

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ETON PHARMACEUTICALS, INC.,
Petitioner,

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner.

PGR2020-00068
Patent 10,583,155 B1

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

PAULRAJ, *Administrative Patent Judge*.

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

I. INTRODUCTION

Eton Pharmaceuticals, Inc. (collectively, “Petitioner”) filed a Petition requesting post-grant review of claims 1–30 (the “challenged claims”) of U.S. Patent No. 10,583,155 (Ex. 1001, “the ’155 patent”). Paper 1 (“Pet.”). Exela Pharma Sciences, LLC (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). We have jurisdiction under 35 U.S.C. § 324.

To institute a post-grant review, we must determine whether the information presented in the petition “would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a). After considering the Petition and the Preliminary Response, we determine, for the reasons set forth below, that Petitioner has failed to demonstrate that it is “more likely than not” that any of the challenged claims are unpatentable based on the grounds presented. Therefore, we do not institute a post-grant review of those claims.

A. *Real Parties in Interest*

Petitioner identifies itself as the real party in interest. Pet. 3–4. Patent Owner identifies itself as the real party in interest. Paper 4, 2.

B. *Related Matters*

The ’155 patent is the subject of the following litigation matters: *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, Case No. 1:20-cv-00365-MN (D. Del., filed March 16, 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. 3–4; Paper 4, 2.

Petitioner filed a petition for post-grant review against a related patent, U.S. Patent No. 10,478,453 B1 (“the ’453 patent”), for which we previously denied institution. Pet. 4; PGR2020-00064, Paper 12.

Petitioner lists the following related patents and published applications: Appl. No. 16/248,460 (“the ’460 application,” which issued as the ’453 patent); Appl. No. 16/746,028; U.S. Appl. No. 16/773,563 (issued as U.S. Patent No. 10,653,719 B1); U.S. Appl. No. 16/850,726; U.S. Appl. No. 16/850,962; and U.S. Application No. 16/850,973. Pet. 4–5.

C. The ’155 Patent

The ’155 patent, titled “Stable, Highly Pure L-Cysteine Compositions for Injection and Methods of Use,” discloses stable L-cysteine compositions for injection. Ex. 1001, (54), (57). The ’155 patent issued from Application No. 16/665,702, which is a continuation of the ’460 application filed on January 15, 2019. *Id.*, (63).

L-cysteine is a “conditionally essential” sulfur-containing amino acid involved in growth and protein synthesis. *Id.* at 1:21–29. L-cysteine supplements may be administered to preterm infants who lack the natural ability to synthesize L-cysteine due to biochemical immaturity of the enzyme cystathionase. *Id.* at 1:29–37. Although L-cysteine compositions were known in the prior art, the ’155 patent states that these prior art compositions for infusion failed to address issues related to aluminum and cystine impurities, and thus were considered less safe for preterm infants, pediatric patients, and critically ill adults. *Id.* at 4:25–31.

According to the ’155 patent, “[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 4:31–36.

Moreover, the patent discloses 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.

Id. at 4:43–49.

The ’155 patent discloses that “known L-cysteine compositions contain up to 5000 ppb Aluminum.” *Id.* at 7:16–17. In contrast, the patent describes “compositions that provide a therapeutically effective amount of L-cysteine, while containing less than 250 ppb Aluminum.” *Id.* at 7:18–22. The patent further discloses that reduced aluminum compositions “permits 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 7:29–35.

The ’155 patent 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 25:4–9. 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 25:51–59.

Example 1 of the '155 patent describes a method of compounding an L-cysteine composition as follows:

40±1.0 kg of Water for Injection, USP (WFI) was added . . . A target 65 water temperature of NMT 60° C. was maintained throughout WFI addition using a heat exchanger. With continuous mixing at a speed of 126 rpm, Argon overlaying of the WFI began in the mixing bag and continued until the dissolved oxygen was NMT 1 ppm; then the mixing bag was allowed to cool to a temperature of NMT 30° C.

. . . L-Cysteine Hydrochloride, Monohydrate, USP (L-Cysteine) was added . . . The mixing continued for NLT 15 minutes or until complete dissolution was observed. . . . Argon overlaying continues until the dissolved 15 oxygen was NMT 1 ppm.

