

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ETON PHARMACEUTICALS, INC.,
Petitioner,

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner.

PGR2020-00086
Patent 10,653,719 B1

Before ULRIKE W. JENKS, SUSAN L. C. MITCHELL, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

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

Eton Pharmaceuticals Inc. (“Petitioner”) filed a Petition requesting a post-grant review of claims 1–27 (“the challenged claims”) of U.S. Patent 10,653,719 B1(Ex. 1106, “the ’719 patent”). Paper 1 (“Pet.”). Exela Pharma Sciences, LLC (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). With our authorization (*see* Ex. 1124 at 14–20), Petitioner filed a reply to Patent Owner’s Preliminary Response (Paper 8 (“Pet. Reply”)), and Patent Owner filed a Sur-reply (Paper 10 (“Sur-reply”)). We granted the additional briefing to allow Petitioner to file a copy of the request for rehearing it filed in related proceedings, PGR2020-00064 and PGR2020-00068, and to respond to assertions made in Patent Owner’s Preliminary Response.

We have authority to determine whether to institute a post-grant review. 35 U.S.C. § 324. After considering all the papers submitted and cited evidence, for the reasons discussed below, we deny the Petition and do not institute a post-grant review.

I. BACKGROUND

A. *Real Parties in Interest*

Petitioner identifies itself as the real party in interest. Pet. 2. Patent Owner identifies itself as the real party in interest. Paper 3, 2.

B. *Related Proceedings*

The parties identify a related litigation matter, *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, Case No. 1:20-cv-00365-MN (D. Del., filed March 16, 2020) (the “District Court Action”). Pet. 2; Paper 3, 2.

The parties also identify U.S. Patent No. 10/478,453, which is the subject of a post-grant review in PGR2020-00064, U.S. Patent No. 10,583,155, which is the subject of a post-grant Review in PGR2020-00068.

Pet. 3–4; Paper 3, 2. The parties also identify related applications U.S. Patent Appl. No. 16/746,028, U.S. Patent Appl. No.16/773,641, U.S. Patent Appl. No.16/850,726, U.S. Patent Appl. No.16/850,962, and U.S. Patent Appl. No.16/850,973. Pet. 3–4; Paper 3, 3.

C. The '719 Patent (Ex. 1106)

The '719 patent is titled “STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE.”

Ex. 1106, code (54). The '719 patent issued from Application No. 16/773,563 (“the '563 application”), filed January 27, 2020. *Id.* at (21), (22).

The '719 patent describes stable L-cysteine compositions for injection, comprising: L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL, and aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb. *Id.* at (57).

“L-cysteine is a sulfur-containing amino acid that can be synthesized de novo from methionine and serine in adult humans.” *Id.* at 1:26–28. Because L-cysteine can be synthesized by the body, it is considered a non-essential amino acid. *Id.* at 1:33–34. “L-cysteine can be conditionally essential in preterm infants due to biochemical immaturity of the enzyme cystathionase that is involved in L-cysteine synthesis. Thus, there are a number of circumstances in which L-cysteine supplementation can be desirable.” *Id.* at 1:37–42.

According to the specification, “[i]t has now been found that L–cysteine compositions for injection can be prepared using the methods described herein whereby the compositions unexpectedly comprise exceedingly low levels of Aluminum and other undesirable impurities, such

as cystine, pyruvic acid, certain heavy metals and certain ions.” *Id.* at 4:37–

43. Moreover, the specification discloses that:

[T]he 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.

Id. at 4:51–56.

The specification discloses that “known L-cysteine compositions contain up to 5000 ppb Aluminum.” *Id.* at 7:21–22. In contrast, the specification describes “compositions that provide a therapeutically effective amount of L-cysteine, while containing less than 250 ppb Aluminum.” *Id.* at 7:25–26. The specification discloses that reduced aluminum 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 7:35–38.

The specification expressly defines the term “stable.”

the term “stable” refers to a composition that has the component profiles described herein, for example. Aluminum, L-Cystine, and pyruvic acid, at the levels described and for the amount of time identified. In other words, a stable composition will remain in the specified levels of all components for [a] sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting.

Id. at 16:41–48. For example, the specification discloses compositions wherein “cystine is present in the composition in an amount not more than 2.0 wt % relative to L-cysteine after storage at ambient temperature for a period of 6 months.” *Id.* at 25:6–9. The specification also discloses

compositions wherein “pyruvic acid is present in the composition in an amount not more than 2.0 wt % relative to L-cysteine after storage at ambient temperature for a period of 6 months.” *Id.* at 26:5–8.

