KeyCite Blue Flag – Appeal Notification
Appeal Filed by EXELA PHARMA SCIENCES, LLC v. DR. REDDY'S LABORATORIES S.A., Fed.Cir., October 12, 2022

620 F.Supp.3d 108
United States District Court, D. Delaware.

EXELA PHARMA SCIENCES, LLC, Plaintiff,
v.
ETON PHARMACEUTICALS, INC., Defendant.

C.A. No. 20-365 (MN)
|
Signed August 8, 2022

Synopsis

Background: Patentee brought action against competitor pursuant to Hatch-Waxman Act, alleging infringement of three patents covering an injectable L-cysteine composition containing low aluminum levels and methods of using such composition.

Holdings: The District Court, Maryellen Noreika, J., held that:

[1] competitor directly infringed patent claim covering a method of treating a patient with an adverse health condition responsive to L-cysteine administration;

[2] prior art product did not anticipate claim;

[3] foreign manufacturer's certificate of analysis for single lot of prior art product was insufficient to prove anticipation;

[4] competitor failed to establish by clear and convincing evidence that it was obvious to use prior art product with particular vials;

[5] patentee's product filled long-felt need for low-aluminum cysteine composition; and

[6] competitor failed to meet its burden of proving patent claims were obvious with respect to specific aluminum-over-time and cystine-over-time claim limitations of each asserted claim.

Ordered accordingly.

Procedural Posture(s): Judgment.

West Headnotes (56)

[1] **Patents** Questions of law or fact

The ultimate question of the proper construction of a patent is a question of law, although subsidiary fact-finding is sometimes necessary.

[2] **Patents** Plain, ordinary, or customary meaning in general

Patents State of the art

The words of a patent claim are generally given their ordinary and customary meaning, which is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.

[3] **Patents** Context

Although the patent claims themselves provide substantial guidance as to the meaning of particular claim terms, the context of the surrounding words of the claim also must be considered.

[4] **Patents** Plain, ordinary, or customary meaning in general

Patents State of the art

The ordinary meaning of a patent claim term is its meaning to the ordinary artisan after reading the entire patent.

[5] **Patents** Specifications and Drawings; Written Description

The patent specification is always highly relevant to the claim construction analysis, as it is the single best guide to the meaning of a disputed term.

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[6] **Patents** Contemporaneous construction

It is possible that the patent specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess; in such cases, the inventor's lexicography governs.

[7] **Patents** Preferred embodiment

Even when the patent specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.

[8] **Patents** Rejection and Amendment of Claims; Prosecution History

In addition to the patent specification, a court construing the claims of a patent should also consider the patent's prosecution history, if it is in evidence.

[9] **Patents** Rejection and Amendment of Claims; Prosecution History

A patent's "prosecution history," which is intrinsic evidence, consists of the complete record of proceedings before the Patent and Trademark Office (PTO) and includes the prior art cited during the examination of the patent.

[10] **Patents** Rejection and Amendment of Claims; Prosecution History

A patent's prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.

[11] **Patents** Extrinsic Evidence

"Extrinsic evidence," for purposes of construing the claims of a patent, consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.

[12] **Patents** Expert and inventor testimony

Expert testimony can be useful, for purposes of construing the claims of a patent, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field; nonetheless, courts must not lose sight of the fact that expert reports and testimony are generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence.

[13] **Patents** Extrinsic Evidence

Although extrinsic evidence may be useful to a court construing the claims of a patent, it is less reliable than intrinsic evidence, and its consideration is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence.

[14] **Patents** Extrinsic Evidence

Where the intrinsic record unambiguously describes the scope of a patented invention, reliance on any extrinsic evidence, for purposes of claim construction, is improper.

[15] **Patents** In general; comparison with patent claims

Courts employ a two-step analysis in making a patent infringement determination: first, a court must construe the asserted claims; next, the trier of fact must compare the properly-construed

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claims to the accused infringing product. 35 U.S.C.A. § 271(a).

[16] **Patents** In general; comparison with patent claims

Literal patent infringement occurs where every limitation in a patent claim is found in an accused product, exactly. 35 U.S.C.A. § 271(a).

[17] **Patents** Filing of applications for drug approval

In a patent infringement action brought pursuant to the Hatch-Waxman Act, the infringement inquiry is whether, if a particular drug were put on the market, it would infringe the relevant patent. 35 U.S.C.A. § 271(e)(2)(A).

[18] **Patents** As to Patentability and Validity

An issued patent is presumed to be valid. 35 U.S.C.A. § 282.

[19] **Patents** Degree of proof

To invalidate a patent, the party seeking invalidation must carry its burden of proof by clear and convincing evidence. 35 U.S.C.A. § 282.

[20] **Patents** Degree of proof

"Clear and convincing evidence," for purposes of the burden of proof of the party seeking to invalidate a patent, is evidence that proves in the mind of the trier of fact an abiding conviction that the truth of the factual contentions is highly probable. 35 U.S.C.A. § 282.

[21] **Patents** Questions of law or fact

Patent anticipation is a question of fact. 35 U.S.C.A. § 102(a).

