

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Nexus Pharmaceuticals, LLC,
Petitioner

v.

Exela Pharma Sciences, LLC,
Patent Owner

Case No.: Unassigned
Patent No. 11,642,370

**PETITION FOR POST GRANT REVIEW OF
U.S. PATENT NO. 11,642,370
UNDER 35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.200 *ET SEQ.***

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PETITIONER’S EXHIBIT LIST

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Exhibit 1001	U.S. Patent No. 11,642,370 (“the ’370 patent”)
Exhibit 1002	’370 Patent File History
Exhibit 1003	Declaration of Pasquale N. Confalone Ph.D.
Exhibit 1004	Affidavit of Christopher Butler
Exhibit 1005	Sandoz Label Way Back Machine Screenshots of https://web.archive.org/web/20170403170533/http://drugsdb.eu/drug.php?d=L-cysteine%20Hydrochloride&m=Sandoz%20Inc&id=083366d6-0437-4ee0-90d4-440a5b5d03b5.xml and https://web.archive.org/web/20160824090050/http://drugsdb.eu/drug.php?d=L-cysteine%20Hydrochloride&m=Sandoz%20Inc&id=083366d6-0437-4ee0-90d4-440a5b5d03b5.xml
Exhibit 1006	A. Hernandez-Sanchez et al., <i>Aluminum in Parenteral Nutrition: A Systematic Review</i> , 67 Eur. J. Clinical Nutrition 230 (2013)
Exhibit 1007	<i>Exela Pharma Sciences, LLC v. Eton Pharmaceuticals, Inc.</i> , 620 F.Supp.3d 108 (D. Del. 2022)
Exhibit 1008	D. Bohrer et al., <i>Influence of the Glass Packing on the Contamination of Pharmaceutical Products by Aluminum. Part II: Amino Acids for Parenteral Nutrition</i> , 15 J. Trace Elements Med. & Biology 103 (2001) (“Bohrer II”)
Exhibit 1009	P. Nasa, <i>A Review on Pharmaceutical Packaging Material</i> , World J. of Pharm. Res., vol. 3, Issue 5, 344-368 (2015)
Exhibit 1010	Reserved
Exhibit 1011	D. Bohrer et al., <i>Ion-exchange and potentiometric characterization of Al-cystine and Al-cysteine complexes</i> , J. Biol Inorg. Chem. 11, 991-991 (2006)

<u>Exhibit No.</u>	<u>Description</u>
Exhibit 1012	D. Bohrer et al., <i>Influence of the Glass Packing on the Contamination of Pharmaceutical Products by Aluminum. Part III: Interaction Container-Chemicals During the Heating for Sterilisation</i> , 17 J. Trace Elements med. & Biology 107 (2003) (“Bohrer III”)
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Exhibit 1015	United States Patent No. 10,583,155 (“the ’155 patent”)
Exhibit 1016	United States Patent No. 10,905,713 (“the ’713 patent”)
Exhibit 1017	Reserved
Exhibit 1018	United States Patent No. 10,912,795 (“the ’795 patent”)
Exhibit 1019	United States Patent No. 10,478,453 (“the ’453 patent”)
Exhibit 1020	Loyd V. Allen, <i>L-Cysteine Hydrochloride 50 mg/mL Injection</i> , 36 U.S. Pharmacist 41 (Sept. 20, 2011)
Exhibit 1021	Essential of Pharmaceutical Chemistry (Donald Cairns ed., 4 th ed. 2012).
Exhibit 1022	United States Patent No. 10,933,089 (“the ’089 patent”)
Exhibit 1023	’089 patent file history
Exhibit 1024	’453 patent file history
Exhibit 1025	Drug Facts and Comparison (2015)
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Exhibit 1034	Farideh Jalilehvand et al., <i>Lead(II) Complex Formation with LCysteine in Aqueous Solution</i> , 54 Inorg. Chem. 2160 (2015)
Exhibits 1035-1053	Reserved
Exhibit 1054	<i>Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition</i> , 63 Fed. Reg. 176 (Jan. 5, 1998) (codified at 21C.F.R. 201)
Exhibit 1055	<i>Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition</i> , 65 Fed. Reg. 4103 (Jan. 26, 2000) (codified at 21 C.F.R. 201)
Exhibits 1056-1060	Reserved
Exhibit 1061	Len Okabe, <i>Studies on the Solubility of Cystine Under Various Conditions, and On A New Method of Cystine Preparation</i> , 8 Biochem J. 441 (1927)
Exhibits 1062-1075	Reserved

Petitioner Nexus Pharmaceuticals, LLC (“Petitioner” or “Nexus”) requests post grant review of claims 1-30 (“the challenged claims”) of U.S. Patent No. 11,642,370 (“the ‘370 patent”) (Ex. 1001) pursuant to 35 U.S.C. §§ 321-329 and 37 C.F.R. § 42.200.

For the reasons explained below, Nexus is likely to prevail in its assertion that claims 1-30 of the ‘370 patent are not enabled to their full scope pursuant to 35 U.S.C. § 112(a) or are obvious pursuant to 35 U.S.C. §103. Nexus requests that the Board institute PGR and cancel each of claims 1-30 of the ‘370 patent.

I. INTRODUCTION

All the claims of the ‘370 patent recite solutions of L-cysteine that contain “no more than” a claimed amount of aluminum and “no more than” a claimed amount of oxygen, which it is further claimed yields a stable formulation free of visible particulate matter after 12, 18, or 24 months of storage in a vial. The patent, however, does not justify the scope of the varying amounts of aluminum and oxygen that are claimed. These are supposedly critical limitations, but the specification gives a limited example (Example 6) while the claims cover broad ranges. The Patent Owner cannot argue in response that a person of ordinary skill in the art could have run tests that comprise routine and not undue experimentation. That is because the Patent Owner defeated exactly that contention by arguing the opposite, and succeeded in persuading both the Patent

Office and district court from finding the asserted claims obvious on the basis of routine optimization.

In particular, in related proceedings, the Patent Owner showed that a person of ordinary skill in the art would not know which amounts of aluminum and oxygen, in combination with other variables, would result in a formulation that would meet the claimed stability requirements. The '370 patent claims are very similar to claims in several related patents for the litigated family. See *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, 620 F.Supp.3d 108 (D. Del. 2022) (Patent Owner asserted U.S. Patent Nos. 10,583,155 (“the '155 patent”), 10,905,713 (“the '713 patent”), and 10,912,795 (“the '795 patent”); PGR2020-00064 (challenged U.S. Patent No. 10,478,453 (“the '453 patent”)) ; PGR 2020-00068 (challenged the '155 patent). All these patents are part of a family of patents issued from a string of continuation applications that ultimately claim priority to the same patent application that issued as the '453 patent.

The district court decision is important because it rejected obviousness only by accepting the Patent Owner’s argument that aluminum and oxygen levels, along with other variables, were critical and that a person of ordinary skill in the art could not figure them out on their own without undue experimentation. The district court found that the related '155, '713, and '795 patents were not obvious, and similarly the Patent Trial and Appeal Board (“PTAB”) did not institute post

grant review of the '155 nor of the '453. PGR2020-00064, Paper 12, PGR2020-00068, Paper 11. None of these decisions addressed Section 112 challenges. The written description and enablement grounds presented in this petition were not previously addressed by the PTAB nor by the district court. Thus, the Petition presents the following core argument: because the Patent Owner defeated obviousness by asserting aluminum and oxygen criticality, but the patent specification does not show what ranges of these components work or do not work (especially when combined with other variables), the patent claims are not enabled or described to their full scope.

When discussing obviousness, the district court in the related litigation found L-cysteine formulations to be “complex and unpredictable” and that “varying the amount of aluminum in a cysteine formulation can impact other aspects of the formulation, including the appearance of precipitates” Ex. 1007 at 28. In the PGRs challenging the related '453 and '155 patents—also on obviousness grounds—the Patent Owner argued that the patent claims covering L-cysteine solutions were not obvious in part because “L-cysteine parenteral solutions are sensitive to an array of multivariate and interrelated interactions.” PGR2020-00064, Paper 6, Prelim. Resp. at 60; PGR2020-00068, Paper 6, Prelim. Resp. at 55. In sum, these decisions rely upon and accept the Patent Owner’s view that the complexity and unpredictability of L-cysteine solutions makes all claims in

the patent family not obvious. As discussed below, the Patent Owner is estopped from arguing anything differently now. So if a person of ordinary skill in the art could not have figured out what formulations worked and did not work without undue experimentation, the '370 patent specification does not fill in the blanks, and fails to provide guidance that substantiates the full scope of the claims. The specification discloses one example (Example 6), but the claims are broader than that and face the same issues that the Patent Owner already argued a person of ordinary skill in the art could not figure out and must now live with the consequences of that argument: the claims are not enabled and lack written description.

The prior decisions all rested on the premise that there is a precise and delicate balance between aluminum, oxygen, and other variables that is required to make a stable formulation. The scope of that assertion, however, is not demonstrated in the patent specification, shared by the '370 patent and all others in the family. Yet the claims are broader than anything disclosed in the patent, and a person of ordinary skill in the art is left with a guessing game of what might work or what might not work—even though entire ranges are claimed. In fact, even though the claims of the '370 patent cover the combination of claimed ranges of L-cysteine, aluminum, oxygen content, and pH, to create a stable formulation, the specification discloses no examples of such a formulation that is also stable for 12

months—the minimum time period in all '370 patent claims. Worse, the '370 patent claims relate to broad ranges of the supposedly critical values of aluminum (0-150 ppb in the narrowest claims) and oxygen (0-5%), but no formulation in the specification comes close to justifying these ranges (aluminum 2.9-5.6ppb and oxygen .19%-1.2%). Ex. 1001, 49:53-50:55, Examples 6 and 7.

Multiple decisions—both at the district court and the Patent Office—accepted the Patent Owner's assertion that testing aluminum and oxygen levels, among other variables, is an unpredictable and complex exercise, involving interrelated variables that are not explained or tested in the patent specification. Thus, especially given those findings but even based on a fresh review, a person of ordinary skill in the art would not be able to practice the claimed invention to its full scope without conducting undue experimentation: extensive trial-and-error experiments to determine which combination of variables meets the recited limitations. In other words, the '370 patent is only an invitation to test the same variables that the prior art outlined to test, but the district court and Patent Office found were insufficient to render obvious even a part of the claims. The specification simply does not substantiate the full scope of the claims. Accordingly, the claims of the '370 patent are not enabled to their full scope and lack written description.

Finally, if for some reason Patent Owner is now allowed to argue that the claims are enabled and described because a person of ordinary skill in the art could test workable solutions, then the same analysis would apply to the prior art. Therefore, Petitioner includes an alternative invalidity ground of obviousness similar to what was presented in the district court litigation and the earlier PGRs. But Section 112 defenses were not presented in those earlier proceedings. Therefore, this obviousness submission is made in the alternative to show that Patent Owner cannot have it both ways: either the claims of the '370 patent are not enabled because a person of ordinary skill in the art would have to do undue experimentation to figure out what worked and what did not work within the claimed range, or else if a person of ordinary skill in the art would find such testing routine and not undue, then the asserted claim would have been obvious.

The Board, therefore, should institute this proceeding and cancel the challenged claims as non-enabled, lacking written description, or obvious.

II. NOTICES, STATEMENTS AND PAYMENT OF FEES

A. Real Party In Interest Under 37 C.F.R. § 42.8(b)(1)

Nexus Pharmaceuticals, LLC is the real party in interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any related matters involving the '370 patent.

However, Petitioner is aware of 15 other issued patents and 1 pending patent applications that are in the same family and which claim priority to the same

application as the '370 patent through a chain of continuation applications, to Application No. 16/248,460 (“the '460 application”) now Pat. No. 10,478,453 (“the '453 patent”). The issued patents and pending application in the family of the '370 patent are as follows:

U.S. Patent/U.S. Patent App. No.	Filing Date
Pat. No. 10,478,453	Jan 15, 2019
Pat. No. 10,583,155	Oct. 28, 2019
Pat. No. 10,478,453	Jan. 15, 2019
Pat. No. 10,933,089	Jan. 17, 2020
Pat. No. 10,653,719	Jan. 27, 2020
Pat. No. 10,905,713	Jan. 27, 2020
Pat. No. 10,912,795	April 16, 2020
Pat. No. 10,905,714	April 16, 2020
Pat. No. 10,918,662	April 16, 2020
Pat. No. 11,510,941	Feb. 1, 2021
Pat. No. 11,510,942	March 1, 2021
Pat. No. 11,672,824	Sep. 22, 2022
Pat. No. 11,684,636	Sep. 22, 2022
Pat. No. 11,648,262	Dec. 16, 2022

Pat. No. 11,826,383	June 9, 2023
App. No. 18/520,172	Nov. 27, 2023

The related '453 and '155 patents were the subjects of petitions for Post Grant Review filed by Eton Pharmaceuticals, Inc. ("Eton"), again asserting only obviousness invalidity grounds, PGR2020-00064 and PGR2020-00068, and not Section 112 grounds. The Patent Trial and Appeal Board did not institute review of either patent.