Example 1 of the '719 patent describes a method of compounding an L-cysteine composition. *See id.* 41:60–42:32. Example 2 describes a test for aluminum levels in L-cysteine injections compounded as per Example 1. *Id.* at 42:34–60. The bulk solution was filled into uncoated Schott Type 1 USP glass vials. *Id.* Although “[t]he product was quite stable for all the time points tested up to 12 months[,] . . . the product resulted in an unacceptably high aluminum content.” *Id.* at 42:43–49. The aluminum levels are shown in Table 6, reproduced below. *Id.*

TABLE 6			
Aluminum Levels			
6 Months			
Lot #	Release	25°	40°
		C./60% RH	C./75% RH
XMHH1609	212 ppb	569 ppb	1,306 ppb
XMHH1610	199 ppb	748 ppb	1,374 ppb
XMHH1611	230 ppb	726 ppb	1,044 ppb

Example 6 also describes the stability of L-cysteine injections compounded as per Example 1. *Id.* at 49:55–50:22. The bulk solution was filled into Schott Type 1 USP Plus glass, which is internally coated with silicon dioxide. *Id.* Unlike Example 2, the L-cysteine compositions stored in coated glass vials did not show increased aluminum content when stored upright at room temperature for 9 months at 25° C/60% RH. *Id.* The stability data is shown in Table 18, reproduced-in-part below. *Id.*

TABLE 18			
Characterization of L-Cysteine Composition for Injection			
Test	XMHJ1705	XMHJ1706	XMHJ1707

L-Cysteine HCl	Up 100.4%	Up 101.3%	Up 101.2%
Related Compounds			
L-Cystine	0.3%	0.3%	0.3%
Pyruvic Acid	0.1%	0.2%	0.1%
Aluminum Content	3.2 ppb	2.9 ppb	5.6 ppb

D. Illustrative Claim

Claim 1 of the '719 patent is illustrative and reproduced below (with added bracketing for reference):

1. A solution of L-cysteine comprising,
[A] a pharmaceutically acceptable carrier,
[B] about 50 mg/mL of L-cysteine hydrochloride monohydrate, or equivalent amount of a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof,
[C] *less than about 150 ppb of aluminum*,
[D] a pH from about 1.0 to about 2.5, and
[E] wherein the solution is substantially free of visually detectable particulate matter and suitable for use as an additive in a parenteral nutrition composition for administration to an individual.

Ex. 1106, 58:34–44 (emphasis added).

E. Prior Art

Petitioner relies upon the following prior art reference¹ (Pet. 6):

References	Patent / Publication	Exhibits
Sandoz Label	L-CYSTEINE HYDROCHLORIDE – cysteine hydrochloride injection, solution Sandoz Inc.	Ex. 1005

¹ Petitioner additionally cites references in support of the knowledge of a person of ordinary skill in the art. *See* Pet. 30–35.

In addition, Petitioner relies on the affidavit of Christopher Butler of the Internet Archive (Ex. 1004) and its attached exhibits to establish the availability of the reference.

F. Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–27 of the ’719 patent on the following ground (Pet. 6):

Claim(s) Challenged	Basis	Reference(s)
1–27	§ 103	The Sandoz Label in view of the knowledge of a person of ordinary skill in the art

Petitioner also relies on the Declarations of Barrett Rabinow, Ph.D. (Ex. 1003) and Harry “Warren” Johnson (Ex. 1022, Ex. 1116) to support its assertions. Patent Owner relies on the Declaration of Robert J. Kuhn, PharmD (Ex. 2001) in support of its Patent Owner Preliminary Response.

II. DISCUSSION

Petitioner contends that claims 1–27 would have been obvious over the combination of the Sandoz Label and the knowledge of a person of ordinary skill in the art. *See* Pet. 25–54; Pet. Reply 1–9. Patent Owner opposes. *See* Prelim. Resp. 18–63; Sur-reply 1–10. We begin by providing an overview of the prior art, followed by our analysis of the merits.

A. Overview of Petitioner’s Reference

“Sandoz Label” (Ex. 1005)

The Sandoz Label² describes a solution containing 50 mg of L-cysteine hydrochloride monohydrate and water, with the air replaced with

² Petitioner identifies “the Sandoz Label” as including the product, package insert, and package label. *See* Pet. 26–29, 43 (citing Ex. 1003 ¶ 109; Ex. 1022 ¶ 15). Patent Owner contends that Petitioner’s identified “label”

nitrogen, and the solution having a pH 1.0–2.5. Ex. 1005, 5. The Sandoz Label indicates that the solution is supplied in either 10 ml or 50 ml containers. *Id.* at 9. “L-Cysteine is a sulfur-containing amino acid. In premixed solutions of crystalline amino acids, cysteine is relatively unstable over time, eventually converting to insoluble cystine.” *Id.* at 1. The indicated use of L-cysteine hydrochloride injection as described in the Sandoz Label is for dilution as an additive to crystalline amino acid injections to meet the intravenous amino acid nutritional requirements of infants receiving total parenteral nutrition. *Id.* at 2. The label describes that “[a]ny unused portion of the vial must be discarded within 4 hours after initial entry.” *Id.* at 9.

