

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEXUS PHARMACEUTICALS, LLC,
Petitioner,

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner.

PGR2024-00016
Patent 11,642,370 B1

Before ULRIKE W. JENKS, SUSAN L. C. MITCHELL, and
CYNTHIA M. HARDMAN, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. § 324

I. INTRODUCTION

A. Background and Summary

Nexus Pharmaceuticals, LLC (“Petitioner”) filed a Petition requesting post-grant review of claims 1–30 (“the challenged claims”) of U.S. Patent No. 11,642,370 B1 (Ex. 1001, “the ’370 patent”). Paper 1 (“Pet.”). Exela Pharma Sciences, LLC (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). With our authorization (Ex. 3001), Petitioner filed a Petitioner’s Preliminary Reply to Patent Owner’s Preliminary Response (Paper 7, “Prelim. Reply”) and Patent Owner filed Patent Owner’s Pre-Institution Sur-Reply (Paper 8, “Prelim. Sur-reply”).

Under 35 U.S.C. § 324(a), a post-grant review may be instituted only if “the information presented in the petition . . . demonstrate[s] that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” Post-grant review is available for patents that issue from applications that at one point contained at least one claim with an effective filing date on or after March 16, 2013. *See Leahy-Smith America Invents Act*, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), §§ 3(n)(1), 6(f)(2)(A).

After considering the briefing and the evidence of record, for the reasons set forth below, we exercise discretion to deny institution under § 325(d). Accordingly, we do not institute a post-grant review of the challenged claims of the ’370 patent.

B. Real Parties in Interest

The parties identify themselves as real parties-in-interest. Pet. 6; Paper 4, 1.

C. Related Matters

Petitioner states they are “not aware of any related matters involving the ’370 patent.” Pet. 6. Petitioner lists fifteen issued patents and one pending patent application as being in the same family as the ’370 patent because they claim priority through a chain of continuation applications to the same application as the ’370 patent, i.e., Application No. 16/248,460 (“the ’460 application”) now Pat. No. 10,478,453 (“the ’453 patent.”). *Id.* at 6–7. Of these related patents and application, Petitioner states that the ’453 patent and U.S. Patent No. 10,583,155 (“the ’155 patent”) were the subject of PGR2020-00064 (“the ’453 PGR”) and PGR2020-00068 (“the ’155 PGR”), respectively, which were filed by Eton Pharmaceuticals, Inc. (“Eton”). *Id.* at 7–8.

Patent Owner identifies the same post-grant proceedings and additionally identifies PGR2020-00086 (“the ’719 PGR”), involving U.S. Patent No. 10,653,719 (“the ’719 patent”), as a related matter. Paper 4, 1.

The parties also note that related patents were asserted in *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, Case No. 1:20-cv-00365-MN (D. Del., filed May 14, 2020). Pet. 8; Paper 4, 1. Petitioner further states that related patents were asserted in *Exela Pharma Sciences, LLC v. Sandoz Inc.*, Case No. 1:20-cv-00645-MN (D. Del., filed May 14, 2020) and *Exela Pharma Sciences, LLC v. Sandoz Inc.*, Case No. 1:20-cv-01393 (D. Colo., filed May 15, 2020). Pet. 8.

D. The ’370 Patent (Ex. 1001)

The ’370 patent is titled “Stable, Highly Pure L-Cysteine Compositions for Injection and Methods of Use.” Ex. 1001, code (54). The

'370 patent was filed as Application No. 18/067,287 on December 16, 2022, and is a continuation of Application No. 17,950,964, filed on September 22, 2022, which is a continuation of Application No. 17/188,922, filed on March 1, 2021 (issued as Pat. No. 11,510,942), which is a continuation of Application No. 16/746,028, filed on January 17, 2020 (issued as Pat. No. 10,933,089 (“the '089 patent”)), which is a continuation of Application No. 16/665,702, filed on October 28, 2019 (issued as the '155 patent), which is a continuation of Application No. 16/248,460 (the '460 application), filed January 15, 2019 (issued as the '453 patent). *Id.*, codes (21), (22), (63).

The '370 patent discloses “compositions for parenteral administration comprising L-cysteine that are stable and have desirable safety attributes for extended periods of time.” Ex. 1001, 1:24–26. According to the '370 patent, “L-cysteine performs a variety of metabolic functions,” such as being involved with growth, protein synthesis, and being a precursor for glutathione, an intracellular antioxidant. *Id.* at 1:32–35. The '370 patent explains that L-cysteine “can be synthesized in small amounts by the human body” but “L-cysteine can be conditionally essential in preterm infants due to biochemical immaturity of the enzyme cystathionase that is involved in L-cysteine synthesis.” *Id.* at 1:36–44.