. . . [T]he solution's pH was adjusted to a target of 1.8 with concentrated Hydrochloric Acid, NF and/or 5.0 N Sodium Hydroxide, NF.

. . . [T]he solution was q.s.'d with the WFI to a final weight of 50.6 kg and allowed to mix for approximately 10 minutes. The final solution weight, solution temperature, solution pH, and dissolved oxygen was then measured and recorded. Following these steps, the mixing bag was fully inflated with Argon and capped, and the solution was transferred from the mixing bag to the solution holding bag.

Id. at 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 43–49. The aluminum levels are shown in Table 6, reproduced below. *Id.*

TABLE 6

Aluminum Levels			
6 Months			
Lot #	Release	25° C./60% RH	40° 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 49:54–50:22. The bulk solution was filled into Scott 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 increases 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 Claims

Petitioner challenges claims 1–30 of the '155 patent, of which claims 1, 27, and 28 are independent. Claim 1 is representative of the independent claims and recites:

1. A method of treating a subject having an adverse health condition that is responsive to L-cysteine administration, said method comprising:

parenterally administering to said subject a parenteral composition comprising a mixture of one or more amino acids, intravenous fluid, and a stable L-cysteine composition, wherein said stable L-cysteine composition contributes to said parenteral composition:

a therapeutically effective amount of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof;

per Liter of said stable L-cysteine composition, from about 1.0 mcg to about 250 mcg of Aluminum;

not more than about 2.0 wt % of cystine relative to L-cysteine; and,

not more than about 2.0 wt % of pyruvic acid relative to L-cysteine.

Ex. 1001, 56:34–50.

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–30 would have been unpatentable based on the following grounds. Pet. 7. Petitioner also offers the Declarations of Barrett Rabinow, Ph.D (Ex. 1003) and Harry “Warren” Johnson (Ex. 1022) in support of the Petition.

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–16, 18, 23, 24, 26–30	103	Sandoz Label, ¹ Hospira Label, ² knowledge of POSITA

¹ Sandoz, Inc., *L-CYSTEINE HYDROCHLORIDE*, DrugsDB.eu. (Revised June 2010) (Ex. 1005) (“Sandoz Label”) (characterized as archived on August 24, 2016 by Internet Archive organization’s “Wayback Machine,” see Ex. 1004).

² Hospira, Inc., *AMINOSYN*, DrugsDB.eu. (Revised October 2004) (Ex. 1009) (“Hospira Label”) (characterized as archived on August 31, 2018 by Internet Archive organization’s “Wayback Machine,” see Ex. 1010).

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
17, 19–22, 25	103	Sandoz Label, Hospira Label, Hospira Package Insert, ³ Federal Register Notice, ⁴ knowledge of POSITA

II. ANALYSIS⁵

A. *Level of Ordinary Skill in the Art*

Petitioner proposes that a person of ordinary skill in the art (“POSITA”) “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. 29 (citing Ex. 1003 ¶ 26). Petitioner adds that “[s]pecific experience with processes and techniques for minimizing impurities in and improving the stability of pharmaceutical drug products during manufacture and storage would have been a must.” *Id.* (citing Ex. 1003 ¶ 26).

Patent Owner contends Petitioner’s definition “misses the mark at least because it ignores the clinical nature of the ’155 patent’s claims.” Prelim. Resp. 21. Patent Owner contends Petitioner’s definition of the POSITA does not extend to the claimed clinical features, “or otherwise suggest that the alleged POSITA would, for example, have had knowledge or experience in preparing pharmaceutical admixtures in a clinical setting for

³ Hospira, Inc., 7.25% Cysteine Hydrochloride Injection, USP (0.5 g Cysteine), Package Insert (1986) (Ex. 1092) (“Hospira Package Insert”).

⁴ *Determination that Cysteine Hydrochloride Injection, USP, 7.25%, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness*, 75 Fed. Reg. 31,790 (June 4, 2010) (Ex. 1091) (“Federal Register Notice”).