The label indicates that the product contains no more than 5000 mcg/L [(5000 ppb)³] of aluminum. *Id.* at 5, 10. The Sandoz Label provides a warning that the product contains aluminum that may be toxic. *Id.* at 2. “Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.” *Id.* (emphasis omitted).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v.*

reaches three distinct sources of alleged prior art: the product itself, the package label, and the package insert (i.e., printed matter). Prelim. Resp. 29. Patent Owner contends that each source should be treated as separate prior art. *Id.* at 31. We address Patent Owner’s arguments below.

³ 5000 mcg/L corresponds to 5000 ppb. *See* Ex. 1003 ¶ 32; Ex. 2001 ¶ 20.

VSI Int'l Inc., 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that the ordinary skilled artisan “would have had a Ph.D. in chemistry or biochemistry and at least 2 years of work experience with pharmaceutical drug product formulation analysis, development, optimization, and manufacture.” Pet. 23–24 (citing Ex. 1003 ¶ 25).

Patent Owner asserts that Petitioner’s definition of an ordinary skilled artisan misses the mark because it ignores the need for the artisan⁴ to also have “knowledge or experience in assessing whether a solution is suitable for administration in a clinical setting, in interpreting pharmaceutical drug labels, or consulting with someone who routinely does these things.” Prelim. Resp. 26 (citing Ex. 2001).

We note that the descriptions asserted by Petitioner and Patent Owner suggest that the level of skill in the art is considerably high. Patent Owner’s description is more limiting than Petitioner’s description in that it requires the person of ordinary skill also have clinical knowledge that is pertinent to interpreting pharmaceutical drug labels. Prelim. Resp. 26. Patent Owner, however, does not propose its own alternative definition of a person of ordinary skill in the art, acknowledging instead that the Petition fails even under Petitioner’s construction. *Id.* at 27 (“the Board need not resolve the

⁴ To the extent that Patent Owner challenges Petitioner’s expert, Dr. Rabinow, as lacking the foundation necessary to opine as a person of ordinary skill in the art in interpreting pharmaceutical drug labels, we address the weight to be given to his testimony in our obviousness analysis. Prelim Resp. 26, 41.

level of ordinary skill in the art in order to deny the Petition because, even under Eton’s definition, the Petition falls short.”).

We find that the record as a whole supports Petitioner’s description of the level of ordinary skill in the art. For purposes of our analysis in this Decision, we hereby adopt Petitioner’s definition of a person of ordinary skill in the art. We also note that Petitioner’s proposed definition appears to be consistent with the cited prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. Claim Construction

Petitioner proposes constructions for several claim terms: “about” “substantially free” and “essentially free.” *See* Pet. 24–25 (citing Ex. 1106 at 17:61–18:5, 57:63–58:6). Patent Owner contends that there is no need to resolve any claim construction terms. Prelim Resp. 25.

Because this decision declining to institute trial does not turn on the adoption of any particular claim construction, we need not construe any terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that “we 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)).

D. Analysis

The relevant statute provides that a determination whether to institute a post-grant review shall be made based on “the information presented in the petition.” 35 U.S.C. § 324(a). Under 35 U.S.C. § 324(a), a post-grant review can be instituted only if it is more likely than not that the petitioner would prevail with respect to at least one of the claims challenged in the petition.

Id. In addition, 35 U.S.C. § 322(a)(3) provides that the petition may be considered only if it 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.” Section § 42.22(a)(2) of Title 37 of the US Code of Federal Regulations provides that each petition must include, “[a] full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence including material facts, and the governing law, rules, and precedent.” *See also* 37 C.F.R. § 42.204 (2020).

In a post-grant review, as in an *inter partes* review, “the petitioner has the burden from the onset to *show with particularity* why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (emphasis added) (citing 35 U.S.C. §312(a)(3) as applied to *inter partes* review, which is equivalent to 35 U.S.C. § 322(a)(3) as applied to post-grant review). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in AIA trials).

1.) The Parties’ Contentions

Petitioner contends that the challenged claims would have been obvious based on the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art. Pet. 43–72. Petitioner provides a detailed analysis of how each claim element is allegedly described by the prior art. *Id.* Petitioner also relies on the declaration of Dr. Rabinow to support this challenge. *See id.*

We focus our analysis on representative claim 1 and particularly element 1(C)'s requirement of a range of aluminum as measured in ppb that is not taught by the asserted art. Because each challenged claim includes this or a similar requirement, it is dispositive of our conclusion to deny institution.

Petitioner contends that claim elements 1(A), 1(B), 1(D) and 1(E) are disclosed in the Sandoz Label. Pet. 44–45. With respect to element 1(C), Petitioner contends that “[t]he Sandoz Label discloses a product that ‘[c]ontains no more than 5,000 mcg/L [*i.e.*, 5000 ppb] of aluminum,’ which encompasses the claimed range of ‘less than about 150 ppb of aluminum.’” *Id.* 42 (citing Ex. 1003 ¶ 109; Ex. 1005, 5, 10; Ex. 1004, 8, 13). Petitioner argues that there is nothing unexpected or surprising about the claimed range and that the claimed range is the expected result of optimizing the “Sandoz L-Cysteine Product in response to regulatory and market pressures.” *Id.* at 43.