The '370 patent states prior art L-cysteine compositions had impurity profiles that made those products less safe, particularly for preterm and term infants, pediatric patients aged 1 month to 1 year, and critically ill adults. Ex. 1001, 4:32–38. According to the '370 patent, other “formulations fail to address the issues related to the amounts of Aluminum and cystine, among other impurities, that can be routinely present and co-administered with

L-cysteine” and “known L-cysteine compositions contain up to 5000 ppb Aluminum.” *Id.* at 4:38–41, 7:24–25.

In view of this, the ’370 patent describes L-cysteine compositions having “an exceptional safety, purity, and stability profile.” Ex. 1001, 1:47–50. Specifically, the ’370 patent discloses “compositions that provide a therapeutically effective amount of L-cysteine, while containing less than 250 ppb Aluminum.” *Id.* at 7:26–29. According to the ’370 patent, such compositions “permit[] exposure to less than or equal to 4-5 micrograms per kilogram per day ($\mu\text{g/kg/d}$) to avoid or minimize Aluminum toxicity while still providing therapeutically effective L-cysteine in a stable composition.” *Id.* at 7:37–41.

The ’370 patent further states that

without being bound to theory, it has been found that the problems of safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace as well as certain heavy metals and certain ions that may leach or be extracted out of the container closure.

Ex. 1001, 4:53–59. For instance, the ’370 patent states that two L-cysteine residues will form a disulfide covalent bond in the presence of oxygen to form L-cystine, which has a lower solubility than L-cysteine and can be visually observed in some cases. *Id.* at 57:17–21. Therefore, the ’370 patent discloses the preparation of compositions in which the head space oxygen is reduced to about 5.0% to 0.5% before sealing a composition’s container. *Id.* at 35:46–67.

E. Illustrative Claim

Independent claim 1 of the ’370 patent is illustrative and reproduced below.

1. A solution of L-cysteine for use in total parenteral nutrition (TPN) comprising,
about 10 mg/mL to about 100 mg/mL of L-cysteine or a pharmaceutically acceptable salt or hydrate thereof, in a pharmaceutically acceptable carrier;
wherein:
after 12 months of storage in a sealed vial at room temperature:
the total amount of oxygen within the sealed vial is no more than about 5%; and
the solution:
contains no more than 250 ppb aluminum,
is substantially free of visually detectable particulate matter, and
has a pH from 1.0 to 2.5.

Ex. 1001, 58:53–67.

F. Asserted Grounds

Petitioner asserts that claims 1–30 are unpatentable on the following grounds (Pet. 10):

Claim(s) Challenged	35 U.S.C. §¹	Reference(s)/Basis
1–30	112	Lack of Enablement
1–30	112	Lack of Written Description
1–30	103	Sandoz label, ² knowledge of one of ordinary skill in the art

¹ The Leahy-Smith America Invents Act, Pub. L. No. 112–29, 125 Stat. 284 (2011) (“AIA”), amended 35 U.S.C. §§ 103 and 112. Because the challenged claims of the ’370 patent have an effective filing date after the effective date of the applicable AIA amendment, we refer to the AIA versions of 35 U.S.C. §§ 103 and 112.

² Screenshots of Internet Archive webpages <https://web.archive.org/web/20170403170533/http://drugsdb.eu/drug.php?d=Lcysteine%20Hydrochloride&m=Sandoz%20Inc&id=083366d6-0437-4ee0-90d4-440a5b5d03b5.xml> and <https://web.archive.org/web/20160824090050/http://drugsdb.eu/>

Petitioner also relies on the Declaration of Pasquale N. Confalone, Ph.D., (Exhibit 1003) to support its assertions. Patent Owner relies on the Declaration of Dennis R. Jenke, Ph.D. (Ex. 2001).

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art:

would have had an advanced degree like a Ph.D. or equivalent in chemistry, biochemistry, pharmaceuticals, pharmacy, or a related pharmaceutical field, with at least two years of experience in pharmaceutical formulation development, analysis, optimization and manufacturing, including experiences with processes and techniques for minimizing impurities in, and improving the stability of, pharmaceutical drug products during manufacture and storage.

Pet. 27 (citing Ex. 1003 ¶ 24). Petitioner also states that one of ordinary skill in the art “may also have lesser levels of education but more years of experience” and “[a] multi-disciplinary team consisting of individuals with different skills and experience could also suffice.” *Id.*

Patent Owner argues that:

A person of ordinary skill in the art has attained a Pharm. D., or M.S. or Ph.D. in chemistry, chemical engineering, or a related field; has three or more years of experience in developing aqueous drug formulations; and has access to other scientists to collaborate and consult with on, for example, characterizing the drug formulation, manufacture of the drug formulation, and clinical use and effect of the drug formulation.