⁵ Patent Owner does not challenge the eligibility of the ’155 patent for post grant review. We assume *arguendo* that the ’155 patent is eligible for post-grant review for purposes of our analysis herein.

administration to patients, in interpreting pharmaceutical drug labels, or consulting with someone who routinely does these things.” *Id.* Patent Owner, however, does not propose its own alternative definition of a POSITA. *See id.* at 21–22.

For purposes of our analysis in this Decision, we hereby adopt Petitioner’s definition of a POSITA. Although we recognize that the claimed method is directed to treating a subject having an adverse health condition that is responsive to L-cysteine administration, the focus of the invention described in the ’155 patent is on the stable L-cysteine composition and the method of formulating such a composition rather than any particular clinical techniques associated with the administration of the composition. 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) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

Petitioner proposes constructions for two claim terms: “about” and “stable.” *See* Pet. 29–30. Patent Owner contends that there is no need to resolve any claim construction terms. Prelim Resp. 20. 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)).

C. Grounds 1 and 2: Obviousness under 35 U.S.C. § 103

Petitioner contends that claims 1–16, 18, 23, 24, and 26–30 are obvious over the combination of the Sandoz Label, the Hospira Label, and the knowledge of a POSITA. Pet. 45–69. Petitioner further contends that claims 17, 19–22, and 25 are obvious over the combination of the Sandoz Label, the Hospira Label, the Hospira Package Insert, the Federal Register, and the knowledge of a POSITA. For these grounds, we provide an overview of the prior art, followed by our analysis of the merits.

1. Overview of the Prior Art

a) Sandoz Label (Ex. 1005)

The “Sandoz Label” includes product information for L-CYSTEINE HYDROCHLORIDE (cysteine hydrochloride injection, solution) manufactured by Sandoz, Inc. Ex. 1005. The reference bears a revision date of “06/2010.” *Id.* at 11. Petitioner contends “[t]he Sandoz Label was available by no later than 2016.” Pet. 31. Patent Owner does not challenge the reference’s status as a printed publication. *See generally* Prelim. Resp.

The Sandoz Label discloses that “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. The Sandoz Label discloses that:

Each 0.5 gram of L-Cysteine Hydrochloride Monohydrate should be combined aseptically with 12.5 grams Crystalline Amino Acid Injection, such as that present in 250 mL of 5% Crystalline Amino Acid Injection. The admixture is then diluted with 250 mL of dextrose 50% or such lesser volume as indicated.

Equal volumes of 5% Crystalline Amino Acid Injection and dextrose 50% produce a final solution which contains Crystalline Amino Acid 2.5% Injection in dextrose 25%, which is suitable for administration by central venous infusion. Administration of the final admixture should begin within one hour of mixing. Otherwise, the admixture should be refrigerated immediately and used within 24 hours of the time of mixing.

Id. at 3.

The Sandoz Label further describes product packaging disclosing that the product “contains no more than 5,000 mcg/L of aluminum.” *Id.* at 5.

The Sandoz Label includes the following warning:

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

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. at 2.

b) Hospira Label (Ex. 1009)

The “Hospira Label” includes product information for AMINOSYN (isoleucine, leucine, lysine acetate, methionine, phenylalanine, threonine, tryptophan, valine, alanine, arginine, histidine, proline, serine, tyrosine and glycine injection, solution) manufactured by Hospira, Inc. Ex. 1009. The reference bears a revision date of “October 2004.” *Id.* at 9. Petitioner contends the Hospira Label “was available no later than 2013.” Pet. 34.

Patent Owner does not challenge the reference's status as a printed publication. *See generally* Prelim. Resp.

The Hospira Label discloses a crystalline amino acid solution containing the following amino acids:

Essential Amino Acid	(mg/100 mL)
Isoleucine	360
Leucine	470
Lysine (excluding acetate)	360
Methionine	200
Phenylalanine	220
Threonine	260
Tryptophan	80
Valine	400

Ex. 1009, 1–2.

c) Hospira 7.25% Cysteine HCl Package Insert (Ex. 1092)⁶

The “Hospira Package Insert” includes product information for 7.25% Cysteine Hydrochloride Injection, USP (0.5 g Cysteine) distributed by KabiVitrum, Inc. Ex. 1092. The reference bears a date of “March 1986.” *Id.* at 9. Petitioner contends the Hospira 7.25% Package Insert “was available no later than July 2017.” Pet. 35. Patent Owner does not challenge the reference's status as a printed publication. *See generally* Prelim. Resp.

