaration that "C1-INH is one of the most highly glycosylated plasma proteins," that "[l]ike many highly glycosylated proteins, C1-INH has a high viscosity," and that "plasma-derived C1-INH is particularly prone to aggregation due to the presence of certain co-eluates." Ex. 1003 ¶ 13. In contesting this statement, Petitioner's formulation expert, Dr. Winter, asserts that he was unaware of any reports prior to March 2013 that C1-INH was "particularly prone to aggregation," but even "assuming a small baseline tendency for plasma-purified proteins to aggregate, a skilled formulator would not expect C1-INH to be difficult to formulate at high concentrations based on its molecular weight and glycosylation pattern." Ex. 1015 ¶ 50; *see also id.* ¶ 100.

Likewise, in contesting Dr. Schranz's statements concerning a long-felt need for more convenient delivery of C1-INH, that early clinical trials examining subcutaneous administration of C1-INH had been unsuccessful, that there had been safety and efficacy concerns over increasing C1-INH concentrations in formulations, and that there had been a consensus in the field that it would not be feasible to develop high-concentration formulations of C1-INH (Ex. 1003 ¶¶ 14, 20, 23), Petitioner's medical expert, Dr. Craig, asserts that "Dr. Schranz's unsupported assertions are incorrect and do not

reflect the state of the art with respect to C1-INH therapies for treating HAE as of March 2013." Ex. 1012 ¶ 16. But neither of Petitioner's experts point to any specific statements in the Schranz Declaration that were factually incorrect. Nor do they address the corroborating evidence the applicant submitted in support of the Schranz Declaration during prosecution. Rather, Petitioner's experts merely express a difference of opinion as to whether a person of ordinary skill at the time would have expected to encounter difficulties in developing an sc formulation of C1-INH. Under the circumstances, we do not believe that Petitioner's expert declarations provide a sufficient justification for the Board to reconsider that issue in this proceeding.

We also recognize that Petitioner relies upon certain additional evidence concerning the efforts to develop a more concentrated formulation of C1-INH by both Petitioner and Patent Owner. *See* Pet. 5–6 (discussing separate evaluations of more concentrated preparations of Berinert and Cinryze, respectively by Petitioner and Patent Owner's collaborator Sanquin); Ex. 1008 (internal memo by Petitioner's predecessor ZLB Behring discussing feasibility and stability of a 10-fold concentration (500 U/mL) of Berinert); Ex. 1014 (declaration by Dr. Hubert Metzner, Petitioner's Director of Process Development, discussing efforts to develop a concentrated C1-INH formulation for sc administration); Ex. 1050 (research report by Sanquin discussing Cinryze formulations in concentrations of up to 500 U/mL); Ex. 1051 (internal email by ViroPharma scientists discussing Sanquin report). Petitioner contends that this evidence demonstrates that the companies had independently tested the higher concentration formulations without difficulty. Pet. 24–25. As noted by Patent Owner and

acknowledged by Petitioner, however, this evidence was not publicly available prior to the effective filing date of the '788 patent. Prelim. Resp. 7; Pet. 6. In an *inter partes* review, unpatentability challenges under 35 U.S.C. § 102 and § 103 can be made "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). As such, we are not persuaded that this previously non-public evidence cited in the Petition presents a sufficient basis to institute despite the Office's prior consideration of the relevant art that was publicly available.

IV. CONCLUSION

In considering the record as a whole, we determine that the same or substantially the same prior art or arguments that Petitioner asserts were presented to the Office during examination of the '111 patent and the '788 patent as well as in IPR2017-01512. 35 U.S.C. § 325(d). Moreover, Petitioner has not shown sufficiently how the Examiner erred in evaluating the asserted prior art or the Schranz Declaration. Thus, when we consider the interests of conservation of resources and finality of prior Office determinations—the policy objectives underlying § 325(d) and the *Becton Dickinson* factors—we determine that the circumstances in this case weigh strongly in favor of exercising our discretion to not institute an *inter partes* review. Accordingly, we do not institute *inter partes* review of the challenged claims based on the challenge presented in the Petition.

V. ORDER

In consideration of the foregoing, it is hereby ORDERED that the Petition is *denied*.

For PETITIONER:

Anthony Tridico
Amanda Murphy
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP
Anthony-tridico@finnegan.com
Amanda.murphy@finegan.com

For PATENT OWNER:

Edgar Haug
Brian Murphy
Angus Chen
Andrew Wasson
Andrew Roper
Kaitlin Abrams
HAUG PARTNERS LLP
ehaug@haugpatners.com
bmurphy@haugpartners.com
achen@haugpartners.com
awasson@haugpartners.com
arope@haugpartners.com
kabrams@haugpartners.com