Prelim. Resp. 18. Patent Owner further asserts that “[p]ractical experience, either in industry or academia, can compensate for less or different formal

drug.php?d=Lcysteine%20Hydrochloride&m=Sandoz%20Inc&id=083366d6-0437-4ee0-90d4-440a5b5d03b5.xml (last visited May 1, 2020 (Ex. 1005)).

education, and more formal education can compensate for less practical experience.” *Id.* at 18–19 (citing Ex. 2019 ¶¶ 39–41).

Our determination does not turn on any difference between these definitions. We note that both parties acknowledge that the person of ordinary skill in the art has attained advanced skills either by education or experience relevant for the purpose of making pharmaceutical formulations. Petitioner’s proposed definition is consistent with the disclosure of the ’370 patent and the prior art of record, and we adopt it for purposes of this Decision. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that the prior art itself may “reflect[] an appropriate level” of ordinary skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

Petitioner asserts that “stable” and “about” are expressly defined by the ’370 patent and should be construed accordingly. Pet. 28 (citing Ex. 1001, 16:44–55, 58:9–21). Petitioner further states that the Delaware District Court “construed ‘stable’ as a composition that ‘will contain the specified levels of all components for sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting.’” *Id.* (citing Ex. 1007, 25–26).

Patent Owner states that there is no need to construe any claim terms at this stage. Prelim. Resp. 18.

Because this Decision declining to institute trial does not necessitate the application of any express claim construction, we need not construe any terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are

in controversy, and only to the extent necessary to resolve the controversy.”” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

C. Post-Grant Review Eligibility

As a threshold issue, we must determine whether the ’370 patent is eligible for post-grant review. There are two requirements that must be met for post-grant review to be available. First, post-grant review is only available if the petition is filed within nine months of the issuance of the challenged patent. 35 U.S.C. § 321(c). Here, the Petition was filed on February 8, 2024, which is within nine months of the ’370 patent’s May 9, 2023, issue date. Pet. 1; Ex. 1001, code (45).

Second, post-grant review is available only for patents that issue from applications that at one point contained at least one claim with an effective filing date of March 16, 2013, or later. *See Leahy-Smith America Invents Act*, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”) §§ 3(n)(1), 6(f)(2)(A). The “effective filing date” for a claim is either the application’s actual filing date or the filing date of the earliest application that supports the claim. 35 U.S.C. § 100(i) (2018). A patent claiming the benefit of priority of an application filed before March 16, 2013, must have written description support for all claims in the earlier-filed application in order to avoid PGR-eligibility. *Id.*

Petitioner contends that the ’370 patent is eligible for post-grant review because the ’370 patent’s earliest possible filing date is that of Application No. 16/248,460, which is January 15, 2019. Pet. 9. Patent Owner does not dispute that the ’370 patent is eligible for post-grant review. *See generally* Prelim. Resp.

On the current record, we determine that Petitioner has sufficiently shown that the '370 patent is eligible for post-grant review.

D. Discretionary Denial Under 35 U.S.C. § 325(d)

Patent Owner argues we should exercise discretion under § 325(d) and deny institution of review on the basis of the USPTO's prior consideration of substantially the same arguments and art. Prelim. Resp. 19–35; Prelim. Sur-reply 1. Petitioner provides opposing arguments. Pet. 10–16; Prelim. Reply 1. For the reasons discussed below, we invoke our discretion to deny institution under § 325(d).

1. Legal Framework

Under § 325(d), in determining whether to institute a post-grant review, “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.”³ Our § 325(d) analysis employs a two-prong framework: (1) whether the arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of those arguments. *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (“*Advanced Bionics*”), 8 (PTAB Feb. 13, 2020) (precedential).

We consider several non-exclusive factors as set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”), which “provide useful insight into how to apply the

³ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

framework” under § 325(d). *Advanced Bionics*, 9. These non-exclusive factors include:

- (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, 17–18 (formatting added). “If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office, then factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office.” *Advanced Bionics*, 10.

2. Whether the Arguments and Art Are the Same or Substantially the Same as Previously Presented to the Office

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office.

Advanced Bionics, Paper 6 at 8.

a) Enablement

Petitioner argues that the “Petition does not duplicate the Eton PGRs (PGR2020-00064 and PGR2020-00068) which challenged the validity of related ’453 and ’155 patents, respectively, on non-Section 112 grounds.”

Pet. 10. Petitioner states that “[i]n fact, if anything the Petition accepts and relies upon those proceedings to substantiate Section 112 invalidity,” asserting that, while the Petition’s grounds are distinct, the ’453, ’155, and ’370 patents “claim very similar subject matter.” *Id.* at 10–12. Petitioner contends that Eton challenged the validity of the ’453 and ’155 patents “only on the basis of prior art, namely the Sandoz label (Ex. 1005), alone or in combination with the Hospira label, in view of a POSA’s knowledge.” *Id.* at 12 (citing PGR2020-00064, Paper 1, 6; PGR2020-00068, Paper 1, 7).