⁶ Petitioner submits an alternative version of the Hospira 7.25% Package Insert as Ex. 1093.

The Hospira Package Insert discloses that “7.25% Cysteine Hydrochloride Injection, USP (0.725 as the monohydrate), is a sterile, nonpyrogenic solution. Each 10 ml provides 0.5 g cysteine and 4.13 mEq of chloride in Water for Injection, USP. The pH range is 1.0 to 2.5.” Ex. 1092, 9. The Hospira Package Insert discloses that the product “is indicated for use as an additive to amino acids solutions to meet nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN.” *Id.* at 10.

d) The Federal Register Notice - 75 Fed. Reg. 31,790 (Exhibit 1091)

The Federal Register Notice was published June 4, 2010 and discloses the Food and Drug Administration’s (FDA) determination that “that Cysteine Hydrochloride Injection, USP, 7.25% (Cysteine HCl), was not withdrawn from sale for reasons of safety or effectiveness.” Ex. 1091, 1. The Federal Register Notice further discloses that:

Cysteine HCl is the subject of NDA 19–523, most recently held by Hospira, Inc. (Hospira), and initially approved on October 22, 1986. Cysteine HCl is indicated for use as an additive to amino acid solutions to meet the nutritional requirements of newborn infants requiring total parenteral nutrition (TPN) and of adult and pediatric patients with severe liver disease who may have impaired enzymatic processes and require TPN. It can also be added to amino acid solutions to provide a more complete profile of amino acids for protein synthesis.

Id. at 2.

2. *Analysis of Ground 1 (Obviousness based on the Sandoz Label and the Hospira Label)*

Petitioner contends that claims 1–16, 18, 23, 24, and 26–30 are obvious over the combination of the Sandoz Label, the Hospira Label, and the knowledge of a POSITA. Pet. 45–69. 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 as it is dispositive to our conclusion.

Petitioner contends that the preamble of claim 1, reciting “a method of treating a subject having an adverse health condition that is responsive to L-cysteine administration” is disclosed by the Sandoz Label. *Id.* at 46–47 (citing Ex. 1003 ¶ 105; Ex. 1005, 2, 7).

With respect to the step of “parenterally administering . . . a parenteral composition,” Petitioner relies on the Sandoz Label’s dosing instructions to combine the L-Cysteine composition with crystalline amino acids injection and dilute the admixture with dextrose solution, i.e., an intravenous fluid. *Id.* at 47–48 (citing Ex. 1003 ¶ 106, Ex. 1005, 3, 9).

With respect to the limitation of a “stable L-cysteine composition,” Petitioner contends that a POSITA would have been motivated to “optimize the product disclosed by the Sandoz Label to be ‘stable’ as that term is defined in the ’155 patent.” *Id.* at 48 (citing Ex. 1003 ¶ 107). Specifically, Petitioner contends that the “POSITA would have been motivated to remove oxygen during manufacture and storage of the L-Cysteine composition to prevent [] oxidative degradation.” *Id.*

Petitioner further contends the components of the “stable L-cysteine composition” would have been obvious to a POSITA applying the Sandoz

Label and the Hospira Label. *Id.* at 49–52. With respect to “a therapeutically effective amount of L-cysteine,” Petitioner contends “the combination of the Sandoz and Hospira Labels teaches that the Sandoz Label product contributes 142 mg/kg/day of L-Cysteine.” *Id.* at 49 (citing Ex. 1003 ¶¶ 109–110).