The related '155, '713, and '795 patents were asserted in the following civil actions:

- *Exela Pharma Sciences, LLC v. Eton Pharms., Inc.*, Case No. 1:20-cv-00365-MN (D. Del. Filed May 14, 2020), decision issued at 620 F.Supp.3d 108 (D. Del. 2022), appeal pending;
- *Exela Pharma Sciences, LLC v. Sandoz Inc.*, Case No. 1:20-cv-00645-MN (D. Del. Filed May 14, 2020), dismissed August 7, 2020; and
- *Exela Pharma Sciences, LLC v. Sandoz Inc.*, Case No. 1:20-cv-01393 (D. Colo. filed May 15, 2020), dismissed August 7, 2020.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Nexus designates lead and back-up counsel as noted below. Powers of attorney pursuant to 37 C.F.R. § 42.10(b) accompany this Petition.

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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

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E. Grounds for Standing Under 37 C.F.R. § 42.204(a)

Pursuant to 37 C.F.R. § 42.204(a), Nexus certifies that the '370 patent is available for post grant review, and that Petitioner is not barred or estopped from requesting post grant review based on the grounds herein.

The '370 patent is available for post grant review pursuant to the America Invents Act ("AIA"), Pub. L. No. 112-29, § 3(n)(1), 125 Stat. 284, 293 (2011), because the earliest possible filing date that any of the challenged claims could possibly claim the benefit of is the January 15, 2019 filing dated of Application No. 16/248,460, now issued as U.S. Patent No. 10,478,453. *See* Ex. 1001, Related U.S. Application Data. Thus, as required by the AIA, at least one claim has an effective filing date on or after March 16, 2013.

F. Fees Under 37 C.F.R. § 42.203

The undersigned authorizes the Office to charge the fee set forth in 37 C.F.R. § 42.15(b) for this Petition to Deposit Account No. 012300. The undersigned further authorizes payment for any additional fees that may be due in connection with this Petition to be charged to the above-referenced deposit account.

III. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.204(b)

Nexus requests cancellation of the challenged claims as unpatentable under 35 U.S.C. § 112 and § 103. It is more likely than not that claims 1-30 are unpatentable in view of the following unpatentability grounds and prior art references:

Grounds	Claims	Statutory Basis	Prior Art References
1.	1-30	35 U.S.C. § 112 Lack of Enablement	
2.	1-30	35 U.S.C. § 112 Lack of Written Description	
3.	1-30	35 U.S.C. § 103 Obviousness	Sandoz label (Ex. 1005) and POSA's knowledge

IV. NEXUS'S GROUNDS OF UNPATENTABILITY ARE DISTINCT FROM THOSE PRESENTED BY ETON

This Petition does not duplicate the Eton PGRs (PGR2020-00064 and PGR2020-00068) which challenged the validity of related '453 and '155 patents, respectively, on non-Section 112 grounds. In fact, if anything the Petition accepts and relies upon those proceedings to substantiate Section 112 invalidity. While the

invalidity grounds are distinct, the related '453 (Ex. 1019), '155 (Ex. 1015) and '370 (Ex. 1001) patents claim very similar subject matter. All three patents claim stable L-cysteine solutions with a limited amount of precipitates¹ and covering varying levels of aluminum. The '370 and '453 patents also cover varying levels of oxygen.

Claim Limitation	'370 patent	'453 patent	'155 patent
Limited precipitates	“no visible particulate matter”	“L-cysteine in an amount from about 0.001wt% to about 2.0 wt% relative to L-cysteine”	“not more than about 2.0wt% of cystine relative to L-cysteine” ²
Aluminum content	“not more than 250 ppb”	“from about 1.0 [mcg/L] ³ to about 25[mcg/L]	“1 [ppb] to about 250 ppb”

¹ The '370 patent claims require the absence of visible particulate matter while the '453 and '155 patents limit the amount of cystine in the solution. *See, e.g.*, Ex.1019 at 59:10-11 and Ex. 1015 at 58:47-48. Cystine is the less soluble product of L-cysteine's oxidation which forms precipitates. Ex. 1003, ¶ 32; Ex. 1007 at 20, 29.

² Cystine or L-cystine are impurities associated with cysteine or L-cysteine formulations.

³ Micrograms per liter (“mcg/L”) is equivalent to parts per billion (“ppb”).

Claim Limitation	'370 patent	'453 patent	'155 patent
Oxygen content in storage vial	“total oxygen with the sealed vial is no more than about 5%”	“headspace oxygen . . . from about 0.5% v/v to 4/0% v/v)” and “dissolved oxygen from about 0.1 [ppm] to about 5 ppm”	

Eton challenged the validity of the related patents only on the basis of prior art, namely the Sandoz label (Ex. 1005), alone or in combination with the Hospira label, in view of a POSA’s knowledge. *See* PGR2020-00064, Paper 1 at 6; PGR2020-00068, Paper 1 at 7. The obviousness defense presented during the related district court litigation relied on the same prior art to argue obviousness of the ’155 patent.⁴

This Petition includes new grounds of unpatentability, namely non-enablement pursuant to § 112 (Ground 1) and lack of written description (Ground 2), which are not “the same or substantially the same” as the Eton grounds which were solely based on prior art pursuant to §§ 102 and 103. 35 U.S.C. § 325(d).

⁴ The district court litigation also addressed two other patents related to the ’370 patent: the ’713 and ’795 patents. The district court concluded that its findings regarding the obviousness inquiry applied to all three patents, in particular in regard to the “aluminum-over-time and cystine-over-time claim limitations.” Ex. 1007 at 31.

In addition, the non-enablement and written description grounds presented here was not previously considered and indeed are supported by arguments and findings from the earlier proceedings. For example, the Patent Owner during the earlier PGR proceedings and during the district court litigation argued that the recited compositions were not obvious because of complex interactions between components and the unpredictability of the formulation properties. The district court findings and Patent Owner's arguments regarding the complexity and unpredictability of the recited L-cysteine solutions support the non-enablement grounds presented here.

Accordingly, the Board has not previously considered non-enablement and written description grounds presented here, and Petitioner respectfully suggests that review should be instituted. In the alternative, the Board has also not considered the tension between Section 112 and obviousness, so if the '370 patent claims are found to be enabled, then the challenged claims would have been obvious.

V. OVERVIEW OF THE '370 PATENT AND PROSECUTION HISTORY

A. The '370 Patent Specification

The '370 patent is generally directed to stable L-cysteine compositions for injection as well as "compositions for a total parenteral nutrition regimen and methods for their use." Ex. 1001 at Abstract. L-cysteine is an amino acid that

performs “a variety of metabolic functions” in humans. Ex. 1001 at 1:32-33. The ’370 patent states that known formulations containing L-cysteine have impurity profiles that “make the product less safe to be used by patients, in particular, preterm and term infants . . . as well as critically ill adults.” *Id.* at 3:35-38.

Specifically, one issue the patent claims cover is a broad range of aluminum levels. But according to the patent specification, prior art L-cysteine formulations allegedly “fail to address the issues related to the amounts of Aluminum and cystine, among other impurities, that can be routinely present and co-administered with L-cysteine.” *Id.* at 3:38-40. That teaching suggests removing aluminum altogether, because aluminum can be toxic, but then there is no teaching that zero-aluminum formulations would work and to the contrary requires at least some aluminum. The ’370 patent asserts that the cystine precipitate “may have been exacerbated by reduction in Aluminum since Aluminum in solution may have a stabilizing effect. Consequently, removing Aluminum may have the unintended consequence of increased precipitation and product failure in the presence of even small amount of oxygen in the container.” *Id.* at 5:20-25. This stabilizing effect was characterized as “unexpected.” *Id.* at 5:25. The specification does not test or describe ranges of combinations that demonstrate the claimed stability across the claimed scope, which has broad ranges for multiple components—including for aluminum—far beyond tests in the specification.

Similarly, another supposed issue is oxygen levels. The '370 patent specification asserts that “[i]n the presence of oxygen, two L-Cysteine residues will form a disulfide covalent bond forming L-Cystine” which has a lower solubility than L-cysteine so tends to precipitate out of solution. Ex. 1001, 57:17-21. Accordingly, a POSA would have recognized based on the prior art and before the '370 patent was filed that the “particulate matter” recited in the claims would include insoluble cystine formed by oxidative degradation of L-cysteine. Ex. 1003, ¶¶ 31-32. Again, this suggests removing oxygen altogether, but instead the examples in the patent all require—and even add—oxygen to the formulation. Furthermore, the specification does not test or describe ranges or combinations that demonstrate the claimed stability across the claimed scope, which has broad ranges for oxygen levels, far beyond what the specification tests.

The '370 patent specification also asserts that the problems of “safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace as well as certain heavy metals and certain ions that may leach or be extracted out of the container closure.” Ex. 1001 at 4:54-59. The specification describes efforts to make an L-cysteine for injection product that would be acceptable to infants, pediatric, and adult patients. *Id.* at 4:60-62. It was reportedly found that glass containers were a source of unsafe levels of aluminum. *Id.* at 4:64-

5:3; *see also* Example 2. However, replacing the glass vials with plastic containers supposedly resulted in unacceptable levels of oxidation products (cystine precipitate) likely because oxygen entered the plastic containers. *Id.* at 5:8-19; *see also* Example 3. Hence, the specification introduces container choice as yet another variable that could affect formulation stability, but again was not studied or tested to support the claimed stability across the scope of claimed ranges of aluminum and oxygen levels.

B. The '370 Patent Claims

Independent claim 1 is directed to an L-cysteine solution for use in total parenteral nutrition having a certain composition after 12 months of storage in a sealed vial and is set for the below:

1. A solution of L-cysteine for use in total parenteral nutrition (TPN) comprising,

about 10 mg/mL to about 100 mg/mL of L-cysteine or a pharmaceutically acceptable salt or hydrate thereof, in a pharmaceutically acceptable carrier;

wherein:

after 12 months of storage in a sealed vial at room temperature:

the total amount of oxygen within the sealed vial is no more than about 5%; and

the solution:

contains not more than 250 ppb aluminum,
is substantially free of visually detectable particulate matter, and

has a pH from 1.0 to 2.5.

Claims 2-9 depend directly or indirectly from claim 1 and recite additional limitations related oxygen content (claim 2), aluminum content (claim 3), properties of the vial (claim 4), and methods for preparing solution using inert gases to reduce oxygen content (claims 5-9). Claim 28 also depends from claim 1 and recites an L-cysteine concentration of “about 34.5mg/mL to 50 mg/mL.

Independent claim 10 is the same as claim 1 with the exception that the storage time is increased to 18 months. Claims 11-18 and 29 depend directly or indirectly from claim 10. The additional limitations recited in these claims are identical to the limitations recited in corresponding dependent claims 2-9 and 28.

Independent claim 19 is the same as claim 1 with the exception that the storage time is increased to 24 months. Claims 20-27 and 30 depend directly or indirectly from claim 19. The additional limitations recited in these claims are identical to the limitations recited in corresponding dependent claims 2-9 and 28.

C. The Prosecution History of the ‘370 Patent

The ‘370 patent issued from Application No. 18/067,287 (“the ‘287 application”) filed December 16, 2022 which was a continuation of Application No. 17/950,964 (“the ‘964 application”) now Pat. No. 11,672,824, which is a continuation of Application No. 17/188,922 (“the ‘922 application”) now Pat. No. 11,510,942 (“the ‘942 patent”), which is a continuation of Application No. 16/746,028 (“the ‘028 application”) now Pat. No. 10,933,089 (“the ‘089 patent”) which is a continuation of application No. 16/665,702 (“the ‘702 patent”), now Pat. No. 10,583,155 (“the ‘155 patent”) which is a continuation of Application No. 16/248,460 (“the ‘460 application”) now Pat. No. 10,478,453 (“the ‘453 patent”). Applicants filed the ‘287 application with the same 30 claims that issued in the ‘370 patent. Ex. 1002 at 108-113.

The Examiner issued a non-final office action on March 8, 2023 that rejected the claims only pursuant to nonstatutory double patenting over U.S. Patent Nos. 10,905,713; 10,933,089; 10,583,155; 10,478,453; and 11,510,942, stating that “[a]lthough the claims at issue are not identical, they are not patentably distinct from each other because the patents are all directed to compositions and stored compositions of L-cysteine having low levels of aluminum over extended periods with pH values below 2.5 and substantially free of visually detectable particulate matter.” Ex. 1002 at 159-160. The Examiner also provisionally rejected the

pending claims on the ground of nonstatutory double patenting over copending Application Nos. 17/950,979, (subsequently issued as U.S. patent no. 11, 684,636); 17/950,964 (subsequently issued as U.S. patent no. 11,672,824); 18/067,397; and 18/067,605 for the same reasons. Ex. 1002 at 160.

Because the only rejection was curable, based on double patenting over non-patentably distinct claims, Applicants submitted terminal disclaimers over all these patent and applications. Ex. 1002 at 189.

The Examiner issued a Notice of Allowance on March 22, 2023. Ex. 1002 at 201.

The parent '089 patent: The prosecution of the parent '089 patent is relevant. There, Patent Owner initially filed claim 1-27 generally directed to L-cysteine solutions having less than 150 ppb aluminum after at least 6 months from date of manufacture. Ex. 1023 at 26-29.

