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Paper No. 12
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ETON PHARMACEUTICALS, INC,
Petitioner,

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner.

PGR2020-00064
Patent US 10,478,453 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 1–22 ("the challenged claim") of Patent US 10,478,453 B1(Ex. 1001, "the '453 patent"). Paper 1 ("Pet."). Exela Pharma Sciences, LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). With our authorization (Paper 7), Petitioner filed a reply to Patent Owner's Preliminary Response (Paper 9 ("Pet. Reply")), and Patent Owner filed a Sur-reply (Paper 11 ("Sur-reply")). We granted additional briefing to allow Petitioner to clarify the record with respect to assertions made in Patent Owner's preliminary response, and to allow Patent Owner the opportunity to address alleged conflicting arguments made in a related proceeding.

We have authority to determine whether to institute a post-grant review. 35 U.S.C. § 324. After considering all the papers submitted, 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

Petitioner identifies as related matter *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, Case No. 1:20-cv-00365-MN (D. Del., filed March 16, 2020) ("District Court Action"); *Exela Pharma Sciences LLC v. Avadel Legacy Pharms., LLC*, No. 1:20-cv-00024-MN (D. Del., filed January 7, 2020); *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. 3; Paper 3, 1.

Petitioner also identifies U.S. Patent No. 10,583,155, U.S. Patent Appl. No. 16/746,028, U.S. Patent Appl. No.16/773,563 (now U.S. Patent No. 10,653,719), 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 as claiming benefit of priority to U.S. Application No. 16/248,460 which issued as the '453 patent. Pet. 3–4; Paper 3, 2.

C. The '453 Patent (Ex. 1001)

The '453 patent is titled "STABLE, HIGHLY PURE L-CYSTEINE COMPOSITIONS FOR INJECTION AND METHODS OF USE." Ex. 1001, (54). The '453 patent issued from Application No. 16/248,460 ("the '460 application"), filed January 15, 2019. *Id.* at (21), (22).

The '453 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 1:14–16. Because L-cysteine can be synthesized by the body, it is considered a non-essential amino acid. *Id.* at 1:20. "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 1:26–31.

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 4:25–30. 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 4:37–43.

The specification discloses that "known L-cysteine compositions contain up to 5000 ppb Aluminum." *Id.* at 7:8–9. In contrast, the specification describes "compositions that provide a therapeutically effective amount of L-cysteine, while containing less than 250 ppb Aluminum." *Id.* at 7:10–13. The specification discloses that reduced aluminum compositions "permit[ ] exposure to less than or equal to 4–5 micrograms per kilogram per day (μg/kg/d) to avoid or minimize Aluminum toxicity while still providing therapeutically effective L-cysteine in a stable composition." *Id.* at 7:21–25.

The specification expressly defines the term "stable" as a composition that will contain the specified levels of all components, e.g., Aluminum, cystine, and pyruvic acid, "for [a] sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting." *Id.* at 16:41–52. 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.

D. Illustrative Claim

Claim 1 of the '453 patent is illustrative and reproduced below (with added bracketing for reference):

> A stable L-cysteine composition for parenteral administration, comprising:
>
> [(A)] 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;
>
> [(B)] Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb;
>
> [(C)] L-cystine in an amount from about 0.001 wt% to about 2.0 wt % relative to L-cysteine;
>
> [(D)] pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt % relative to L-cysteine;
>
> [(E)] a pharmaceutically acceptable carrier, comprising water;
>
> [(F)] headspace oxygen that is from about 0.5% v/v to 4.0% v/v from the time of manufacture to about 1 month from manufacture when stored at room temperature;
>
> [(G)] dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature,
>
> [(H)] wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.

Ex. 1001, 59:2–25.

E. Prior art

Petitioner relies upon the following prior art references[1] (Pet. 6):

References	Patent / Publication	Exhibits
Sandoz Label	L-CYSTEINE HYDROCHLORIDE – cysteine hydrochloride injection, solution Sandoz Inc.	Ex. 1005
Hospira Label	AMINOSYN® A Crystalline Amino Acid Solution	Ex. 1009
Allergy Process	Exhibit A (Declaration of Harry "Warren" Johnson)	Ex. 1022

Petitioner relies on affidavits of Christopher Butler of the Internet Archive (Ex. 1004; Ex. 1010) and the attached exhibits to establish the availability of certain references.

F. Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–22 of the '453 patent on the following grounds (Pet. 6):

Ground	Claim(s) Challenged	Basis	Reference(s)
1	1–14	§ 103	The Sandoz Label in view of the knowledge of a person of ordinary skill in the art
2	15–20, 22	§ 103	The Sandoz Label and the Hospira Label, in view of the knowledge of a person of ordinary skill in the art
3	21	§ 103	The Sandoz Label and the Allergy Process, 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) to support its assertions.

[1] Petitioner additionally cites references in support of "the knowledge of POSITA [(person of ordinary skill in the art)]." *See* Pet. 27–34.

Patent Owner relies on the Declaration of Robert J. Kuhn, PharmD (Ex. 2001) in support of its Patent Owner Preliminary Response.[2]

II. DISCUSSION

A. Overview of Petitioner's References

1.) "Sandoz Label" (Ex. 1005)

The Sandoz Label[3] describes a solution containing 50 mg of L-cysteine hydrochloride monohydrate, water, with the air replaced with nitrogen, and the solution having a pH 1.0–2.5. Ex. 1005, 5. The product comes 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.

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[2] To the extent a genuine issue of material fact arises from the testimony of Dr. Kuhn, we view that issue in the light most favorable to Petitioner solely for purposes of this Decision. *See* 37 C.F.R. § 42.108(c).

[3] Petitioner identifies "the Sandoz Label" as including the product, package insert, and package label. Pet. 1. Patent Owner contends that the "label" 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 a separate prior art. *Id.* at 31.

The label indicates that the product contains no more than 5000 mcg/L [(5000 ppb)[4]] of aluminum. 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.*

2.) "Hospira Label" (Ex. 1009)

Hospira Label describes Aminosyn® as sterile crystalline amino acid solution for intravenous infusion. Ex. 1009, 1. Aminosyn provides crystalline amino acids to promote protein synthesis and wound healing and to reduce the rate of endogenous protein catabolism. *Id.* at. 2.

3.) "Allergy Process" from the Johnson Declaration (Ex. 1022)

Allergy Laboratories, Inc. ("Allergy"), manufactured the Sandoz product that is the subject of the Sandoz Label. Pet. 33 (citing Ex. 1022 ¶¶ 8–9). The Allergy Process[5] included the following steps:

a. Stirring water for injection, USP (WFI) in a vessel at temperature not more than (NMT) about 60ºC;

b. Allowing the vessel to cool to a temperature of NMT 30ºC;

c. Contacting the WFI with L-Cysteine Hydrochloride, Monohydrate, USP (L-Cysteine) for not longer than (NLT) 15 minutes;

[4] 5000 mcg/L corresponds to 5,000 ppb. *See* Ex. 1003 ¶ 98; Ex. 2001 ¶ 20.
[5] Patent Owner contends that the Allergy Process does not qualify as prior art. *See* Prelim Resp. 19–28. Because we deny the Petition on the merits we do not address the prior art status of the Allergy Process.

d. Adjusting the pH, if needed, with concentrated Hydrochloric Acid, NF and/or 5.0N Sodium Hydroxide, NF;

e. Mixing for a minimum of about 10 minutes;

f. Capping the vessel and allowing to stand;

g. Filling said mixture into container of use;

h. Reducing the head space oxygen in said containers of use; and

i. Sealing said containers of use.

Pet. 33 (citing Ex. 1022 ¶¶ 16–18). The product made by the Allergy Process contained Aluminum at the very low end (e.g., typically < 100 ppb) of the no more than 5,000 mcg/L (i.e., ppb) range disclosed by the Sandoz Label. *Id.* (citing Ex. 1022 ¶ 15).

B. The Parties' Contentions

Petitioner contends that the challenged claims are obvious based primarily on the Sandoz Label. Pet. 43–72.

Petitioner's first obviousness ground, challenging claims 1–14, relies on the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art.[6] Pet. 43. Petitioner contends that claim elements 1(A), 1(B), 1(E), and 1(H) are disclosed in the Sandoz Label. Pet. 44–47, 50.

[6] Petitioner identifies 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. 24. Patent Owner contends that Petitioner's definition misses the mark because it ignores the need for the artisan to also have "knowledge or experience in interpreting pharmaceutical drug labels or consulting with someone who did." Prelim. Resp.18. We note the parties' differences with respect to level of skill in the art, but because we deny institution for other reasons, we do not need to resolve this conflict here.