In response, Patent Owner argues that the Petition does not provide “any explanation as to why a [person of ordinary skill in the art] would have had a reasonable expectation of success in solving the ‘*decades old*’ aluminum problem through mere alleged ‘routine’ optimization.” Prelim Resp. 10. Patent Owner contends that the Petition lacks the particularity required by 35 U.S.C. §322(a). Specifically, Patent Owner contends that

Eton relies on a “Sandoz product” manufactured by Allergy Labs, and refers to this product interchangeably with the Sandoz label and package insert at Exhibit 1005 (“Sandoz Label”). Eton never establishes that any product, let alone a product with characteristics beyond those described in the Sandoz Label, qualifies as prior art. Yet Eton relies on characteristics of a product made by Allergy Labs that were

either unknowable to the POSITA [(person of ordinary skill in the art)] (e.g., as-tested aluminum levels of the product before release to the public), or for which there is zero evidence in the record (e.g., as-tested aluminum levels of the product from 1-24 months) beyond the say-so of an interested declarant with a huge financial interest in Eton succeeding in this PGR proceeding. Eton must be limited to the product characteristics described in the Sandoz Label, and that label makes clear the product may contain up to 5,000 ppb of aluminum during its shelf life.

Prelim Resp. 11 (emphasis omitted) (footnote omitted). Patent Owner contends that “[t]he Petition repeatedly conflates a so-called ‘Sandoz product’ with the ‘Sandoz Label’ (i.e., the Sandoz package label and package insert, Ex. 1005), treating them as a single prior art source (Ex. 1005) so as to back-door unproven product characteristics to try to show obviousness.” *Id.* at 29.

Additionally, Patent Owner argues that nothing in the record suggests that Petitioner’s expert is “qualified to interpret labels for parenteral products that are intended for use by clinicians or that he has any experience in doing so.” *Id.* at 41. Patent Owner argues that Petitioner’s routine optimization argument is infected with hindsight assumptions and ignores the complexity of the environmental conditions that contribute to the aluminum levels in parenteral solutions. *See id.* at 44–56. Finally, Patent Owner argues that we should exercise our discretion and deny institution under 35 U.S.C. § 324(a).⁵ *See id.* at 64–66.

⁵ We acknowledge Patent Owner’s position that we should deny institution under 35 U.S.C. § 324(a) because it would be inefficient and wasteful of the Board’s resources and that the same issues will be addressed in the co-pending district court litigation. Prelim. Resp. 12; *see also* Pet. Reply 9 (“If

In its Reply, Petitioner contends that the person of ordinary skill in the art would have been motivated to reduce aluminum levels in the Sandoz Label product by removing sources of aluminum contamination.

Pet. Reply 2. Petitioner contends that Patent Owner does not cite any failed attempts in solving the aluminum problem. *Id.* at 3. Petitioner cites aluminum levels measured by Allergy Labs a producer of the Sandoz Label product to establish low levels of aluminum in the Sandoz product right after manufacture. *Id.* Petitioner contends that Patent Owner is introducing complexity in the manufacture of the product when the solution of minimizing or preventing aluminum contamination was simple and straight forward. *Id.* at 4. Petitioner contends that Patent Owner fails to establish the relatedness of aluminum contamination and particulate matter formation. *Id.* at 7.

In its Sur-reply, Patent Owner argues that Petitioner has improperly presented new theories of unpatentability in Petitioner's Reply. Specifically, Patent Owner contends that Petitioner now argues that a person of ordinary skill in the art "would have a reasonable expectation of success *regardless* of how the Sandoz label is interpreted." Sur-reply 2. Patent Owner contends that "the Schott Type I Plus vial with the silicon dioxide lining was available at least as early as 2006. Yet, as of May 2019 Sandoz still had not solved the problem and instead sought to license Exela's low-aluminum ELCYS® product within weeks of Exela's NDA approval." *Id.* at 4 (footnote omitted)

the PO is truly interested in avoiding parallel proceedings and purportedly unnecessary litigation, it can join Petitioner's motion and urge the district court to stay that action."). Because we deny institution on the merits, we do not address the issues raised under 35 U.S.C. § 324(a).

(citing Ex. 1014, 2, 8; Prelim. Resp. 5–6). Patent Owner reiterates that Eton conflates the Sandoz Label and the “Sandoz product” in order to backfill information not found in the label. *Id.* at 7. Patent Owner contends that Eton has not established that “any particular product qualifies as prior art” or how a person of ordinary skill in the art would have had access to the product before its release. *Id.* at 8–9.

We address the parties’ contentions below.