Petitioner argues that the Petition’s lack of enablement and written description challenges are new grounds of unpatentability, “which are not ‘the same or substantially the same’ as the Eton grounds which were solely based on prior art pursuant to §§ 102 and 103.” Pet. 12. Petitioner asserts that the Petition’s § 112 grounds were not previously considered and “are supported by arguments and findings from the earlier proceedings.” *Id.* at 13. Specifically, Petitioner contends that “Patent Owner during the earlier PGR proceedings and during the district court litigation argued that the recited compositions were not obvious because of complex interactions between components and the unpredictability of the formulation properties,” and “[t]he district court findings and Patent Owner’s arguments regarding the complexity and unpredictability of the recited L-cysteine solutions support the non-enablement grounds presented here.” *Id.*

Patent Owner asserts that “[t]he Petition references § 325(d) only once, without citing *Advanced Bionics* or providing any substantive discussion of how the arguments in the Petition could meet the standards.” Prelim. Resp. 19 (citing Pet. 12). Patent Owner argues that Petitioner is careful to say that the Petition’s § 112 grounds were not at issue in the Eton

PGRs “but Petitioner does not mention here that the Examiner extensively discussed the same enablement argument during prosecution of the priority application, No. 16/248,460 [the ’460 application, now issued as the ’453 patent].” *Id.* at 20. According to Patent Owner, “Petitioner admits [that] the claims of the ’453 patent, the ’155 patent, and the ’370 patent ‘claim very similar subject matter.’” *Id.*; *see id.* at 22–23 (providing a comparison between claim 1 of the ’460 application and claim 1 of the ’370 patent); Pet. 11–12 (presenting a table comparing claim limitations between the ’370, ’453, and ’155 patents).

Patent Owner argues that during prosecution of the ’460 application (which issued as the ’453 patent), Examiner rejected all claims due to lack of enablement. Prelim. Resp. 21, 26. According to Patent Owner, Examiner addressed the unpredictability of the art, breadth of the claims, specification’s guidance, and quantity of experimentation—the same factors that underly the enablement arguments Petitioner now raises. *Id.* at 26–27 (citing Ex. 1024, 378–380).

During prosecution, Patent Owner addressed the enablement rejection by acknowledging “that ‘the cited art reports on the problem at hand, which after many years was still unsolved prior to the present inventors’ solution as described in the present application.’” Prelim. Resp. 27 (citing Ex. 1024, 408). During prosecution Patent Owner “directed the Examiner to the portions of the specification that explained the nature of the problem” and “also addressed the Examiner’s discussion of the *Wands* factors by pointing out the relevant portions of the specification that address these problems, including the extensive testing data.” *Id.* at 27–28 (citing Ex. 1024, 408); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (In analyzing undue

experimentation, the following factors are considered: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”). Patent Owner argues that “Examiner agreed with the evidence presented in the specification and determined that the claims are enabled.” Prelim. Resp. 28 (citing Ex. 1024, 415). Patent Owner emphasizes that Examiner already considered and rejected the same arguments presented by Petitioner regarding the unpredictability of the art, breadth of the claims, guidance provided by the specification, and the experimentation needed during prosecution. *Id.* at 29–30 (citing Ex. 1024, 378–380, 420).

In response, Petitioner argues that “the non-enablement ground is not the same or substantially the same as what the Patent Office addressed during prosecution of a parent application.” Prelim. Reply 1. Specifically, Petitioner asserts that the non-enablement ground “is presented in tension with Patent Owner’s new non-obviousness arguments in later PTAB and district court proceedings—and the decisions in those proceedings—all after the ’460 Application prosecution closed.” *Id.* (citing Pet. 12–13, 27–37, 40, 44–45). According to Petitioner, “Patentee made contradictory arguments in different fora,” and “[t]he Examiner did not and could not have considered the arguments in the Petition.” *Id.*

Patent Owner maintains their position that Petitioner’s lack of enablement arguments “are not new” because the Office already considered them. Prelim. Sur-reply 1 (citing Prelim. Resp. 26–30). Patent Owner disputes any contradictions between “statements [made] during prosecution

and in later PTAB and district court proceedings.” *Id.* Patent Owner argues that “statements in the later proceedings were about the *prior art*, and why the inventors’ solution was not obvious in view of that prior art,” and “[b]ecause those statements were addressing non-obviousness, they do not speak to the teachings in [Patent Owner]’s own specification, which of course must be the starting point for any enablement analysis.” *Id.* (citing Prelim. Resp. 4–5, 35–37). According to Patent Owner, the Patent Office considered the unpredictability of the prior art, including the very same file history as the enablement rejection that Patent Owner overcame. *Id.* (citing Prelim. Resp. 12–14).