Petitioner concedes that elements 1(C), 1(D), 1(F), and 1(G) are not recited in the Sandoz Label, but contends that these elements would be obvious in light of the knowledge of a person of ordinary skill in the art. *See* Pet. 47 ("[T]he claimed ranges are the reasonably expected result of taking art-recognized steps to prevent oxidative degradation of L-Cysteine to L-Cystine during manufacture and storage." (citing Ex. 1003 ¶¶ 100–105)); 48 ("[T]he claimed range encompasses what was known in the art . . . ." (citing Ex. 1003 ¶¶ 107, 109–110; Ex. 1027, Ex. 1029), 49 ("[T]he claimed range encompasses dissolved oxygen levels known in the prior art . . . ." (citing Ex. 1003 ¶ 112; Ex. 1082)). With respect to independent claim 1, Petitioner contends 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. Pet. 49 (citing Ex. 1003 ¶ 113). Petitioner contends that dependent claims 2–14 would have similarly been obvious based on the Sandoz Label in conjunction with the knowledge of one of ordinary skill in the art and/or based on routine optimization. *See* Pet. 50–56 (citing Ex. 1003 ¶¶ 50, 54–58, 117–134, 136, 138, 139, 141–147, 150–156, 158; Ex. 1006; Ex. 1007; Ex. 1008; Ex. 1011; Ex. 1012; Ex. 1013; Ex. 1014; Ex. 1027; Ex. 1036; Ex. 1038; Ex. 1039; Ex. 1048; Ex. 1064; Ex. 1070; Ex. 1071).

Petitioner's second obviousness ground, challenging claims 15–20 and 22, relies on the Sandoz Label and the Hospira Label in conjunction with the knowledge of a person of ordinary skill in the art. Pet. 56–67. Petitioner contends that claim elements of claim 15 corresponding to claim elements 1(A), 1(B), 1(E), and 1(H) are disclosed in the Sandoz Label. Pet. 56–57. Petitioner contends that claim elements corresponding to additional

amino acid compositions as recited in claim 15 are taught by the Hospira Label. Petitioner concedes that the claim elements in claim 15 that correspond to claim elements 1(C), 1(D), 1(F), and 1(G) are not recited in the Sandoz Label, but contends that these elements would be obvious in light of the knowledge of a person of ordinary skill in the art. *See* Pet. 58–59.

Petitioner's third obviousness ground, challenging claim 21, relies on the Sandoz Label and the Allergy Process in conjunction with the knowledge of a person of ordinary skill in the art. Pet. 67–72 (citing Ex. 1003 ¶¶ 48–49, 195, 198–207; Ex. 1022 ¶ 16; Ex. 1027; Ex. 1028; Ex. 1031; Ex. 1032; Ex. 1033; Ex. 1036; Ex. 1041; Ex. 1069; Ex. 1082).

In response, Patent Owner argues that Petitioner is using additional references, specifically Waterman,[7] Yaman,[8] and Butler,[9] as more than just evidence of the knowledge of the person having ordinary skill in the art, but instead Petitioner is using these references to try and establish that specific claim elements were taught in the art. Prelim. Resp. 33 (citing *Adaptics Limited v. Perfect Company*, IPR2018-01596, Paper 20 at 20–23 (PTAB Mar. 6, 2019) (Informative Decision); *see also EnergySource Materials, LLC v. Terralithium LLC*, IPR2019-01605, Paper 7 at 30 (PTAB Apr. 6, 2020)). Waterman, Yaman, and Butler describe techniques for removing

[7] Kenneth C. Waterman et al., *Stabilization of Pharmaceuticals to Oxidative Degradation*, 7 Pharm. Develop. & Tech, 1–32 (2002) (Ex. 1027).
[8] Alpaslan Yaman, *Chapter 7: Engineering Considerations in Sterile Powder Process*, *in Sterile Pharmaceutical Products: Process Engineering Application* (Kenneth. E. Avid ed., 1995) (Ex. 1029).
[9] Ian B. Butler et al., *Removal of Dissolved Oxygen from Water a Comparison of Four Common Techniques*, 41 Talenta 211–215 (1994) (Ex. 1082).

oxygen from either the headspace or from a liquid carrier as recited in claim elements 1(F) and 1(G). Patent Owner argues that, by taking a "catch-all" approach without identifying what specific combinations are intended and instead placing everything under the umbrella of either "routine optimization" or "knowledge of the ordinary artisan," the Petition lacks the required particularity that would allow Patent Owner a fair opportunity to formulate a response to the intended combinations. Prelim. Resp. 33 ("These 'back door' combinations should be rejected . . . .").