The Examiner rejected all 27 pending claims as obvious over the Sandoz label (Ex. 1005) in view of papers by Hernandez-Sanchez (Ex. 1006), Bohrer (Ex. 1008), Asquith, and Waterman (Ex. 1027), and U.S. Patent No. 4,835,086. Ex. 1023 at 246-247. The Examiner explained that the Sandoz label disclosed an L-cysteine solution and the other references taught the need to reduce aluminum and methods to do so. Ex. 1023 at 247. The cited articles also disclosed the oxygen sensitivity of L-cysteine and methods to limit its degradation. *Id.*

In response to the rejection, Applicants argued that the prior art did not render the pending claims obvious and to the contrary showed that the problem of making a L-cysteine formulation with reduced levels of aluminum “went unsolved for decades.” Ex.1023 at 284. Applicants also cited the December 6, 2019 Declaration of John Geissler (submitted during unfair competition and deceptive trade practices litigation brought by Exela against Sandoz, Inc. *Exela Pharma Sciences LLC v. Sandoz, Inc.*, Case No. 19-cv-318 (W.D.N.C.)) which purportedly showed that a prior art L-cysteine formulation contained more than double the amount of aluminum in the pending claims after two and a half months (i.e., before the six months recited in the pending claims). Ex.1023 at 284. Applicants also argued that reducing aluminum in L-cysteine solutions was a complex problem involving interrelated variables in an unpredictable art:

Reducing aluminum levels in L-cysteine parenteral solutions proved to be a surprisingly complex undertaking because of the chemistry of L-cysteine. The present inventors discovered in solving the problem that one has to consider and balance multiple variables, including interactions of the active, its concentration, trace components, the excipients, the solvent, the packaging, the pH, and the manufacturing among other things. The art did not predict and could not have predicted how those variables would interact under the specific conditions of the presently claimed L-cysteine parenteral solution, let alone how changing one variable would affect the other variables.

Ex. 1023 at 7. Applicants also directed the Examiner to his previous conclusion during prosecution of the parent '453 patent (summarized below) “that the ‘unpredictable nature of the art’ belies any obvious solution because ‘while aluminum contamination is a known problem, it is unknown how to reduce the aluminum content of formulations.’” Ex. 1023 at 285-286. Applicants also argued that long felt need and failure of others to solve the problem of reduced aluminum L-cysteine formulations was evidence on non-obviousness. Ex. 1023 at 288-289. The Examiner issued a Notice of Allowance on January 13, 2021. Ex. 1023 at 325.

The parent '453 patent: The '453 patent issued from the '460 application, which was the first in the string of continuation applications from which the '370 patent claims priority.

On January 15, 2019 Applicants filed the '460 application with 22 claims. Ex. 1024 at 90-94. Claims 1-20 were directed to an L-cysteine formulation comprising, along with other components, aluminum in ranges of 1-250 parts per billion (“ppb”). Claim 21 was directed to methods of preparing the composition recited in claim 1 and claim 22 was an independent claim reciting a method of preparing a reduced aluminum composition comprising 1-250 ppb aluminum.

On June 19, 2019, the Examiner rejected all the pending claims for failing to comply with enablement requirement under 35 U.S.C. § 112(a). The Examiner explained that the recited subject matter was “unpredictable” and while the

problem of aluminum contamination is known “it is unknown how to reduce the aluminum content of formulations.” Ex. 1024 at 378-379. The Examiner also stated that the claims were broad and that the specification provided “no direction or guidance for practicing the claimed invention in its ‘full scope.’” *Id.* at 379. Accordingly, a person skilled in the art would have to engage in “undue experimentation.” The Examiner further stated that the specification discloses only “mixing L-cysteine with minimum contaminants (see ex claim 22) but there is no disclosure how the compound is made pure or [how to] avoid impurities known in the art.” *Id.* at 380.

The Examiner also rejected claims 1-13 and 15-22 as obvious under 35 U.S.C. § 103. *Id.* at 380-381. The Examiner supported the § 103 rejection by relying on a combination of a Sigma-Aldrich product information brochure for L-Cysteine Hydrochloride Monohydrates—teaching that L-Cysteine is soluble in water—and Whiting *et al.* (Ex. 1032)—disclosing that head space oxygen can allow microbial spore outgrowth and toxin production. Specifically, the Examiner stated:

It would have been obvious . . . to store the solution of Sigma-Aldrich in an oxygen reduced atmosphere to reduce the chances of undesired reactions causing side products.

While the references do not disclose the impurity content, given the disclosure is for the compound per se, it is reasonably expected that the impurity content is below the claimed amount where the disclosure above suggest the impurities come from combination products.

With regard to the steps of claim 21, where the end result is reduced oxygen exposure, it would have been obvious to use an alternate gas when mixing to reduce the oxygen absorption during formulation.

Ex. 1024 at 381. The Examiner also rejected claims 1 and 14 as obvious in view of Jalilehvand *et al.* (Ex. 1034), which disclosed lead in an aqueous solution of L-Cysteine. Ex. 1024 at 381.

On September 6, 2019, Applicants responded, referencing an August 28, 2019 interview with the Examiner. Applicant described the substance of the interview as follows:

We discussed the criticality of the aluminum impurity and what was required to lower the amount to the claimed range. We also discussed which steps were expected to reduce the contaminate, yet didn't, leading to unpredictability in the art.

Ex. 1024 at 407, 422. In response to the enablement rejection, Applicants argued that the specification “addressed many variables and describes the factors that the present inventors used to overcome the Aluminum safety issues at hand, for

example: ‘the problems of safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace . . .’” Ex. 1024 at 408 citing Ex. 1001 at 5:53-57⁵. Applicants also argued that the patent examples and the stability and purity data for three batches found in Table 18 “show that controlling for Aluminum and oxygen by the processes described in the present specification result in the lowest impurity profile obtained for the claimed compositions.” *Id.* at 408. Applicants concluded that the examples and data in the specification amount to a “reduction to practice of the resulting compositions. As such, all of the present claims are enabled.” *Id.* at 409.

Applicants’ argument was misleading at least because a reduction to practice of one embodiment does not equate to enablement across the full scope of what is claimed. Broad claims, such as those in the ’370 patent, require a broad disclosure to enable the claims to their full scope. As the Supreme Court recently ruled, “the more a party claims, the broader the monopoly it demands, the more it must enable.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 613 (2023). As described below, the

⁵ Sep. 9, 2019 Response cites specification in the ’460 application which is shared with the ’370 patent. The ’370 patent specification is cited above for ease of reference.

'370 patent does not provide a sufficiently enabling disclosure. *See generally* Ex. 1003, ¶¶ 77-129.

In response to the obviousness rejection, the applicants argued that the Sigma-Aldrich L-cysteine product combined with teachings to reduce oxygen content would not “suggest (or even implicitly disclose) a reasonably reliable or reproducible impurity content, let alone, each element of the present claims.” Ex. 1024 at 409. Applicants also suggested that there was no reason a POSA would have “looked at the Office Action’s combination of references to achieve the claimed invention described, let alone, with a reasonable expectation of success.” *Id.* at 409. Indeed, Applicants argued, “it was only after the present inventors addressed and overcame the problem of Aluminum that they were confronted with the problem of stability and precipitate formation.” Ex. 1024 at 409. Or, “[p]ut another way, the art did not know about the additional problems.” Ex. 1024 at 409.

The specification does not solve these problems for the ranges of components that are claimed, leaving unchanged the task that a POSA already had based on the prior art: the POSA would have to test each and every combination, across the full scope, for at least a year to determine which formulation conditions meet the claimed stability requirement and which do not. Applicants’ arguments that the L-cysteine solutions were not obvious because of their complexity and unpredictability further supports the lack of an enabling disclosure for the full

scope of the claims. No claims of the '370 patent are limited to the examples disclosed in the specification, or even narrowly tailored to fit what was shown and tested.

The Examiner withdrew both the § 103 and § 112 rejections and issued a Notice of Allowance on October 3, 2019. Ex. 1024 at 415. The Examiner provided the following reasons for allowance:

As noted by Applicants, while compositions with L-cysteine have been known in the art, the contaminant of aluminum hinders the further use of the product, especially for certain patient populations where the contaminant is beyond what is allowable for FDA approval. As such, Applicants have used multiple means disclosed in the specification and in the claims to achieve a composition which is far below the FDA demand, filling an unmet need which has been present for quite a number of years. Because each step taken independently did not demonstrate the desired result and there was no obvious reason to combine the steps actually taken, the product as claimed cannot be viewed as obvious. Instead, the unexpected result is due to the Applicants unexpected findings resulting from testing combinations of theories with no expectation of success.

Ex. 1024 at 420. The Examiner's Reasons for Allowance did not directly address the non-enablement rejection, and particularly did not address at all the full scope enablement issue presented here. Thus, the '453 patent subsequently issued without any further prosecution. Ex. 1024 at 436.

VI. LEVEL OF ORDINARY SKILL IN THE ART

Claims 1-30 of the '370 patent are directed to a solution of L-cysteine for use in parenteral nutrition having certain amounts of oxygen, aluminum, and particulate matter after being stored in a sealed vial and methods for making such a solution. A POSA as of the January 2019 priority date would have had an advanced degree like a Ph.D. or equivalent in chemistry, biochemistry, pharmaceuticals, pharmacy, or a related pharmaceutical field, with at least two years of experience in pharmaceutical formulation development, analysis, optimization and manufacturing, including experiences with processes and techniques for minimizing impurities in, and improving the stability of, pharmaceutical drug products during manufacture and storage. Ex. 1003, ¶ 24. A POSA may also have lesser levels of education but more years of experience. For example, a POSA may have had an M.S. with at least 3-5 years of experience or a B.S. with a minimum of 6 years of work experience as described above. A multi-disciplinary team consisting of individuals with different skills and experience could also suffice. Ex. 1003, ¶ 24.

VII. CLAIM CONSTRUCTION

The Board construes disputed claim terms using the *Phillips* standard which determines “the ordinary and customary meaning of [each] claim as understood by a person of ordinary skill in the art and the prosecution history pertaining to the

patent.” 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005). To the extent useful or relevant, the terms “stable” and “about” are expressly defined in the specification, and therefore can and should be construed accordingly. Ex. 1001, at 16:44-55 and 58:9-21. The district court construed “stable” as a composition that “will contain the specified levels of all components for sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting.” Ex. 1007 at 25-26.

VIII. THE CHALLENGED CLAIMS ARE INVALID

A. District Court Opinion

The ’370 patent is related to, and covers similar subject matter as, the ’155, ’713, and ’795 patents”. All four patents share substantially the same specification and claim priority, through a chain of continuation applications, back to the ’453 patent. The validity of the ’155, ’713 and ’795 patents was challenged in district court on non-Section 112 grounds. Ex. 1007 at 8. (*Exela Pharma Sciences, LLC v. Eton Pharmaceuticals, Inc.*, 620 F.Supp.3d 108 (D. Del. 2022)).

Along with infringement and anticipation, the district court addressed the obviousness of the asserted patents. The district court found that each of the asserted claims in the ’155 (claim 27), ’713 (claims 8-10), and ’795 (claims 1, 19, and 27) patents required a stable L-cysteine solution or composition in which the

amount of aluminum is not more than 150 ppb for a period of time (*e.g.*, 3 months, 12 months, or 24 months). *Id.* at 19. Each of the asserted claims also required an L-cysteine solution or composition with a limited amount of impurities or precipitates. As shown in the table below, the asserted patents, recite, like the '370 patent, stable L-cysteine solutions with limited precipitates and limited aluminum content.

Claim Limitation	'713 patent	'155 patent	'795 patent
Limited precipitates	"a pharmaceutically acceptable amount of cystine for at least about 12 months from the time of manufacture"	"per Liter of said stable L-cysteine composition" . . . "not more than about 2.0 wt% of cystine relative to L-cysteine"	"Substantially free of visually detectable particulate matter" after 12 months
Aluminum content	"150 ppb of aluminum for at least about 12 months from the time of manufacture"	"1 [ppb] to about 250 ppb"	"Containing no more than 150 ppb of aluminum;"

The district court found that the obviousness argument is generally the same as to all the claims and addressed the claims collectively, as the parties had done.

Ex. 1007 at 28. As described below, the Patent Owner made arguments and the district court made findings in addressing obviousness that apply equally to the '370 patent, given the similarity of the claimed subject matter.

Defendant based its obviousness argument on a prior art Sandoz product, as defined by its label, (“the Sandoz Label”, Ex. 1005) and the knowledge of a POSA regarding leaching of aluminum and coated vials. Ex. 1007 at 19. The Sandoz Label described an L-cysteine solution that contained no more than 5,000 mcg/L of aluminum and contains a warning that “[t]his product contains aluminum that may be toxic.” Ex. 1005 at 2. The district court found that it was well-known at the time that aluminum was toxic in L-cysteine solutions and a POSA would have been motivated to reduce the amount of aluminum. Ex. 1007 at 15-17, 20-22, and 30.

The district court found that the aluminum levels in the Sandoz product varied across lots (and within lots) and increased over time in storage. Ex. 1007 at 14-15. The Sandoz product was made with the use of oxygen controls (such as nitrogen sparging, use of a nitrogen blanket during manufacturing and filling, or dissolved or headspace oxygen measurements). *Id.* at 15. There was no data provided for the specific amount of cystine in the Sandoz product. *Id.* at 15. The district court recognized that cystine, when formed, results in particulate matter. Ex. 1007 at 13, 20. The Sandoz Label does not identify the container used other than noting it was a clear glass vial. *Id.* at 15.

The district court also made findings regarding a POSA's knowledge at the time of filing. The district court summarized articles authored by D. Bohrer et al. that address aluminum leaching in total parenteral nutrition ("TPN") products. The papers show that a number of different variables, including affinity for aluminum, time, temperature, pH, and oxygen affect the amount of aluminum leaching. *Id.* at 16; Ex. 1008 at 4; 1012 at 4-5; Ex. 1011 at 7. Bohrer also found that cysteine, in comparison to other amino acids in TPN products, had the highest affinity for aluminum. Ex. 1007 at 16; Ex. 1008 at 4, Fig. 2. Cystine, the degradation product of cysteine, had the next highest affinity for aluminum. *Id.*

The district court also found that Bohrer further demonstrated that the aluminum leaching continues to increase over time, and, even after almost a year, it continues to rise. Ex. 1007 at 16; Ex. 1008 at 4. Therefore, the time that amino acid solutions are in contact with glass affects how much aluminum is leached. Ex. 1007 at 125.

