

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 PGR2024-00016
Patent No. 11,642,370

**PATENT OWNER'S
PRELIMINARY RESPONSE**

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EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Dr. Dennis R. Jenke
2002	Aileen B. Sedman et al., <i>Evidence of Aluminum Loading in Infants Receiving Intravenous Therapy</i> , 312 NEW ENG. J. MED. 1337 (1985)
2003	Nicholas J. Bishop et al., <i>Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions</i> , 336 NEW ENG. J. MED. 1557 (1997)
2004	ELCYS [®] Label, Exela Pharma Sciences, LLC
2005	Amended Complaint (Redacted), <i>Exela Pharma Sciences, LLC v. Sandoz, Inc.</i> , No. 1:20-cv-00645-MN (D. Del. June 1, 2020), ECF No. 12
2006	Amended Complaint, <i>Exela Pharma Sciences, LLC v. Eton Pharmaceuticals, Inc.</i> , No. 20-365-MN (D. Del. July 28, 2020), ECF No. 14
2007	Declaration of Mark Hartman (Redacted), <i>Exela Pharma Sciences, LLC v. Sandoz Inc.</i> , No. 19-cv-00318-MR (W.D.N.C. Dec. 6, 2019), ECF No. 26-1
2008	Megan Fortenberry et al., <i>Evaluating Differences in Aluminum Exposure Through Parenteral Nutrition in Neonatal Morbidities</i> , 9 NUTRIENTS 1249 (2017)
2009	Kathleen M. Gura, <i>Aluminum Contamination in Parenteral Products</i> , 17 CURR. OPIN. CLIN. NUTR. & METAB. CARE 551 (2014)
2010	Gordon L. Klein et al., <i>Hypocalcemia Complicating Deferoxamine Therapy in an Infant with Parenteral Nutrition-Associated Aluminum Overload: Evidence for a Role of Aluminum in the Bone Disease of Infants</i> , 9 J. PED. GASTR. & NUTR. 400 (1989)
2011	Jay M. Mirtallo, <i>Aluminum Contamination of Parenteral Nutrition Fluids</i> , 34 J. PARENTERAL & ENTERAL NUTR. 346 (2010)
2012	Robert L. Poole et al., <i>Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation</i> , 32 J. PARENTERAL & ENTERAL NUTR. 242 (2008)
2013	PGR2020-00064, Paper 12 (herein, “453 PGR Decision”)

2014	PGR2020-00068, Paper 11 (herein, “155 PGR Decision”)
2015	PGR2020-00086, Paper 11 (herein, “719 PGR Decision”)
2016	<i>Exela Pharma Scis., LLC v. Eton Pharms., Inc.</i> (20-cv-365-MN) Day 1 Trial Transcript
2017	Toru Ogawa, Makoto Miyajima, Naoki Wakiyama & Katsuhide Terada (2015) Aluminum elution and precipitation in glass vials: effect of pH and buffer species, <i>Drug Development and Industrial Pharmacy</i> , 41:2, 315-321.
2018	PGR2020-00064, Paper 1 (herein, “453 PGR Petition”)
2019	Redacted Excerpt of Dr. Dennis Jenke Rebuttal Expert Report
2020	<i>Exela Pharma Scis., LLC v. Eton Pharms., Inc.</i> (20-cv-365-MN) Day 3 Trial Transcript
2021	<i>Exela Pharma Scis., LLC v. Eton Pharms., Inc.</i> (20-cv-365-MN) Stipulation, D.I. 266.
2022	Driscoll, M; Driscoll, D.F., Calculating aluminum content in total parenteral nutrition admixtures. <i>Am. J. Health-Syst. Pharm.</i> 2005:62:312-5.
2023	Roethlisberger, D.; Mahler, H.C.; Altenburger, U. Pappenburger, A. If Euhydric and Isotonic Do Not Work, What Are Acceptable pH and Osmolality for Parenteral Drug Dosage Forms? <i>Journal of Pharmaceutical Sciences</i> 106: 446-456 (2017)
2024	Carta, L.; Tola, G.; Solubilities of L-Cystine, L-Tyrosine, L-Leucine, and Glycine in Aqueous Solutions at Various pHs and NaCl Concentrations, <i>J. Chem. Eng. Data</i> 1996, 41, 414-417.
2025	Beg, S.; Application of Design of Experiments (DoE) in Pharmaceutical Product and Process Optimization; <i>Pharmaceutical Quality by Design</i> , 2019, Ch. 3. https://doi.org/10.1016/B978-0-12-815799-2.00003-4 .

I. INTRODUCTION

Exela's U.S. Patent No. 11,642,370 ("the '370 patent"; Ex. 1001) relates to inventions for stable, highly pure L-cysteine compositions to nourish preterm and underweight infants during their fragile first days, weeks, and sometimes months of life. While prior L-cysteine formulations contained up to 5,000 ppb (parts per billion) of toxic aluminum, the inventive compositions contain no more than 250 ppb of aluminum. Unlike prior L-cysteine compositions, which had aluminum levels known to increase over time, Ex. 1008 (Bohrer) at 1, 4, Table 2 and Fig. 2, the aluminum and other impurity levels in the claimed compositions are stable over time and remain safe for administration to infants throughout the product's shelf life. Exela's invention solved what was by 2013 already a "decades old and still unresolved" problem. Exela's invention resulted in its successful ELCYS® product, filling the longstanding need in the market for a total parenteral nutrition product that maintains safe, low aluminum levels over time for the vulnerable patients who need it.

The Office has awarded Exela several patents for its invention and the Petition presents the *fifth* invalidity challenge to patents in the family. Industry competitor Eton filed three PGRs against related patents with very similar claims. The Board denied institution for each of the three PGRs. Eton also challenged validity of three related patents before the district court. After a bench trial, the

court entered judgment of no invalidity. Petitioner repeats the very arguments the Office, this Board, and the district court have already rejected.

Petitioner's primary argument (Ground 1) is enablement, and the Examiner rejected this argument during examination of the priority application for the '370 patent. The Examiner issued a non-final office action rejecting the pending claims for the same reasons Petitioner now asserts: unpredictability of the art, breadth of the claims, the specification's guidance about the full scope of the claims, and the quantity of experimentation. Ex. 1024 ('453 File History) at 376-382. After considering Exela's response, the Examiner allowed all pending claims and issued U.S. Patent No. 10,478,453. *Id.* at 11-13. Petitioner admits the claims of the '453 Patent and the '370 Patent "claim very similar subject matter." Paper 1 at 11-12. Petitioner does not assert—much less explain how—the Examiner made a material error in deciding the claims are enabled.

For Petitioner's next argument, written description (Ground 2), Petitioner simply asserts that for "substantially the same reasons as discussed above for non-enablement, all claims of the '370 patent lack written description." *Id.* at 64. The Petition's ***two-page*** argument substantively fails for the same reasons the enablement argument fails. It also fails because it lacks the particularity requirement of 35 U.S.C. § 322(a)(3).

Petitioner's last argument is obviousness (Ground 3), and it is admittedly just a reprise of Eton's three failed PGRs and failed district court invalidity case brought against related Exela patents. Petitioner admits that Ground 3 involves the same prior art (the Sandoz label), same argument, and similar claims: "This obviousness ground is similar to grounds presented in PGR2020-00064, and - 00068 for related patents, '453 and '155, respectively. *See* Ex. 2013 (PGR2020-00064, Paper 12 denied institution of U.S. Patent No. 10,478,453 ("'453 PGR Decision")); Ex. 2014 (PGR2020-00068, Paper 11 denied institution of U.S. Patent No. 10,583,155 ("'155 PGR Decision")). It is also like the obviousness defense raised in the *Exela* case." Paper 1 at 66. Rather than claiming that the Board erred in not instituting the earlier PGRs, Petitioner *embraces* the prior decisions and uses them as the foundation for its non-enablement argument. Petitioner has not alleged, much less proven, a material error in the Board's decision to deny institution of the earlier PGRs. And its arguments also fail as lacking particularity, just as the arguments in the earlier non-instituted petitions.

The Board should exercise its discretion under 35 U.S.C. § 325(d) to deny institution of this request for post-grant review. This fifth challenge to this patent family raises no new arguments and makes no showing of any purported material error in the prior decisions. The Board has considered the obviousness issues raised in the Petition three times and declined to institute. *See* Ex. 2013 ('453 PGR

Decision); Ex. 2014 ('155 PGR Decision); Ex. 2015 (PGR2020-00086, Paper 11 (“’719 PGR Decision”)). The Delaware court had a bench trial on the same obviousness issues and ruled that the patents are valid. *See* Ex. 1007, *Exela Pharma Scis., LLC v. Eton Pharms., Inc.*, 620 F. Supp. 3d 108 (D. Del. 2022), *appeal dismissed sub nom. Exela Pharma Scis., LLC v. Dr. Reddy’s Lab’ys S.A.*, No. 2023-1026, 2023 WL 6492309 (Fed. Cir. Oct. 5, 2023). The Office previously considered the same enablement argument made here and decided in favor of issuance. And the written description argument presented is conclusory, lacks merit, and fails to support institution of post grant review.

Further, even if the Board were to consider anew the merits of the Petition, it would be fruitless. Petitioner has failed to show that it is more likely than not that the claims lack enablement or written description or would have been obvious.

A fundamental flaw of Petitioner’s non-enablement argument is that it is premised on a mischaracterization of Exela’s statements *about the prior art* in the prior proceedings. Petitioner asserts that the full range of the claims is not enabled because Exela has claimed in other proceedings that a POSA 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” and that a POSA “could not figure them out on their own without undue experimentation.” Paper 1 at 2. But Exela’s statements concern the level of

experimentation that a POSA would have needed *before* Exela's patent. Exela has never represented that a POSA—*with the benefit of Exela's patent specification*—could not arrive at the claimed inventions. The specification is the road map that solved this decades-old problem. And the POSA, of course, gets the full benefit of that roadmap for enablement.

Petitioner also has not found a single claimed embodiment that does not work. Petitioner wrongly asserts that even with the benefit of the '370 patent's 46-page disclosure a "POSA would have to engage in trial-and-error research to practice the claimed invention." Paper 1 at 53. Unlike the industry competitors who have copied Exela's low-aluminum, stable L-cysteine, Petitioner has not even tried to make a claimed embodiment and instead just criticizes the disclosure in the specification and makes unsupported assertions about the amount of testing that a POSA would supposedly need to do to practice the claims.

The Board should deny institution regarding written description for the same reasons, as Petitioner admits its written description argument and enablement argument are "substantially the same." Moreover, contrary to Petitioner's argument that "[t]here are no examples in the specification that demonstrate the claimed stability," Paper 1 at 64, the specification lists many examples that comprise the full claimed range. *See, e.g.,* Ex. 1001 ('370 Patent) at 36:3-41.44. The specification also includes testing data showing the inventors were in

possession of a stable formulation for the claimed periods. Although the Petition cites Table 18, it *ignores* other tables that have test data for the same lots (XMHJ1705 XMHJ1706 XMHJ1707). For example, the Petition does not mention Table 22, which shows test results for multiple representative batches (comprising over 10,000 vials, as shown in Table 23) at twelve months at room temperature conditions and six months at accelerated storage conditions. Nor does the Petition acknowledge that six months of *accelerated* stability data is an industry standard for demonstrating a product's stability for *twenty-four* months at normal (in this case, room temperature or long-term) storage conditions. The test data shows the inventors possessed the claimed L-cysteine formulations.

As to obviousness, Petitioner acknowledges that “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.” Paper 1 at 71. And yet, the problem went unsolved for years, including by Sandoz whose work on L-cysteine injection products dates to 2008, and who had the resources and economic incentive to solve the problem. Despite repeated pleas from the medical and academic communities for manufacturers to cut the aluminum contamination of parenteral products, more than a decade later neither Sandoz nor anyone else had solved the problem. *See* Ex. 2012 (Poole) at 1; Ex. 2011 (Mirtallo) at 2; Ex. 1006 (Hernandez-Sanchez) at 1; Ex. 2009 (Gura) at 1.