[22] **Patents** Single reference disclosing every element or limitation of claim

Patents Inherent anticipation

A patent claim is anticipated if each and every limitation is found, either expressly or inherently, in a single prior art reference. 35 U.S.C.A. § 102(a).

[23] **Patents** Prior Art and Relation of Claimed Invention Thereto

The test for patent anticipation mirrors, to some extent, the test for infringement, and it is axiomatic that which would literally infringe, if later, anticipates, if earlier. 35 U.S.C.A. § 102(a).

[24] **Patents** Single reference disclosing every element or limitation of claim

In order to anticipate a patent, a reference must show all of the limitations of the claims arranged or combined in the same way as recited in the claims. 35 U.S.C.A. § 102(a).

[25] **Patents** Prior knowledge or use in general

If an invention was known to or used by others in the United States before the date of the patentee's invention, the later inventor has not contributed to the store of knowledge, and has no entitlement to a patent. 35 U.S.C.A. § 102(a).

[26] **Patents** Accessibility to public of prior art; concealed inventions

For prior art to anticipate a patent claim because it has been "used," the use must be accessible to the public. 35 U.S.C.A. § 102(a).

[27] **Patents** Prior knowledge or use in general

The prior knowledge and use of prior art by a single person is sufficient to anticipate a patent claim. 35 U.S.C.A. § 102(a).

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[28] **Patents** Incorporation by reference

Material not explicitly contained in a single prior art document may still be considered, in determining whether a patent claim is anticipated, if that material is incorporated by reference into the document. 35 U.S.C.A. § 102(a).

[29] **Patents** Incorporation by reference

"Incorporation by reference," for purposes of determining whether a patent claim is anticipated, provides a method for integrating material from various documents into a host document by citing such material in a manner making clear that the material is effectively part of the host document as if it were explicitly contained therein. 35 U.S.C.A. § 102(a).

[30] **Patents** In general; multiple factors

Patents Questions of law or fact

Patent obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. 35 U.S.C.A. § 103(a).

[31] **Patents** Combination of prior art references; "teaching, suggestion, or motivation" test

Patents Expectation or probability of success; predictability

Patents Level of Ordinary Skill in the Art

To prove that a patent is obvious, a party must demonstrate that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so. 35 U.S.C.A. § 103(a).

[32] **Patents** Combination of prior art references; "teaching, suggestion, or motivation" test

Although an analysis of any teaching, suggestion, or motivation to combine known elements is useful to a patent obviousness analysis, the overall obviousness inquiry must be expansive and flexible. 35 U.S.C.A. § 103(a).

[33] **Patents** Level of Ordinary Skill in the Art

Patents Time of evaluation; hindsight

The use of hindsight is not permitted when determining whether a patent claim would have been obvious to one of ordinary skill in the art. 35 U.S.C.A. § 103(a).

[34] **Patents** In general; multiple factors

To protect against the improper use of hindsight when assessing patent obviousness, the court is required to consider objective or secondary considerations, or indicia, of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. 35 U.S.C.A. § 103(a).

[35] **Patents** Particular products or processes

Patents Drugs and medicines

Term "about," as used in patent claim covering a method of treating a subject having an adverse health condition that is responsive to L-cysteine administration, meant approximately, and was not indefinite.

[36] **Patents** Particular products or processes

Patents Drugs and medicines

Term "pharmaceutically acceptable amount of cystine," as used in patent for stable and highly pure L-cysteine compositions for injection and methods of use, meant an amount of cystine that was compatible chemically and/or toxicology with the other ingredients comprising

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a formulation and/or the mammal being treated therewith, and was not indefinite.

[37] **Patents** Drugs and medicines

Term "stable L-cysteine composition," in patent claim for method of treating a subject having an adverse health condition that is responsive to L-cysteine administration, meant an L-cysteine composition that had the component profiles described therein, for example, aluminum, L-cystine, and pyruvic acid, at the levels described and for the amount of time identified; in other words, a stable composition that contained the specified levels of all components for sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting.

[38] **Patents** Drugs and medicines

Term "pyruvic acid relative to L-cysteine not more than about 2.0 wt %," as used in patent claim covering a method of treating a subject having an adverse health condition that was responsive to L-cysteine administration, had its plain and ordinary meaning, which set a limit to the amount of pyruvic acid when present, but did not require the presence of pyruvic acid.

[39] **Patents** Drugs and medicines

Competitor's abbreviated new drug application (ANDA) product met all limitations of patent claim covering a method of treating a patient with an adverse health condition responsive to L-cysteine administration, and thus competitor directly infringed claim, even if ANDA product did not contain pyruvic acid, where court construed asserted claim to require only that the amount of pyruvic acid not exceed the maximum stated, such that claim did not require any amount of pyruvic acid to be present. 35 U.S.C.A. § 271(e)(2).

[40] **Patents** Filing of applications for drug approval

What an Abbreviated New Drug Application (ANDA) applicant asks for and receives approval to market, if within the scope of a valid claim, is a patent infringement. 35 U.S.C.A. § 271(e)(2).