C. Claim Construction

Petitioner proposes constructions for two claim terms: "about" and "stable." *See* Pet. 25–26 (citing Ex. 1001, 16:40–51; 58:28–39). Patent Owner contends that there is no need to resolve any claim construction terms, but notes that the term "stable" requires that the composition must be stable over certain minimum time period. Prelim Resp. 18.

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.*, 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

1.) Particularity Requirement

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. 35 U.S.C. § 324(a). In addition, 35 U.S.C. § 322(a)(3) provides that the petition identify "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 includes, "[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.

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 the 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).

Consistent with the statute and case law, our Consolidated Trial Practice Guide[10] advises that petitioners should "avoid submitting a

[10] Consolidated Trial Practice Guide Update, 59 (Nov. 2019), available at www.uspto.gov/trialpracticeguideconsolidated, ("TPG").

repository of all the information that a judge could possibly consider, and instead focus on concise, well-organized, easy-to-follow arguments supported by readily identifiable evidence of record." TPG 39.

In this case, we agree with Patent Owner that the Petition suffers from a lack of particularity because it is not clear what aspects of the numerous references cited in the body of the Petition, but not listed in the grounds of unpatentability, Petitioner relies on to establish a basis for "routine optimization" as the reason for arriving at claim elements 1(C), 1(D), 1(F), and 1(G). By not including references in the formulation of the ground unpatentability Petitioner is not providing an articulated reason that allows Patent Owner the ability to respond and leaves Patent Owner, and the Board for that matter, to guess how the references are applied to each particular ground. Prelim. Resp. 33 ("[Petitioner] is relying on its 'additional references' to create back-up obviousness combinations without identifying those combinations to Exela and the Board." (emphasis omitted)); *cf. In re Hoch*, 428 F.2d 1341, 1342 n.3 (CCPA 1970) ("Where a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of rejection.").

Petitioner relies on the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art to arrive at the L-cysteine composition as recited in independent claim 1. *See* Pet. 43–50. Patent Owner argues that Petitioner relies on more than the general knowledge of the ordinary artisan because Petitioner uses Waterman and Yaman to establish a headspace oxygen range that meets the claim requirements, yet does not

recite these references in the stated ground of unpatentability. Prelim Resp. 32 (citing Ex. 1027 and Ex. 1029).

For example, Petitioner contends that the oxygen sensitivity of L-cysteine is well-known in the art and easily addressed. *See* Pet. 38–40. Petitioner notes that in "the Sandoz Label, headspace air is replaced with nitrogen to address L-Cysteine's oxygen sensitivity." Pet. 39 (citing Ex. 1003 ¶ 31; Ex. 1005, 1), 48 (citing Ex. 1003 ¶ 109; Ex. 1029, 41; Ex. 1027, 27). Petitioner then notes that given the disclosure of the Sandoz Label in conjunction with teachings in Yaman and Waterman, "the percent oxygen in the vial headspace" of the Sandoz Label encompasses the claimed range based on what was known in the art. Pet. 48. Here, the Petition cites Yaman and Waterman to establish the oxygen level in the headspace of the product described in the Sandoz Label. *Id.* (citing Ex. 1003 ¶¶ 107–108). The Petition, however, does not cite these references in the ground of unpatentability, and instead, Petitioner appears to be relying on routine optimization based on the knowledge of one of ordinary skill in the art to arrive at the conclusion that the Sandoz Label meets the claimed elements.

Another example of Petitioner's reliance on more than just the knowledge of the ordinary artisan is with respect to the dissolved oxygen range in water as disclosed in Butler. *See* Pet. 49 (citing Ex. 1082), Prelim Resp. 32 (citing Ex. 1082). Butler describes several techniques to remove dissolved oxygen from a liquid. These are: purging with nitrogen, argon, or a similar inert gas; boiling at 1 atm; sonication under "vacuum"; and boiling under "vacuum." Ex. 1082, 1. Butler concludes that a nitrogen purge is an efficient method for removing dissolved oxygen from deionized water but concludes "it is a poor method to preserve solutions containing redox-