Instead, in May 2019, Sandoz approached Exela for a license to sell Exela's low-aluminum, FDA-approved L-cysteine product (ELCYS®) that embodies the '370 patent (this was just two months after FDA approval of ELCYS®). Ex. 2007 (Mark Hartman Decl., *Exela Pharma Sciences, LLC v. Sandoz Inc.*, No. 19-cv-00318-MR (W.D.N.C. Dec. 6, 2019), ECF No. 26-1) ¶¶ 6, 11. Sandoz's motivation for seeking a license could have only been because of the merits of the product; at that time Exela's patent applications were not public knowledge. After Exela declined, Sandoz filed an ANDA seeking FDA approval of a generic (i.e., copy) of Exela's ELCYS® product. Ex. 2005 (Amended Complaint, *Exela Pharma Sciences, LLC v. Sandoz, Inc.*, No. 1:20-cv-00645-MN (D. Del. June 1, 2020), ECF No. 12) ¶ 12. Exela promptly sued Sandoz for patent infringement, which resulted in dismissal and no market entry of Sandoz's product to-date.

Sandoz was not alone in seeking Exela's inventive solution to the long-standing aluminum problem for L-cysteine. Eton, in collaboration with AL Pharma (which manufactured an L-cysteine injection for Sandoz), also failed to solve the problem and resorted to copying Exela's invention. Eton tried and failed to invalidate Exela's patents in both district court and before the Board, and ultimately reached a settlement in which it licensed Exela's patents. Ex. 2021 (*Exela v. Eton* Stipulation, D.I. 266), ¶ 1. Both Eton and Sandoz were uniquely positioned with manufacturing and analytical facilities to modify the Sandoz high-

aluminum L-cysteine, and had economic incentives, yet they both failed for years and instead resorted to copying Exela's inventive solution. Petitioner has not shown it is more likely than not that any of the challenged claims would have been obvious in view of the Sandoz label.

In short, the Board should exercise its discretion to deny institution under § 325(d) because the Petition does not raise new arguments, and because the old arguments it raises have repeatedly and correctly been rejected by the Office, the Board, and the district court. And if the Board should get to the merits, it will find that Petitioner has not shown it is more likely than not that any of the challenged claims would have been obvious or lack enablement or written description support, and, for that additional reason, institution should be denied.

II. BACKGROUND

A. L-Cysteine is an essential amino acid, primarily administered to infants, that posed devastating health risks due to its high aluminum content before Exela's invention.

L-cysteine is an amino acid that performs various metabolic functions and is important for human life. While healthy adults can naturally synthesize small amounts of L-cysteine, certain high-risk populations require supplementation by parenteral administration (e.g., intravenous infusion or injection). These high-risk populations include preterm and low birth weight infants and other individuals with renal compromise (i.e., impaired kidney function). *See* Ex. 1006 (Hernandez-

Sanchez) at 2.

For these patients, L-cysteine is administered as a component of a nutritional regimen, typically referred to as Total Parenteral Nutrition (“TPN”) or Parenteral Nutrition (“PN”). Ex. 2016 (Exela v. Eton Day 1 Trial Tr. (Kuhn)) at 75:10-77:13. A TPN regimen involves administering—typically intravenously—a formulation that is a mixture (called an “admixture”) of various parenteral nutrition components. *Id.* at 78:18-79:22. Thus, L-cysteine is first manufactured as a stand-alone component, then admixed with various other components, and ultimately administered by IV to the patient as part of a TPN regimen. *Id.* at 77:14-78:7.

Aluminum is a known contaminant in TPN formulations. *See* Ex. 2002 (Sedman) at 1; Ex. 2012 (Poole) at 1 (“Aluminum is a contaminant of parenteral nutrition (PN) solution components.”); Ex. 1003 (Confalone Decl.), ¶ 26. As the *Journal of Parenteral and Enteral Nutrition* reported in 2008, “there have been numerous reports of aluminum toxicity from the contamination of [parenteral nutrition] solutions over the past 3 decades.” Ex. 2012 (Poole) at 3. Aluminum toxicity can cause “serious central nervous system and bone toxicities,” as well as liver damage and anemia. *Id.* Several components in a TPN solution can contribute to the total amount of aluminum after admixing, with L-cysteine formulations historically being a substantial contributor of aluminum. Ex. 1006

(Hernandez-Sanchez) at 2; Ex. 2012 (Poole) at Table 5; Ex. 2016 (Exela v. Eton Day 1 Trial Tr. (Kuhn)) at 80:12-82:5.

Before the '370 patent's inventions, the amount of toxic aluminum in L-cysteine formulations was known to increase over the product's two-year shelf life, due at least in part to aluminum leaching into the solution from its glass container. Ex. 1008 (Bohrer) at 1, 4, Table 2 and Fig. 2.

The vulnerable infants who receive TPN (most generally while in the Neonatal Intensive Care Unit (NICU)) are “predispose[d]” to a “high risk for aluminum toxicity.” Ex. 2008 (Fortenberry) at 1; *see also* Ex. 2016 (Exela v. Eton Day 1 Trial Tr. (Kuhn) at 81:23-82:5. These infants are particularly susceptible because they have immature kidneys, which impairs elimination of aluminum from the body. Ex. 1006 (Hernandez-Sanchez) at 2; *see also* Ex. 2016 (Exela v. Eton Day 1 Trial Tr. (Kuhn) at 81:10-15. As aluminum is prone to accumulate in bones, the central nervous system, and other tissues in the body, their risk is exacerbated by the prolonged TPN treatment they often require. Ex. 1006 (Hernandez-Sanchez 2013) at 2.

The consequences to preterm infants are sobering. A 1997 study found that preterm infants receiving the standard, high-aluminum TPN solutions lost one point per day on the 100-point Bayley Mental Development Index (MDI). Ex. 2003 (Bishop) at 1; *see also* Ex. 2012 (Poole) at 2. Infants receiving the standard

TPN solutions were also twice as likely to have MDI scores below 85 (the MDI level predictive of delayed neurodevelopment and subsequent educational problems) at 18 months, compared to infants treated with aluminum-depleted solutions. *Id.* Other studies have shown that the aluminum contamination in TPN solutions impairs bone calcium uptake and contributes to osteopenia, and can lead to significantly reduced hip bone mass, lumbar spine bone mineral content, and total bone area by age 13-15 years. Ex. 2010 (Klein) at 1; *see also* Ex. 1006 (Hernandez-Sanchez) at 6.

Because of the serious health risks associated with aluminum toxicity, the FDA since 2004 has required the labels for parenteral nutrition components to contain a “WARNING” that aluminum levels should not exceed 4 to 5 mcg/kg/day in vulnerable patients, like those with impaired kidney function. 21 C.F.R. § 201.323; Fed. Reg. 4103, 4111 (Jan. 26, 2000); 68 Fed. Reg. 32,979 (June 3, 2003); Ex. 1006 (Hernandez-Sanchez) at 7.

But it would take nearly fifteen years before someone (Exela) finally developed an injectable L-cysteine composition with acceptably safe aluminum levels that would enable practitioners to comply with this warning. *See* Ex. 2012 (Poole); Ex. 2016 (Exela v. Eton Day 1 Trial Tr. at 110:10-111:8 (explaining the market switch when ELCYS® became available in spring/summer 2019).

B. The patented invention solved the long-standing and complex problem to fulfill an unmet need for a stable, low-aluminum L-cysteine TPN component.

The inventors of the '370 patent finally solved the aluminum problem with parenteral L-cysteine compositions decades after its first recognition. Despite repeated pleas from the medical and academic communities for manufacturers to cut the aluminum contamination of parenteral products, Sandoz still had not solved the problem more than a decade later. *See* Ex. 2012 (Poole) at 1; Ex. 2011 (Mirtallo) at 2; Ex. 1006 (Hernandez-Sanchez) at 1; Ex. 2009 (Gura) at 1. Not only were the inventors able to develop L-cysteine compositions with low aluminum levels (no more than 120 ppb as embodied in the ELCYS® product and specifically covered by dependent claim 3's 150 ppb maximum), but the inventors' compositions are highly pure and remain stable over time. The stable compositions "contain the specified levels of all components for sufficient [*sic*] period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting." Ex. 1001 ('370 Patent) at 16:48-51.

In developing the patented inventions, the inventors had to overcome certain "unexpected technical hurdles." Ex. 1024 ('453 File History) at 407. Before Exela solved the long-standing aluminum problem, the kinetics and equilibrium chemistry of the various L-cysteine and L-cystine (an oxidative degradant of L-

Cysteine) species in any particular L-cysteine solution were considered complex and influenced by multiple interacting variables of that environment, including oxygen levels, pH, and the presence of trace metals. *See, e.g.*, Ex. 1020 (Allen) at 3; Ex. 1001 ('370 Patent) at 23:1-9; Ex. 1061 (Okabe) at 3-5. Moreover, multiple variables, including pH and L-cystine concentration, could affect the extent of aluminum leaching from the glass containers then used to store L-cysteine compositions. *See, e.g.*, Ex. 1012 (Bohrer) at 7; Ex. 2001 (Jenke Decl.), ¶ 30.

The art did not predict—nor could it have predicted—how those variables would interact under the specific conditions of the claimed L-cysteine parenteral solution, let alone how changing one variable would affect the other variables. For example, the inventors unexpectedly encountered that “removing Aluminum may have the unintended consequence of increased [L-cystine] precipitation and product failure in the presence of even small amounts of oxygen in the container.” Ex. 1001 ('370 Patent) at 5:22-25. As explained during prosecution, “the art did not know about the additional problems” of instability and L-cystine precipitate formation upon significant reduction of the aluminum concentration. Ex. 1024 ('453 File History) at 409. The inventors first discovered 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 (’370 Patent) at 4:53-59; *see also* Ex. 1024 (’453 File History) at 408.

Nonetheless, and despite “the unpredictable nature of the art,” as the Examiner acknowledged, the inventors addressed and overcame these multivariate problems to arrive at the patented invention. Ex. 1024 (’453 File History) at 378–79. In the Notice of Allowance for the first patent in the family, the Examiner explained that the inventors had “achieve[d] a composition which is far below the FDA demand [for aluminum levels], filling an unmet need which has been present for quite a number of years.” *Id.* at 420. The Examiner further recognized that this “unexpected result is due to the Applicants [*sic*] unexpected findings resulting from testing combinations of theories with no expectation of success.” *Id.*

Exela’s invention, disclosed and claimed in the ’370 patent, is embodied in ELCYS®, the first FDA-approved, low-aluminum L-cysteine hydrochloride injection product, which is labeled as containing no more than 120 ppb of aluminum throughout its two-year shelf life. Ex. 2004 (ELCYS® Label) § 11. “Stability testing of ELCYS under accelerated conditions shows that its registration batches contained between 6 ppb and 9 ppb of aluminum throughout its 24-month shelf life when stored at 25°C and 60% relative humidity.” Ex. 1007, *Exela*, 620 F. Supp. 3d at 120. “ELCYS contains headspace oxygen between 1.9% and 2.3% at release and between 0.9% and 2.8% one month from manufacture

when stored at room temperature, and dissolved oxygen between 0.39 and 1.59 ppm at release, and between 0.51 and 1.04 ppm one month from manufacture when stored at room temperature.” *Id.*

C. The earlier PGRs and district court invalidity challenges confirmed Exela’s inventions are not obvious.

a. PGRs

In 2020, Eton Pharmaceuticals Inc. filed three Petitions requesting post-grant review of the claims of Exela’s U.S. Patent Nos. 10,478,453 (PGR2020-00064), 10,583,155 (PGR2020-00068), and 10,653,719 (PGR2020-00086). The ’453 patent issued from Application No. 16/248,460 (the priority application), the first of a series of continuation applications leading to the ’370 patent. The ’155 and ’719 patents are continuations of the priority ’460 Application. Ex. 1007, *Exela*, 620 F. Supp. 3d at 116-19. Accordingly, the ’370 Patent and the three related patents (’453, ’155, and ’719) share a specification and are all directed to stable, highly pure L-cysteine compositions. As described by the Board in the first non-institution decision, “[t]he ’453 patent describes stable L-cysteine compositions for injection, comprising: L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL, and aluminum in an amount from about 1.0 parts per billion (ppb) to about 250 ppb.” Ex. 2013 (’453 PGR Decision) at 3. In its PGR petitions, Eton asserted that the three patents were obvious based on the Sandoz Label by itself or combined

with other references. *See* Ex. 2013 ('453 PGR Decision) at 6 (Sandoz Label, Sandoz Label combined with Hospira Label, and Sandoz Label combined with Allergy Process); Ex. 2014 ('155 PGR Decision) at 7-8 (Sandoz Label combined with Hospira Label, and Sandoz Label combined with Hospira Label, Hospira Package Insert, and Federal Register Notice); Ex. 2015 ('719 PGR Decision) at 7 (Sandoz label).