Petitioner acknowledges that the ’453 (Ex. 1019), ’155 (Ex. 1015), and ’370 (Ex. 1001) patents claim very similar subject matter: stable L-cysteine solutions with a limited amount of precipitates covering varying levels of aluminum, and that the ’370 and ’453 patents also cover varying levels of oxygen. *See* Pet. 11; Prelim. Resp. 22–23.

During the prosecution of the ’460 application⁴ leading to the ’453 patent, Examiner rejected claim 1 as lacking enablement. *See* Ex. 1024, 378–380. Specifically, Examiner asserted that “[t]he claims are broadly drawn to a composition having claimed properties, but with no disclosure or limitations as to how those properties are achieved.” Ex. 1024, 379. Examiner asserted that the specification provides no direction or guidance for practicing the invention, and that it would require undue experimentation to practice the claimed subject matter. *Id.* Examiner stated that “the only disclosure appears to be mixing L-cysteine with minimum contaminants [sic]

⁴ The ’460 application is the first application in this patent family; the family contains numerous continuation applications. *See above* I.D.

. . . but there is no disclosure how the compound is made pure or avoid[s] impurities known in the art. Instant claim [] suggests using reduced head space oxygen, but it is unclear how that will reduce contaminants [sic] already present.” *Id.* at 380.

To better understand Patent Owner’s rebuttal to Examiner’s enablement arguments made during prosecution, we briefly review the teachings of the ’460 application specification. According to the ’460 application, “Aluminum in solution may have a stabilizing effect [on L-cysteine]. Consequently, removing Aluminum may have the unintended consequence of increased precipitation and product failure in the presence of even small amounts of oxygen in the container. This was unexpected.” Ex. 1024, 234; Ex. 1001, 5:20–25.

The ’460 application further explains that “because cystine is an oxidation product of L-cysteine, it is possible that the amount of cystine can increase over time.” Ex. 1024, 237; Ex. 1001, 7:1–3. “L-Cystine has a lower solubility (0.112 mg/mL) than L-Cysteine (50 mg/mL), [thus] in some cases the degradant [in the form of a precipitate] can be visually observed.” Ex. 1024, 311; Ex. 1001, 57:19–21. The ’460 application explains “that the problems of safety, purity and stability [of an L-cysteine solution] are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace as well as certain heavy metals and certain ions that may leach or be extracted out of the container closure.” Ex. 1024, 233; Ex. 1001, 4:53–59.

Patent Owner in their response to Examiner’s enablement rejection argued the following:

Turning again to the present specification, the variables to be addressed and the factors used are described, *inter alia*, in the

Examples beginning on page 61. Here, it is described to the person of ordinary skill how to make the claimed compositions as well as how unexpected technical issues and product failures were overcome. The Examples disclose at the very least: how to compound and fill representative L-cysteine compositions (Example 1, page 61); how lack of control for Aluminum leaching ultimately results in Aluminum levels that while lower than known products, are still deemed unacceptably high (levels that are outside the scope of the present claims)(Example 2, page 62); how plastic vials while achieving exceedingly low Aluminum levels unexpectedly result in unacceptable precipitate formation within one month (Example 3, pages 62-63); and how to accomplish head space oxygen reduction using a lyophilizer (Example 4, pages 63-68) or automated filling equipment (Example 5, pages 69-72). Further, in Example 6, the present specification provides additional experimental evidence in Table 18 on page 72, in the form of test data for purity and long-term stability of three batches compounded and filled by the processes taught in the present specification. The data in Table 18 and the Figures show that controlling for Aluminum and oxygen by the processes described in the present specification result in the lowest impurity profile obtained for the claimed compositions.

Ex. 1024, 408.

In response to Patent Owner's arguments, Examiner withdrew the enablement rejection and allowed the claims. Ex. 1024, 415.

To summarize, during prosecution, Examiner asserted that "[t]he claims are broadly drawn to a composition having [the] claimed properties, but with no disclosure or limitations as to how those properties are achieved." Ex. 1024, 380. These arguments made during prosecution by Examiner are similar to the arguments presented here by Petitioner. *See* Pet. 39 (stating "[i]mportantly, the patent specification of the '370 patent did not fill in the blanks for the information Patent Owner asserted would be undue for a POSA to determine: aluminum amount, oxygen amount, container

choice, and interactions between these and other variables to achieve a sufficiently stable formulation”). Examiner, therefore, made the same or substantially the same enablement argument during prosecution that Petitioner presents here in the Petition. *Compare* Ex. 1024, 377–380, with Pet. 37–64.

During prosecution, Patent Owner overcame the enablement rejection by explaining that it was a combination of reduced oxygen, pH, the use of a coated vial, as well as the presence of some aluminum that was required to achieve the stated L-cysteine stability. *See* Ex. 1024, 408 (the ’460 application “addressed many variables and describes the factors that the present inventors used to overcome the Aluminum safety issues at hand, for example: ‘the problems of safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace’”).