[41] **Patents** Scope of inquiry and power of court in general

Competitor, whose abbreviated new drug application (ANDA) product met all limitations of patentee's patent claim covering a method of treating a patient with an adverse health condition responsive to L-cysteine administration, waived its argument in parties' infringement dispute that if claim limitation "not more than" could mean zero, then patent claim was invalid, where competitor raised argument for the first time in post-trial brief, and did not present argument at trial or in pre-trial order.

[42] **Patents** Drugs and medicines

Competitor's abbreviated new drug application (ANDA) product, which met all limitations of patent claim covering a method of treating a patient with an adverse health condition responsive to L-cysteine administration, was not the same as prior art product, and thus prior art product did not anticipate claim; ANDA product and prior art product differed as to amount of aluminum over time, ANDA product required additional sterilization step and oxygen controls that were material to integrity of product, prior art product used different vial which could affect how much aluminum leached into product, and products were made with cysteine sourced from different companies, which sold ingredients with different impurity profiles. 35 U.S.C.A. § 102(a).

[43] **Patents** Drugs and medicines

Foreign manufacturer's certificate of analysis for single lot of prior art product, which competitor alleged anticipated patent claim

covering a method of treating a patient with an adverse health condition responsive to L-cysteine administration, was insufficient to prove anticipation, even if manufacturer prepared other lots of product for public use or sale in the United States; there was no evidence that single lot was in public use, on sale, or otherwise available to public at time of invention, aluminum levels of lots were highly variable, and single lot's certificate of analysis was only certificate, among many submitted as evidence, that met aluminum limit claimed. 35 U.S.C.A. § 102(a).

[44] **Patents** Drugs and medicines

Competitor, whose abbreviated new drug application (ANDA) product infringed three patents for an injectable L-cysteine composition containing low aluminum levels and methods of using such composition, failed to establish by clear and convincing evidence that it was obvious to use prior art product with particular vials, which allegedly reduced amount of aluminum leaching into product; reduction of aluminum in a cysteine formulation was not wholly independent of all other properties and characteristics of formulation, including acceptable levels of impurities, and complex chemistry of cysteine was not always predictable in a practical setting. 35 U.S.C.A. § 103(a).

[45] **Patents** Drugs and medicines

Competitor, whose abbreviated new drug application (ANDA) product infringed three patents for an injectable L-cysteine composition containing low aluminum levels and methods of using such composition, failed to establish by clear and convincing evidence that a person of ordinary skill in the art would have chosen to use particular vials to reduce aluminum levels in cysteine products; problem of aluminum leaching remained unresolved for duration of period that prior art product was on sale, and a person of ordinary skill in the art would not have been motivated to try particular vials with cysteine formulations by prior art patent disclosing use of coated vials to reduce aluminum precipitation in lysine formulation. 35 U.S.C.A. § 103(a).

[46] **Patents** Time of evaluation; hindsight

An analysis of patent obviousness requires a form of amnesia that "forgets" the invention and analyzes the prior art and understanding of the problem at the date of invention. 35 U.S.C.A. § 103(a).

[47] **Patents** Drugs and medicines

Competitor, whose abbreviated new drug application (ANDA) product infringed three patents for an injectable L-cysteine composition containing low aluminum levels and methods of using such composition, failed to establish that a person of ordinary skill in the art would have had a reasonable expectation of success in reducing aluminum in cysteine compositions by using particular vial with prior art product, and thus, patents were not obvious on such basis; no one, including prior art product manufacturer, tried using vials despite strong motivation to reduce aluminum in cysteine compositions. 35 U.S.C.A. § 103(a).

[48] **Patents** Time of evaluation; hindsight

The use of an inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. 35 U.S.C.A. § 103(a).

[49] **Patents** Level of Ordinary Skill in the Art

What matters in determining whether a patent claim would have been obvious is the path that a person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art. 35 U.S.C.A. § 103(a).

[50] **Patents** Drugs and medicines

Patentee's product, which was an embodiment of patent claims covering injectable L-cysteine composition containing low aluminum levels

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and methods of using such composition, filled long-felt need for low-aluminum cysteine composition, as would support determination that claims were not obvious; for over two decades before patentee's inventions, clinical community recognized that aluminum contamination of cysteine used for total parenteral nutrition (TPN) was a long-standing problem, Food and Drug Administration (FDA) implemented regulations requiring labels to report maximum content, and product was first to provide a stable, low-aluminum cysteine composition that allowed clinicians to administer TPN solutions without exceeding FDA's recommended daily maximum aluminum amount. 35 U.S.C.A. § 103(a).

[51] **Patents** Drugs and medicines

Competitor, whose abbreviated new drug application (ANDA) product infringed three patents for an injectable L-cysteine composition containing low aluminum levels and methods of using such composition, failed to establish that prior art product had already filled, at time of patentee's inventions, long-felt need for low-aluminum cysteine composition, as would weigh against determination that patent claims were not obvious; clinicians acknowledged and called for a solution to the problem of high aluminum contamination in cysteine used for total parenteral nutrition (TPN) during period in which product was sold, product contained more than twice the Food and Drug Administration's (FDA) recommended daily maximum aluminum amount, and aluminum levels in product were highly variable. 35 U.S.C.A. § 103(a).