The Board declined to institute reviews for any of the patents. First, among its findings in the first decision denying institution of the '453 petition, the Board concluded “we are not persuaded that the Petition establishes that it is ‘more likely than not’ that any of claims 1–22 of the '453 patent are unpatentable under 35 U.S.C. § 103(a) based on the grounds presented.” Ex. 2013 ('453 PGR Decision) at 23. In particular, the Board found the Sandoz Label—precisely the same reference Petitioner relies on here for obviousness in Ground 3—did not disclose a range of aluminum contamination from 0 ppb to 5,000 ppb and that the claimed low amounts of aluminum could not be achieved with routine optimization. *Id.* at 22-23. The Board applied substantially the same reasoning in denying institution of the related PGRs. Ex. 2014 ('155 PGR Decision) at 19 (“[W]e do not find that the indication in the Sandoz Label that the product ‘[c]ontains no more than 5,000 mcg/L of aluminum’ reasonably suggests a range of 0–5,000 mcg/L of the

aluminum amount that would be subject to routine optimization.”); Ex. 2015 (’719 PGR Decision) at 26 (same).

Second, the Board found that Eton had not met the particularity requirements of 35 U.S.C. § 322(a)(3) for any of the arguments (which are similar to those made by Petitioner here) attempting to combine the Sandoz Label with the knowledge of a POSA:

Based on the above examples, we agree with Patent Owner and find that the Petition fails to meet the particularity requirement of 35 U.S.C. § 322(a)(3) with regard to Petitioner’s assertion that the subject matter of claims 1–14 would have been obvious over the Sandoz Label in conjunction with the knowledge of a person of ordinary skill in the art, and we decline to institute a post-grant review on that ground.

Ex. 2013 (’453 PGR Decision) at 17.

b. District Court

Petitioner properly summarizes some aspects of the Delaware court’s description of the Sandoz product prior art:

- “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.”
- “There was no data provided for the specific amount of cystine in the Sandoz product.”
- “The Sandoz Label does not identify the container used other than noting it was a clear glass vial.” Paper 1 at 30.

But Petitioner misstates the Delaware court’s findings about whether oxygen controls were used in making the Sandoz product. Petitioner incorrectly says: “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).” But the Delaware court found the opposite: “Allergy Labs [Sandoz’s predecessor] did *not* employ oxygen controls (such as nitrogen sparging, use of a nitrogen blanket during manufacturing and filling, or dissolved or headspace oxygen measurements) in manufacturing the Sandoz product.” Ex. 1007, *Exela*, 620 F. Supp. 3d at 124. Thus, unlike the patented invention, the Sandoz product did not adequately control for oxygen and there is no evidence it used a coated glass vial.

III. CLAIM CONSTRUCTION

The Board need not resolve the meaning of claim terms to deny institution.

IV. LEVEL OF ORDINARY SKILL IN THE ART

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

compensate for less or different formal education, and more formal education can compensate for less practical experience. Ex. 2019 (Jenke Reb. Rpt.), ¶¶ 39-41.

V. THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION UNDER § 325(D).

The Board has the authority to decline to institute post grant review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). In evaluating whether to exercise its discretion to deny institution under § 325(d), the Board employs a two-part framework: (1) whether the same or substantially the same art or arguments were presented to the patent office; and (2) whether the petitioner has shown that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH, No. IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential).

The Petition references § 325(d) only once, without citing *Advanced Bionics* or providing any substantive discussion of how the arguments in the Petition could meet the standards:

This Petition includes new grounds of unpatentability, namely nonenablement 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).

Paper 1 at 12.

Here, in its only discussion of § 325(d), Petitioner is careful to say that Ground 1 (enablement) and Ground 2 (written description) were not at issue *in the Eton PGRs*, but Petitioner does not mention here that the Examiner extensively discussed the same enablement argument during prosecution of the priority application, No. 16/248,460. The '460 Application is the first of a series of continuation applications that led first to the '453 Patent, and later to the '155 Patent, the '719 Patent, and the '370 Patent. Petitioner admits the claims of the '453 patent, the '155 patent, and the '370 patent “claim very similar subject matter.” Paper 1 at 11-12.

While Petitioner makes no mention of Ground 3 (obviousness) in its discussion of § 325(d), in other parts of the Petition it acknowledges—as it must—that Ground 3 relies on the same prior art and argument that the Board addressed in the earlier PGRs. Paper 1 at 66 (“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.”)

The first prong of the *Advanced Bionics* test is therefore satisfied. The Board has previously considered Petitioner’s obviousness challenge; the Office has

previously considered Petitioner’s enablement challenge; and Petitioner acknowledges its written description challenge is the same as its enablement challenge. The second prong is also satisfied, as the Petitioner has not shown—indeed, does not even attempt to explain—how the Board and the Examiner materially erred.

A. The first prong of the *Advanced Bionics* test is satisfied.

a. The prior decisions involved related patents that had claims directed to “very similar subject matter.”

The Office and Board have considered family member patents “that claim very similar subject matter” to the claims that Petitioner challenges in the ’370 Patent and addressed the same or similar arguments, easily meeting the first prong of the *Advanced Bionics* test. Paper 1 at 11. *See Passage Bio, Inc. v. The Trustees of the Univ. of Pennsylvania, et al.*, No. PGR2021-0073, Paper 13, 26 (PTAB Oct. 6, 2021) (“Having reviewed the prosecution histories, however, we find that Petitioner’s arguments are the same or substantially the same as those previously presented to the Office during the prosecution of the ’218 application **and the priority applications**” (emphasis added).) On June 19, 2019, the PTO issued an Office Action rejecting all claims of application No. 16/248,460 on the grounds of lack of enablement. The ’460 Application is the first of a series of continuation applications that led first to the ’453 Patent, and later to the ’155 Patent, the ’719 Patent and the ’370 Patent. Petitioner never mentions the PGR decision for the

'719 patent. But in discussing the other two PGRs, Petitioner admits that the claims of the '453 Patent and '155 Patent are like the '370 patent: "All three patents claim stable L-cysteine solutions with a limited amount of precipitates and covering varying levels of aluminum. The '370 and '453 patents also cover varying levels of oxygen." Paper 1 at 11. The Petition even includes a table showing the similarity of the claims for the '370 Patent, the '453 Patent, and the '155 Patent. *Id.* at 11-12. Below is claim 1 of the '460 Application, which became claim 1 of the '453 Patent. Claim 1/460 recites oxygen levels at one month and recites pyruvic acid levels, whereas Claim 1/370 recites oxygen levels at one year and pH levels; but, otherwise, as shown below, they are directed to the same subject matter. *See* Ex. 1024 ('453 File History) at 90.

Claim 1 of the '460 Application	Claim 1 of the '370 Patent
1. (Original) A stable L-cysteine composition for parenteral administration, comprising: L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof in an amount from about 10 mg/mL to about 100 mg/mL; Aluminum (Al) in an amount from about 1.0 parts per billion (ppb) to about 250 ppb; L-cystine in an amount from about 0.001 wt% to about 2.0 wt% relative to L-cysteine; pyruvic acid in an amount from about 0.001 wt% to about 2.0 wt%	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:

<i>relative to L-cysteine; a pharmaceutically acceptable carrier, comprising water;</i> headspace oxygen that is from about 0.5% v/v to 4.0% v/v from the time of manufacture to about <i>1 month</i> from manufacture when stored at room temperature; dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture to about 1 month from manufacture when stored at room temperature, wherein the composition is enclosed in a single-use container having a volume of from about 10 mL to about 100 mL.	contains no more than 250 ppb aluminum, is substantially free of visually detectable particulate matter, and <i>has a pH from 1.0 to 2.5.</i>
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b. Obviousness

As Petitioner admits, its obviousness argument is the same or substantially the same as the obviousness argument Eton presented (and lost on) in the earlier PGRs: “This obviousness ground is similar to grounds presented in PGR2020-00064, and -00068 for related patents, ’453, and ’155, respectively.” Paper 1 at 66. It is also the same or substantially the same obviousness argument Eton presented in the ’719 Patent PGR, which Petitioner ignores. *See* Ex. 2015 (’719 PGR Decision) at 7 (Asserting § 103 obviousness in light of the Sandoz Label). Indeed, by Petitioner’s own admission, the only “difference is that, in this Petition, the obviousness ground is in the alternative and should be applied only if the claims

are found to be enabled to their full scope, in which case the decision cannot be reconciled with prior non-obviousness decisions.” Paper 1 at 66.

Specifically, Petitioner asserts the *same prior art*—the Sandoz label—and makes *the same argument* that the Board previously considered and rejected. *Id.* at 66. For example, just like the arguments in the ’453 PGR, the Petition here asserts all claims would have been obvious based on the Sandoz Label in view of a POSA’s knowledge. *Id.* at 10, 68-70.

'453 PGR Petition ¹	Nexus's Petition ²	'453 PGR Decision ³
“[A]ccording to the Sandoz Label, the Sandoz product ‘[c]ontains no more than 5,000 mcg/L of aluminum.’ Ex. 1003, ¶ 32; Ex. 1005 at 5, 10; Ex. 1004 at 8, 13. Thus, the claimed 1 ppm to 250 range falls within the 0 to 5,000 ppb range disclosed by the Sandoz Label and is thus <i>prima facie</i> obvious.” <i>In re Peterson</i>, 315 F.3d 1324, 1330 (Fed. Cir.).	“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 <i>prima facie</i> obvious.” <i>In re Peterson</i>, 315 F.3d 1324, 1330 (Fed. Cir.).	“Petitioner attempts to further bolster its routine optimization argument by urging that the recitation of ‘[c]ontains no more than 5,000 mcg/L of . . . aluminum’ in the Sandoz Label should be interpreted as a disclosure of an aluminum range from 0 to 5000 ppb. Based on this interpretation, Petitioner concludes that it would have been obvious to optimize the aluminum content in a parenteral solution.”

The panel in the '453 PGR found, among other things, that the Sandoz label did not teach all of the claim elements, and that the combination of the Sandoz label

¹ Ex. 2020 ('453 PGR Petition) at 44-45 (cleaned up).

² Paper 1 at 75.

³ Ex. 2013 ('453 PGR Decision) at 19-20 (cleaned up). *See also* Ex. 2014 ('155 PGR Decision) at 15; Ex. 2015 ('719 PGR Decision) at 22-23.

and knowledge of the POSA did not render obvious claims that are similar to the '370 claims. Paper 1 at 10-11. The panels in the '155 PGR and the '719 PGR reached the same conclusion. Ex. 2014 ('155 PGR Decision) at 21; Ex. 2015 ('719 PGR Decision) at 26. This Petition raises the same obviousness argument the Board has rejected three times. Paper 1 at 10-11. Petitioner also admits that during Examination of U.S. Patent No. 10,933,089, which is another parent to the '370 patent, the Examiner considered whether the claims were obvious in view of the Sandoz label and the knowledge of the POSA. Paper 1 at 19-21. Because both the Board and the Office have considered this argument, the first prong of the *Advanced Bionics* test is met for Ground 3.

c. Enablement

The Office already considered and rejected the same enablement argument the Petition makes here. In the June 19, 2019, non-final office action, the Examiner rejected all pending claims in the '460 Application for lack of enablement on the grounds that the claimed subject matter is unpredictable, the claims are too broad, and the specification fails to disclose to a POSA how to practice the claimed invention without undue experimentation. As shown in the table above (*supra* at § V.A.a) then pending claim 1 of the '460 Application is very similar to claim 1 of the '370 patent. The Examiner explicitly addressed the enablement arguments Petitioner now raises:

- ***Unpredictability of the art:*** “The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art.... while aluminum contamination is a known problem, it is unknown how to reduce the aluminum content of formulations.” Ex. 1024 (’453 File History) at 378-79.
- ***Breadth of the claims:*** “The claims are broadly drawn to a composition having claimed properties, but with no disclosure or limitations as to how those properties are achieved.” *Id.* at 379.
- ***Specification’s guidance about the full scope of the claims:*** “The specification provides no direction or guidance for practicing the claimed invention in its ‘full scope.’ No reasonably specific guidance is provided concerning useful protocols for carrying out the invention as claimed, other than the prophetic process at pg 51, which does not provide an explanation or evidence that the contamination content will be lower than already commonly present.” *Id.*
- ***The quantity of experimentation:*** “Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its ‘full scope’ a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success.” *Id.* at 379-80.