sensitive species." *Id.* at 5. Here, Petitioner acknowledges that the Sandoz Label does not disclose dissolved oxygen content in the carrier, but finds that purging with nitrogen is a known way to reduce oxygen levels. Pet. 49 (citing Ex. 1003 ¶ 112; Ex. 1082, 1; Ex. 1069, 1; Ex. 1032 at 17–18; Ex. 1033, 13; Ex. 1027, 27). There is nothing in the Sandoz Label that suggests that the carrier was purged with nitrogen. Thus, Petitioner is relying on teachings in Waterman, Butler, and others to establish an oxygen range for water and a reason to reduce the oxygen content in the liquid carrier of the product described in the Sandoz Label. *Id.* (citing Ex. 1003 ¶¶ 111–113). Again, rather than citing these references in the ground of unpatentability, which necessitates articulating a rationale to combine the teachings of the references with a reasonable expectation of success, Petitioner instead is relying on routine optimization based on the insufficiently articulated knowledge of one of ordinary skill in the art to arrive at the conclusion that the Sandoz Label meets the claimed elements.

Petitioner contends that "L-Cysteine was known to oxidatively degrade to L-Cystine, which can form undesired particulate matter." Pet. 46 (citing Ex. 1003 ¶ 42; Ex. 1020 at 3; Ex. 1031 at 2; Ex. 1061 at 1–2). Patent Owner argues that Petitioner has not demonstrated that the oxidative behavior of L-cysteine in the pH range of 1.0–2.5 as listed on the Sandoz Label converts the L-cysteine to the unwanted cystine. Prelim. Resp. 47 (citing Ex. 1020, 3 ("In neutral or slightly alkaline aqueous solutions, [cysteine hydrochloride] is oxidized to cystine by air. It is more stable in acidic solutions."). Patent Owner contends that the Petition has not articulated a reason why a person having ordinary skill in the art would have sought to reduce aluminum concentrations by optimizing the cystine levels

in a composition that has the recited low pH. *Id.* 49. In other words, Patent Owner's contention is that Petitioner has not explained why one of ordinary skill in the art would have thought that cystine levels would have had any bearing on the aluminum content of the composition. We agree with Patent Owner that the Petition does not sufficiently explained why one of ordinary skill in the art would want to look at cystine levels in the product disclosed in the Sandoz Label in the first place and what reason there is to maintain it within the recited range.

Based on the above examples, we agree with Patent Owner and find that the Petition fails to meet the particularity requirement of 35 U.S.C. § 322(a)(3) with regard to Petitioner's assertion that the subject matter of claims 1–14 would have been obvious over the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art, and we decline to institute a post-grant review on that ground. We also decline to identify and analyze all possible permutations of prior art combinations that Petitioner may have sought to include in this ground but did not expressly articulate.

2.) Routine Optimization

According to Petitioner, the Sandoz Label already warns that aluminum may be toxic to certain patient populations. Pet. 44. 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. 35. 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). The FDA in communication with Patent Owner indicated that the aluminum dose associated with the L-cysteine drug product in their new drug application "should be limited to ≤ 0.6 mcg/kg/day. To comply with this dose level, a limit of ≤ 145 mcg/L aluminum is needed." Ex. 1019, 1. This aluminum level in the FDA demand is even lower than the previously recited aluminum dose for parenteral nutrition enacted in July 2004. *Compare* Ex. 1019, 1 (aluminum limited to limited to ≤ 0.6 mcg/kg/day) *with* Ex. 1007, 2 (aluminum dose of 4 to 5 mcg/kg/ day). The letter to Patent Owner also noted that due to the extremely low pH of their drug product, pH 1–2.5, it is also necessary to assess the leachables/extractables from any new container Exela Pharma Sciences may wish to use. Ex. 1009, 2. Based on these disclosures, we agree with Petitioner that the evidence supports the position that there is motivation to lower aluminum contamination in total parenteral nutritional solutions, specifically, to avoid aluminum toxicity.

Motivation alone, however, is not sufficient for reaching a conclusion of obviousness. Obviousness also requires a reasonable expectation of success. *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 aluminum threshold goal does not say anything about *how* to achieve the goal. Prelim. Resp. 61. In other words, knowing the FDA's goal may provide a motivation to try and lower aluminum levels in total parenteral nutritional supplements but that does not

provide a path of how to achieve the stated goal. Prelim Resp. 61–62 (citing *Endo Pharm. Inc. v. ActavisLLC*, 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 HCl Extended Release Capsule Patent Litig.*, 676 F.3d 1063, 1074 (Fed. Cir. 2013) (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 further 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 range from 0 to 5000 ppb. Pet. 44–45 (citing Ex. 1003 ¶ 32; 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. *Id.* (citing *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *ClearValue, Inc. v. Pearl Rivers Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012)).