The district court also found that Bohrer demonstrated that temperature also influences the amount of aluminum leaching. *Id.* at 16. Specifically, that sterilization by heat increases the ability of all amino acids to leach aluminum "dramatically." Ex. 1007 at 16; Ex. 1012 at 4-5. Sterilization by heat most increases cysteine and cystine's capacity to leach. *Id.* The district court also summarized the findings of a third paper by Dr. Bohrer that found L-cysteine and

cystine aluminum leaching persists longer in formulations if exposed to oxygen than if not exposed to oxygen. Ex. 1007 at 16; Ex. 1011 at 7.

The district court also summarized publications showing that a POSA would have considered aluminum content a well-known toxin and problem in TPN products. For example, a paper by A. Hernandez-Sanchez et al. gathered and reported information related to aluminum in parenteral nutrition products. Ex. 1007 at 16-17; Ex. 1006. Hernandez-Sanchez reports that the aluminum toxicity “problem in parenteral nutrition solutions (PNS) is decades old and is still unresolved.” Ex. 1007 at 16; Ex. 1006 at Abstract. Hernandez-Sanchez identified cysteine hydrochloride as one of the three largest contributors of aluminum in TPN solutions. Ex. 1007 at 17; Ex. 1006 at 2. The paper recommended that manufacturers of L-cysteine should improve manufacturing techniques to provide low aluminum products. Ex. 1007 at 17; Ex. 1006 at 8.

Like Bohrer, Hernandez-Sanchez explained that parenteral products should be stored in containers that do not interact physically or chemically with the solution. Ex. 1007 at 17; Ex. 1006 at 2. According to the prior proceedings, Hernandez-Sanchez also taught away from glass vials, reporting a substantial reduction in aluminum when packaging changed glass to polyethylene vials. Ex. 1007 at 17; Ex. 1006 at 2. Finally, the district court explained that Hernandez-

Sanchez also discloses “high lot-to-lot variation” in aluminum content in TPN products. Ex. 1007 at 17; Ex. 1006 at Abstract.

The district court also addressed a POSA’s knowledge regarding a certain type of vial called a Schott Type I Plus vial. The brochure for this vial advertises it for the purposes of reducing aluminum leaching. Ex. 1007 at 17. The vial is lined with a barrier layer that “prevents depletion of glass container by drug formulation.” Ex. 1007 at 17. The district court noted that the Schott brochure did not contain information specific to cysteine products and suggests individually testing a given products “fit for the vial.” Ex. 1007 at 17.

The defendant in the *Exela* case relied on the Sandoz Label and a POSA’s knowledge regarding leaching of aluminum and coated vials. Ex. 1007 at 19. The district court found that the Sandoz product was stored in an unidentified glass vial and data for three batches indicated less than 150 ppb aluminum after one month but more than 150 ppb aluminum at 24 months. Ex. 1007 at 20.

In conducting its invalidity analysis, the district court compared the Sandoz product with another L-cysteine solution referred to as the ANDA product. The district court pointed out differences in the manufacturing process that the evidence showed would make a difference in the composition of the L-cysteine solution. For example, application of terminal sterilization was used in the ANDA product but not the Sandoz product. Ex. 1007 at 18. Terminal sterilization uses heat which

increases the rate aluminum leaches from glass vials as well as cysteine's capacity for leaching aluminum. *Id.* The two products also used different oxygen control measures. *Id.* The two products also had different suppliers of the active ingredient, L-cysteine hydrochloride. The district court concluded that impurities in the L-cysteine starting materials can impact the end product. *Id.* The district court also noted that the two products used different glass vials and the "the vial can impact how much aluminum is leached and thus the aluminum content of the product." Ex. 1007 at 18-19.

The district court recognized that all these differences, while significant on their own, could interact in a way that was unpredictable:

Not only are the individual difference between the Sandoz product and the ANDA significant, but they also have the capacity to interact and affect the product in *unpredictable* ways. As Dr. Jenke explained, "the impact or the mechanism by which time and temperature influences leaching is different than the mechanism by which the solution impacts leaching, but the combined effect, the effect that dictates how much aluminum is actually in the product is caused by the interacting phenomenon of both the solution and time and temperature.""

Ex. 1007 at 19 (emphasis added). The district court similarly found the interrelatedness and unpredictability of the properties and characteristics of L-cysteine solutions was supported by evidence that showed that "varying the

amount of aluminum in a cysteine formulation can impact other aspects of the formulation, including the amount of cystine and the appearance of precipitate. And how that happened is complex and unpredictable. Ex. 1007 at 28.

The district court also found that “Aluminum has a stabilizing effect on an L-cysteine solution.” Ex. 1007 at 13. The district court based this decision on experiments performed by Exela and a third party Avadel Legacy Pharmaceutical LLC (“Avadel”); Ex. 1007 at 13, 20. When Exela reduced the aluminum levels in its cysteine product to very low levels, its product failed because the product contained visible particulate matter. *Id.* at 20. This finding appears to be based on the data in Example 3 of the ’370 patent. Ex. 1001 at 42:65-43:32. The district court also found Exela determine that the visible particulate matter was cystine. Ex. 1007 at 20.

The district court also described Avadel’s similar experience. *Id.* at 20. Avadel prepare six batches of its cysteine formulation that were identical except for the vial used. Half the batches were in lined Schott Type I Plus vials, and the other half were stored in normal, unlined Type I vials. *Id.* The lined Schott Type I Plus vials showed aluminum at less than 5 ppb through 24 months while aluminum levels in the unlined vials measured from 45 ppb at manufacture and 102 ppb at 3 months, up to 221 ppb at 12 months. *Id.* “The lined vials with (extremely low

levels of aluminum) unexpectedly generated precipitates that Avadel later determine to be cystine precipitates, resulting in product failure.” *Id.*

B. Previous PGRs on Related Patents

Eton, in addition to being party to the district court litigation summarized above, also filed a petition for post grant review of the ’155 patent. PGR2020-00068, Paper 1. Eton made similar obviousness arguments in its petition and in the district court. Eton argued that reducing aluminum (compared to levels reported in a prior art formulation) would have been obvious because the negative health effects of aluminum in parenteral solutions was well known and reducing cystine would be a matter of routine optimization. *Id.* at 42-52.

The PTAB did not institute review, but Patent Owner filed a preliminary response in which it argued repeatedly that the claimed L-cysteine solutions have unpredictable behavior. For example, the Patent Owner argued that the stability of an L-cysteine parenteral solution is “highly dependent on its environment.” PGR2020-00068, Prelim. Resp., Paper 6 at 53. The patent owner listed pH, available oxygen, presence of trace metals (such as iron or copper) as important variables or parameters and concludes:

In short, L-cysteine parenteral solutions are sensitive to an array of multivariate and interrelated interactions. . . . the system here is not ‘a system that allows independent change of one variable with little or no predictable or material effect on other variable’; rather, it is a

‘system where the change to one variable [can] result in changes to the others.

Id. at 55 (citing *HZNP Medicines LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 703 (Fed. Cir. 2019)).

Patent Owner also admitted that the claimed L-cysteine solutions are sensitive to an “array of multivariate and interrelated interactions” and are not susceptible to simply changing one variable without having other unforeseen effects on the formulation. *Id.* at 55.

Eton also filed a similar PGR petition against the related ’453 patent which also covers stable L-cysteine solutions having certain amounts of aluminum, oxygen, and cystine. PGR2020-00064, Paper 1. Again, Eton asserted invalidity grounds based on the Sandoz Label and a POSA’s knowledge. *Id.* at 6. Patent Owner, in its Preliminary Response made arguments similar to those described and quoted above about the complexity and unpredictability of L-cysteine solutions. *See, e.g.*, PGR2020-00064, Paper 6, at 57-58 and 60. The PTAB also declined to institute review of the ’453 patent. PGR2020-00064, Paper 12.

C. Ground 1: Non-Enablement

Judicial estoppel prevents Patent Owner from now taking a contrary position regarding the complexity and unpredictability of L-cysteine solutions. *New Hampshire v. Maine*, 532 U.S. 742, 749-50 (2001). More broadly, regulatory

agencies use the same standard applying Supreme Court law: “[w]hen an issue of fact or law is actually litigated and determined by a valid and final judgment, and the determination is essential to the judgment, the determination is conclusive in a subsequent action between the parties, whether on the same or a different claim.”

B&B Hardware, Inc. v. Hargis Indus., Inc., 575 U.S. 138, 148 (2015) (quoting Restatement).

New Hampshire establishes three non-exhaustive criteria for the application of judicial estoppel: (1) the party’s later position must be “clearly inconsistent” with its earlier position; (2) the party must have succeeded in persuading the tribunal to accept its earlier position; and (3) accepting the party’s later inconsistent position would give the party an “unfair advantage or impose an unfair detriment on the opposing party.” *New Hampshire*, 532 U.S. at 750-51. As detailed above, patent owner argued to the Patent Office and the district court that the claimed L-cysteine solution were complex and unpredictable. *See* Sections VIII(A) and (B), above. The Patent Office and the district court accepted these arguments and found substantially similar L-cysteine formulation claims to be not invalidated by the prior art. *Id.* If Patent Owner were allowed to now argue that the claimed L-cysteine solutions are not complex and unpredictable, then that would be inconsistent and impose an unfair advantage to Petitioner’s detriment here. Patent Owner obtained and maintained patent protection for its L-cysteine product by

persuading the Patent Office and the district court of the unpredictability and complexity of L-cysteine solutions. It would ignore judicial estoppel if Patent Owner were now permitted to argue to the contrary in response to the enablement ground presented here.

Importantly, the patent specification for the '370 patent did not fill in the blanks for the information Patent Owner asserted would be undue for a POSA to determine: aluminum amount, oxygen amount, container choice, and interactions between these and other variables to achieve a sufficiently stable formulation. To meet the enablement requirement of 35 U.S.C. § 112, the specification must teach a POSA how to make and use the full scope of the claimed invention without “undue experimentation.” *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988)). “[W]hen a range is claimed, there must be reasonable enablement of the scope of the range.” *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). It is not enough for the specification to “provide[] a starting point from which one of skill in the art can perform further research in order to practice the claimed invention.” *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1198 (Fed. Cir. 1999). A specification that requires a skilled artisan to “engage in an iterative, trial-and-error process to practice the claimed invention”

does not provide an enabling disclosure. *Alza Corp. v. Andrx Pharmas., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

The Supreme Court recently reiterated the proper standard for enablement finding that “the more a party claims, the broader the monopoly it demands, the more it must enable.” *Amgen*, 598 U.S. at 613. A patent that discloses only a “trial-and-error method for finding” the claimed subject matter is not enabling. *Id.* at 614. Here, the ’370 patent specification does not enable a POSA to make and use a solution of L-cysteine having, after storage in a sealed vial, the recited amounts of oxygen, aluminum, and particulate matter required by each of claims 1-30. Ex. 1003, ¶¶ 77-129.

Here, based on the prior district court and Patent Office proceedings concluding that the claimed stability limitations are not inherently based on prior art L-cysteine formulations that already avoided aluminum and used Schott vials, the ’307 patent claims are not enabled. The claims of the ’370 patent list various variables in broad ranges, even though the Patent Owner conceded that the variables are critical and even though the specification lists tiny one-off examples compared to the claim scope. And those examples do not even demonstrate stability for the minimum claimed period of the ’307 patent, which is at least 12 months. Add to that the Patent Owner’s prior arguments that different variables in the claim work in unpredictable ways together, and that trial-and-error testing will

be required, and all that a POSA is left with is the outline of a research project to figure out the full scope of the claimed invention.

All of those prior statements are binding here, because under the doctrine of judicial estoppel, Patent Owner cannot now contradict arguments that it made to support non-obviousness in prior proceedings, and which the district court and Patent Office accepted.

1. The '370 Patent Does Not Enable a POSA To Make Stable L-Cysteine Solutions Substantiating the Full Scope Of the Invention

The '370 patent does not provide sufficient guidance for a POSA to be able to practice the full scope of the claims without engaging in a trial-and-error research project. That is because the patent examples are very limited, referring to one-off embodiments, but the purported claim scope is vast – including oxygen and aluminum amounts that are 5 to 25 times higher, respectively, than the specifications' examples tested for stability. In addition, there are no tests that show stability for 12, 18, or 24 months – as required by all the claims in the '370 patent. The longest test is for data collected after only nine months of storage. Ex. 1001 at 49:64. Thus, a POSA would not know which amounts within the claimed ranges to use for any of the claimed variables—especially aluminum and oxygen—and how choosing an amount of one could affect the amount used for the other. Instead, the scope of the claims would require the POSA to do all the work that

was not done or even discussed in the '370 patent specification, showing that the specification simply does not show a POSA how to make or use the full scope of the asserted claims without undue experimentation. As detailed below, the claims cover numerous variables that would need to be assessed, and then not one by one but also to assess the alleged interrelatedness of solution components, all while acknowledging Patent Owner's assertions regarding the complexity and unpredictability of L-cysteine solutions within the claimed scope. *See, e.g.*, Sections VIII(A) and (B).

a. "no more than [150ppb/250ppb] aluminum"

All the independent claims of the '370 patent require "no more than 250 ppb aluminum," and some dependent claims require "no more than 150 ppb aluminum." Patent Owner successfully argued to the district court and Patent Office that the aluminum level is critical, and that aluminum effects on formulation stability are unpredictable. But the limited disclosure in the specification does not support either the full scope of the '370 patent claims, either higher or lower than the one-off disclosures in the patent specification. Remarkably, despite the broad claim scope, there is not the usual "bracketing" test disclosure in the specification, where data extends along an entire range of options, and the claim scope covering only those options that work for their intended purpose. Here, the patent only discloses a small dot of examples, and still claims entire lines of ranges.