In overcoming these arguments, Exela acknowledged that “the cited art reports on the problem at hand, which after many years was still unsolved prior to the present inventors’ solution as described in the present application.” *Id.* at 408. Exela directed the Examiner to the portions of the specification that explained the nature of the problem: “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....” *Id.* (citing the specification at page 6, lines 25-28). Exela also addressed the Examiner’s discussion of the *Wands* factors by pointing out the relevant portions of the specification that address these problems, including the extensive testing data:

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

Ex. 1024 (’453 File History) at 408 (emphasis added).

The Examiner agreed with the evidence presented in the specification and determined that the claims are enabled. *Id.* at 415. Petitioner now asserts the

claims are not enabled and lack written description for the same reasons the Examiner considered and rejected.

- ***The Petition alleges the art is unpredictable:*** “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.” Paper 1 at 5.

The Examiner has already considered and rejected this argument as well. Ex. 1024 (’453 File History) at 378, 420.

- ***The Petition asserts the claims are broad:*** “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.” Paper 1 at 40.

Once again, the Examiner considered and rejected this argument. Ex. 1024 (’453 File History) at 378-79, 420.

- ***The Petition alleges the specification does not teach how to practice the full scope of the claims:*** “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.” Paper 1 at 42.

Yet again, the Examiner considered and rejected this argument. Ex. 1024 (’453 File History) at 379, 420.

- ***The Petition alleges that it would take “trial and error” experimentation to figure out whether the claims are enabled:*** “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.” Paper 1 at 40-41.

As with all the other enablement arguments in the Petition, the Examiner considered this argument too. Ex. 1024 (’453 File History) at 379-80.

Thus, the Examiner considered and rejected each of the enablement arguments that Petitioner now asserts as Ground 1 and which also underlie Petitioner’s written description challenge (Ground 2). Thus, the first prong of the *Advanced Bionics* test is met for Ground 1 and, as shown below, also for Ground 2.

d. Written description

The first prong of the *Advanced Bionics* test is met for Ground 2 because, as Petitioner acknowledges, the Petition’s written description argument is “substantially the same” as the enablement argument that the Examiner considered during prosecution of the ’460 Application. Indeed, Petitioner’s two-page written description argument is simply an echo of its twenty-seven-page enablement argument. Petitioner admits the similarity of its enablement and written description arguments and states that the claims lack written description for the same reasons they are not enabled: “For substantially the same reasons as discussed above for non-enablement, all claims of the ’370 patent lack written description.” Paper 1 at 64.

* * *

In summary, the first prong of the *Advanced Bionics* test is met because Ground 1 makes the same non-enablement arguments the Examiner made and that Exela overcame during prosecution of the priority '460 application; Ground 2 is the same failed arguments from Ground 1 simply repackaged as a written description challenge; and Ground 3 is the same obviousness challenge the Board considered and rejected in the three failed PGRs.

B. The second prong of the *Advanced Bionics* test is satisfied.

The second prong of the *Advanced Bionics* test is satisfied because Petitioner has not shown that the Board or Examiner erred—let alone in a manner material to patentability—when they previously considered and rejected the same art and arguments Petitioner relies on here. Petitioner does not even allege the Board made a mistake when it denied institution for the three earlier PGRs challenging obviousness. Nor does Petitioner allege that the Office made a mistake when it decided the claims of the '460 Application are enabled. On this basis alone, the Board should deny institution. *See Vital Connect Inc. v. Bardy Diagnostics, Inc.* IPR2023-00381, Paper 7 at 19-20 (July 11, 2023) (denying institution where petition is “silent on material error”). “If a condition in the first part of the framework is satisfied and the petitioner *fails to make a showing of material error*,”—like Petitioner here—“the Director generally will exercise discretion not to institute *inter partes* review.” *Advanced Bionics*, 8–9 (emphasis added).

Petitioner even goes so far as to *embrace* the Board’s prior PGR decisions, stating: “In fact, if anything the Petition accepts and relies upon those proceedings to substantiate Section 112 invalidity.” Paper 1 at 10. Petitioner asserts that because the claims are not obvious, they must not be enabled—as if these are the only two possibilities:

[T]his 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.

Paper 1 at 6. This is a false dichotomy that was rejected by the Federal Circuit. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015). Petitioner ignores the critical fact that the specification supplies the road map to solving the problem that had perplexed the industry for over a decade. The Board need not decide the merits of this argument because it has already done so, and Petitioner has not shown that the Board materially erred in doing so.

The Board should deny institution because the Petition does not assert—much less prove—any material error during prosecution. *See Vital Connect Inc. v. Bardy Diagnostics, Inc.* IPR2023-00381, Paper 7 at 19-20 (July 11, 2023) (denying institution where petition is “silent on material error”). “[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record

unless material error is shown.” *Advanced Bionics*, at 9. The Petition is *silent* about how the Office erred in deciding that the claims are enabled. In its overview of the patent section, the Petition mentions the Examiner’s non-enablement rejection and mentions the Examiner reversed that rejection, but it does not explain how the Examiner erred in allowing the claims to issue. Paper 1 at 21-22, 26. Petitioner may disagree with the Examiner’s conclusion that the claims are enabled, but that disagreement is not a basis for institution: “When analyzing the second prong, [i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 7 (cleaned up).

C. Section 325(d) is sufficiently implicated such that the Board should deny institution on all grounds.

Although the Examiner did not issue a written description rejection, the Examiner addressed the enablement arguments that underlie Petitioner’s written description challenge. The Petition’s two-page written description argument is the same as Petitioner’s enablement argument. Petitioner admits this: “For substantially the same reasons as discussed above for non-enablement, all claims of the ’370 patent lack written description.” Paper 1 at 64.

The Board should thus deny institution on Ground 2 for the same reason it denies institution on Ground 1—they are the same argument. Here, § 325(d) is

“sufficiently implicated” that its statutory purpose would be undermined by instituting review. In addition, it would waste Board resources to institute under § 324(a) on the one ground that is only superficially raised, particularly where (as discussed in section VI.D.c. below) the argument is premised on a fundamental misunderstanding of basic stability testing principles. The crux of Petitioner’s written description argument is that the “longest stability test” in the specification is 9 months, “which of course is less than the 12/18/24 months required by the claims.” Paper 1 at 64. But the patent also includes 12-month data at long-term conditions, as well as 6-month data at accelerated conditions. *See, e.g.*, Ex. 1001 (’370 Patent) at Table 22. It is a basic principle in the art that **6 months** of **accelerated** stability data is used to represent the product’s stability over **24 months** at long-term storage (in this case, room temperature) conditions. Ex. 2001 (Jenke Decl.), ¶¶ 34-35. This is how FDA evaluates drug product stability in approving the filings. Petitioner, who files FDA applications regularly, ignores this well-known and accepted stability principle.

The Petition is treading over well-trodden arguments. There is no reason for the Board to consider a fourth PGR to this family of patents. *Passage Bio*, No. PGR2021-0073, Paper 13, 7 (“[W]e determine that 35 U.S.C. § 325(d) is sufficiently implicated that instituting review on all grounds would undermine the statutory purpose of 35 U.S.C. § 325(d)”).

Furthermore, if the Board finds that while most of the claim limitations have been previously decided but is convinced that one or two challenges to limitations may have a reasonable likelihood of success, the Board can also deny institution under § 314(a) if it believes the pursuit is not worth the Board's time and resources. *See Chevron Oronite Co. LLC v. Infineum USA L.P.*, No. IPR2018-00923, Paper 9 at 11 (PTAB Nov. 7, 2018) ("On this record, instituting a trial with respect to all twenty claims based on evidence and arguments directed to dependent claims 3 and 4 is not an efficient use of the Board's time and resources. Thus, we do not institute an inter partes review"); *Deeper, UAB v. Vexilar, Inc.*, Case IPR2018-01310, Paper 7 at 43 (PTAB Jan. 24, 2019).

Therefore, the Board should deny institution under § 325(d).

VI. THE PETITION DOES NOT SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS ARE NOT ENABLED OR DESCRIBED.

Even if the Board considers the merits, the challenge to the claims on enablement, written description, and obviousness fails for the same reasons they previously failed.

A. There is no judicial estoppel because Exela is not taking inconsistent positions about the complexity of the problem and the efficacy of its solution.

Petitioner asserts that Exela should be judicially estopped from asserting the claims are enabled, but Petitioner's argument is based on a misrepresentation of

what Exela said during the earlier proceedings. Exela has consistently said *the prior art did not enable* a POSA to make a stable, low-aluminum L-cysteine.

Exela has also consistently asserted that *its patent specification enables* a POSA to make a stable, low-aluminum L-cysteine. These statements are not inconsistent.

Rather, they are the two sides of Exela's invention story: why the problem remained unsolved and how Exela solved it.

The problem of aluminum in L-cysteine *was* "complex and unpredictable" *before Exela solved it*. The prior art knew aluminum was a problem but did not know how to solve it. First, as the patent specification explains, the amount of aluminum leaching from the vial was higher than expected: "It was however found that glass containers contribute more significantly than expected to the Aluminum content of L-cysteine compositions stored therein...." Ex. 1001 ('370 Patent) at 4:64-66. Second, while trying to reduce the amount of aluminum, the inventors made the additional unexpected discovery that oxygen was also contributing to the instability of L-cysteine:

As such, efforts were focused on identifying the sources of Aluminum in the product and attempts to minimize it in the product. These efforts led to the *unexpected discovery* that simply removing a source of Aluminum by replacing glass with plastic did not result in a product having the desired properties. Additional efforts to identify the root cause for the product failure led to the finding that *the product likely failed because oxygen entered the plastic container* and into the product at a rate higher than previously expected or predicted. For example, the plastic container product failed in some

cases in less than 1-2 months. See Example 3. This finding was also *unexpected. Increased oxygen levels in the product led to unacceptable levels of oxidation products, such as cystine*, which precipitated and caused particulates in the product.

Ex. 1001 ('370 Patent) at 5:2-16.

Finally, the inventors unexpectedly discovered that there is a complex relationship between the amount of aluminum, the amount of oxygen, and the stability of the product. As the specification explains, even small amounts of oxygen can lead to failure when aluminum levels are low, because as Exela discovered, the aluminum may have a stabilizing effect that prevents precipitation:

However, the *precipitation 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 amounts of oxygen in the container. This was *unexpected*.

Ex. 1001 ('370 Patent) at 5:20-25. The inventors figured out this complex and unexpected relationship between aluminum, oxygen, and product stability:

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

Id. at 4:53-59. The problem the inventors tackled *was* complex and unpredictable—a POSA could not solve it by looking only at the prior art—and the inventors solved it.

Exela has *never* said a POSA could not derive a stable, low-aluminum L-cysteine *after* reading the specification. To the contrary—the specification supplies the road map for solving this decades’ old problem. It explains the problem, shows the solution, and supplies extensive test data confirming the solution works. Exela’s statements about the problem being complex and unpredictable are completely consistent with its position that its patent enables the solution. Because Exela has not taken inconsistent positions, judicial estoppel does not apply. *See Cross Med. Prod., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1316 (Fed. Cir. 2005) (“Because the positions are not entirely inconsistent, judicial estoppel does not apply.”)

B. The specification teaches how to make and use the full range of claimed L-cysteine solutions.

Nexus’s reliance on *Amgen v. Sanofi* is misplaced because that case is about claims to a broad genus of compounds with minimal supporting examples—where the patentee “freely admit[ted] that it seeks to claim for itself an entire universe of antibodies.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 613 (2023). Exela’s ’370 claims, in stark contrast, are directed to a single pharmaceutical solution with one specific chemical, L-cysteine. Each claim also includes a low and narrow range of aluminum novel for L-cysteine, and further narrows the scope to cover specific and narrow ranges for oxygen, pH, and concentration. Moreover, the inventors

chose—and tested—oxygen levels that enable L-cysteine to be stable even when aluminum levels are low. After a year of testing, the inventors patented exactly what they invented, what they described in their specification, and what their testing confirmed. Indeed, the facts here are more like those of *Alcon Research Ltd. v. Barr Laboratories, Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014), where the Federal Circuit found enablement when “the patents disclose exemplary compositions within the scope of the claims, detail how those example compositions are prepared from commercially-available ingredients,” and “identify the various [components] that can be used and a range of suitable concentrations for both components, including narrow preferred embodiments.”