[52] **Patents** Drugs and medicines

Third-party pharmaceutical company's work developing a stable L-cysteine product with low aluminum at the same time patentee was developing invention claimed by three patents for an injectable L-cysteine composition containing low aluminum levels and methods of using such composition did not demonstrate that patent claims were obvious, in infringement action brought by patentee against competitor, whose abbreviated new drug application (ANDA) product infringed patents; simultaneous invention, on its own, could not support finding of obviousness, and pharmaceutical company's experience developing its product demonstrated that claimed invention was unexpected and complicated. 35 U.S.C.A. § 103(a).

[53] **Patents** Simultaneous invention

A single instance of simultaneous invention cannot alone support a finding of obviousness. 35 U.S.C.A. § 103(a).

[54] **Patents** Drugs and medicines

Competitor, whose abbreviated new drug application (ANDA) product infringed three patents for an injectable L-cysteine composition containing low aluminum levels and methods of using such composition, failed to meet its burden of proving patent claims were obvious with respect to specific aluminum-over-time and cystine-over-time claim limitations of each asserted claim, which encompassed periods of time sufficient for the product to be administered in a clinical setting. 35 U.S.C.A. § 103(a).

[55] **Patents** Drugs and medicines

Competitor, whose abbreviated new drug application (ANDA) product infringed patent claims covering a cysteine product containing specified levels of mercury and/or lead, failed to meet its burden of proving patent claims were obvious, where competitor's only basis for obviousness argument was that a prior art product was the same as ANDA product, and competitor failed to establish by clear and convincing evidence that ANDA product and prior art product were the same with respect to lead and mercury content. 35 U.S.C.A. § 103(a).

[56] **Patents** In general; utility

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US Patent 10,583,155, US Patent 10,905,713, US Patent 10,912,795. Not Invalid, Infringed.

Go to Markman Construed Terms

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MEMORANDUM OPINION

NOREIKA, UNITED STATES DISTRICT JUDGE:

Plaintiff Exela Pharma Sciences, LLC ("Exela" or "Plaintiff") brought this Hatch-Waxman action against Defendant Eton Pharmaceuticals, Inc. ("Eton" or "Defendant"). Eton has filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to market a generic version ("ANDA product") of Exela's ELCYS ® product before expiration of several patents owned by Exela. Plaintiff alleges ***115** that Eton's ANDA product will infringe claim 27 of the 10,583,155 patent ("the '155 patent"), claims 8, 9, and 10 of the 10,905,713 patent ("the '713 patent") and claims 1, 19, and 27 of the 10,912,795 patent ("the '795 patent"). The parties stipulated to infringement of all asserted claims of the '713 and '795 patents (D.I. 199), leaving only infringement of claim 27 of the '155 patent disputed. Eton asserts that all asserted claims are invalid.

The Court conducted a three-day bench trial from March 14, 2022 to March 16, 2022. (*See* D.I. 205-207 ("Tr.")). The parties completed post-trial briefing on April 18, 2022. (D.I. 209, 212, 220, 222, 228, 229). With their briefing, the parties submitted proposed findings of fact. (D.I. 210, 211, 221). [1]

Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, and after having considered the entire record and the applicable law, the Court concludes that: (1) the ANDA product infringes claims 8, 9, and 10 of the '713 patent and claims 1, 19, and 27 of the '795 patent; (2) Exela has proven that Defendant's ANDA product directly and contributorily infringes and induces infringement of claim 27 of the '155 patent; (3) Eton has failed to prove that claim 27 of the '155 patent is invalid as anticipated, and (4) Eton has failed to prove that claim 27 of the '155 patent, claims 8, 9, and 10 of the '713 patent or claims 1, 19, and 27 of the '795 patent are invalid for obviousness. This opinion constitutes the Court's findings of fact and conclusions of law.

I. FINDINGS OF FACT

A. Introduction

1. Exela is a limited liability corporation existing under the laws of Delaware, having its principal place of business in North Carolina. (D.I. 177, Ex. 1 ¶ 2).

2. Eton is a corporation organized and existing under the laws of Delaware, having its principal place of business in Illinois. (D.I. 177, Ex. 1 ¶ 4).

3. Exela owns the '155, '713, and '795 patents, which are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" ("the Orange Book"), as having at least one claim that covers Exela's ELCYS product. (D.I. 177, Ex. 1 ¶ 50).

4. On December 9, 2019, Eton submitted ANDA No. 214082 to FDA under 21 U.S.C. § 355(j)(5)(B)(iii) seeking FDA approval to engage in the commercial manufacture, use, or sale of its ANDA product (*i.e.*, Cysteine Hydrochloride Injection, USP, 500 mg/10 mL (50 mg/mL) Single Dose Vials). (D.I. 177, Ex. 1 ¶¶ 68, 69). Defendant's ANDA contains certifications for each of the patents in this case. (D.I. 177, Ex. 1 ¶ 71). [2]

B. Witnesses

1. Fact Witnesses

5. Dr. Phanesh Koneru, a named inventor of the '155, '713, and '795 patents and Exela's co-founder and CEO, testified live at trial about Exela's development of ELCYS. (Tr. 153:1–231:9).