Patent Owner argues that "[a] pharmacist reading the label would treat it as disclosing a maximum aluminum content of 5,000 ppb (mcg/L)

aluminum, and would have used this value to prepare a formulation for administration to an infant." Prelim. Resp. 63. 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.

It is known that

> 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.

Here, the evidence supports the position that the Sandoz product label recites the contamination level at the expiration date. Even if the concentration of the aluminum level before that date is actually lower, the evidence in the record does not support the position that the Sandoz Label teaches the aluminum concentration in the product to be zero or even within the claimed range of 1 to 250 ppb.

The evidence of record shows that it was known in the art that

> [a]mino acids complex metals; the aluminium complexes of glutamic and aspartic acids have known stability constants, and although the stability constant for cys-Al is not found in the literature, cysteine must interact with Al as it interacts with other metals; this could explain its great leaching action on the aluminium present in glass. . . . Cysteine is a ligand for

> aluminium [and the affinity is] as strong[] as citrate or oxalate.

Ex. 1008, 4. Thus, when glass containers are used for storing cysteine as well as its oxidation product cystine, the aluminum concentration in the solution continues to increase during storage. *Id.* at 5.

> Aluminum contamination in products comes from many sources.
>
> The results of all investigated container materials revealed an aluminium content of 1.57% Al in glass, 0.05% in plastic and 4.54% in rubber. The sterilization procedure showed that even pure water was able to extract Al from glass and rubber, 22.5 ± 13.3 µg/L and 79.4 ±22.7 µg/L respectively, while from plastic the [amount of] aluminium leached was insignificant.

Ex. 1012, Abstract.

We agree with Patent Owner that the recitation of "contains no more than 5000 mcg/ml (i.e. 5000 ppm) aluminum" is reasonably interpreted to be the upper end of the aluminum concentration that is expected in the product. We also do not find that zero is a reasonable starting point for the aluminum concentration in a cysteine containing composition based on the record before us. Here, 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[11] ¶ 15 ("L-Cysteine Products (*i.e.*, within several weeks of manufacture) were typically below about 100 ppb."), Exhibit B (showing aluminum concentration of as high as 61 ppb after manufacture)). The evidence, therefore, does not support Petitioner's

[11] In this decision, we accept the disclosures for the matter asserted in the Johnson declaration (Ex. 1022). We do not address whether the disclosure of the Allergy Process presented in the Johnson declaration qualifies as prior art based on the sale of the product or whether the process qualifies as prior art under public use. *See* Pet. Reply. 6; Pet. 9.

position that "the Sandoz product contained aluminum in the range of 0 ppb to 5,000 ppb." Pet. 40–41 (citing Ex. 1003 ¶ 32; Ex. 1005, 5). Because we do not find that the product described in the Sandoz Label discloses a range for aluminum from 0 ppb to 5,000 ppb, we are not persuaded by Petitioner's position that there is a reasonable expectation that routine optimization would lead to aluminum concentrations as recited in claim 1 of the '453 patent based on optimizing overlapping ranges. *See* Pet. 42.

On this record, we agree with Patent Owner that Petitioner 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 recited in claim 1 of the '453 patent. With respect to claims 2–14, Petitioner relies on the same underlying arguments as presented for claim 1 that we find unpersuasive.

3.) Second and Third Grounds

The second ground of unpatentability as recited in the Petition relies on the addition of the Hospira Label with the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art. *See* Pet. 56–67. The addition of the Hospira Label does not address the underlying issue as discussed above for ground 1, specifically, that the Sandoz Label does not disclose a range of aluminum contamination from 0 ppb to 5,000 ppb. Because the Hospira Label is not relied upon to rectify the underlying shortcoming of the Sandoz Label (*see above* II.D.1 and II.D.2), we conclude that the evidence presented in the Petition does not support the contention that the claims 15–20 are 22 are unpatentable.

The third ground of unpatentability as recited in the Petition relies on the addition of the Allergy Product with the Sandoz Label in conjunction

with the knowledge of a person of ordinary skill in the art. *See* Pet. 67–72. The Allergy Product is not relied upon to rectify the underlying shortcoming of the Sandoz Label (*see above* II.D.1 and II.D.2), and therefore, we conclude that the evidence does not support Petitioner's contention that the claim 21 is unpatentable.

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 1–22 of the '453 patent are unpatentable under 35 U.S.C. § 103(a) based on the grounds 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.

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