Below is a discussion of the elements of the claims that Petitioner alleges are not enabled.

a. Aluminum

The Petition erroneously asserts that the specification shows a “small dot of examples” and does not support the full scope of the range of aluminum claimed. Paper 1 at 42. The specification teaches how to reduce aluminum to less than 1 ppb. In doing so, it necessarily enables a POSA to make a L-cysteine with *more* aluminum.

The specification explains exactly how to reduce the amount of aluminum in L-cysteine below the threshold necessary for safe use in the NICU. Ex. 1001 ('370

Patent) at 7:35-41, 7:64-8:3. When Exela filed the '460 Application in 2019, the state of the art was 900 ppb aluminum—which was toxic for preterm infants. *Id.* at 7:25-26.

It was known in the art that aluminum could leach from the glass vial. Example 2 in the specification shows the problem. The inventors placed L-cysteine in glass vials and then tested for aluminum at release and then again at six months:

- Lot XMHH1609: testing aluminum levels in uncoated glass vials (at release, six months, and six months accelerated)
- Lot XMHH1610: testing aluminum levels in uncoated glass vials (at release, six months, and six months accelerated)
- Lot XMHH1611: testing aluminum levels in uncoated glass vials (at release, six months, and six months accelerated)

At six months, the data showed that the product already had “an unacceptably high aluminum content.” Ex. 1001 ('370 Patent) at 42:47-48. Example 2 failed but confirmed a critical point: to make a stable, low-aluminum L-cysteine, the inventors would have to prevent aluminum from leaching from glass vials.

The inventors experimented with vials that would not leach aluminum or allow oxygen to seep into the vial. The prior art provided no help: “Up to now, there has been no guidance with regard to the compatibility of L-cysteine with coated glass vials or that any vials could be used to provide L-cysteine compositions having low levels of Aluminum.” The inventors conceived of at

least three examples of vials they believed could hold L-cysteine compositions and maintain low levels of aluminum and oxygen: (1) vials with an external pouch; (2) plastic vials thick enough to prevent oxygen penetration; and (3) coated glass vials. Ex. 1001 ('370 Patent) at 22:58-23:60. The inventors selected coated glass vials, tested them, and showed they worked. *See, e.g., id.* at Table 18 and Table 22.

The inventors also looked to reduce aluminum leaching from the stoppers. They selected and tested stoppers coated with “a special non-reactive inert coating that minimizes interaction with the drug product.” *Id.* at 23:61-24:13. The specification identifies by product name and number a specific coated stopper suitable for this application. *Id.* at 23:61-24:10. The inventors’ testing showed these stoppers resulted in a “minimal contribution to Aluminum levels in the drug product.” *Id.* at 24:10-13.

The inventors succeeded in reducing aluminum to levels below quantitation (i.e., less than 1 ppb). *Id.* at Table 22 (showing aluminum levels below quantitation level); 32:6-11 (what the quantitation level is). The specification describes how to do this, specifically by reducing the leaching of aluminum from the glass vial and stopper while limiting the total oxygen in the vial to below 5%. *Id.* at 23:10-24:13 (explains what vials, stoppers, and coating to use to reduce aluminum leaching); *id.* at 29:17-44 (methods for controlling oxygen levels). *See*

also id. at Examples 1 and 4 (manual processes for controlling oxygen); Example 5 (automated process for controlling oxygen).

Because aluminum is toxic, the inventors targeted a solution with the least amount of it possible: “it is essential that aluminum levels in the L-Cysteine drug product are carefully controlled and kept at as low as possible.” *Id.* at 10:22-24.

They claimed a solution having NMT 250 ppb aluminum because that was understood as safe for preterm infants, but the goal was to reduce aluminum levels as low as possible:

Most preterm and low birth weight infants tend to require parenteral nutrition with amino acid supplementation during their hospital stay. However, as mentioned above, infants are a particularly high-risk population for Aluminum toxicity. To address such issues, in certain embodiments, the compositions comprise about 34.5 mg/mL of L-cysteine measured as a base ... and no more than 250 ppb, preferably about 120 ppb, or lower, of Aluminum.

Ex. 1001 ('370 Patent) at 7:62-8:3. Aluminum levels tend to increase over time, so the initial aluminum level in the L-cysteine product must be low enough so that it will not exceed 250 ppb by the end of its shelf life.

Because the specification teaches how to reduce aluminum from 900 ppb to less than 1 ppb, it necessarily enables claims for a L-cysteine with *more* aluminum, such as claim 1 (NMT 250 ppb aluminum) and claim 3 (NMT 150 ppb aluminum). The same techniques that allow a POSA to create L-cysteine with 1 ppb aluminum allow the POSA to create L-cysteine with higher aluminum levels.

In summary, to lower the Aluminum level to even greater extent as described herein, the container, the stopper, the drug substance, the water for injection, and any other excipients can be chosen such that the Aluminum concentration in the drug product is from about 1.0 ppb to about 250 ppb, or as described in the other embodiments provided herein.

Id. at 24:58-64. Indeed, as the specification teaches, oxygen is more of a problem at lower levels of aluminum, and thus increasing the amount of aluminum only makes the solution more stable. Ex. 2001 (Jenke Decl.), ¶ 28. The Petition offers no reason why a POSA could not make L-cysteine with *more* aluminum than the examples in the specification.

b. Oxygen

Petitioner erroneously asserts 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.” Paper 1 at 46. The specification shows how to reduce headspace oxygen to as low as 0.16% and dissolved oxygen as low as 0.12 ppm. Ex. 1001 (’370 Patent) at Table 18. In doing so, the specification necessarily enables a POSA to make a L-cysteine with *more* oxygen.

The inventors showed that controlling aluminum leaching was not sufficient and that a failure to control oxygen could lead to an unstable solution with visual particulates. The inventors unexpectedly encountered that “removing Aluminum may have the unintended consequence of increased [L-cystine] precipitation and

product failure in the presence of even small amounts of oxygen in the container.”

Ex. 1001 (’370 Patent) at 5:23-25. As Exela explained during prosecution, “the art did not know about the additional problems” of instability and L-cystine precipitate formation upon significant reduction of the aluminum concentration. Ex. 1024 (’453 File History) at 409.

The inventors experimented with ways to reduce dissolved oxygen and oxygen in the head space. The specification describes the inventors’ techniques to reduce dissolved oxygen including:

- “The dissolved oxygen content in the carrier can be reduced to at or below a predetermined level before the L-cysteine is added to the carrier.” Ex. 1001 (’370 Patent) at 21:49-52.
- “[B]lanketing a container for housing the composition in an inert gas, such as nitrogen, argon, or the like, prior to introducing the carrier or composition into the carrier.” *Id.* at 21:53-56.
- “[B]ubbling the carrier or composition with an inert gas, such as nitrogen, argon, or the like, at ambient or reduced atmospheric pressure prior to and/or during addition and mixing of L-cysteine.” *Id.* at 21:58-61.

Similarly, the specification describes the inventors’ methods for reducing the amount of oxygen in the headspace:

The amount of oxygen present in the headspace of the container can be controlled by filling the headspace with an inert gas, such as nitrogen or argon. Alternatively, the head space oxygen may be controlled by vacuum operation without using an inert gas. In another aspect, the head space oxygen may be controlled by a combination of vacuum operation and inert gas overlay. In one particular aspect, the head space oxygen is controlled by repeated pulses of vacuum and

inert gas overlay in tandem such that the process may start first with vacuum operation followed by inert gas overlay followed by vacuum operation. The combination of vacuum operation and inert gas overlay (or inert gas overlay and vacuum operation) is considered one pulse when both steps are used together. A typical head space control operation may comprise from one to eight pulses.

Id. at 19:17-31. Example 4 and Example 5 show that these methods reduce the amount of dissolved oxygen and the amount of headspace oxygen and provide more specific details on how those results were achieved. *Id.* at 44:1-49:50. In Example 4, the L-cysteine compound was “overlaid with Argon until the dissolved oxygen levels were no more than (NMT) 1 part per million (PPM).” *Id.* at 44:1-49:50. The inventors filled vials with the compound and monitored different steps in the manufacturing process, including “1) Compounding; 2) Pre-Filling; 3) Filling; 4) Post Filling; and 5) Head Space Reduction.” *Id.* at 44:17-20. The inventors measured the dissolved oxygen levels at each stage and included these results as FIG. 1 and FIG. 2. The inventors showed that “a reduction of dissolved oxygen to an average of 0.50 ppm after headspace reduction” was possible. *Id.* at 47:27-28, 47:66-48. Example 5 shows how the inventors reduced head space oxygen using automated filling equipment. The inventors’ testing shows that even after one month of storage headspace oxygen was between 0.4 and 1.5%. *Id.* at 48:35-37.

By reducing the initial total oxygen to below 5% the inventors ensured that oxygen would not increase above 5% over time. Ex. 2001 (Jenke Decl.), ¶¶ 41-44; Ex. 1001 ('370 Patent) at Table 12 (Oxygen content), 47:49-48:4, Fig. 4 (% Headspace Oxygen), Fig. 5 (L-Cysteine HCL – Dissolved vs Headspace Oxygen). The specification states, “the dissolved oxygen levels and the head space oxygen levels within a sealed container of L-Cysteine compositions described herein may reach an equilibrium at some time point during its shelf-life” and “the numbers are expected to stay within the ranges disclosed herein.” Ex. 1001 ('370 Patent) at 28:49-53, 28:59-60. Thus, once in a sealed container, the total oxygen will not increase—only decrease as L-cysteine is oxidized to form the unwanted byproduct cystine. Ex. 2001 (Jenke Decl.), ¶¶ 39-44; Ex. 1001 ('370 Patent) at 21:43-45, 28:49-29:3.

The specification demonstrates how to keep headspace oxygen levels as low as 0.16%. Ex. 1001 ('370 Patent) at 50:24-55. Because the specification teaches how to reduce headspace oxygen to 0.16%, it necessarily enables claims for headspace oxygen below 5% and total oxygen below 5%. The same techniques disclosed in the specification that allow a POSA to create L-cysteine with 0.16% headspace oxygen would also allow the POSA to create L-cysteine with higher oxygen levels. For example, Figure 4, shows a stable L-cysteine with 3% headspace oxygen after one month. *See also id.* at Table 16 (2.8%).

Similarly, the specification shows how to keep dissolved oxygen as low as 0.012 ppm. Ex. 1001 ('370 Patent) at Table 18. The specification explains that once you have low dissolved oxygen levels, they are expected to remain that low. *Id.* at 21:43-45 (“Additional time points beyond the 1-month from time zero data point are expected to provide similar dissolved oxygen levels”).

The specification provides data showing the efficacy of the methods it describes. For example, the specification includes the dissolved oxygen levels during the manufacturing process, *id.* at Table 10, the dissolved oxygen levels in held vials, *id.* at Table 12, a comparison of post head space dissolved oxygen (ppm) and head space oxygen content, *id.* at Table 13, the dissolved oxygen levels at time zero and in one month, *id.* at Table 17, and the final dissolved oxygen levels in the characterization of the L-cysteine composition, *id.* at Table 18. A POSA can follow the processes and achieve the low dissolved oxygen levels in the claimed ranges.

c. Storage for 12 to 24 months

The Petition asserts that “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.” Paper 1 at 50. This is incorrect. As shown below in Section VI.D, the specification has extensive stability test data for

representative batches of a product containing over 10,000 vials showing a stable, low aluminum L-cysteine over a twelve-month period under normal storage conditions and—critically—***over a six-month period at accelerated stability conditions***. As discussed in Section VI.D.c, it is standard practice in the industry to use six months of accelerated stability data as a proxy for the product’s stability over ***24 months*** at normal storage conditions. (*See infra* § VI.D.c.)

d. Vials

The Petition also erroneously asserts that “the ability of a particular vial to meet the claim would not have been predictable.” Paper 1 at 51. The specification explains which types of vials work and which do not work. The specification’s extensive testing shows that a coated glass vial can produce a low aluminum, stable L-cysteine. Lots PROT-000213, XMHJ1705, XMHJ1706, and XMHJ1707 used coated glass vials. These lots had a stable, low-aluminum L-cysteine after twelve months at long-term and six months at accelerated storage conditions. Ex. 1001 (’370 Patent) at Table 22. In addition, the specification discusses two other types of vials that work:

It should be recognized that vials which are impermeable with an internal coating, vials which are stored in a pouch that protects the product from atmospheric oxygen ingress, and relatively thick vials made of impermeable plastic or glass can be suitable for the L-Cysteine product disclosed herein.