2.) *Particularity*

Petitioner relies on “[t]he Sandoz Label [as] disclos[ing] a product that ‘[c]ontains no more than 5,000 mcg/L [*i.e.*, 5000 ppb] of aluminum,’ which encompasses the claimed range of ‘less than about 150 ppb of aluminum.’” Pet. 42 (citing Ex. 1003 ¶ 109; Ex. 1005, 5, 10; Ex. 1004, 8, 13); *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness”); *see also ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012) (disclosure of “150 ppm or less” teaches “50 ppm”)), *see also* Pet. 38 (“As reported by the Sandoz Label, the Sandoz product contained aluminum in the range of 0 ppb to 5,000 ppb. Ex. 1003 ¶ 32; Ex. 1005, 5, 10; Ex. 1004, 8, 13.”). Petitioner reasons that a person of ordinary skill in the art *could* have easily determined the aluminum levels in “the Sandoz product disclosed by the Sandoz Label by testing the product. The aluminum levels in the Sandoz product were typically less than 100 ppb shortly after manufacture and increased to several hundred ppbs during storage.” Pet. 43 (citing Ex. 1003 ¶ 109; Ex. 1022 ¶ 15). In other words, Petitioner’s position is that if a person of ordinary skill in the art *had* tested the Sandoz product,

they would have determined that right after manufacture, the aluminum levels were at the low end of the alleged 0 to 5000 ppb range.

Petitioner's recited ground of unpatentability, however, relies solely on the Sandoz Label in view of the knowledge of a person of ordinary skill in the art. Based on that articulated ground, we agree with Patent Owner that the Petition suffers from a lack of particularity because the Petition "improperly mixes-and-matches two different types of alleged prior art under the 'Sandoz Label' umbrella—(1) the contents of a printed publication, and (2) alleged features of a 'Sandoz product' associated with that label that are neither described by the label nor substantiated with any evidence." Prelim Resp. 27–28, *see also id.* at 29 ("The Petition repeatedly conflates a so-called 'Sandoz product' with the 'Sandoz Label' (i.e., the Sandoz package label and package insert, Ex. 1005), treating them as a single prior art source (Ex. 1005) so as to back-door unproven product characteristics to try to show obviousness."); Sur-reply 7–9. Petitioner's expert, Dr. Rabinow in his declaration similarly mixes-and-matches the two different types of prior art under the Sandoz Label. *See* Ex. 1002 ¶¶ 31–33, 106–113 (citing Ex. 1022).

"In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Technology, Inc.*, 815 F.3d 1356, 1363 (2016). "Section 312(a)(3)'s particularity requirement is designed, at least in part, to ensure that a patent owner has sufficient notice of the challenge against which it must defend." *Cuozzo Speed Technologies, LLC v. Lee*, 136 S.Ct. 2131, 2154 (2016) Section 312(a) relates to *inter partes* reviews (IPRs) and the similarly worded Section 322(a) relates to post-grant reviews (PGRs); we interpret

these two statutory sections similarly. Here, by mixing the two different types of art Petitioner is asking us read information into the Sandoz Label that is not there, and this does not satisfy the notice requirement under section 322(a). Accordingly, we agree with Patent Owner that the Petition lacks particularity.

3.) Range

We additionally find that Petitioner's argument that a person of ordinary skill in the art would have understood the Sandoz Label to teach a range of 0 to 5,000 ppm aluminum is not supported by the evidence of record. The Sandoz Label (i.e., the package label and container labeling) states: "L-Cysteine Hydrochloride Injection, USP, 50 mg/ml, is a sterile, nonpyrogenic solution. Each ml contains: 50 mg of L-Cysteine Hydrochloride Monohydrate USP; Water for Injection, USP q.s.; Air replaced With Nitrogen. pH 1.0-2.5." Ex. 1005, 1; *see also id.* at 5, 10. The Sandoz Label describes that the product "L-Cysteine Hydrochloride Injection, USP is intended for use only after dilution as an additive to Crystalline Amino Acid Injections to meet the intravenous amino acid nutritional requirements of infants receiving total parenteral nutrition." *Id.* at 2. The Sandoz Label explains that the product contains aluminum. *Id.* ("WARNING: This product contains aluminum that may be toxic." (emphasis omitted)); *see* Ex. 1003 ¶ 32; Ex. 2001 ¶ 19). The Sandoz Label states that the product contains "no more than 5,000 mcg/L aluminum" (corresponding to 5000 ppb). Ex. 1005, 5, 10; *see* Ex. 1003 ¶ 32; Ex. 2001 ¶ 21.

Patent Owner contends nothing in the record suggests that Petitioner's expert, Dr. Rabinow, is "qualified to interpret labels for parenteral products

that are intended for use by clinicians or that he has any experience in doing so.” Prelim Resp. 41. Patent Owner argues that clinical knowledge is pertinent to interpreting pharmaceutical labels such as the Sandoz Label. *Id.* at 26 (citing Ex. 2001). Patent Owner challenges Petitioner’s expert conclusion that one of ordinary skill in the art would interpret the Sandoz Label as reciting a range of 0 to 5000 ppb. Prelim Resp. 40 (citing *See Innovations4Flooring NV v. Valinge Innovation AB*, IPR2017-02130, Paper 36, 57–58 (PTAB Mar. 25, 2019) (assigning “limited weight” to expert’s testimony where expert did not possess the “practical experience” that a person of ordinary skill in the art would have possessed))).