On the upper end, the maximum aluminum amount shown in the patent specification that was even tested for stability was between 2.9 ppb and 5.6 ppb aluminum. *See* Ex. 1001 at 50:1-20, Example 6, and Table 18; Ex. 1003, ¶ 101. The claims are far broader. By comparison, the claims include on the high end up to about 25 times more aluminum for the 150ppb claims—and about 45 times more aluminum for the 250ppb claims. There is simply no disclosure for whether those claimed aluminum amounts will work at all, much less to make a stable formulation that meets the claimed storage requirements. In fact, even for the formulations with 2.9-5.6 ppb, the longest stability storage test result in the specification is 9 months, while the shortest stability requirement in the '370 patent claims is 12 months (claim 1). *See* Ex. 1003, ¶¶ 87, 104.

The '370 patent discloses the aluminum content of other L-cysteine solutions in Tables 6 and 8. Table 6 shows aluminum levels well above the highest claimed threshold of 250 ppb limitation in the '370 patent claims, so those are inapplicable. Ex. 1003, ¶ 102.

On the other end of the spectrum, the claims start at zero, but there is no disclosure for successful formulations with no aluminum, and in fact teachings that aluminum is required. There is no doubt the claimed amount includes zero, as the specification even defines the phrase “not more than” as including the “possibility” of zero. Ex. 1001 at 32:18-21. Yet the patent specification itself shows that very

low aluminum amounts near zero do not work. For example, the solutions in Table 8 do show very low aluminum content—down to 1-2 ppb—but exhibited particulate matter and so did not satisfy the stability limitations from the '370 patent claims. Ex. 1003, ¶ 102. Moreover, the patent specification spells out expressly that what the '370 patent claims will not work because aluminum “may have a stabilizing effect”: “Consequently, removing Aluminum may have the unintended consequence of increased precipitation and product failure in the presence of even small amount of oxygen in the container.” Ex. 1001, at 5:20-25.

In sum, the narrow range of aluminum embodiments actually disclosed in the specification for stability testing—2.9 ppb to 5.6 ppb—does not enable the full scope of 0 to 250 ppb or 0 to 150 ppb aluminum, particularly in light of the admitted complexity and unpredictability of the claimed L-cysteine solution. Accepting Patent Owner’s argument on this same issue, the district court previously recognized that the amount of aluminum in the formulation has a complex and unpredictable interaction with the other properties and components of the solution:

The evidence at trial showed that reduction of aluminum in a cysteine formulation is not wholly independent of all the other properties and characteristics of the formulation, including acceptable levels of impurities, such as cystine. Rather, the evidence indicated that varying the amount of aluminum in a cysteine formulation can impact other aspects of the formulation, including the amount of cysteine and the appearance of precipitates. *And how that happen is complex and unpredictable.*

Ex. 1007 at 28 (emphasis added). The district court also found that “[t]he evidence shows that the levels of aluminum are not independent of the amount of impurities in a cysteine product.” Ex. 1007 at 20. The district court also found, and the ’370 patent asserts, that “aluminum has a stabilizing effect on an L-cysteine solution.” Ex. 1007 at 13; Ex. 1001 at 5:21-22. This finding, in particular, emphasizes the interconnected nature of the various components of L-cysteine solutions. simply reducing aluminum to a very low level would not result achieve the claimed invention. A POSA would have to engage in a trial-and-error research project to determine whether or not L-cysteine solutions that cover the full scope of the claimed composition resulted in the recited levels of aluminum—and other claimed limitations—after storage. Ex. 1003, ¶¶ 103-105.

Non-enablement is particularly strong here where, where the specification itself concedes that the full scope of what the ’370 patent ended up claiming will not work. The “specification’s teaching is itself evidence” of non-enablement. *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234 (Fed. Cir. 2003). A POSA would have to just do the work to run all the experiments using trial and error, which is exactly what the district court already found insufficient. *See Crown Operations Intern., Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1380 (Fed. Cir. 2002) (citing *In re Cook*, 439 F.2d 730, 735 (C.C.P.A. 1971)). The patent specification does not enable the full scope of the ’370 patent claims.

- b. “total amount of oxygen with the sealed vial is no more than about 5%”

The independent claims 1, 10, and 19 of the '370 patent require that “the total amount of oxygen within the sealed vial is no more than about 5%” after storage. Again, the minimum storage time is 12 months (claim 1), although other claims are for longer periods of time (18 or 24 months). And once again, the maximum storage time in the patent specification is only nine months, for a formulation that actually fits within the claimed levels of aluminum, oxygen, and particulate matter testing. Ex. 1001 at 49:55-50:20. After a 9-month test period, the oxygen content was found to be between 0.12 and 0.14 ppm of dissolved oxygen and between 0.16 and 0.89% in the headspace. Ex. 1001 at 50:1-20, Table 18; Ex. 1003, ¶ 96. Example 7 shows the effect of oxygen on four other L-cysteine solutions, but only after one week of storage in unidentified vials—nowhere near the 12 month minimum for the asserted claims—and still does not include information about the absence of visually detectable particulates. Ex. 1001 at 50:30-55; Ex. 1003, ¶ 97.

The discrete examples in the specification do not justify the entire claimed range of oxygen levels, and did not even show the disclosed formulations met the claimed stability criteria. The headspace oxygen levels in Example 7 are 20% and 1.2%. Ex. 1001 at 50:25-40, Table 19; Ex. 1003, ¶¶ 98-100. The solutions with 20% oxygen in the headspace also had about 8 ppm dissolved oxygen. *Id.* One

sample had 1.2% oxygen in the headspace and 0.5 ppm dissolved oxygen. *Id.* The amount of cystine⁶ was measured, but the '370 patent does not report whether the samples exhibited visible particulate matter or not, so did not show they met the claimed stability requirement. *Id.* The higher-oxygen-content samples had between 0.5 and 0.8% cystine. The lower-oxygen-content sample had 0.1% cystine. No information was provided as to whether the amounts of cystine measured in the Table 19 resulted in visible particulate matter, the stability limitation required by all of the '370 patent claims. *Id.* Accordingly, Example 7 provides no confirmation about even the specific embodiments testing, much less guidance about the full scope claimed, regarding whether an L-cysteine product with varying oxygen content would meet the claimed stability limitations. Ex. 1003, ¶¶ 99-100.

In sum, the claims recite a much broader range of oxygen content, namely from zero to five percent, compared to anything disclosed in the patent specification with or without stability testing; the specification shows ranges of approximately 0.19% to 1.2% oxygen disclosed in Examples 6 and 7. A POSA could not simply assume that the 1.2% oxygen content reported in Example 7 met all the requirement of the claims, and the patent does not show stability testing for 12 months or more. Ex. 1003, ¶¶ 99-100. The claims require a solution

⁶ Cystine is the oxidative degradation product of L-cysteine that would be the likely source of any particulate matter. Ex. 1003, ¶ 135; Ex. 1001, 16:62-64.

“substantially free of particulate matter,” but Example 7 reports only the percentage of cystine found, not whether there was any visible particulate matter. Thus, a POSA would have to engage in a trial-and-error testing to determine whether the full scope of the oxygen content recited in the claims—from 0% and up to 5%—actually results in L-cysteine formulations having the impurity profile and properties recited in the claims. Ex. 1003, ¶ 100.

c. Concentration of L-Cysteine

Claims 1-27 of the '370 patent cover the expansive range for drug concentration from about 10 mg/ml to about 100 mg/ml of L-cysteine or a pharmaceutically acceptable salt or hydrate thereof. Dependent claims 28-30 recite 34.5 mg/mL to 50 mg/mL of active ingredient. But there is only one concentration disclosed in the patent specification: all the solutions of L-cysteine studied in the '370 patent have an L-cysteine hydrochloride concentration of 50 mg/ml. Ex. 1003, ¶ 79; Ex. 1001 at 41:58-42:32, Example 1. Example 1 describes how the 50 mg/ml L-cysteine hydrochloride solution was compounded. *Id.* It is this solution that is studied in all the '370 patent examples.

One concentration of L-cysteine does not enable the entire claimed 10-100 mg/ml range of possible concentrations recited in the claim. This is especially so when Patent Owner argued, and the district court accepted, that higher drug concentration would result in higher impurity levels. In particular, the district

court found, and a POSA would understand, that the prior art taught that L-cysteine—and its oxidative degradation product, cystine—had high affinity for aluminum (compared to other amino acids) and so would be more likely to leach aluminum from the vial and formulation. Ex. 1007 at 16; Ex. 1008 at 4, Fig. 2, Ex. 1003, ¶ 81. Therefore, the leaching properties of the solution depend not only on the starting concentration of L-cysteine, but also on the amount of oxygen present which would react with L-cysteine to form cystine, because both leach aluminum. Ex. 1003, ¶¶ 65, 83.

The district court also found that it was reported in the literature that aluminum leaching continues to increase over time, and, even after almost a year, it continues to rise. Ex. 1007 at 16; Ex. 1008 at 4, Fig. 2; Ex. 1003, ¶¶ 64, 81. Therefore, the time that L-cysteine solutions are in contact with glass affects how much aluminum is leached. Ex. 1007 at 16; Ex. 1003, ¶ 82. Given the complex behavior of the interrelated variables in L-cysteine solutions—including the concentration of L-cysteine—a POSA would have to engage in trial-and-error experimentation to determine if L-cysteine solutions having 10-100 mg/ml of L-cysteine met the claimed requirements including aluminum content and absence of particulate matter. Ex. 1003, ¶ 83. The synergistic effect of oxygen and drug concentration on aluminum leaching was not tested, much less demonstrated, across the full scope of the claimed drug concentration range.

d. “12 months of storage”

Claim 1 requires certain amounts of aluminum and oxygen after 12 months of storage in a vial. Other claims require even longer periods of time. All claims requires that the solution be ‘substantially free of visually detectable particulate matter’ and maintain a pH from 1.0 to 2.5. But the ’370 patent does not disclose any data for an L-cysteine solution that meets the claimed oxygen/aluminum amounts that was actually stored for 12 months required by claim 1, much less the 18 or 24 months required by other claims in the ’370 patent. Instead, as discussed above, the only examples in the ’370 patent that tested results for the claimed stability was done over a *9-month* testing period, during which the samples were stored upright at room temperature 25°C/60% relative humidity (“RH”). This limited data stopped short well before the claim scope begins, so cannot possibly enable the full scope of the claims which require longer 12, 18, or 24 months storage while maintaining stability. Ex. 1003, ¶¶ 85-86

A POSA would not have relied on 9-month stability data when the claims require 12-24 months of storage. Ex. 1003, ¶ 87. The district court recognized and a POSA would have understood that the composition of an L-cysteine solution can depend on the amount of time in storage. Ex. 1007 at 16; Ex. 1003, ¶¶ 78-83, 87. For example, and as described above, the amount of aluminum in the solution from aluminum leaching varies over time and depends on a variety of factors, including

the amount of L-cysteine and cystine in the solution and oxygen in the solution, and the type of vial, as described below.

e. “sealed vial”

All the claims of the '370 patent require storage in a “sealed vial.” The independent claims do not require a particular type of vial, opening the door to yet another list of possibilities even though the specification does not justify or support the full scope of this claim. In fact, the district court recognized and a POSA would have understood that different types of vials would affect the amount of aluminum, oxygen, and cystine in the solution—particularly over the long, claimed storage times of a year or more. For example, the district court found that the prior art recommended non-glass vials to reduce aluminum leaching from glass. Ex. 1007 at 17; Ex. 1006 at 2. A POSA also would have understood that there are a wide array of possible vials in which parenteral preparations could be stored. Ex. 1003, ¶¶ 91-93. All of these are covered by the claim, which permits any “sealed vial” material. Accordingly, a POSA would need to try various types of vials in order to determine if the claimed solution met at least the aluminum, oxygen and particulate matter requirements after storage. Ex. 1003, ¶ 94. Given the complexity of L-cysteine solutions, the ability of a particular vial to meet the claim would not have been predictable. Ex. 1003, ¶ 94.

Once again, the '370 patent does not provide sufficient guidance to enable the broad range of possible storage vials. To the contrary, the patent provides the general disclosure that the storage container can be made of “a variety of materials . . . provided that it can both prevent oxygen penetration and minimize aluminum [and other] contamination.” Ex. 1001, 22:58-64. But it does not say what those are, beyond the one embodiment listed in the examples. Accordingly, the behavior of the claimed L-cysteine solutions in a certain vial was not predictable, and a POSA would have had to engage in trial-and-error experiments using a variety of vials, along with the other variables already mentioned. Ex. 1003, ¶ 94.

f. “pH from 1.0 to 2.5”

During PGR2020-00068, the Patent Owner further added that pH was one of the interrelated variables that impacts L-cysteine solutions:

the kinetics and equilibrium chemistry of the various L-cysteine and cystine species in any particular L-cysteine solution are complex and influenced by multiple interacting variables of the environment, including oxygen levels, pH, and the presence of trace metals. Moreover, multiple variables, *including pH* and cystine concentration, can further affect the extent of aluminum leaching from the glass containers historically used to store l-cysteine compositions.