Based on these disclosures in the prosecution record, we agree with Patent Owner that the Petition presents the same or substantially the same argument that was previously presented to the Office.

b) Written Description

Petitioner asserts that “the patent specification fails to show that the named inventors were in possession of any formulation that remained stable according to the claims, and for the time period required by the claims.” *See* Pet. 64–65.

With regard to the Petition’s written description ground, Patent Owner asserts that Petitioner acknowledges that “the Petition’s written description argument is ‘substantially the same’ as the enablement argument that the Examiner considered during prosecution of the ’460 Application [now the

'453 patent].” Prelim. Resp. 30. Specifically, Patent Owner contends that “Petitioner admits the similarity of its enablement and written description arguments and states that the claims lack written description for the same reasons they are not enabled: ‘For substantially the same reasons as discussed above for non-enablement, all claims of the ’370 patent lack written description.’” *Id.* (citing Pet. 64). Patent Owner argues that § 325(d) is sufficiently implicated. *Id.* at 33–35.

Patent Owner acknowledges, and we agree, that “Examiner did not issue a written description rejection, [but] the Examiner addressed the enablement arguments that underlie Petitioner’s written description challenge.” Prelim. Resp. 33. We understand that written description and enablement are separate requirements. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1340 (Fed. Cir. 2010) (en banc). On this record, however, Petitioner asserts that lack of written description and non-enablement are based on the “same reasons.” Pet. 64. Thus, we agree with Patent Owner that in evaluating the Petition’s written description arguments under the first prong of the *Advanced Bionics* framework, it is reasonable for us to render our conclusion based on what we determined in the enablement section. Therefore, based on our discussion above (*see II.D.2.a*) we agree with Patent Owner that the Petition presents the same or substantially the same argument that was previously presented to the Office.

c) Obviousness

With regard to the Petition’s obviousness ground, Patent Owner argues that Petitioner does not address this challenge when discussing § 325(d). The Petition acknowledges “that Ground 3 relies on the same prior art and argument that the Board addressed in the earlier PGRs.” Prelim.

Resp. 20 (citing Pet. 66). Patent Owner contends that “[a]s Petitioner admits, its obviousness argument is the same or substantially the same as the obviousness argument Eton presented (and lost on) in the earlier PGRs.” *Id.* at 23 (citing Pet. 66). Patent Owner further asserts that the obviousness ground “is also the same or substantially the same obviousness argument Eton presented in the ’719 Patent PGR.” *Id.* (citing Ex. 2015, 7). According to Patent Owner, Petitioner admits that “the only difference is that, in this Petition, the obviousness ground is in the alternative and should be applied only if the claims are found to be enabled to their full scope, in which case the decision cannot be reconciled with prior non-obviousness decisions.” *Id.* at 23–24 (citing Pet. 66).

Patent Owner further argues that the obviousness ground asserts the same prior art, the Sandoz label, “and makes the same argument that the Board previously considered and rejected.” Prelim. Resp. 24 (citing Pet. 66) (emphasis omitted). Patent Owner provides a comparison chart to support their argument that “just like the arguments in the ’453 PGR, the Petition here asserts all claims would have been obvious based on the Sandoz Label in view of a POSA’s knowledge.” *Id.* at 24–25 (citing Pet. 68–70).

According to Patent Owner, “[t]he panel in the ’453 PGR found, among other things, that the Sandoz label did not teach all of the claim elements, and that the combination of the Sandoz label and knowledge of the POSA did not render obvious claims that are similar to the ’370 claims.” *Id.* at 25–26 (Pet. 10–11). Patent Owner argues that “[t]he panels in the ’155 PGR and the ’719 PGR reached the same conclusion.” *Id.* at 26 (citing Ex. 2014, 21; Ex. 2015, 26). Patent Owner contends that the “Petition raises the same

obviousness argument the Board has rejected three times.” *Id.* (citing Pet. 10–11).

We agree with Patent Owner that we have previously considered and rejected similar arguments made in the Eton PGRs that are based on the Sandoz Label in conjunction with knowledge of the ordinarily-skilled artisan. *See* Ex. 2013; Ex. 2014; Ex. 2015. For example, in the ’453 PGR we were not persuaded that Eton had demonstrated that it was more likely than not that “the skilled artisan would have relied on routine optimization using well-known techniques to achieve the reasonably expected result of preventing oxidative degradation of L-Cysteine.” Ex. 2013, 9–22. We explained that identifying a motivation to try and lower aluminum levels in total parenteral nutritional supplements does not provide a path of how to achieve the stated goal. *Id.* at 18–19. We concluded that Eton has not “provided a sufficient evidentiary basis from which to conclude that there is a reasonable expectation for making L-cysteine containing solutions having the requisite aluminum content” as claimed. *Id.* at 22.