6. Dr. John Hofstetter, a former employee of Allergy Laboratories ("Allergy Labs") and currently the Managing Member of Dry Creek Project, LLC, testified live at trial. (Tr. 285:25–346:4). Dr. Hofstetter ***116** testified about Allergy Labs work manufacturing an L-cysteine product for Sandoz and its later submission of an NDA to market its own L-cysteine product. Dr. Hofstetter has a financial interest in this case, as his company will receive 12.5% of Eton's profit from its proposed ANDA product. (Tr. 337:9–339:4, PTX-33, PTX-35).

7. Sean Brynjelsen, Eton's founder and CEO, testified live at trial as a fact witness. (Tr. 346:8–374:20). Mr. Brynjelsen testified about his work in the pharmaceutical industry, including on sterile injectable products and total parenteral nutrition ("TPN") solutions as well as Eton's ANDA product.

8. Warren Johnson, the former owner of Allergy Laboratories, Inc. and the Vice President of AL Pharma, Inc., testified by deposition. (Tr. 376:8–380:5). Mr. Johnson testified about the L-cysteine product Allergy Labs manufactured for Sandoz and Allergy Labs's later decision to submit an NDA to market its own L-cysteine product

9. Dr. John Maloney, a named inventor of the '155, '713, and '795 patents and Exela's Head of Research and Development, testified by deposition about his work developing ELCYS. (Tr. 380:6–389:16).

10. Dr. Aruna Koganti, a named inventor of the '155, '713 and '795 patents, testified by deposition. Dr. Koganti was not involved with developing the drug product, but was responsible for preparing and submitting the New Drug Application ("NDA") for ELCYS and communicating with the FDA. (Tr. 389:22–395:25).

11. Dr. Olu Aloba, Vice President of Chemistry, Manufacturing, and Controls at Camargo Pharmaceutical Services, testified by deposition regarding AL Pharma's submission of an NDA for an L-cysteine product and about how Camargo made recommendations to improve and validate AL Pharma's manufacturing process. (Tr. 550:18:–556:3).

2. Plaintiffs' Expert Witnesses

12. Dr. Christian Schoneich is the Chair of the Department of Pharmaceutical Chemistry at the University of Kansas. (Tr. 232:15–21). Dr. Schoneich received a diploma in chemistry in 1987 and a Ph.D. from the Technical University in Berlin, where he studied the reaction of vials including cysteine, including oxidation reactions. (Tr. 232:22–233:10). At the University of Kansas, Dr. Schoneich teaches and performs research related to amino acid chemistry, including cysteine. (Tr. 233:5–234:4, 235:5–11, 236:4–22). Dr. Schoneich has authored more than 60 papers related to pharmaceutical chemistry, and has more than 30 publications related to cysteine chemistry. (Tr. 237:5–14). The Court recognized Dr. Schoneich as an expert in pharmaceutical and amino acid chemistry, specifically with respect to cysteine chemistry. (Tr. 239:3–14).

13. Dr. Dennis Jenke is a consultant in the medical and pharmaceutical industries who holds a master's degree in geochemistry and a Ph.D. in analytical chemistry. (Tr. 556:24–557:2, 559:17–19). Prior to his consulting career, Dr. Jenke spent thirty-four years at Baxter Health Care where he worked on at least one hundred aqueous drug formulations and developed expertise in extractables and leachables. (Tr. 557:3–15, 558:10–23, 559:9–16). The Court recognized Dr. Jenke as an expert in aqueous drug formulations and packaging. (Tr. 560:4–7).

14. Dr. Robert Kuhn is a pediatric clinical pharmacist at the Kentucky Children's Hospital at the University of Kentucky and is a professor of pharmacy at the University of Kentucky College of Pharmacy. (Tr. 71:25–72:4). Dr. Kuhn received his bachelor's degree in pharmacy from ***117** Ohio State in 1980 and a Pharm.D. from the University of Texas in 1984. (Tr. 72:14–21). Dr. Kuhn has compounded TPN solutions for more than forty years (Tr. 72:22–25, 104:16–25) and has published research on aluminum in TPN solutions (PTX-179, Tr. 74:17–21). The Court recognized Dr. Kuhn as an expert in pharmacy and total parenteral nutrition. (Tr. 75:3–8).