Petitioner’s expert, Dr. Rabinow recognizes that the Sandoz Label warns that “this product contains aluminum that may be toxic.” Ex. 1003 ¶ 32. Dr. Rainbow never the less avers that the recitation “[c]ontains no more than 5,000 mcg/L [*i.e.*, 5,000 ppb] of aluminum” in the Sandoz Label would have been understood by a person of ordinary skill in the art “to mean aluminum in an amount falling somewhere within the range of 0 ppb to 5,000 ppb.” *Id.* As explained in our trial practice guide, the relative weight that we assign expert testimony is subject to various factors. *See, e.g.*, Consolidated Trial Practice Guide⁶ 40 (“Opinions expressed without disclosing the underlying facts or data may be given little or no weight.”). In this case, we find that a recognition in the Sandoz Label that the product contains aluminum reasonably undercuts a conclusion that the lower limit of

⁶ A copy of the Trial Practice Guide is available at:
<https://www.uspto.gov/TrialPracticeGuideConsolidated>

the Sandoz Label is zero. (Ex. 1005, 8 (“WARNING: This product contains aluminum that may be toxic” (emphasis omitted))).

Patent Owner’s expert, Dr. Kuhn avers that a pharmacist reading the label would interpret “[c]ontains no more than 5,000 mcg/L [i.e., 5,000 ppb] of aluminum” as being the maximum aluminum content. Ex. 2001 ¶ 15 (“In 2004, the Food and Drug Administration . . . issued a rule requiring that additives used to compound TPN [(total parenteral nutrition)] have the maximum aluminum content at expiration listed on the product label.”); Ex. 1007, 1 (“Manufacturers currently label these products with the maximum aluminum content at the time of expiry.”). Dr. Kuhn further explains that when

calculating the potential aluminum exposure for a patient receiving TPN solution that uses the Cysteine HCl Product [, a pharmacist] would use the 5,000 mcg/L aluminum concentration to do so. The package label expressly teaches the product could contain up to 5,000 mcg/L of aluminum, and any prudent pharmacist would use that maximum aluminum level to calculate potential aluminum exposure so as to not underestimate the content of the potential for aluminum toxicity.

Ex. 2001 ¶ 21.

The evidence in the record (*see* Ex. 1007, 2) supports Dr. Kuhn’s position that the Sandoz Label recites the maximum aluminum contamination level at the product expiration date. Furthermore, the Sandoz label expressly warns that the Sandoz product contains aluminum which can be toxic to certain individuals. Ex. 1005, 8 (“WARNING: This product contains aluminum that may be toxic” (emphasis omitted))).

We have considered Petitioner's arguments and evidence. We do not find Dr. Rabinow's testimony to be entitled to persuasive weight because, as Dr. Kuhn explains, the recitation of "contains no more than 5,000 mcg/L of aluminum" would be understood by a person of ordinary skill in the art to be a maximum aluminum level and not a recitation of a range. Because the label specifically warns about the presence of aluminum we do not find Dr. Rabinow's testimony with respect to the Sandoz Label teaching a range of 0 to 5,000 ppm to be supported by the evidence in the record.

4.) Optimization

Petitioner relies on "routine optimization" as the reason for arriving at claim element 1(C) directed to a solution of L-cysteine comprising "less than about 150 ppb of aluminum." Petitioner contends that a person of ordinary skill in the art would have addressed "well-known" sources of potential aluminum contamination, including: (1) component ingredients; (2) other amino acid compositions combined with the parenteral drug product; and (3) container closure systems such as "glass containers, which were known to leach aluminum into the drug product." *See* Pet. 32–33 (citing Ex. 1003 ¶¶ 58–62; Ex. 1006, 2; Ex. 1007, 1–2; Ex. 1008, 1; Ex. 1011, 1; Ex. 1012, 3; Ex. 1014, 8; Ex. 1038, 3, tbl.1; Ex. 1048, 12; Ex. 1070, 1; Ex. 1071, 5–7; Ex. 1101, 14), *see also id.* at 37–39 (citing Ex. 1003 ¶¶ 28–55, 58–62, 109, 115, 118, 121, 124, 127, 146, 163). Petitioner further contends that a person of ordinary skill in the art would have been motivated to prevent the "known oxidative degradation of oxygen sensitive drugs such as L-Cysteine." *Id.* at 33–34 (citing Ex. 1003 ¶¶ 42, 46–48), *see id.* at 40 (citing Ex. 1003 ¶¶ 63–75).