Patent Owner further argues that Petitioner “admits that during Examination of U.S. Patent No. 10,933,089, which is another parent to the ’370 patent, the Examiner considered whether the claims were obvious in view of the Sandoz label and the knowledge of the POSA.” *Id.* at 26 (citing Pet. 19–21).

According to Examiner during the prosecution of the ’089 patent, “[t]he Sandoz Label discloses L-Cysteine Hydrochloride injections, 50mg/mL, available in single-dose vials. Sandoz label notes the product contains water and air replaced with Nitrogen, with a pH 1.0-2.5. The label further states the product contains no more than 5,000 mcg/L (5,000 ppb) of

aluminum. Sandoz Label further discloses a warning about aluminum which suggest[s] premature neonates should not receive levels of more than 4 mcg to 5 mcg/kg/day accumulate aluminum levels.” Ex. 1023, 246–247.

Examiner acknowledges that the “Sandoz Label does not teach methods to remove aluminum contaminant.” *Id.* at 247. Examiner relies on the teachings of additional references to arrive at a conclusion that it would have been obvious to arrive at the product as claimed. *Id.* Examiner acknowledges “the contamination content problem was known to be caused by various elements of the overall process of developing and storing the product, and each step had known means to reduce the contamination. While such steps had not been applied in the industry, the skilled artisan would have recognized the solutions based on the art and would simply have to implement them into the overall process as outlined above.” *Id.* at 248. Here, Examiner not only relied on the Sandoz Label in the obviousness rejections but also relied on additional references to support the position that the claims in the prosecution of the ’089 patent⁵ would have been obvious. Patent Owner presented arguments to overcome the rejection, resulting in the allowance of the claims. *See* Ex. 1023, 283–289 (Patent Owner’s arguments), *id.* at 329 (Notice of Allowance).

⁵ Claim 1 of the ’089 patent is similar to the claims in the ’370 patent and reads as follows: A solution of L-cysteine comprising, a pharmaceutically acceptable carrier, about 50 mg/mL of L-cysteine hydrochloride monohydrate, or equivalent amount of a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof, less than about 150 ppb of aluminum for at least about 6 months from the time of manufacture of the solution, and a pH from about 1.0 to about 2.5, wherein the solution is suitable for use as an additive in a parenteral nutrition composition for administration to an individual. Ex. 1023, 351.

Because the Eton PGRs relied on the Sandoz Label in conjunction with knowledge of the ordinary artisan, and the same art and arguments were also used in the prosecution record, we agree with Patent Owner that the Petition presents the same or substantially the same argument that was previously presented to the Office.

3. Whether Petitioner Has Demonstrated Material Error

Because we find that the same or substantially the same art or arguments were previously presented to the Office, we turn to whether Petitioner demonstrates that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 8, 10; *see Becton, Dickinson*, Paper 8 at 24. We conclude that Petitioner has failed to do so.

a) Enablement

Petitioner asserts that the Petition “explains how the Examiner erred in considering the patentability of those ’460 Application claims.” Reply 1. According to Petitioner, “the Petition explains that the Examiner failed to apply the appropriate standard for enablement later defined in *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023).” *Id.* (citing Pet. 24–26, 40). Petitioner argues that “the Examiner did not have and could not have considered the standard the Supreme Court set only after prosecution of the ’460 Application closed” and “[t]he Petition therefore raises new grounds for review.” *Id.*

Patent Owner asserts that “Petitioner has not shown that the Board or Examiner erred—let alone in a manner material to patentability—when they previously considered and rejected the same art and arguments Petitioner relies on here.” Prelim. Resp. 31. Patent Owner argues that “Petitioner does not even allege the Board made a mistake when it denied institution for the

three earlier PGRs challenging obviousness.” *Id.* Petitioner also does not argue “that the Office made a mistake when it decided the claims of the ’460 Application are enabled.” *Id.*

According to Patent Owner, Petitioner embraces the Board’s prior PGR decisions for the Petition’s § 112 grounds. Prelim. Resp. 32 (citing Pet. 10). Patent Owner contends that Petitioner’s argument that the challenged claims must not be enabled if they are not obvious is a false dichotomy. *Id.* (citing *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015), which states that “[t]he obviousness inquiry turns on what the prior art would have taught a person of ordinary skill in the art and whether the claimed invention would have been obvious in view of the *prior art*. . . . In contrast, the enablement inquiry turns on whether the skilled artisan, after reading the specification would be able to make and use the claimed invention without undue experimentation, based on the ordinary skill in the art.”). Patent Owner further argues that “Petitioner ignores the critical fact that the specification supplies the road map to solving the problem that had perplexed the industry for over a decade.” *Id.*