3. Defendant's Expert Witness

15. Dr. Stephen Baertschi is the President of Baertschi Consulting LLC, which provides consulting services to pharmaceutical companies pertaining to issues such as stability, degradation and impurities. (Tr. 400:13–401:4). Dr. Baertschi holds a Ph.D. from Vanderbilt University in organic chemistry. (Tr. 401:13–17). Prior to his consulting career, Dr. Baertschi worked at Eli Lilly for twenty-five years, where he held a variety of technical roles. (Tr. 402:6–18). Dr. Baertschi worked with L-cysteine as a graduate student (Tr. 403:10–15) and helped organize an extractables and leachables group while at Eli Lilly (Tr. 404:19–25). Dr. Baertschi has worked on more than two dozen parenteral products throughout his career. (Tr. 405:1–6). The Court recognized Dr. Baertschi as an expert in pharmaceutical chemistry and formulation including with respect to impurities and degradation. (Tr. 407:5–11).

C. The Asserted Patents

1. The '155 Patent

16. The '155 patent is titled "Stable, Highly Pure L-Cysteine Compositions for Injection and Methods of Use" and issued on March 10, 2020, from U.S. Patent Application No. 16/665,702, which is a continuation of the '460 Application, filed January 15, 2019, now U.S. Patent No. 10,478,453. (D.I. 177, Ex. 1 ¶ 12). The '155 patent claims priority to the '460 Application. (D.I. 177, Ex. 1 ¶¶ 19, 20).

17. The named inventors of the '155 patent are John Maloney, Aruna Koganti, and Phanesh Koneru. (D.I. 177, Ex. 1 ¶ 13).

18. Exela asserts claim 27 of the '155 Patent, which claims:

> A method of treating a subject having an adverse health condition that is responsive to L-cysteine administration, said method comprising:
>
> parenterally administering to said subject a parenteral composition comprising a mixture comprising a stable L-cysteine composition, wherein said stable L-cysteine composition contributes to said parenteral composition:
>
> a therapeutically effective amount of L-cysteine or a pharmaceutically acceptable salt thereof and/or hydrate thereof;
>
> per Liter of said stable L-cysteine composition, not more than 150 mcg of Aluminum;
>
> cystine relative to L-cysteine not more than about 2.0 wt %; and,
>
> pyruvic acid relative to L-cysteine not more than about 2.0 wt %.

(JTX-2 at 60:15–31).

2. The '795 Patent

19. The '795 patent is titled "Stable, highly pure L-cysteine compositions for injection and methods of use" and issued on February 9, 2021, from U.S. Patent Application No. 16/850,726 filed on April 16, 2020, which ultimately (through a series of continuation applications) is a continuation of the '460 Application. (D.I. 177, Ex. 1 ¶ 28). The '795 patent claims priority to the '460 Application. (D.I. 177, Ex. 1 ¶¶ 34, 35). [3]

***118** 20. The named inventors of the '795 patent are listed as John Maloney, Aruna Koganti, and Phanesh Koneru. (D.I. 177, Ex. 1 ¶ 29).

21. Exela asserts claims 1, 19, and 27 of the '795 patent. Claim 1 claims:

> A solution of L-cysteine comprising,
>
> a pharmaceutically acceptable carrier, and
>
> about 50 mg/mL of L-cysteine hydrochloride monohydrate, or
>
> equivalent amount of a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof;
>
> wherein the solution is stored in a single-use vial;
>
> wherein for at least 12 months from the time of manufacture of the solution, the solution will remain:
>
> substantially free of visually detectable particulate matter, at a pH from about 1.0 to 2.5, and
>
> containing no more than 150 ppb of aluminum; and
>
> wherein the solution is safe for use as an additive in a parenteral nutrition composition for intravenous administration to an individual for at least 12 months from the time of manufacture of the solution

(JTX-5 at 58:34–49).

22. Claim 19, which depends from claim 1, claims:

> The solution of claim 1, wherein for at least 24 months from the time of manufacture of the solution, the solution will remain:
>
> substantially free of visually detectable particulate matter, at a pH from about 1.0 to 2.5, and
>
> containing no more than 150 ppb of aluminum; and
>
> wherein the solution is safe for use as an additive in a parenteral nutrition composition for intravenous administration to an individual for at least 24 months from the time of manufacture of the solution.

(JTX-5 at 60:11–24).

23. Claim 27, which also depends from claim 1, claims:

> The solution of claim 1, wherein for at least 24 months from the time of manufacture of the solution, the solution will remain:
>
> substantially free of visually detectable particulate matter, at a pH from about 1.0 to 2.5, and
>
> containing no more than 150 ppb of aluminum; and
>
> wherein the solution is safe for use as an additive in a parenteral nutrition composition for intravenous administration to an individual for at least 24 months from the time of manufacture of the solution.

(JTX-5 at 60:38-48).

3. The ’713 Patent

24. The ’713 patent is titled “Stable, highly pure L-cysteine compositions for injection and methods of use” and issued on February 2, 2021, from U.S. Patent Application No. 16/773,641 filed January 27, 2020. (D.I. 177, Ex. 1 ¶ 21). Like the ’155 and ’795 patents, the ’713 patent is ultimately a continuation of the ’460 Application, and claims priority to that application. (D.I. 177, Ex. 1 ¶¶ 26, 27).

25. The named inventors of the ’713 patent are listed as John Maloney, Aruna Koganti, and Phanesh Koneru. (D.I. 177, Ex. 1 ¶ 22).