Id. at 23:10-16. The specification explains why uncoated glass vials do not work: the L-cysteine causes aluminum in the glass to leach into the solution. *Id.* at 42:34-60; Ex. 2001 (Jenke Decl.), ¶ 50. Example 2 (Table 6) describes how glass vials leach aluminum. After twelve months, the solution was stable, but “the product resulted in an unacceptably high aluminum content.” Example 2 is not a claimed embodiment because the aluminum levels exceed 250 ppb, yet it provides a POSA with useful information about the types of vials that do not work.

The specification also explains why plastic vials do not work: oxygen permeates the plastic, increasing the total oxygen in the vial, which leads to the formation of cystine and instability. Ex. 1001 (’370 Patent) at 42:34-60. Example 3 (Tables 7 and 8) describes how plastic vials allow oxygen permeation. This solution had low levels of aluminum (Table 8) but the “product was not stable beyond 1 month at accelerate storage conditions and failed at room temperature conditions by the third month data point.” *Id.* at 43:3-6. Example 3 is not a claimed embodiment because the oxygen levels are too high, *id.* at 5:8-19, but it too supplies useful information about the importance of oxygen controls.

The specification describes the types of vials that work and do not work and teaches how to test them. It would not require undue experimentation for a POSA to test a new or different vial in light of those teachings. Ex. 2001 (Jenke Decl.), ¶¶ 50-51; *see also Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed.

Cir. 1999) (“[A] patent specification complies with the statute even if a ‘reasonable’ amount of routine experimentation is required in order to practice a claimed invention.”).

e. Concentration and pH

The Petition erroneously asserts that the specification does not support the full ranges for the claimed concentrations of L-cysteine and pH. The specification discloses a range of concentrations and pH levels that work and provides test data for a mid-point in the claimed ranges. The specification discloses extensive testing of a 50 mg/mL concentration of L-cysteine having a pH of 1.8. Ex. 1001 (‘370 Patent) at Table 18 and Table 22. This concentration and pH match the prior art Sandoz Label, which had a pH of 1.0 to 2.5 and a concentration of 50 mg/mL. Ex. 1005 (Sandoz Label). At the time the inventors conducted their testing, the Sandoz Label was commercially available and used in the medical field. *Id.* at 5, 11.

L-cysteine is strongly acidic, *see* Ex. 2004 (ELCYS® Label), and the specification explains that an L-cysteine product with a pH of 3.0 can disrupt coating inside the container and result in leaching. Ex. 1001 (‘370 Patent) at 23:1-9. The prior art taught that aluminum leaching increases exponentially when the pH exceeds 4.0, *see* Ex. 2017 (Ogawa) at 316-318; Fig. 4, and also taught a workable range of 1.0 to 2.5. Ex. 1005 (Sandoz Label) at 1. The inventors reasoned that a pH below 3.0 would minimize leaching and confirmed this through

testing. Ex. 1001 ('370 Patent) at 23:1-9 (“Therefore, up to now, the success of the product was uncertain until the products described herein were manufactured and studied in real time for prolonged periods as described herein.”)

The specification states tests were run using L-cysteine with a 1.8 pH, and explains how to adjust pH using concentrated Hydrochloric Acid, NF and 5.0 N Sodium Hydroxide, NF. *Id.* at 41:44-46.

The specification also enables the range of the claimed concentration of 10 mg/mL to 100 mg/L. Example 1 teaches a POSA how to compound an l-cysteine hydrochloride injection for 50 mg/mL. *Id.* at 41:58-42:32. That same method is used for Example 6. *Compare id.* at Table 18 (aluminum levels at 3.2 ppb, 2.9 ppb, and 5.6 ppb), *with id.* at claim 1 (contains no more than 250 ppb). Example 6 and Table 18 show measurements for the variables—e.g, aluminum, cystine, headspace and dissolved oxygen—to be on the much lower end of the claimed ranges. *Id.*

Dr. Confalone asserts that the specification does not enable the upper end of the range for concentration, 100 mg/mL, because a POSA would know that the more L-cysteine present, the more aluminum that would be leached. Ex. 1003 (Confalone Decl.), ¶ 8. The numerous data points in the specification showing consistently low levels of aluminum indicate that the leaching of aluminum from the vial or stopper under the manufacturing conditions described is not influenced

by the concentration of L-Cysteine in the vial. But even if the aluminum levels in Example 6 were to be doubled to account for double the concentration, the result would still be well within the claim limitations. Dr. Confalone has not shown that a concentration at 100 mg/mL would not work.

C. The Petition does not show any claimed embodiment that is not enabled.

Neither the Petition nor its accompanying 77-page expert declaration shows a single claimed embodiment that does not work. As a legal matter, a claim can be enabled even when many embodiments do not work. *See Durel Corp. v. Osram Sylvania Inc.*, 256 F.3d 1298, 1306–07 (Fed. Cir. 2001) (if a “significant percentage” of embodiments encompassed by the claims are inoperable it *might* be sufficient to prove invalidity); *Cook*, 439 F.2d at 735 (noting a broad claim reading on a large number of inoperative embodiments is not necessarily invalid because the POSA could figure out with minimal effort which embodiments work as intended); *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (“It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.”). But here, as a factual matter, the Petition does not identify even one claimed embodiment that does not work. Nor does the Petition even hypothesize a set of conditions under

which a claimed embodiment might not work. Instead, it relies on statements Exela, the Office, and the Delaware court made about the unpredictability of the problem *before* the inventors solved it.

Nor has Petitioner or Dr. Confalone provided any test data to show inoperability of any claimed embodiment. Instead, Petitioner suggests 7,680 experiments a POSA could conduct, without naming one that does not work. It is Petitioner's burden to prove that the experimentation would be undue and that the claims are not enabled, and Petitioner has not done so by the "more likely than not" standard of 35 U.S.C. § 324(a).

Petitioner's failure to show a single claimed embodiment that does not work is not an oversight. The declaration of Dr. Jenke confirms that a POSA would expect the full claimed range to work. He confirms that, if the total oxygen is kept below 5 %, the aluminum is kept below 250 ppb, and the pH is from 1.0 to 2.5, then the claimed L-cysteine solution will remain stable and free of visually detectable particulate matter for twenty-four months. Ex. 2001 (Jenke Decl.), ¶ 48.

D. A POSA would not have to engage in "trial-and-error" testing because the specification's ample testing data already proves the claimed L-cysteine formulations are enabled.

Petitioner ignores the extensive testing data showing how to manufacture and store stable, low-aluminum L-cysteine. Petitioner erroneously asserts that "given the unpredictable nature of L-cysteine solutions and the interrelated

variables, it would have been necessary to perform trial-and-error testing of various solutions.” Paper 1 at 53. Petitioner mischaracterizes the specification’s testing data as “tiny one-off examples,” “very limited,” and “a small dot of examples.” *Id.* at 40-42. Petitioner erroneously asserts there is only a single example in the specification (Example 6) that Exela is relying on to support the full range of claims, and it mischaracterizes the specification as disclosing “no examples” of a claimed formulation stable for twelve months. *Id.* at 4. To the contrary, the specification documents the testing of multiple exhibit batches representing over 10,000 vials, multiple experiments showing what works and what doesn’t work, and test results at many points in time. *See* Ex. 1001 at Tables 13, 16, 18, 20, 22, and 23.

For example, the specification includes extensive test data for three lots of L-cysteine having a concentration of 50 mg/mL and a pH of 1.8 and stored in coated glass vials: XMHJ1505, XMHJ1506 and XMHJ1707. As shown in Table 23, these lots represent over 10,000 vials. The specification includes stability testing for these lots over a twelve-month period both under normal storage conditions and over a six-month period under accelerated storage conditions, which is an industry standard for simulating what the sample would look like at 24 months if stored under normal conditions. Ex. 2001 (Jenke Decl.), ¶ 35.

- Lot XMHG1705: testing aluminum levels, dissolved oxygen and head space oxygen in coated glass vials (during manufacturing, release, one month, one month accelerated, three months, three months accelerated, six months, six months accelerated, nine months, and twelve months).
- Lot XMHG1706: testing aluminum levels, dissolved oxygen and head space oxygen in coated glass vials (during manufacturing, release, one month, one month accelerated, three months, three months accelerated, six months, six months accelerated, nine months, and twelve months).
- Lot XMHG1707: testing aluminum levels, dissolved oxygen and head space oxygen in coated glass vials (during manufacturing, release, one month, one month accelerated, three months, three months accelerated, six months, six months accelerated, nine months, and twelve months).

Tables 13, 16, 18, 20, 22, and 23 show the test data for these lots and demonstrate that the claimed L-cysteine solution is stable for twenty-four months.

a. The testing data shows aluminum levels did not exceed 150 ppb over twelve months at room temperature or six months at accelerated stability conditions.

Unlike the prior art products, which had aluminum levels of 5,000 ppb, the inventors had created L-cysteine formulations with aluminum levels safe for NICU patients. Table 22 shows aluminum levels for a claimed embodiment at one month, three months, six months, nine months, and twelve months at room temperature conditions, as well as at one month, three months, and six months at accelerated stability conditions. The twelve-month data in Table 22 shows that aluminum levels did not exceed 150 ppb after twelve months. Indeed, most of the vials showed aluminum levels in the single digit ppb. In addition, the six-month accelerated data in Table 22 shows aluminum levels below the level of

quantitation, thus showing they would not exceed 150 ppb even after twenty-four months. Federal Drug Administration, *Guidance for Industry ANDAs: Stability Testing Drug Substances and Products Questions and Answers*, at 4 (May 2014), <https://www.fda.gov/files/drugs/published/ANDAs--Stability-Testing-of-Drug-Substances-and-Products--Questions-and-Answers.pdf> (herein, “FDA Guidance 2014”). The testing documented in Table 22, which involves multiple batches, often tested in triplicates, and representing over 10,000 vials of product, is far from a “limited example,” as Petitioner asserts.

Petitioner erroneously says, “there is no disclosure for successful formulations with no aluminum.” Paper 1 at 43. Table 22 discloses many times when the amount of aluminum is “< QL,” which means less than the quantitation limit of 1 ppb. Ex. 1001 (’370 Patent) at 31:45-32:10, 32:18-27 (defining the quantitation limit for aluminum). In sum, the specification includes a rich body of test data showing the inventors achieved what the industry had failed to achieve: aluminum levels NMT 250 ppb throughout the claimed periods.

b. The testing data shows that oxygen remained below the claimed limits.

The specification shows testing data for oxygen levels at the time of manufacture (Tables 10-16) and again at one week (Table 19), one month (Table 17), and nine months (Table 18). Example 4 shows the success of various

techniques to reduce the amount of head space oxygen. Ex. 1001 ('370 Patent) at 44:1-48:4. Example 5 shows the success of various techniques to reduce dissolved oxygen. *Id.* at 48:6-49:50. Example 7 shows various oxygen concentrations one week after manufacture. The one-month testing data (Table 17) shows the glass vial did not allow oxygen permeation, which is what a POSA would have expected. *See* Ex. 2001 (Jenke Decl.), ¶ 43. Table 18 confirms that at nine months the total oxygen level has still not increased from the amount present when the vial was manufactured. A POSA would understand from the data at release, one month, and nine months that if the total oxygen had not increased during the first nine months that it would remain below 5% throughout the twenty-four-month period. *Id.* at ¶¶ 43-44.

The Petition criticizes the lack of oxygen testing at twelve months, Paper 1 at 50, but the specification has other data from which a POSA can conclude that the amount of oxygen would not exceed the claimed amounts at twelve (or twenty-four) months. The inventors tested lots XMHJ1705, XMHJ1706, and XMHJ1707 for oxygen at nine months (Table 18). That testing showed dissolved oxygen between 12 ppm and 14 ppm and head-space oxygen between 0.16% and 0.89%. Since oxygen levels would decrease over time, a POSA would infer that the head-space oxygen, dissolved oxygen, and total oxygen would all be below the claimed amounts at twelve (and twenty-four) months. Ex. 2001 (Jenke Decl.), ¶¶ 43-44.

The inventors tested these same lots at twelve months of long-term and six months accelerated conditions and did not report that the solution was unstable, as they did in other circumstances where oxygen had permeated the vial (e.g., Table 7), conveying to the POSA that the oxygen levels were in the acceptable claimed range. Ex. 1001 ('370 Patent) at Table 22.