With respect to the recited range of “from about 1.0 mcg to about 250 mcg of Aluminum” per Liter of said stable L-cysteine composition, Petitioner contends that the Sandoz Label teaches a range of 0 to 5,000 mcg/L of aluminum by disclosing that the Sandoz L-Cysteine Product “[c]ontains no more than 5,000 mcg/L of aluminum,” thereby encompassing the claimed range.⁷ *Id.* at 49–50 (citing Ex. 1003 ¶¶ 34, 111; Ex. 1005, 5, 10; Ex. 1004, 8, 13). Petitioner further contends that a POSITA would have optimized the Sandoz product to meet the regulatory and market pressures to substantially reduce aluminum. *Id.* at 50 (citing Ex. 1003 ¶¶ 112–113). Petitioner further contends that the aluminum levels in the Sandoz product disclosed by the Sandoz Label “were typically less than 100 ppb shortly after manufacture and increased to several hundred ppb[] during storage.” *Id.* at 50–51 (citing Ex. 1003 ¶ 112; Ex. 1022 ¶ 15). Petitioner contends that “by optimizing the product disclosed by the Sandoz Label, its method of manufacture, and its container to substantially reduce and eliminate aluminum, the POSITA would have reasonably expected to achieve aluminum levels within the claimed range during manufacture and storage, including for 3–24 months post-manufacture.” *Id.* at 51 (citing Ex. 1003 ¶ 113).

⁷ Petitioner contends mcg/L is interchangeable with ppb. Pet. 50.

Additionally, with respect to the claimed aluminum range, Petitioner contends that in 2004 the FDA issued a rule governing aluminum content in compositions used to prepare parenteral nutrition solutions (“PNS”). Pet. 36 (citing Ex. 1003 ¶¶ 31-32; Ex. 1006, 1; Ex. 1007, 1–2). The 2004 Rule required PNS compositions to include a standardized warning describing the presence of aluminum in the products, aluminum’s risk to infants, and a recommended maximum daily aluminum dose of 4 to 5 mcg/kg/day. *Id.* at 37 (citing Ex. 1003 ¶ 32; Ex. 1006, 7; Ex. 1007, 1–2). Petitioner contends that, given the ongoing concerns about aluminum toxicity, the FDA imposed stricter aluminum limits on parenteral drug products in August 2017. *Id.* at 28 (citing Ex. 1053). For example, Petitioner contends that FDA instructed Patent Owner that “the aluminum dose delivered by your drug product, L-Cysteine Hydrochloride Injection, 0.5g/10mL should be limited to ≤ 0.6 mcg/kg/day. To comply with this dose level, a limit of ≤ 145 mcg/L [*i.e.*, ≤ 145 ppb] aluminum is needed.” *Id.* at 38 (citing Ex. 1003 ¶ 36; Ex. 1019, 1).

Petitioner contends that a POSITA 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) “glass containers, which were known to leach aluminum into the drug product.” *Id.* at 39 (citing Ex. 1003 ¶¶ 56–60). Petitioner further contends that a POSITA would have also been motivated to prevent the “known oxidative degradation of oxygen sensitive drugs such as L-Cysteine.” *Id.* at 41 (citing Ex. 1003 ¶¶ 50–53). Petitioner contends that “oxidative degradation can be prevented by adding antioxidants or by removing dissolved oxygen and/or replacing headspace air with an inert gas, such as nitrogen or argon, during manufacture and storage.” *Id.* (citing Ex. 1003 ¶ 51). For example, Petitioner contends that the Sandoz Label

describes replacing headspace air with nitrogen. *Id.* (citing 1003 ¶ 33; Ex. 1005, 1, 6; Ex. 1004, 5, 11). Petitioner contends that a POSITA would have also used an oxygen impermeable container, such as silicon dioxide coated glass containers which did not leach aluminum. *Id.* at 41–42 (citing Ex. 1003 ¶ 59; Ex. 1014, 8).

With respect to the recited ranges of “not more than about 2.0 wt % of cystine,” and “not more than about 2.0 wt % of pyruvic acid,” both relative to L-cysteine, Petitioner acknowledges that the Sandoz Label does not expressly disclose the amount of cystine or pyruvic acid in the composition. *Id.* at 51–52. Petitioner, however, contends that a POSITA would have taken art-recognized steps to prevent the oxidative degradation of L-Cysteine, such as replacing the headspace air with nitrogen. *Id.* (Ex. 1003 ¶ 116; Ex. 1005, 1, 6). Petitioner contends that a POSITA would have known that preventing oxidative degradation of L-Cysteine would avoid its oxidative degradation products, i.e., cystine, which further degrades into pyruvic acid. *Id.* (citing Ex. 1003 ¶ 114–119).