***119** 26. Exela asserts claims 8, 9, and 10 of the ’713 patent. These terms depend from unasserted claim 1, which recites:

> A solution of L-cysteine comprising,
>
> a pharmaceutically acceptable carrier,
>
> about 50 mg/mL of L-cysteine hydrochloride monohydrate, or equivalent amount of a pharmaceutically acceptable L-cysteine or a salt or hydrate thereof,
>
> a pharmaceutically acceptable amount of cystine for at least about 12 months from the time of manufacture of the solution,
>
> less than about 150 ppb of aluminum for at least about 12 months from the time of manufacture of the solution,
>
> a pH from about 1.0 to about 2.5, and
>
> wherein the solution is enclosed in a single-use vial.

(JTX-4 at 60:52–64).

27. Claims 8 through 10 add:

> 8. The solution of claim 1, further comprising lead in an amount from about 1 ppb to about 10 ppb.
>
> 9. The solution of claim 1, further comprising mercury in an amount from about 0.2 ppb to about 5.0 ppb.
>
> 10. The solution of claim 9, further comprising lead in an amount from about 1 ppb to about 10 ppb.

(JTX-4 at 61:9–14).

D. ELCYS®

28. Exela is the holder of NDA No. 210660, submitted on July 27, 2018, which sought FDA approval for the marketing and sale of ELCYS, an injectable L-cysteine hydrochloride product containing low aluminum levels. The FDA approved the NDA for ELCYS on April 16, 2019. (D.I. 177, Ex. 1 ¶¶ 48, 49).

29. ELCYS is a stable solution of L-cysteine hydrochloride indicated for use as an additive to amino acid solutions to meet

the nutritional requirements for patients requiring TPN. (D.I. 177, Ex. 1 ¶ 57).

30. TPN is a method of providing, via an intravenous solution, nutrients such as amino acids, carbohydrates, electrolytes, pediatric multivitamins and fats to patients who cannot feed orally. (Tr. 73:1–7, 78:11–79:22). TPN provides all needed calories and manages electrolytes and fluids. (Tr. 75:14–22).

31. TPN is primarily used for neonates (children who are less than thirty days old), including premature infants and children who cannot use their gut to obtain the calories they need. In the United States, there are approximately 4,000 to 6,000 neonates receiving TPN on a given day. (Tr. 75:14–76:15).

32. Neonates cannot make certain amino acids, such as cysteine, which are necessary for their growth and development. Accordingly, formulations of amino acids that include cysteine need to be added into their TPN solutions. (Tr. 76:16–77:4, 79:15–22).

33. TPN solutions with toxins present a significant risk to neonates because they are small and have undeveloped kidneys. (Tr. 77:5–13).

34. Aluminum, a common impurity in TPN solutions, is toxic to neonatal patients. (Tr. 80:12–17). Cysteine is known to contribute aluminum levels in TPN solutions. (Tr. 81:16–22).

35. Two other known impurities in cysteine products are cystine and pyruvic acid, which are both degradation products of cysteine. (Tr. 164:14–17).

36. ELCYS contains 50 mg/mL of cysteine hydrochloride (equivalent to 34.5 mg/mL of cysteine) in water for injection. The chemical name of cysteine hydrochloride is cysteine hydrochloride monohydrate. (D.I. 177, Ex. 1 ¶ 58).

***120** 37. ELCYS contains no more than 120 mcg/L (or 120 ppb) [4] of aluminum. Stability testing of ELCYS 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. (D.I. 177, Ex. 1 ¶ 59).

38. ELCYS contains no more than 1.0 wt % of cystine. Stability testing of ELCYS shows that its exhibit batches contained between 0.2% and 0.8% of cystine throughout its 24-month shelf life when stored at 25°C and 60% relative humidity and remained essentially free of visible particulate matter. In approving ELCYS, the FDA concluded that it contains a pharmaceutically acceptable amount of cystine. The cystine present in ELCYS forms as a result of oxidation. (D.I. 177, Ex. 1 ¶ 60).

39. ELCYS contains pyruvic acid, in an amount of no more than 1.0 wt % relative to cysteine, as set forth in the NDA's release and stability specifications for the product, which provide for no more than 0.5% of two specified impurities attributable to pyruvic acid (RRT 0.56 and 0.76) throughout the 24-month shelf life of the product. The pyruvic acid present in ELCYS forms as a result of, for example, oxidation of cysteine. (D.I. 177, Ex. 1 ¶ 61).

40. 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. (D.I. 177, Ex. 1 ¶ 62).

41. ELCYS is a commercial embodiment of all asserted claims of the ’795 patent and the ’713 patent. (D.I. 201 ¶ 6). ELCYS is also a commercial embodiment of claim 27 of the ’155 patent. [5]

E. Exela's Development of ELCYS

42. The ’155, ’713, and ’795 patents arose from Exela's development of ELCYS. (Tr. 196:6–8).

43. Exela's development of ELCYS reflects the complex nature of developing a low-aluminum L-cysteine product with a safe impurity profile.