The specification also shows test data (Table 19) on the impact that headspace and dissolved oxygen have on product purity. When the headspace oxygen measured at over 20% and dissolved oxygen over 8 ppm, the purity of the L-cysteine product suffered—more L-cystine was present (between 0.5%-0.8%). But where the headspace oxygen was 1.2% and dissolved oxygen was 5 ppm, well below the claimed 5% total oxygen content, L-cystine was only 0.1%.

In sum, the test data shows the inventors controlled the amount of oxygen within the claimed ranges throughout the claimed periods. In light of that disclosure, there would have been no undue experimentation required for a POSA to practice the claimed invention. Ex. 2001 (Jenke Decl.), ¶ 55.

c. The testing data shows the product is stable over 24 months.

Table 22 shows testing at twelve months long-term and six months accelerated conditions. From this data, a POSA would understand the solution would remain stable at twenty-four months. In its *Guidance for Industry*, the FDA

addresses stability testing and specifically the question of “[w]ill 6 months of accelerated data equal[] 24 months at long-term”:

Data from the three ANDA submission batches (i.e., 6 months), accelerated data meeting all criteria (without significant change per ICH Q1A(R2)), and 12 months long-term data without variability will not need statistical evaluation, and with appropriate post approval stability commitments, *can be used to support extrapolation to a 24 months shelf life.*

FDA Guidance 2014 at 4. The answer is plainly *yes*.

Focusing on Table 18, which shows nine-month data, Petitioner wrongly asserts there “are no tests that show stability for 12, 18, or 24 months.” Paper 1 at 41. Table 22 shows twelve-month real time data and six-month accelerated data. Dr. Confalone’s assertion that accelerated conditions are improper here because “it [is] beneficial to control heat during compounding or sterilization to prepare stable L-cysteine solutions,” misses the point. Ex. 1003 (Confalone Decl.), ¶ 109. The fact the L-cysteine is stable after six months under these harsher conditions shows a POSA that it would be stable after 24 months under normal conditions. Ex. 2001 (Jenke Decl.), ¶¶ 35, 37. That is the very premise behind the FDA’s guidance of allowing a 6-month accelerated temperature study as a proxy for the product’s stability over 24 months at normal (in this case, room temperature) conditions.

d. The testing data shows the invention works with commercially available concentrations of L-cysteine.

The specification shows extensive testing involving a 50 mg/mL concentration of L-cysteine having a pH of 1.8. This concentration and this pH are near the midpoints of the claimed ranges of 10 to 100 mg/mL and 1.0 to 2.5 pH. They are also representative of the commercial L-cysteine products available at the time of the invention.

Petitioner has not submitted evidence suggesting there is any concentration or pH level within the claimed ranges that would not work. Ex. 2001 (Jenke Decl.), ¶ 55. Nor would it require undue experimentation to conduct additional tests involving a concentration of 10 mg/mL and 100 mg/mL and a pH of 1.0 and 2.5 to confirm that the entire range works. *See Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (“It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.”). Petitioner’s arguments are speculation with no scientific basis.

Based on all the above, *Wands* factors 1, 2, 3, 6, and 8 all strongly support enablement here, factors 4, 5, and 7 are neutral when properly viewed in light of

the extensive guidance in the specification, and no factor suggests a lack of enablement.

e. To show non-enablement, Nexus must do more than critique the scope of the testing.

It is not enough to make conclusory statements that the invention is not enabled because there are many variables at play. Nor is it sufficient to create a list of claimed embodiments that the inventors did not test. The Federal Circuit rejected this reasoning in *Alcon Rsch.. Ltd. v. Barr Laboratories, Inc.*:

Adjusting variables may be relevant to optimizing the stability of a given prostaglandin composition, but [the expert] proffered no evidence that any experimentation, let alone undue experimentation, with those variables would be necessary in order to practice the claimed invention. Without that evidence, there is no foundation for the district court's nonenablement ruling.

745 F.3d 1180, 1189 (Fed. Cir. 2014); *see also Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013) (“Unsubstantiated statements indicating that experimentation would be ‘difficult’ and ‘complicated’ are not sufficient.”); *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). The specification supplies many working examples tested at various points in time. Nexus has not found any claimed embodiment that does not work. Thus, like the patent challenger in *Barr*, it too has “proffered no evidence that any experimentation, let alone undue experimentation, with those variables would be necessary in order to practice the claimed invention.” *Id.*

If a POSA wanted to test whether a particular embodiment worked, that testing would not be undue because the specification explains how to do it. “Where the specification provides ‘guidance in selecting the operating parameters that would yield the claimed result,’ it is fair to conclude that the experimentation required to make a particular embodiment is not ‘undue.’” *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1565 (Fed. Cir. 1996) (cleaned up). The specification describes how to control the amount of oxygen using multiple methods. Ex. 1001 (’370 Patent) at 29:17-44; Example 1, Example 4 (including Table 9), Example 5. It describes how to control aluminum levels down to levels below quantitation. It describes how to adjust pH and concentration. It describes test protocols. Even if a POSA were inclined, as Nexus suggests, to test every possible claimed embodiment, that experimentation would not be undue “where the experiments involve repetition of known or commonly used techniques,” as is the case here. *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1338-39 (Fed. Cir. 2013).

“That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive.” In *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, the Federal Circuit found the claims enabled even though there were thousands of claimed emulsions, 40% of applicant’s experiments had failed, and a POSA would not know beforehand which

combinations would work. 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). The Federal Circuit found the experimentation not to be undue because a POSA had little difficulty in making satisfactory emulsions. *Id.* Here, there is no reason to believe that any claimed embodiment will fail and a POSA would have no difficulty in making a satisfactory L-Cysteine in light of the specification’s extensive disclosures. Ex. 2001 (Jenke Decl.), ¶ 55.

The Board should deny institution of Ground 1 because Petitioner has not shown that the claims more likely than not lack enablement.

E. Petitioner does not show that it is more likely than not that the claims lack written description.

Petitioner admittedly raises substantially the same arguments it made in Ground 1 (enablement) for Ground 2 (written description), and the Board should deny institution for the same reasons. Petitioner argues that “[t]here are no examples in the specification that demonstrate the claimed stability[.]” Paper 1 at 64. Petitioner is factually wrong—the specification has many examples⁴—and it is legally wrong because examples are not a requirement for written description.

⁴ In addition to the extensive testing described above, the specification identifies multiple embodiments that fall within the claimed range. *E.g.*, Ex. 1001 (’370 Patent) at 36:3-41:44.

“[T]he test for sufficiency [of the 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.... Specifically, the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

Petitioner argues, without citation, that the “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.” Paper 1 at 65. But the specification has many data points. It recites many values for aluminum (*see* Ex. 1001 at 36:10-57), dissolved oxygen (*id.* at 37:8-10), and headspace oxygen (*id.* at 39:25-48); it lists different values for concentration and pH (*id.* at 22:18-33); and it identifies vials that work (*id.* at 49:58-59). In combination, these variables comprise the full extent of the claimed ranges.

It is legally irrelevant whether the inventors listed or tested each combination of these variables: “[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.” *Id.* at 1352. Moreover, the “specification need

not expressly recite the claimed range to provide written description support.” *Rai Strategic Holdings, Inc. v. Philip Morris Prod. S.A.*, 92 F.4th 1085, 1090 (Fed. Cir. 2024). “It is not necessary that the application describe the claim limitations exactly, [] but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations.” *Application of Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976) (internal citations omitted). The extensive disclosures regarding the claimed variables more than satisfy this requirement.

The Board should deny institution of Ground 2 because the Petition has not shown it is more likely than not that the claims lack written description.

VII. THE PETITION DOES NOT SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS WOULD HAVE BEEN OBVIOUS.

The Board should deny institution for the same reasons it has already denied institution three times. Petitioner admits the Board has considered the same prior art and arguments (Paper 1 at 66), admits the Office considered the Sandoz label during a related prosecution (*id.* at 19), and has not identified any error in the Board’s or Office’s prior decisions or reason for a different result here. Instead, Petitioner embraces the prior decisions: “[i]n fact, if anything the Petition accepts and relies upon those proceedings to substantiate Section 112 invalidity.” *Id.* at 10.

Petitioner provides no reason to depart from the prior panels' decisions or the Office's determination because the knowledge of a POSA combined with the Sandoz label does not make the claimed invention obvious. Ex. 2013 ('453 PGR Decision) at 23; Ex. 2014 ('155 PGR Decision) at 22; Ex. 2015 ('719 PGR Decision) at 26.

A. The Sandoz label does not show each element of the claims.

All claims of the '370 patent require that claimed solution of L-cysteine contains "no more than 250 ppb aluminum." Ex. 1001 at independent claims 1, 10, 19. The Board has already decided the Sandoz label does not disclose L-cysteine having an aluminum content of no more than 250 ppb. The petitioner in the '453 PGR asserted that the Sandoz label's statement that it contained no more than 5,000 ppb meant it disclosed from 0 to 5000 ppb aluminum. The Board rejected that reading, explaining that "the recitation of 'contains no more than 5000 mcg/ml (i.e. 5000 ppm) aluminum' is reasonably interpreted to be the upper end of the aluminum concentration that is expected in the product. We also do not find that zero is a reasonable starting point for the aluminum concentration in a cysteine containing composition based on the record before us." Ex. 2013 ('453 PGR Decision) at 21.

All claims of the '370 patent also require "no more than about 5%" total oxygen. Ex. 1001 at claims 1, 10, 19. The Board has already decided the Sandoz

label does not disclose how to control for headspace oxygen. Ex. 2013 ('453 PGR Decision) at 15-16; Ex. 2015 ('155 PGR Decision) at 18-19. Petitioner argues that this claim element is met because “the Sandoz Label teaches that vial headspace air is replaced with nitrogen” and that “a POSA would have understood [it] was done to prevent oxidative degradation of L-Cysteine.” Paper 1 at 74. But the petitioner in the '453 PGR made that exact argument: that “the oxygen sensitivity of L-cysteine is well-known in the art and easily addressed and in “the Sandoz Label, headspace air is replaced with nitrogen to address L-Cysteine’s oxygen sensitivity.” Ex. 2013 ('453 PGR Decision) at 15. The Board rejected this argument, finding that “Petitioner appears to be relying on routine optimization based on the knowledge of one of ordinary skill in the art to arrive at the conclusion that the Sandoz Label meets the claimed elements.” *Id.* The Board said the Sandoz Label does not disclose a range of headspace oxygen, and even if a POSA knew about additional references, that knowledge with the Sandoz Label is not enough to establish the percent oxygen range in the claims. *Id.*

Some dependent claims of the '370 patent also require an amount of dissolved oxygen (e.g., claim 5). Ex. 1001 ('370 Patent) at 59:13-14. The Board has already decided that the Sandoz label does not disclose the amount of dissolved oxygen. Ex. 2013 ('453 PGR Decision) at 16. Petitioner argues here, as the prior petitions did, that the Sandoz Label shows that the air in the product is replaced

with nitrogen. Paper 1 at 80. But the Board in the '453 PGR rejected this argument as well, finding that “[t]here is nothing in the Sandoz Label that suggests that the carrier was purged with nitrogen” and the Sandoz Label “does not disclose dissolved oxygen content in the carrier.” Ex. 2013 ('453 PGR Decision) at 7, 16.

All claims of the '370 patent also require the solution to be “substantially free of visually detectable particulate.” Ex. 1001 ('370 Patent) at claims 1, 10, 19. Petitioner acknowledges that this element is like the claim element in the '155 Patent “per Liter of said stable L-cysteine composition” . . . “not more than about 2.0 wt% of cystine relative to L-cysteine.” Paper 1 at 29. The Board has already determined the Sandoz label does not disclose whether any L-cystine is present in the composition and, if so, in what amount. Paper 1 at 30 (Referencing district court’s opinion finding “[t]here was no data provided for the specific amount of cystine in the Sandoz product.”); Ex. 2013 ('453 PGR Decision) at 17. *See also* Ex. 2014 ('155 PGR Decision) at 17-19. In addition, the Board found that the “Petition does not sufficiently explain[] why one of ordinary skill in the art would want to look at cystine levels in the product disclosed in the Sandoz Label in the first place and what reason there is to maintain it within the recited range.” Ex. 2013 ('453 PGR Decision) at 17.