In its Preliminary Response, Patent Owner contends that the Sandoz Label and the Hospira Labels do not disclose the limitations of claim 1. Prelim. Resp. 31. In particular, Patent Owner contends that Petitioner “expressly admits that the Sandoz Label does not disclose the cystine and pyruvic acid limitations” of claim 1. *Id.* Patent Owner further contends that Petitioner “implicitly admits that the Sandoz Label does not disclose the ‘stable’ limitation of each claim by asserting that the Sandoz Label composition would need to be ‘optimize[d] to be stable.’” *Id.* at 31–32.

Additionally, with respect to the recited amount of aluminum, Patent Owner contends that the Sandoz Label discloses a maximum amount of aluminum and not a range of 0–5,000 mcg/L. *Id.* at 34–35. Patent Owner

contends that the amount of 5,000 mcg/L was derived from FDA regulations requiring a disclosure of the maximum amount of aluminum at product expiry. *Id.* (citing Ex. 1007, 1). Patent Owner contends 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.” *Id.* at 35 (citing Ex. 2001 ¶¶ 20–24).

Patent Owner further contends that Petitioner’s “routine optimization” analysis is based on hindsight reasoning for several reasons. *See id.* at 38–59. First, Patent Owner contends that Petitioner does not establish that optimizing “cystine levels [was] relevant to solving the aluminum problem.” *Id.* at 42. Second, Patent Owner contends that Petitioner’s routine optimization “does not explain **why** a POSITA purportedly optimizing the Sandoz Label composition to reduce aluminum would have arrived at the specific claimed amounts of cystine,” and thus lacks evidentiary support. *Id.* at 48–49. Patent Owner contends that Petitioner improperly relies “on the patent’s specification to buttress the assumption that the claimed amounts are the result of routine optimization.” *Id.* at 49. Third, Patent Owner contends that the “stable” limitation requires that the claimed amounts of each component remain stable from the time of manufacturing to the time when “the L-cysteine composition is admixed and administered in a clinical setting, which could be up to two years after manufacture.” *Id.* at 51. Fourth, Patent Owner contends that Petitioner’s “‘routine optimization’ argument . . . fails to account for the complexity of the claimed composition,” which solved an unmet need despite the unpredictable nature of the art. *Id.* at 52–53 (citing Ex. 1002, 378–379, 420; Ex. 1006, 1).

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 is obvious over the combination of the Sandoz Label, the Hospira Label, and the knowledge of a POSITA. In particular, the evidence of record does not show that Petitioner will likely be able to meet its burden of establishing that a POSITA 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 1.0 mcg to about 250 mcg of Aluminum per Liter of said stable L-cysteine composition. 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” reasonably suggests 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/ml (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. 34–38.

As noted above, Petitioner also relies on the FDA regulations and other communications directing a lower amount of aluminum for L-cysteine compositions. Although we agree with Petitioner that this evidence supports the position that there would have been a motivation to avoid aluminum toxicity, the presence of such motivation alone is insufficient 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 an aluminum threshold goal does

not say anything about *how* to achieve the goal. Prelim. Resp. 58. 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. *Id.* at 58–59 (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 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.*

Thus, 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 ’155 patent. With respect to claims 2–16, 18, 23, 24, 26–30 that are also challenged under this ground, Petitioner relies on the same underlying arguments as presented for claim 1 that we find unpersuasive.

3. *Analysis of Ground 2 (Obviousness based on the Sandoz Label, the Hospira Label, the Hospira Package Insert, and the Federal Register Notice)*

Petitioner contends that claims 17, 19–22, and 25 are obvious over the combination of the Sandoz Label and the Hospira Label, in further view of the Hospira Package Insert (or the Federal Register Notice) and the knowledge of a POSITA. Pet. 69–72. The addition of the Hospira Package Insert and the Federal Register Notice as part of this ground 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 additional references do not rectify the underlying shortcoming of the Sandoz Label, we conclude that the evidence presented in the Petition does not support the contention that the claims 17, 19–22, and 25 are 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 1–30 of the ’155 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

In consideration of the foregoing, it is hereby:

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

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