PGR2020-00068, Paper 6, Prelim. Resp. at 17 (emphasis added). As Dr. Confalone explains, a POSA would have known that pH can affect at least the formation of cystine particulates. Ex. 1003, ¶ 108. The literature reported that the solubility of

cystine varies significantly even within the 1.0 to 2.5 pH range recited in the claims. Ex. 1003, ¶ 108; Ex. 1061 at 4-5. The solubility of cystine is significant here as the claims requires the absence of visible particles. Ex. 1003, ¶ 108.

The example L-cysteine solutions that were actually tested for stability in the '370 patent examples, however, all have a target pH of 1.8—as shown in the compounding description from Example 1. Ex. 1001 at 42:16-17. The specification does not provide any data for solutions having any different pH, or even the basis to assume that pH values as low as 1.0 or as high as 2.5 would behave the same as the one formulation pH tested that was 1.8. Accordingly, it would be necessary for a POSA to conduct trial-and-error experiments to determine the full scope of the claimed pH range that results in L-cysteine solutions that meet the stability claim limitations, including lack of visible particulate matter.

2. A POSA Would Have to Engage in Trial-and-Error Research to Practice the Claimed Invention

Given the unpredictable nature of the L-cysteine solutions and the interrelated variables, it would have been necessary to perform trial-and-error testing of various solutions having varied amounts of L-cysteine, oxygen, aluminum, and pH for 12, 18, or 24 months in order to determine if the claimed L-cysteine solutions would meet the claimed requirements. Ex. 1003, ¶¶ 110. As Dr. Confalone explained, in order The amount of time and resources required to conduct such stability testing is substantial. Ex. 1003, ¶¶ 111-115.

As Dr. Confalone, explained, in order to study the interrelated variables present in the claimed L-cysteine solutions, a POSA would use experiments starting with a factorial design to include multiple independent variables in an experiment. In this set of experiments, each variable can have various levels. Each level of each independent variable is combined with each level of the other independent variable to create all possible conditions or runs. The number of experimental conditions or runs is defined by the formula: Number of Runs = $n_1 \times n_2 \times n_3 \times n_4 \times \dots \times n_k$ where “n” is the number of levels for each factor and “k” is the number of factors or variables. The factors can have different numbers of levels. A design with five factors, three with two levels, one with three levels and one with four levels has $2 \times 2 \times 2 \times 3 \times 4 = 96$ experiments. Ex. 1003, ¶ 111.

Given the variables discussed above that are relevant in the claimed L-cysteine solutions—and the wide range of claimed values for each variable—a very large number of experiments would need to be conducted to test the full scope of claimed L-cysteine solutions. Dr. Confalone, designed one possible set of experiments, shown in the table below, that would be necessary to study the full scope of the claimed solutions. Ex. 1003, ¶ 112.

Variable	Number of Settings
L-cysteine concentration (10, 25, 50, 75, 100 mg/ml)	5
Oxygen (0, 1, 2, 3, 4, 5%)	6
Aluminum (0, 10, 25, 50, 100, 150, 200, 250 ppb)	8
pH (1.0, 1.5, 2.0, 2.5)	4

Container closure (2 types)	2
Vial type (4 types)	4
Total number of experiments (5 x 6 x 8 x 4 x 2 x 4)	7680

And each of those experiments, in turn, has to be run for a minimum of 12 months to justify any claim of the '370 patent, and up to 24 months for some claims of the '370 patent.

This proposed outline representing 7,680 experiments is a very conservative number, because the assumptions reduced the number of settings per variable to a bare minimum that a POSA might consider. For example, if rather than testing only 5 L-cysteine concentrations, one opted to test 10 concentrations (every 10 from 10-100), that would already double the number of tests required. Similarly, a POSA could reasonably select added oxygen concentrations at intervals of 0.5%, based on the example in the patent, or aluminum levels at intervals of 10 ppb, based on the patent's disclosure that these variables were critical and unpredictable. The number of experiments is a very high number, and will grow based on later rounds of experiments to further optimize and determine what amounts of the various inter-related variables actually work to achieve the claimed stability within the claimed ranges. That "brute force" type of trial-and-error testing is inefficient, but because the '370 patent specification did not teach

anything more about how to make a formulation other than to make it and see what happens after at least 12 months, the experimentation must be done and is undue.

In addition to controlling and verifying the amount of aluminum in the L-cysteine starting material, a POSA would also have worked to identify and confirm aluminum free containers. Ex. 1003, ¶ 109. A POSA would have understood that both the vial and the stopper could be potential sources of aluminum. *Id.* Indeed, Dr. Confalone explained that rubber stoppers may be a greater source of aluminum than the glass used to make the vials. Ex. 1003, ¶ 93. A POSA would also understand, as the district court found, that aluminum free packaging (such as polyethylene vials) would likely be oxygen permeable. *See* Ex. 1007 at 13 (describing development efforts with plastic vials); Ex. 1003, ¶ 109; Ex. 1009 at 11-12. Thus, these issues present additional hurdles about how a POSA would even attempt to justify the entire claimed ranges from the '370 patent.

The trial-and-error research necessary to practice the full scope of the claimed invention is undue experimentation. As Dr. Confalone explains, a research project of this scope would involve the efforts of a multidisciplinary team over a period of weeks or months to source appropriate starting materials and packaging, compound the ingredients, and fill the various solutions into each of the possible vials. Ex. 1003, ¶ 113. It would also be necessary to use oxygen-control technologies during each step of the process. *Id.* In addition, each vial, would have

to be stored and tested over a period of 24 months. Ex. 1003, ¶ 114. In addition, as described above, each experiment bears the added complications of careful control of aluminum in starting materials, oxygen controls, and various container systems to eliminate aluminum. Ex. 1003, ¶ 109.

The large number of experiments (7,680) would require an expenditure of significant time and money to carry out. Dr. Confalone estimated that this project would require the equivalent of three full time employees at a total cost of \$62,500 per month. Ex. 1003, ¶ 113. There would also be significant additional costs associated with carrying out 1 - 2 year stability studies for each experiment. Ex. 1003, ¶ 113.

In *In re Wands*, The Federal Circuit provided a list of factors that can be considered in determining whether a disclosure requires undue experimentation. *In re Wands*, 858 F.2d at 737. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the unpredictability of the art, and (8) the breadth of the claims. *Id.* As has been described in detail above, factors (1)-(4) and (7)-(8) all weigh strongly in favor of undue experimentation. *See* Section D, below (further detailing the lack of guidance and absence of working

examples). The remaining factors are neutral at best and, in any event, would not outweigh the other factors.

Finally, non-enablement is strengthened here because the claimed composition is not defined by the make-up of the L-cysteine solution, but by functional claim terms relating to stability. The only compositional limitations are the concentration of L-cysteine in a carrier at a certain pH and stored in a vial. The '370 patent requires the recited composition to meet certain functional limitations, namely the existence of certain levels of aluminum and oxygen and lack of particulate matter after storage. The use of broad functional claim limitations “raises the bar for enablement.” *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021).

3. The Dependent claims of the '370 Patent are Also Not Enabled

a. Claim 2

Claim 2 depends from claim 1 and adds the requirement that the “total amount of oxygen within the sealed vial is no more than 4%.” The difference between 4% and 5% does not alter the enablement analysis. Ex. 1003, ¶ 117. For example, if the number of “levels” for oxygen content is reduced to five the total number of experiments necessary to practice the invention in claim 2 (5 x 5 x 8 x 4 x 2 x 4) remains very large, namely 6,400. This claim is not enabled for at least the same reasons claim 1 is not enabled. *Id.*

b. Claim 3

Claim 3 depends from claim 1 and adds the requirement that the solution contain “no more than 150 ppb aluminum.” The difference between 250 ppb aluminum and 150 ppb does not materially change the enablement analysis. Ex. 1003, ¶ 118. Both are many multiples higher than the highest-disclosed aluminum content from the specification, and both require vast additional testing to justify the full scope. For example, the number of experiments necessary to practice claim 3 ($5 \times 6 \times 6 \times 4 \times 2 \times 4$) remains very large, namely 5,760. This claim is not enabled for at least the same reasons claim 1 is not enabled. *Id.*

c. Claim 4

Claim 4 depends from claim 1 and adds that the “vial is configured to substantially prevent atmospheric oxygen ingress and leaching of aluminum into the solution during storage of the solution in the vial.” This additional requirement does not change the enablement analysis. Ex. 1003, ¶ 119. As Dr. Confalone explained, there are various types of materials used to make vials that meet these requirements. Ex. 1003, ¶ 91. Even if the claim were construed to be limited to one type of vial, there would still be a large number of experiments ($5 \times 6 \times 8 \times 4 \times 2 \times 1$) required to practice the full scope of the invention, namely 1920. This claim is not enabled for at least the same reasons claim 1 is not enabled

d. Claim 5

Claim 5 recites a method for preparing the solution in claim 1:

5. A method of preparing the solution of claim 1 comprising,
- applying an inert gas to the carrier to reduce the dissolved oxygen content in the carrier to no more than 2 ppm;
- under an inert gas, mixing the carrier with L-cysteine hydrochloride monohydrate or a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof;
- optionally adjusting the pH of the mixture to from 1.0 to 2.5;
- transferring an amount of the mixture into a vial;
- overlaying the mixture with an inert gas; and
- sealing the vial, wherein the headspace oxygen within the sealed vial is no more than 5%.

Claim 5 differs from claim 1 in that it requires that the headspace oxygen is “no more than 5%” and the dissolved oxygen is “no more than 2 ppm,” while claim 1 recites a “total amount of oxygen” that is not more than 5%. The ’370 specification states that “the total amount of oxygen within the container may be arrived at by adding up the amount dissolved oxygen in the carrier and the amount of head space oxygen.” Ex. 1001 at 29:6-9. The specification further explains that “[t]hese values can be expressed independently in separate units (i.e., dissolved

oxygen as ppm and head space oxygen as % v/v).” Ex. 1001 at 29:9-11. Thus, strangely, dependent claim 5 allows more total oxygen than independent claim 1, and is therefore an inappropriate dependent claim. But in the context of this claim, there is no material difference over claim 1. As Dr. Confalone explained, the addition of 2 ppm of oxygen to 5% is negligible. Ex. 1003, ¶ 120. Therefore, the non-enablement analysis for claim 5 is substantially similar to that for claim 1.

e. Claim 6

Claim 6 depends from claim 5 wherein the dissolved oxygen content is no more than 1 ppm.” The difference between “not more than 2 ppm” and “not more than 1 ppm” dissolved oxygen does not change the non-enablement analysis. Ex. 1003, ¶ 122. Either way, the claim still allows up to 5% total oxygen. Claim 6 is non-enabled for at least same reasons as claim 5 and claim 1.

f. Claim 7

Claim 7 depends from claim 5 and adds the requirement that the headspace oxygen is “no more than 4%.” Similar to claim 2, the difference between 4% and 5% does not alter the enablement analysis. Ex. 1003, ¶ 123. Claim 7 is non-enabled for at least the same reasons as claim 5 and claim 1.

g. Claim 8

Claim 8 depends from claim 5 and adds that the dissolved oxygen content is “no more than 5 ppm.” Claim 8 recites a range of 0-5 ppm while claim 5, from which it depends, only claimed a range of 0-2 ppm. The difference between the

upper limits of 2 ppm and 5 ppm—again for only the dissolved oxygen—is negligible and does not change the enablement analysis. Ex. 1003, ¶ 124. The claim still allows up to 5% total oxygen.

h. Claim 9

Claim 9 depends from claim 5 and adds the requirement that when “transferring an amount of the mixture into a vial, an inert gas is utilized to minimize exposure of the solution to oxygen.” This additional requirement does not alter the enablement analysis. Ex. 1003, ¶ 125. The use of inert gases during packaging would also be used to maintain the oxygen levels required in claims 1 and 5. Ex. 1003, ¶ 125. Claim 9 is non-enabled for at least the same reasons as claim 5 and claim 1.

i. Claims 10-18

Independent claim 10 is the same as claim one other than the storage time is increased from 12 months to 18 months. That change does not alter the non-enablement analysis. Ex. 1003, ¶ 116. Claim 10 is not enabled for at least the same reasons claim 1 is not enabled.

Dependent claims 11-18 depend from independent claim 10 and include the additional limitations that appear in claims 2-9, respectively. Therefore, the non-enablement analyses for claims 2-9 apply equally to claims 11-18. Ex. 1003, ¶ 126.

j. Claims 19-27

Independent claim 19 is the same as claim one other than the storage time is increased from 12 months to 24 months. That change does not alter the non-enablement analysis. Ex. 1003, ¶ 116. Claim 19 is not enabled for at least the same reasons claim 1 is not enabled.