Patent Owner argues that “nowhere does the Petition assert that the Examiner committed *any* error—let alone material error—in finding the related ’460 application claims enabled,” and the Petition did not assert that the Examiner failed to apply the appropriate legal standard for enablement (as articulated in the Supreme Court’s *Amgen* decision), which Petitioner now asserts in their Reply. Sur-reply 1. According to Patent Owner, “the Petition correctly acknowledges that the Supreme Court’s *Amgen* decision simply ‘reiterated the proper standard for enablement.’” *Id.*

Petitioner's argument that there was an intervening change in the law regarding enablement in view of *Amgen* that Examiner could not have considered is misplaced. In *Amgen*, the Supreme Court decision reaffirms the principles of enablement on which Examiner's rejection relied during the prosecution of the '453 patent (the '460 application). *See* Ex. 1024, 377–380; *Amgen*, 598 U.S. at 610 (“If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.”). During the prosecution of the '453 patent, Examiner walked through the *Wands* factors in making the enablement rejection. *See* Ex. 1024, 377–380; *Wands*, 858 F.2d at 737.

In response to Patent Owner's arguments, Examiner withdrew the enablement rejection and allowed the claims. Ex. 1024, 415.

We agree with Patent Owner that the Petition does not explain how the Examiner materially erred during prosecution when deciding that Patent Owner overcame the enablement rejection. Prelim. Resp. 32–33 (citing Pet. 21–22, 26). Examiner during prosecution applied the correct law, that was “reiterated” in *Amgen*. *Compare* Ex. 1024, 377–380, with *Amgen*, 598 U.S. at 610. Petitioner's expert testimony is also silent with respect to identifying Examiner error. *See* Ex. 1003 ¶¶ 77–116.

“Petitioner may disagree with the Examiner's conclusion that the claims are enabled, but that disagreement is not a basis for institution.” Prelim. Resp. 33. “If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a

manner material to patentability. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Advanced Bionics*, 9.

Based on this record, we agree with Patent Owner that Petitioner has not sufficiently established error, let alone material error by the Office. Prelim. Resp. 31–33 (citing Pet. 21–22, 26).

b) Written Description

Petitioner contends that “the longest stability test in the ’370 patent specification is shown in Example 6, and that test lasted for 9 months, which of course is less than the 12/18/24 months required by all the claims.” Pet. 64 (citing Ex. 1001, 49:53–50:23). “Even if the patent specification had one test that showed one formulation met the claimed stability criteria—which it does not—still the claims would not be sufficiently described in the ’370 patent because one data point does not substantiate the full claimed ranges for oxygen and aluminum that all claims allow.” Pet. 65. This argument is essentially the same or similar to the argument presented with respect to enablement. *Compare* Pet. 64, *with* Pet. 40 (“[E]xamples do not even demonstrate stability for the minimum claimed period of the ’370 patent, which is at least 12 months.”).

We are not persuaded that Petitioner has established error by Examiner. Petitioner’s written description argument relies on the same theories as its enablement argument, but it did not show error in the Examiner’s findings underlying the enablement rejection.

Furthermore, Patent Owner contends, and we agree, that the ’370 patent includes 12-month data at long-term conditions, as well as 6-month

data at accelerated conditions. *See, e.g.*, Ex. 1001 ('370 Patent) at Table 22.

As Patent Owner explains,

it is a basic principle in the art that 6-months of accelerated stability data is used to represent the product's stability over 24 months at long-term storage (in this case, room temperature) conditions. Ex. 2001 (Jenke Decl.), ¶¶ 34–35. This is how FDA evaluates drug product stability in approving the filings.

Prelim Resp. 34; *see also* Ex. 2001 ¶ 34 (fn. 20).

Based on this record, we agree with Patent Owner that the Petition has not sufficiently established error, let alone material error by the Office.

Prelim. Resp. 32–33 (citing Pet. 21–22, 26).

c) Obviousness

Patent Owner asserts that the Petition does not explain how the Office materially erred when considering the unpatentability arguments presented in the Eton PGRs or during prosecution when evaluating the Sandoz Label and deciding that the claims would not have been obvious. Prelim. Resp. 32–33 (citing Pet. 21–22, 26).

Here, neither the Petition nor the Reply addresses obviousness in the context of § 325(d). *See generally* Pet.; Reply.

Based on this record, we agree with Patent Owner, that Petitioner has not sufficiently established error, let alone material error by the Office.

d) Summary

After reviewing the parties' arguments and evidence of record, we determine that the same or substantially the same art or arguments previously were presented to the Office, and Petitioner has not demonstrated that the Office erred when considering the prior art or arguments. We, therefore, exercise our discretion to deny institution of post-grant review under 35 U.S.C. § 325(d).

III. CONCLUSION

For the reasons discussed above we deny institution.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

PGR2024-00016
Patent 11,642,370 B1

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