According to Petitioner, the Sandoz Label already warns that aluminum may be toxic to certain patient populations in accordance with U.S. Food and Drug Administration (FDA) mandate. Pet. 30. Petitioner contends that in response to FDA regulatory demand, articulated market pressures, and recognized toxicity, there was a motivation to lower the aluminum content in total parenteral nutrition (TPN) solutions. Pet. 30–32 (citing Ex. 1006, 1; Ex. 1007, 2; Ex. 1003 ¶¶ 28, 29, 57–75). As recognized in the prior art:

[T]o limit the risk of aluminum toxicity, the U.S. Food and Drug Administration (FDA) modified its “Regulations on Aluminum in Large and Small Volume Parenterals Used in Total Parental Nutrition” with the January 2000 Final Rule, enacted in July 2004. The Final Rule limits the aluminum concentration of large-volume parenteral products to 25 mcg/L . . . and a recommended maximum daily aluminum dose of 4 to 5 mcg/kg/ day to prevent accumulation and toxicity

Ex. 1007, 2 (citations omitted).

As noted above, Petitioner relies on the FDA regulations and other industry communications directing a lower amount of aluminum in L-cysteine parenteral compositions as motivation to lower the aluminum levels in the Sandoz product. Although we agree with Petitioner that this evidence supports the position that there would have been a motivation to avoid aluminum toxicity and to lower the levels of aluminum in parenteral products, the presence of such motivation alone is insufficient for reaching a conclusion of obviousness. Obviousness also requires a reasonable expectation of success in achieving the claimed subject matter. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

As Patent Owner argues, Petitioner’s reliance on the FDA regulation regarding maximum aluminum level in a product does not say anything about *how* to achieve the goal. Prelim. Resp. 62 (citing Ex. 1019, 2 (aluminum dose delivered should be ≤ 0.6 mcg/kg/day that would be a limit of ≤ 145 mcg/L in the product); Ex. 2012 (“Large-volume parenteral labeling must state that the product ‘contains no more than 25 mcg/liter’ of aluminum . . . with the maximum aluminum content at the product’s expiry.”). In other words, knowing the FDA’s goal may provide a motivation to try to lower aluminum levels in total parenteral nutritional supplements but that does not provide a path of how to achieve the stated goal. Prelim Resp. 62–63 (citing *Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1376 (Fed. Cir. 2019) (finding that FDA communications did not show a reasonable expectation of success where they merely “recite[d] a goal without teaching how the goal is attained”); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1074 (Fed. Cir. 2012) (reversing obviousness determination and rejecting district court’s reliance on FDA guidance document about approval requirements for extended-release formulations because “knowledge of the goal does not render its achievement obvious” (quoting *Abbott Labs, Inc. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2009))). To be sure, “[o]bviousness does not require absolute predictability of success.” *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). But it is also not permissible to reach an obviousness conclusion by allowing each of numerous possible choices to be tried until one possibly arrived at a successful result. *See id.*

Petitioner attempts to bolster its routine optimization argument by urging that the recitation of “[c]ontains no more than 5,000 mcg/L of . . .

aluminum” in the Sandoz Label should be interpreted as a disclosure of an aluminum range⁷ from 0 to 5000 ppb. Pet. 38 (citing Ex. 1003 ¶ 32; Ex. 1005, 5, 10), 42 (“The Sandoz Label discloses a product that ‘[c]ontains no more than 5,000 mcg/L [i.e., 5000 ppb] of aluminum,’ which encompasses the claimed range of “less than about 150 ppb of aluminum.” (citing Ex. 1003 ¶ 109; Ex. 1005, 5, 10)). Based on this interpretation, Petitioner concludes that it would have been obvious to optimize the aluminum content in a parenteral solution based on overlapping ranges. *Id.* at 42 (citing *Peterson*, 315 F.3d at 1330; *ClearValue*, 668 F.3d at 1345).

Patent Owner argues that “any prudent pharmacist would interpret the Sandoz Label as disclosing up to 5,000 mcg/L of aluminum, and would use that maximum aluminum level in calculating a patient’s aluminum exposure” Prelim. Resp. 39. Patent Owner’s expert, Dr. Kuhn, avers that it was known

that for L-cysteine hydrochloride solutions packaged in glass the aluminum content will increase over time. . . . Ideally, L-cysteine hydrochloride solutions with a longer remaining shelf life would be used for neonatal patients because their aluminum levels might be lower than products with a shorter remaining shelf life (i.e., closer to their expiration date).

Ex. 2001 ¶ 22.

⁷ In Petitioner’s Reply, Petitioner asserts that the Petition additionally articulated a reasonable expectation of success argument that did not require overlapping ranges. *See* Pet. Reply 3 n.5. Patent Owner contends that Petitioner’s argument in the Reply – that regardless of how the Sandoz Label is interpreted there is still reasonable expectation of success – is a new argument. *See* Sur-reply 2 (citing Pet. Reply 1). We have reviewed the Petition and agree with Patent Owner that this is a new argument and, therefore, will not further consider it. *See* Consolidated TPG 74.

Dr. Kuhn's position is reasonably supported in the art that the aluminum levels on a label recite the aluminum concentration at the point of expiration. For example, a prior art article of record indicates:

Aluminum is a contaminant in all parenteral nutrition solutions. Manufacturers currently label these products with the maximum aluminum content at the time of expiry, but there are no published data to establish the actual measured concentration of aluminum in parenteral nutrition solution products prior to being compounded in the clinical setting.