Dependent claims 20-27 depend from independent claim 19 and include the additional limitations that appear in claims 2-9, respectively. Therefore, the non-enablement analyses for claims 2-9 apply equally to claims 20-27. Ex. 1003, ¶ 127.

k. Claim 28

Claim 28 depends from claim 1 and adds the requirement that the concentration of L-cysteine is “about 34.5 mg/mL to about 50 mg/mL.” The difference between “about 10 mg/mL to about 100mg/mL” recited in claim one and the narrower range recited in claim 28 does not substantially alter the enablement analysis. Ex. 1003, ¶ 128. As Dr. Confalone explained, the narrower range of L-cysteine does not substantially alter the non-enablement analysis. This claim is not enabled for at least the same reasons claim 1 is not enabled.

l. Claims 29-30

Claims 29-30 depend from claims 10 and 19, respectively. Like claim 28, they recite that the concentration of L-cysteine is “about 34.5 mg/mL to about 50 mg/mL.” The only difference between independent claim 1 and independent claims 10 and 19 is the storage time: 12 months (claim 1); 18 months (claim 10); and 24

months (claim 19). Accordingly, the enablement analysis for claims 29 and 30 is the same as for claim 28. Ex. 1003, ¶129.

D. Ground 2: Written Description

For substantially the same reasons as discussed above for non-enablement, all claims of the '370 patent lack written description. In particular, the patent specification fails to show that the named inventors were in possession of any formulation that remained stable according to the claims, and for the time period required by the claims. The claims all require an L-cysteine formulation, wherein “after” “storage” for 12/18/24 months (for independent claims 1, 10, and 19 respectively), four different stability results are measured. These four stability results are: (a) total oxygen “no more than about [5%/4%]”, (b) “no more than [250/150] ppb aluminum,” (c) “substantially free of visually detectable particulate matter,” and (d) “a pH from 1.0 to 2.5.”

There are no examples in the specification that demonstrate the claimed stability: the longest stability test in the '370 patent specification is shown in Example 6, and that test lasted for 9 months, which of course is less than the 12/18/24 months required by all the claims. Ex. 1001, at 49:53-50:23. Moreover, even the 9-month test shown in the patent, at Example 6 and Table 18, does not show all four stability conditions. *Id.* As discussed above, given the unpredictability of L-cysteine formulations, and the propensity to degrade and

destabilize over time, the patent specification never demonstrated that the inventors possessed the claimed invention.

The claims in the '370 patent appear to cherry pick from background exemplary ranges mentioned in different parts of the specification, but nowhere tested nor shown to work for the intended purpose. The specification mentions that “[t]he compositions will have been stored at room temperature for less than a year, or for a year, or for more than a year. Such timelines include, for example, for about 15 months, for about 18 months, for about 24 months.” Ex. 1001 at 22:5-17. But the patent contains no support for any of these time points, and only shows 9-month data.

“The test for [written description] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (citation omitted). Even if the patent specification had one test that showed one formulation met the claimed stability criteria—which it does not—still the claims would not be sufficiently described in the '370 patent because one data point does not substantiate the full claimed ranges for oxygen and aluminum that all claims allow. Because the patent specification does not show that the named inventors ever

possessed what they later purported to claim, all claims of the '370 patent lack written description and should be invalidated.

E. Ground 3: Obviousness

In the event the non-enablement ground set forth above is found not to support institution of post grant review, Petitioner presents the following obviousness ground, because if the claims are enabled to their full scope then for the same reasons a POSA would be able to optimize the prior art formulation. Patent Owner cannot have it both ways. Thus, this obviousness section is provided only in the alternative, if the '370 patent claims are found to be enabled to their full scope.

This obviousness ground is similar to grounds presented in PGR2020-00064 and -00068 for related patents, '453 and '155, respectively. It is also similar to the obviousness defense raised in the *Exela* case. The claims of the '370, like the patent addressed in the earlier PGR petitions and asserted in the *Exela* case, claim L-cysteine solutions with aluminum-over-time, oxygen-over-time and stability limitations. *See* Sections IV and VIII, above. The difference is that, in this Petition, the obviousness ground is in the alternative and should be applied only if the claims are found to be enabled to their full scope, in which case the decision cannot be reconciled with prior non-obviousness decisions.

As described above, the district court concluded the patent owner argued that the claimed L-cysteine solutions were not obvious because of their complex, interrelated variables and unpredictable behavior. *See* Section VIII(A) and (B), above. Those findings and patent owner admissions support the non-enablement ground present above. If the recited L-cysteine solutions are not so complex and unpredictable as to be enabled, then the claims are obvious for the reasons set forth below.

1. Legal Standard

“Regardless of the tribunal, the inquiry into whether any ‘differences’ between the invention and the prior art would have rendered the invention obvious to a [POSA] necessarily depends on such artisan’s knowledge.” *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1337 (Fed. Cir. 2020). It is well established that the “mere application of a known technique to a piece of prior art ready for the improvement” is obvious. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 417 (2007). Similarly, design incentives and other market forces can prompt variations to a known product. If a POSA can implement a predictable variation, obviousness likely bars its patentability. *Id.* at 401.

The Board need not “make any finding regarding a motivation to combine” if Petitioner’s obviousness challenge is premised on a single reference. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019). However, if Petitioner’s

ground involves multiple references, “the Board can rely on evidence other than just prior art” to “consider[] the knowledge, motivations, and expectations of a POSA.” *Yeda Research v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018). For example, in the pharmaceutical art, FDA communications are evidence of a POSA’s knowledge and motivations for improving a drug product. *See, e.g., In re Copaxone Consol. Cases*, 906 F.3d 1013, 1029-30 (Fed. Cir. 2018) (affirming district court’s use of FDA disclosures “as evidence of a POSA’s motivations and expectations when reading the prior art at the time of the invention”).

2. Content of the Prior Art

Sandoz Label: The Sandoz Label was available by no later than 2016 and discloses an L-Cysteine Hydrochloride Injection, 50 mg/mL product available in single-dose vials. Ex. 1003, ¶ 27; Ex. 1005 at 4-5, 9-10. Petitioner Eton relied on Sandoz Label as prior art in PGR2020-00064 and -00068. The Patent Owner did not dispute the availability of the Sandoz Label as prior art in its preliminary responses. PGR2020-00064, Paper 6; PGR2020-00068, Paper 6. Similarly, there is no mention of a dispute regarding the status of the Sandoz Label as prior art in the *Exela* opinion.

The Sandoz Label (Ex. 1005), revised in 2010, was publicly available no later than August 24, 2016, on <http://www.drugsDB.eu> (“DrugsDB.eu”). Ex. 1005

at 1, 6. DrugsDB.eu states that the Sandoz Label was reproduced “with permission of U.S. National Library of Medicine.” Ex. 1005 at 1, 5, 6, 11.

PTAB precedent provides guidance for establishing pharmaceutical labels as prior art. In *Sandoz Inc. v. AbbVie Biotechnology Ltd.*, the Board found that a Wayback Machine screenshot, an accompanying Internet Archive affidavit regarding the site, and expert testimony on how a POSITA “exercising reasonable diligence could have located” the label was sufficient to establish the label as prior art for institution. IPR2018-00156, Paper 11, at 10-13 (PTAB June 5, 2018) (precedential); *see also Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29, at 18 (PTAB Dec. 20, 2019) (precedential) (confirming that a screenshot of a website from the Wayback Machine, a declaration from the Internet Archive including the site’s archival records, and expert testimony asserting its public accessibility was “strong indicia that an asserted reference was publicly accessible”). The same evidence is presented here.

Petitioner submits Wayback Machine screen shots of DrugsDB.eu, accompanying Internet Archive affidavits, and expert testimony demonstrating the public accessibility of DrugsDB.eu. Ex. 1004 at 1, 4, 10; Ex. 1005 at 1, 6 . Information regarding the Sandoz Label was also publicly available in the 2015 edition of Drug Facts and Comparisons, a publication bearing a copyright date of 2014 that “has served the drug information needs of pharmacists and other health

care professionals since its inception in 1946.” Ex. 1025 at 22- 23; Ex. 1026 at 1. Accordingly, the Sandoz Label qualifies as AIA § 102(a) prior art. *See Sandoz*, IPR2018-00156, Paper 11, at 9-13.

According to the Sandoz Label, each mL of the Sandoz product 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 at 1, 6. The POSA would have understood that air was replaced with nitrogen in the Sandoz product to stabilize L-Cysteine, which was known to be oxygen sensitive and oxidatively degrade to form L-Cystine and pyruvic acid. *See, e.g.*, Ex. 1003, ¶ 31. The Sandoz Label also states that the Sandoz product “[c]ontains no more than 5,000 mcg/L [i.e., 5000 ppb] of aluminum.” Ex. 1003, ¶ 28; Ex. 1005 at 5, 10. The POSA would have understood that aluminum is a toxic impurity (*see* Ex. 1003, ¶ 29; Ex. 1005 at 2, 8) and have interpreted the Sandoz Label as disclosing a range of aluminum extending from 0-5,000 ppb. *E.g.*, Ex. 1003, ¶ 28.

3. Additional Knowledge of a POSA

Motivation for Lowering Aluminum Levels: In 2004, FDA acknowledged and addressed concerns about aluminum toxicity in total parenteral nutrition (“TPN”) solutions when it issued a rule governing aluminum content in such products. Ex. 1006 at 1-2; Ex. 1003, ¶ 29. Under this rule, TPNs must include a package insert with a warning about the dangers of aluminum and a recommended

maximum daily aluminum dose of 4 to 5 mcg/kg/day. Ex. 1003, ¶ 26; Ex. 1054 at 1; Ex. 1055 at 2-3; Ex. 1006 at 7. Consistent with the FDA’s mandate, the Sandoz Label included that warning. Ex. 1003, ¶ 28; Ex. 1005 at 2, 8.

Further showing motivation, Hernandez-Sanchez observed in 2013 that, even though the industry could and should do more to lower aluminum levels—at least by choosing products with low Al contamination—“Aluminum (Al) toxicity in parenteral nutrition solutions (PNS) has been a problem for decades and is still unresolved” Ex. 1006 at 1, 8; Ex. 1003, ¶ 29.

Thus, prior to the ’370 patent’s effective filing date and in response to regulatory and market demands articulated by FDA and noted in Hernandez-Sanchez, the POSA would have been motivated to substantially reduce and eliminate aluminum from parenteral nutritional drug products such as the Sandoz product disclosed by the Sandoz Label. Ex. 1003, ¶¶ 29-30; *see also* Ex. 1006 at 7.

Strategies to Reduce Aluminum Contamination Were Well-Known: A POSA would have known that the starting materials (L-cysteine, for example) and packaging materials were common sources of potential aluminum contamination in parenteral drug products. *See* Ex. 1003, ¶ 29-30, 109, 139. A POSA would have addressed these known aluminum sources by screening and selecting raw materials substantially free of aluminum and by using a container closure system that did not leach aluminum into the final drug product. Ex. 1003, ¶ 140. By addressing and

eliminating these known sources of aluminum contamination, the POSITA would have had a reasonable expectation of substantially reducing and eliminating aluminum during manufacture and storage of the drug product. Ex. 1003, ¶ 141 .

L-Cysteine's Oxygen Sensitivity Was Well-Known and Easily Addressed:

During prosecution of the parent '453 patent, applicants argued that while solving the alleged problem of aluminum contamination they unexpectedly encountered another problem, L-Cysteine's oxygen instability. *See* Ex. 1024 at 409. But L-Cysteine's oxygen sensitivity, and its tendency to oxidatively degrade into L-Cystine (which can form unwanted particulate matter), were well known and reported in the prior art. Ex. 1003, ¶¶ 31-33; *see also* Ex. 1031 at 2; Ex. 1061 at 1-2.

There were also well-recognized prior art approaches for preventing the known oxidative degradation of oxygen sensitive drugs such as L-Cysteine. Ex. 1003, ¶¶ 34-35. For example, oxidative degradation can be prevented by removing dissolved oxygen and/or replacing headspace air with an inert gas, such as nitrogen or argon, during manufacture and storage. *Id.*; *see also* Ex. 1027 at 27; Ex. 1033 at 33; *see also* Ex. 1029 at 41. Indeed, as noted on the Sandoz Label, headspace air is replaced with nitrogen, which the POSITA would have understood was done to address L-Cysteine's oxygen sensitivity. Ex. 1003, ¶ 135; Ex. 1005 at 1, 6.

In addition, a POSA would have also known to use an oxygen impermeable container for an oxygen sensitive drug such as L-Cysteine, such as a glass vial. Ex. 1003, ¶ 140; Ex. 1014 at 8.

4. Claim 1

Claim 1 of the '370 patent is generally directed to a solution of L-cysteine for use in total parenteral nutrition that, after 12 months of storage in a sealed vial at room temperature, contains no more than 5% total oxygen, no more than 250 ppb aluminum, is substantially free of visible particulate matter, and has a pH from 1.0 to 2.5.

- a. “A solution of L-cysteine for use in total parenteral nutrition (TPN) comprising”

As explained above, the Sandoz Label discloses an L-Cysteine Hydrochloride Injection, 50 mg/ml product for parenteral administration. *See* Section VIII(E)(2); Ex. 1003, ¶ 132; Ex. 1005 at 1.

- b. “about 10 mg/L to about 100 mg/mL of L-cysteine or a pharmaceutically acceptable salt of hydrate thereof, in a pharmaceutically acceptable carrier; wherein:”

The Sandoz Label discloses that the concentration of the Sandoz L-Cysteine Hydrochloride product is 50 mg/mL. Ex. 1003, ¶ 133; Ex. 1005 at 1, 6. Thus, the hydrochloride salt is a pharmaceutically acceptable salt. The Sandoz Label also discloses “Water for Injection” as the carrier. Ex. 1005 at 1, 6.