All claims of the '370 patent also require a “sealed vial” that is capable of satisfying the other claim elements, including limiting aluminum to NMT 250 ppb

and total oxygen to NMT 5%. Ex. 1001 at claims 1, 10, 19. Petitioner admits that “The Sandoz Label does not identify the container used other than noting it was a clear glass vial” (Paper 1 at 30), but argues it was nonetheless obvious to use a coated glass vial (*id.* at 76). The ’155 PGR Decision previously rejected this argument, determining that the Sandoz Label does not establish that a POSA would “have a reasonable expectation of success to lowering the amount of the aluminum content” of the Sandoz product to within the claimed range of 1.0 ppb to 250 ppb through practices such as coated glass vials. *Id.* at 19. The district court made a similar finding. Ex. 1007 at 15.

In sum, the Board has already determined that the Sandoz label did not disclose many claim elements found in the claims of the ’370 Patent, and the Petition admits that others are not disclosed. Given the dearth of any persuasive evidence or arguments presented in the Petition, the Board should adopt its previous findings.

B. The Petition lacks particularity.

Recognizing that the Sandoz label does not teach each claim element, Petitioner tries to rely on the amorphous knowledge of a POSA to fill the gaps. But this argument fails because it lacks particularity, just like the arguments in the prior petitions. The Board should again deny institution because of a lack of

particularity and reject this “catch-all approach.” Ex. 2015 (’719 PGR Decision) at 16-17.

In a post-grant review, as in an *inter partes* review, “the petitioner has the burden from the onset to *show with particularity* why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (emphasis added) (citing 35 U.S.C. §312(a)(3) as applied to *inter partes* review, which is equivalent to the 35 U.S.C. §322(a)(3) as applied to post-grant review). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in AIA trials). Ex. 2013 (’453 PGR Decision) at 13.

The Board has repeatedly cautioned against “catch-all” arguments and using “additional documents” to “fill gaps in the asserted references.” *See Adaptics Limited v. Perfect Co.*, IPR2018-01596, Paper 20, 20–23 (P.T.A.B. Mar. 6, 2019) (Informative Decision). The result of an improper “catch-all” approach is that the Petition is relying on its “additional references” to create back-up obviousness combinations without identifying those combinations.

Just like Eton in the prior PGRs, Petitioner has not met the requirements for an obviousness challenge, including (i) identifying the particular combination of

references that allegedly render the claims obvious, (ii) explaining why a POSA would have been motivated to combine those particular references to solve the problem, and (iii) explaining why the POSA would have had a reasonable expectation of success in combining those particular references. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1373 (Fed. Cir. 2019).

In denying institution of the previous PGRs, the Board rejected this “catch-all” approach for the combination of Sandoz label prior art, finding that the “Petition suffers from a lack of particularity because it is not clear what aspects of the numerous references cited in the body of the Petition, but not listed in the grounds of unpatentability, Petitioner relies on to establish a basis for ‘routine optimization’ as the reason for arriving at claim elements[.]” Ex. 2013 (’453 PGR Decision) at 14 (“By not including references in the formulation of the ground unpatentability Petitioner is not providing an articulated reason that allows Patent Owner the ability to respond and leaves Patent Owner, and the Board for that matter, to guess how the references are applied to each particular ground.”) Nexus’s Petition suffers from the same flaws, and the Board should deny institution again.

C. The knowledge of a POSA cannot fill the gaps in the Sandoz label.

The prior art does not teach the claim elements that the Sandoz label does not disclose. All but one of the prior art references Petitioner cites as “representative” of the “knowledge of a POSA”, Paper 1 at 56, were cited and referenced during the earlier PGRs. Ex. 2013(’453 PGR Decision) at 12; Ex. 2014 (’155 PGR Decision) at 17; Ex. 2015 (’719 PGR Decision) at 17.⁵ The only new reference Petitioner cites is Exhibit 1009, (P. Nasa, A Review on Pharmaceutical Packaging Material, World J. of Pharm. Res., vol. 3, Issue 5, 344-368 (2015)), which Petitioner refers to once in a string citation following references already considered by the Board. Paper 1 at 56. Both the Board and the district court

⁵ The Petition on page 75 also references an Exhibit 1082 but does not include it as an additional reference in the Petition, only the expert report. We believe Exhibit 1082 to be Ian B. Butler et al., Removal of Dissolved Oxygen From Water: A Comparison of Four Common Techniques, 41 TALANTA 211 (1994), which was Exhibit 1082 in the ’453 PGR that Nexus’s Petition copies Eton’s petition verbatim when discussing that reference. *Compare* Ex. 2023 (’453 PGR Petition) at 49 (“Specifically, Butler discloses...), *with* Paper 1 at 75 (“Specifically, Butler discloses...).

found these references, listed below, do not teach the claim elements missing from the Sandoz label, and Petitioner makes no contrary showing:

- Hernandez-Sanchez (Ex. 1006)⁶
- Bohrer (Ex. 1008)
- Bohrer (Ex. 1011)
- Bohrer (Ex. 1012)
- Akers (Ex. 1014)
- Allen (Ex. 1020)
- Essentials of Pharmaceutical Chemistry (Ex. 1021)
- Drug Facts and Comparison (2015) [Ex. 1074 in the '453 Patent PGR]
- Waterman (Ex. 1027)
- Yaman (Ex. 1029), Patel (Ex. 1031)
- Whiting (Ex. 1032) [Ex. 1080 in the '453 Patent PGR]
- Zhu (Ex. 1033)
- Jalilehvand (Ex. 1034) [Ex. 1081 in the '453 Patent PGR]
- 21 CFR 201 – 1998 (Ex. 1054)

⁶ Unless otherwise indicated, the exhibit numbers in this Petition are the same as the exhibit numbers in the '453 Patent PGR Petition, Ex. 2023.

- 21 CFR 201 – 2000 (Ex. 1055) [Ex. 1035 in the '453 Patent PGR].

Here are just two examples of why this list of references is not sufficient to fill the gaps in the Sandoz label. *First*, Petitioner contends that the oxygen sensitivity of L-cysteine is well-known in the art and easily addressed. Paper 1 at 72. Petitioner notes that in “the Sandoz Label, headspace air is replaced with nitrogen, which a POSITA would have understood was done to address L-Cysteine’s oxygen sensitivity.” *Id.* Petitioner cites Dr. Confalone’s declaration (at ¶ 135), which asserts that a POSA would know to address oxygen, citing generally to Ex. 1020 (Allen), Ex. 1031 (Patel), Ex. 1061 (Okabe), and Ex. 1076 (USP23/NF18 (The U.S. Pharmacopeial Convention, 1995)).⁷ But neither Petitioner nor its expert explains (i) how a POSA would have known that removing aluminum from L-cysteine would cause it to become unstable in the presence of even small amounts of oxygen, (ii) why a POSA would have been motivated to use these particular references to solve this unknown problem or (iii) why a POSA would have a reasonable expectation of success.

Second, Exela’s patent says the scope of the oxidation issues observed with cystine were “unexpected,” a point that the Petition does not address. Ex. 1001

⁷ This exhibit is also not listed in the Petition as an additional reference.

(’370 Patent) at 5:8-19. Dr. Confalone does not explain why a POSA would have thought that cystine levels would bear on aluminum content. Instead, he asserts without citation that a “POSA would understand that L-cysteine, with its ability to leach aluminum, would be[] a ‘complexing agent’” and that treated glass would thus be useful. Ex. 1003 (Confalone Decl.), ¶ 140. Dr. Confalone cites Okabe, Ex. 1061, which describes an optimized method of preparing cystine by hydrolyzing horsehair with 20% hydrochloric acid. Neither Petitioner nor Dr. Confalone explain why a POSA would even know of the almost century-old Okabe horsehair reference, much less why a POSA would have thought to apply it to a TPN solution for administration to pre-term infants. Ex. 1061 (Okabe) at 1 (discussing how it was “not easy” to form cystine in certain conditions and how cystine formation was pH-dependent); *id.* at 3–5 (demonstrating that cystine solubility increases at $\text{pH} < 2.6$). Petitioner has not explained why a POSA seeking to reduce the aluminum levels in the Sandoz Label composition would have anticipated needing to optimize L-cystine levels in a low-pH composition.

While the Petition seeks to pick apart each variable and claim it as obvious in light of prior art—with the benefit of hindsight—the analysis is supposed to consider whether a POSA would have had a reasonable expectation of success in achieving the claimed invention as a whole—without Exela’s patent as a roadmap. *See* Ex. 2019 (Jenke Reb. Rpt), ¶ 230. It has not done this.

It was Exela's patent that disclosed the discovery that oxygen caused problems when aluminum levels were low. It was Exela's patent that discussed the interplay between the different variables and how addressing one led to unexpected issues with another. Ex. 1001 ('370 Patent) at 4:60-5:33. Although many competitors in the industry were motivated to produce a low-aluminum L-cysteine, Exela was the first to provide a successful solution. In summary, Petitioner has not shown it is more likely than not that the claims would have been obvious before Exela's patent.

D. A POSA could not achieve the claims through routine optimization.

Petitioner repeatedly relies on "routine optimization" to make its arguments, but it ignores that a POSA would not have had the benefit of the Exela patent specification to teach them how to do this supposedly routine optimization. For this reason, the Board rejected this exact argument when it was previously raised against a related patent. *See* Ex. 2013 ('453 PGR Decision) at 22. The district court also addressed and rejected this hindsight-infected argument. Ex. 1007, *Exela Pharma Scis*, 620 F. Supp. 3d at 144. *See also, e.g., Celltrion, Inc. v. Genentech, Inc.*, IPR2016- 01667, Paper 15, 17 (P.T.A.B. Mar. 2, 2017) ("[p]etitioner's argument relies on impermissible hindsight reconstruction and not a proper demonstration of routine optimization"); *Hyundai Mobis Co. et al. v. Autoliv ASP, Inc.*, IPR2014-01005, Paper 54, 24–26 (P.T.A.B. Jan. 6, 2016) (finding petitioner's

argument that a POSA would have “optimize[d] the length of the chord” at issue to be based on “nothing more than impermissible hindsight”).

There is also a distinction between routine optimization *before* the invention and routine (not undue) experimentation *after* the invention. *Allergan*, 796 F.3d at 1310 (finding that “there is no tension in the district court’s decision that the asserted claims would not have been obvious and also are not invalid for lack of enablement” because “[t]he obviousness inquiry turns on what the prior art would have taught a person of ordinary skill in the art and whether the claimed invention would have been obvious in view of the *prior art*[,]” whereas “[i]n contrast, the enablement inquiry turns on whether the skilled artisan, after reading the *specification*, would be able to make and use the claimed invention without undue experimentation, based on the ordinary skill in the art.” (emphasis in original)). Nexus conflates these two concepts and creates a false dichotomy (discussed above), but they are distinct. The inventors taught the industry how to overcome the problems in the prior art, and the specification provides the road map that those of skill in the art previously lacked.

L-cysteine parenteral solutions are sensitive to an array of multivariate and interrelated interactions. As Exela discovered when it tried to minimize the aluminum concentration in its L-cysteine product, *see* Ex. 1001 (’370 Patent) at 4:53-59, the system here is not “a system that allows independent change of one

variable with little or no predictable or material effect on other variables”; it is a “system where the change to one variable [can] result in changes to the others.”

See HZNP Medicines LLC v. Actavis Labs. UT, Inc., 940 F.3d 680, 703 (Fed. Cir. 2019). Exela figured out the relationship between these variables and taught the world how to make a stable, low-aluminum L-cysteine TPN component. As the Examiner concluded:

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 ('453 File History) at 420.

VIII. CONCLUSION

The Board should deny institution of the Petition under § 325(d) because the Board and Office have considered Petitioner’s arguments, and Petitioner has not shown a material error. The Board should deny institution of Ground 3 for lack of particularity. And it should deny institution on all grounds because the specification describes and enables the creation of an L-cysteine product that

POSAs had been unable to produce based on the prior art, their knowledge, and routine experimentation. The problem was known. It was serious, especially for the vulnerable patients who need parenteral nutrition. And for over a decade no one could solve it—before Exela did so. That is the paragon of a nonobvious invention.

Respectfully submitted,

Date: May 13, 2024

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CERTIFICATION UNDER 37 CFR § 42.24(d)

Under 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for this Patent Owner Response to Petition totals 18,620, which is less than the 18,700 allowed under 37 CFR § 42.24(b)(1).

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4), the undersigned certifies that on May 13, 2024, a complete and entire copy of this Patent Owner's Preliminary Response and accompanying exhibits were provided via email to the Petitioner by serving the correspondence email addresses of record as follows:

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