Ex. 1007, 1.

We do not find that the indication in the Sandoz Label that the product “[c]ontains no more than 5,000 mcg/L of aluminum” reasonably suggests a range of 0–5,000 mcg/L of aluminum that would be subject to routine optimization. We agree with Patent Owner that the recitation of contains no more than 5000 mcg/L (i.e. 5000 ppm) aluminum is more reasonably interpreted to be the upper end of the aluminum concentration that is expected in the product rather than a teaching of any lower limit for the aluminum content that overlaps with the claimed range. Prelim. Resp. 42. Also, based on the record before us, we find that *zero* is not a reasonable endpoint for any range of the aluminum concentration in a cysteine containing composition as set out in the Sandoz Label. In fact, the Sandoz product even right after manufacture contains measurable aluminum, indicating that the level of aluminum in the product is not *zero* at any time. *See e.g.* Ex. 1022 ¶ 15 (“L-Cysteine Products (*i.e.*, within several weeks of manufacture) were typically below about 100 ppb.”)); *id.* at Ex. B (showing aluminum concentration of as high as 61 ppb after manufacture). The evidence, therefore, does not support Petitioner's position that the Sandoz

Label describes a product that “contained aluminum in the range of 0 ppb to 5,000 ppb.” Pet. 40–41 (citing Ex. 1003 ¶ 32; Ex. 1005, 5).

Patent Owner further contends that Petitioner’s “routine optimization” analysis is based on hindsight reasoning. *See* Prelim. Resp. 43–63. First, Patent Owner contends that Petitioner has not established that particulate matter was known to be relevant to solving the aluminum problem with L-cysteine solutions especially in the low-pH environment of the Sandoz solution. *Id.* at 47. Second, Patent Owner contends that Petitioner has not articulated why there would have been a “reasonable expectation of success in solving the decades-old aluminum problem.” *Id.* at 43. Patent Owner contends this is especially apparent because the person of ordinary skill in the art was highly motivated to solve the “alleged problem of aluminum” and yet the problem had “gone unsolved for more than a decade” despite the supposedly “simple and straight forward solutions.” *Id.* at 44–45 (citing *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (“If these discoveries and advances were routine and relatively easy, the record would undoubtedly have shown that some ordinary artisan would have achieved this invention within months of [the prior art patents]. Instead this invention does not appear for more than a decade.”)). Third, Patent Owner contends that “L-cysteine parenteral solutions are sensitive to an array of multivariate and interrelated interactions,” meaning that a change in one variable results in changes in other variables. *Id.* at 58.

Having considered the arguments and evidence of record, we determine that Petitioner has not demonstrated that it is more likely than not that claim 1 would have been obvious over the Sandoz Label in light of the knowledge of a person of ordinary skill in the art. In particular, the evidence

of record does not show that Petitioner will likely be able to meet its burden of establishing that a person of ordinary skill in the art would have had a reasonable expectation of success with respect to lowering the amount of aluminum content within the Sandoz L-cysteine product to within the claimed range of less than 150 ppb of aluminum. Additionally, we do not find that the indication in the Sandoz Label that the product “[c]ontains no more than 5,000 mcg/L of aluminum” would have reasonably suggested a range of 0–5,000 mcg/L of the aluminum amount that would be subject to routine optimization. We agree with Patent Owner that the recitation of “contains no more than 5000 mcg/[L] (i.e. 5000 ppm) aluminum” would have been more reasonably interpreted to be the upper end of the aluminum concentration that is expected in the product rather than a teaching of any lower limit for the aluminum content. Prelim. Resp. 42.

On this record, we agree with Patent Owner that Petitioner has not provided a sufficient evidentiary basis from which to conclude that there would have been a reasonable expectation for making L-cysteine containing solutions having the requisite aluminum content as recited in claim 1 of the ’719 patent. With respect to claims 2–27, which recite similar aluminum content as recited in claim 1, Petitioner relies on the same underlying arguments as presented for claim 1 that we find unpersuasive.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes that it is “more likely than not” that any of claims 1–27 of the ’719 patent are unpatentable under 35 U.S.C. § 103 based on the ground presented. We, therefore, do not institute a post-grant review of those challenged claims based on the current Petition.

IV. ORDER

Accordingly, it is:

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

PGR2020-00086
Patent 10,653,719 B1

For PETITIONER:

Ralph Gabric
Eugene Goryunov
Jeff Wolfson
Judy He
HAYNES AND BOONE LLP
ralph.gabric.ipr@haynesboone.com
eugene.goryunov.ipr@haynesboone.com
jeff.wolfson.ipr@haynesboone.com
judy.he@haynesboone.com

For PATENT OWNER:

Dorothy Whelan
Alana Mannige
FISH & RICHARDSON P.C.
whelan@fr.com
mannige@fr.com