- c. “after 12 months of storage in a sealed vial at room temperature:”

The Sandoz Label discloses a product that was enclosed in a single-use container having a volume of 10mL. Ex. 1003, ¶ 134, Ex. 1005 at 4-5, 9-10. A POSA would have understood that a shelf life of at least 12 months, and more likely 24 months would have been necessary for a commercially viable parenteral product like an L-cysteine solution. Ex. 1003, ¶ 134.

- d. “the total amount of oxygen within the sealed vial is no more than about 5%; and”

The '370 patent states that the “total amount of oxygen” in the vial “may be arrived at by adding up the amount of dissolved oxygen in the carrier and the amount of head space oxygen.” '370 patent, 29:4-9. A POSA would have known to reduce the amount of oxygen in the vial at least because, L-Cysteine was known to oxidatively degrade to L-Cystine, which can form undesired particulate matter. Ex. 1003, ¶ 32; Ex. 1020 at 3; Ex. 1031 at 2; Ex. 1061 at 1-2. Indeed, the Sandoz Label teaches that vial headspace air is replaced with nitrogen, which the POSA would have understood was done to prevent oxidative degradation of the L-Cysteine. Ex. 1003, ¶ 135; Ex 1005 at 1, 6.

Although the Sandoz Label does not disclose the percent oxygen in the vial headspace, the claimed range encompasses what was known in the art. *See, e.g.*, Ex. 1027 at 27 (“For oxygen-sensitive compounds in liquid formulation . . . An

oxygen level between 3 and 8% in the headspace is generally attainable . . .”); Ex. 1003, ¶¶ 34, 136; *see also In re Peterson*, 315 F.3d at 1329 (claimed range is *prima facie* obvious where prior art range overlaps with the claimed range).

Similarly, a POSA would have known common methods to remove oxygen from the “water for injection” disclosed as the carrier in the Sandoz label. Ex. 1005 at 1, 6. Specifically, Butler discloses nitrogen gas purging as a common method for removing dissolved oxygen from water and teaches that residual oxygen levels as low as 0.2-0.4 ppm can be achieved with a nitrogen purge. Ex. 1003, ¶ 137; Ex. 1082 at 1. Moreover, there is nothing unexpected about the claimed range. The claimed range is the reasonably expected result of routine optimization lowering head space and dissolved oxygen to prevent oxidative degradation of L-Cysteine. Ex. 1003, ¶¶ 136-137.

e. “the solution: contains no more than 250 ppb aluminum”

According to the Sandoz Label, the Sandoz product “[c]ontains no more than 5,000 mcg/L of aluminum.” Ex. 1003, ¶ 138; Ex. 1005 at 5, 10. Thus, the claimed no more than 250 ppb range falls within the 0 to 5,000 ppb range disclosed by the Sandoz Label and is thus *prima facie* obvious. *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”).

The claimed range is the expected result of optimizing the Sandoz product in response to regulatory and market pressures to substantially reduce and eliminate aluminum from parenteral drug products. *See* Section VIII(E)(3); *see also* Ex. 1003, ¶¶ 26, 29, 109, 139-141. As the POSA would have recognized the sources of the aluminum and eliminated them, including, the use of a container that did not leach aluminum, such as a silicon dioxide coated glass vial, and low-aluminum starting materials. Ex. 1003, ¶¶ 139-140; *see, e.g.*, Ex. 1014 at 8; Ex. 1008 at 1; Ex. 1012 at 3. A POSA would have reasonably expected that these strategies would result in the recited levels of aluminum. Ex. 1003, ¶ 141.

- f. “is substantially free of visually detectable particulate matter, and”

L-Cysteine was known to oxidatively degrade to L-Cystine, which can form undesired particulate matter. Ex. 1003, ¶ 32; Ex. 1061 at 1-2. Indeed, the Sandoz Label teaches that vial headspace air is replaced with nitrogen, which the POSA would have understood was done to prevent oxidative degradation of the L-Cysteine. Ex. 1003, ¶ 33; Ex. 1005 at 1, 6.

Although the Sandoz Label does not expressly disclose the amount, if any, of L-cystine in the Sandoz product, the absence of visually detectable particulate matter is the reasonably expected result of taking art-recognized steps to prevent

oxidative degradation of L-cysteine to L-cystine during manufacture and storage.

Ex. 1003, ¶ 142.

g. “has a pH form 1.0 to 2.5”

The Sandoz Label states that the L-Cysteine composition has an acidic pH of 1.0 to 2.5. Ex. 1005 at 1.

5. Claim 2

Claim 2 depends from claim 1 and adds the requirement that after 12 months of storage, the total amount of oxygen within the sealed vial is no more than 4%. The difference between 5%—recited in claim 1—and 4% does not negate obviousness. Ex. 1003, ¶ 144. Similar to claim 1, a POSA would have known to reduce the amount of oxygen in an L-cysteine solution and 4% oxygen content would have been readily achieved using well-known techniques. *Id.*

6. Claim 3

Claim 3 depends from claim 1 and adds the requirement that after 12 months of storage, the solution contains no more than 150 ppb aluminum. The difference between 250 ppb—recited in claim 1—and 150 ppb does not negate obviousness. Ex. 1003, ¶ 145. Similar to claim 1, a POSA would have known to reduce the amount of aluminum in an L-cysteine solution and 150 ppb aluminum would have been readily achieved using well-known techniques. *Id.*

7. Claim 4

Claim 4 depends from claim 1 and further requires that the vial “is configured to substantially prevent atmospheric oxygen ingress and leaching of aluminum into the solution during storage of the solution in the vial.” As Dr. Confalone explained, the requirement that packaging material (including a vial) for a parenteral formulation should prevent “atmospheric oxygen ingress and leaching of aluminum” would have been obvious to a POSA based on the need to strictly control and characterize impurities in pharmaceutical products. Ex. 1003, ¶ 146. Both of these goals would be compromised by a vial that was permeable to oxygen and leached aluminum. Accordingly, it would have been obvious to use a container that does not interact chemically with the solution and is impermeable to oxygen. See Ex. 1003, ¶ 146; Ex. 1008 at 1.

8. Claim 5

Claim 5 depends from claim 1 and recites a method of preparing the solution of claim 1. As described below each of the steps was standard procedure for making an L-cysteine solution, rendering the claim obvious. Ex. 1003, ¶¶ 147-152.

The first recited step is “applying an inert gas to the carrier to reduce the dissolved oxygen content in the carrier to no more than 2 ppm.” As Dr. Confalone, explained, the use of sparging techniques to reduce oxygen content in the carrier was a well-known strategy for oxygen sensitive drugs. See Ex. 1003, ¶ 148. The

literature also specifically reports that sparging techniques can reduce dissolved oxygen levels to at least 2 ppm. Ex. 1003, ¶ 148; Ex. 1082 at 1.

Claim 5 next recites “under an inert gas, mixing the carrier with L-cysteine hydrochloride monohydrate or a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof.” The Sandoz Product used L-cysteine hydrochloride in water. Ex. 1005 at 5. Of course, using mixing to combine L-cysteine and water would have been obvious. Dr. Confalone also explained that using a blanket of nitrogen during the preparation of an L-cysteine solution would have been a matter of routine for an oxygen sensitive compound. *See* Ex. 1003, ¶¶ 149.

Claim 5 next recites “optionally adjusting the pH of the mixture to form 1.0 to 2.5.” Using the pH would have been obvious at least because the Sandoz product reports a pH of 1.0 to 2.5. Ex. 1005 at 1; Ex. 1003, ¶ 150.

Claim 5 next recites “transferring an amount of the mixture into a vial.” As is commonly done to liquid parenteral formulations, the Sandoz Label states that the product is packaged in a vial. Ex. 1005 at 3-4. For at least this reason, it would have been obvious to transfer the mixture into a vial. Ex. 1003, ¶ 151.

Claim 5 finally recites “overlaying the mixture with an inert gas and sealing the vial, wherein the headspace oxygen within the sealed vial is no more than 4%.” As described above for claim 1, A POSA would have known to reduce the amount of oxygen in the vial at least because, L-Cysteine was known to oxidatively

degrade to L-Cystine, which can from undesired particulate matter. Ex. 1003, ¶ 32. Indeed, the Sandoz Label teaches that vial headspace air is replaced with nitrogen, which the POSA would have understood was done to prevent oxidative degradation of the L-Cysteine. Ex 1005 at 1, 6. Dr. Confalone also explained that achieving an oxygen level of 4% is the expected result of routine oxygen-control strategies. Ex. 1003, ¶ 152.

Accordingly, claim 5 would have been obvious.

9. Claim 6-9

Claims 6-9 depend from claim 5 and recites additional oxygen content limitations.

Claim 6 requires “dissolved oxygen in the carrier reduced to no more than 1 ppm.” As described for claim 5, a POSA would have known, and the literature corroborates, that sparging techniques are able to reduce dissolved oxygen to levels well below 1 ppm. Ex. 1003, ¶ 154.

Claim 7 requires headspace oxygen within the sealed vial is no more than 4%. This claim would have been obvious for basically the same reasons set forth above for claims 1 and 2. The additional recitation of “headspace” in this claim does not change the analysis. Ex. 1003, ¶ 155.

Claim 8 requires that the dissolved oxygen content of the solution within the vial is no more than 5 ppm. As described for claim 5, a POSA would have known,

and the literature corroborates, that sparging techniques are able to reduce dissolved oxygen to levels well below 1 ppm. Ex. 1003, ¶ 157.

Claim 9 adds an additional requirement to the method of claim 5 wherein, when transferring the solution into a vial, “an inert gas is utilized to minimize exposure of the solution to oxygen. As described above, a POSA would have recognized the oxygen sensitivity of L-cysteine and using a blanket of nitrogen during compounding, filling, and storing of the solution would have been standard practice. *See* Ex. 1003, ¶ 157.

10. Claim 10-18

Independent claim 10 is the same as claim one except the storage time is increased from 12 months to 18 months. That change does not alter the obviousness analysis. Claim 10 would have been obvious for at least the same reasons claim 1 would have been obvious. Ex. 1003, ¶ 158.

Dependent claims 11-18 depend from independent claim 10 and include the additional limitations that appear in claims 2-9, respectively. Therefore, the obviousness analyses for claims 2-9 apply equally to claims 11-18. Ex. 1003, ¶159.

11. Claim 19-27

Independent claim 19 is the same as claim one except the storage time is increased from 12 months to 24 months. That change does not alter the

obviousness analysis. Claim 19 would have been obvious for at least the same reasons claim 1 would have been obvious. Ex. 1003, ¶160.

Dependent claims 20-27 depend from independent claim 10 and include the additional limitations that appear in claims 2-9, respectively. Therefore, the obviousness analyses for claims 2-9 apply equally to claims 20-27. Ex. 1003, ¶161.

12. Claim 28-30

Claim 28 depends from claim 1 and adds the requirement that the concentration of L-cysteine is “about 34.5 mg/mL to about 50 mg/mL.” The difference between “about 10 mg/mL to about 100mg/mL”—recited in claim one—and the narrower range recited in claim 28 does not substantially alter the obvious analysis. Ex. 1003, ¶ 162. The Sandoz Label discloses an L-cysteine solution for parenteral administration comprising 50 mg/mL of L-cysteine hydrochloride which overlaps with the claimed range. Ex. 1005 at 5, 11. Therefore, it would have been obvious to use the claimed concentration of L-cysteine. Ex. 1003, ¶ 162.

Claims 29-30 depend from claims 10 and 19, respectively. Like claim 28, they recite that the concentration of L-cysteine is “about 34.5 mg/mL to about 50 mg/mL.” The only difference between independent claims 10 and 19 and independent claim 1 is the storage times, *i.e.*, 12 months (claim 1); 18 months

(claim 10); and 24 months (claim 19). The altered storage times does not substantially alter the obviousness analysis for claims 29-30 compared to claim 28. Ex. 1003, ¶163. Accordingly, claims 29 and 30 would have been obvious for at least the same reasons claim 28 would have been obvious. Ex. 1003, ¶163.

13. Secondary Considerations of Non-Obviousness

Petitioner is aware that the district court found that there was a long felt need for a “stable, low-aluminum cysteine product.” Ex. 1007 at 30. However, any alleged long felt need does not outweigh the strong evidence of obviousness, as presented here. As Dr. Confalone explained, given the obvious nature of the claimed L-cysteine solutions, any alleged delay in the development of an alternative to the Sandoz L-cysteine product was likely the result of economic or market considerations and not a lack of technical know-how. Ex. 1003, ¶¶ 164-165. In addition, the district court did not discuss nexus between any supposed long felt need for a “low-aluminum” product generally and the specific claimed ranges of less than 250 ppb and less than 150 ppb aluminum formulations. Based on the district court’s assessment that 5 mcg/day aluminum was acceptable (Ex. 1007, at ¶¶ 168, 172), and using the same ratio that the district court considered for converting ppb to mcg/day (Ex. 1007 at 15, (¶75)), then aluminum amounts up to 1785 ppb would have been just as sufficient.

IX. CONCLUSION

Petitioner requests institution of a PGR trial and cancellation of claims 1-30 of the '370 patent.

X. CERTIFICATE OF WORD COUNT

The Petition complies with the type-volume limitations as mandated in 37 FC.F.R. § 42.24, totaling 18,258 words. Counsel has relied on the word count feature provided by Microsoft Word.

Respectfully submitted,

Dated: February 8, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.105 and 42.6, I certify I caused a true and correct copy of the forgoing PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 11,642,370 was served on February 8, 2024, on the patent owner at the correspondence address of record for the subject patent as follows:

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Dated: February 8, 2024

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