44. In October 2015, Exela first reached out to the FDA about pursuing an NDA for a cysteine hydrochloride solution. (Tr. 157:9–16, JTX-13.11181).

45. Prior to October 2015, Exela had periodically made cysteine solutions during drug shortages upon hospital requests. (JTX-13.11230, Tr. 158:9–159:4, 160:25–161:2, 162:12–163:1). The cysteine product that Exela manufactured during this period had a shelf life of only three months, underwent limited testing, and had high levels of impurities such as cystine and pyruvic acid. (Tr. 161:21–162:11, 163:25–164:21).

46. Exela believed that the aluminum levels in its prior product, which measured ***121** at around 400 ppb, were satisfactory, but that its impurity levels were too high. (Tr. 163:13–24). Accordingly, Exela set out to reduce its product's impurity profile. (Tr. 163:25–164:5).

47. To that end, Exela implemented strict oxygen controls throughout its manufacturing process because it believed that impurities result from the degradation of cysteine due to oxidization. (JTX-13.10000-10001, Tr. 164:9–13, 164:22–165:20, 385:3–386:1). Specifically, Exela (1) used an argon overlay to limit the dissolved oxygen content to no more than 1 ppm throughout the mixing process, with dissolved oxygen measurements taken at four steps during the mixing process, (2) removed oxygen at the holding stage, between mixing and vial filling, and (3) removed headspace oxygen by using a series of argon flushes and vacuum pulses. (JTX-13.10000–10001).

48. Exela's strict oxygen controls resulted in total impurities of 0.4%, with cystine at 0.3%. (JTX-13.7914, Tr. 172:6–25).

49. After six months of storage, Exela's initial product contained aluminum levels ranging from 550 to 750 ppb, and under accelerated conditions intending to simulate a two-year shelf life, the aluminum levels ranged from about 1,000 to 1,400 ppb. (JTX-13.7911–7916, Tr. 176:2–176:6).

50. The FDA informed Exela that its NDA was not approvable because the aluminum levels were unacceptable. (Tr. 176:7–25). The FDA later told Exela that an approvable product must have an aluminum level less than or equal to 145 mcg. (PTX-486; Tr. 183:21–184:3).

51. Exela thus committed to reducing the aluminum levels. To do so, Exela maintained its oxygen controls but altered its process in two ways. First, Exela bottled its formulation in plastic containers because, as it explained to the FDA, "[i]t is believed that the glass containers contribute significantly to aluminum levels in the drug product." (JTX-13.11962, Tr. 179:7–181:18). Second, Exela sourced its cysteine from a different vendor which provided product with lower aluminum levels. (JTX-13.11336, Tr. 182:20–183:1).

52. Exela's newly sourced cysteine and plastic vials resulted in significantly reduced initial aluminum levels. (JTX-13.11336, Tr. 181:4–6, 182:2–183:1). One month into stability testing, however, the product contained visible particulate matter. (JTX-13.11801, Tr. 184:15–24). Exela discovered that the particulates were L-cystine, a degradation product that results from the oxidation of L-cysteine. (JTX-13.11801).

53. Exela hypothesized that the particulates arose because of oxidation that occurred in the plastic vials despite the use of strict oxygen controls. (Tr. 186:5–10, 188:7–15). As a result, Exela decided to use Schott Type I Plus glass vials instead while maintaining its manufacturing process. (JTX-13.11802–11803). [6]

54. Schott Type I Plus glass vials had been in use since the early 2000s. (Tr. 498:2–7). But at the time Exela decided to use them, there was no data on this vial's performance with a product having cysteine's low pH (1.0 to 2.5) or affinity for leaching. (Tr. 189:3–190:13, *see* JTX-13.11804–11811).

55. After six months, the product in the Schott Type I Plus vials maintained aluminum levels well below FDA's stated maximum of 145 mcg/L and did not generate particulate matter. (JTX-13.1788–1789, Tr. 192:15–194:10).

***122** 56. Exela attributed its success in reducing particulate matter to the unexpected and counterintuitive realization that aluminum protects cysteine, and so when aluminum is reduced too much it permits cysteine to degrade into cystine. Put simply, aluminum has a stabilizing effect on an L-cysteine solution. (Tr. 197:19–198:15, 199:2–200:13).

F. Person of Skill in the Art

57. Plaintiff's experts defined a person of ordinary skill in the art ("POSA") as a person having:

> 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 additional formal

> education can compensate for less practical experience.

(D.I. 179, Ex. 1 ¶ 45, Tr. 242:8–20, 560:15–25).

58. Defendant's expert defined the POSA as:

> A person having "a bachelor's degree in pharmacy or a related field, along with five years of practical experience in drug formation or a related field. In addition, a [POSA] may have a graduate degree in pharmacy or a related field and three years of practical experience in drug formulation or a related field."

(D.I. 179, Ex. 1 ¶ 46, Tr. 407:18–408:2).

59. Plaintiff's experts, Drs. Schoneich and Jenke, and Defendant's expert, Dr. Baertschi, agreed that their opinions would not change regardless of which definition of a POSA were used. (Tr. 242:22–243:3, 408:4–16, 561:10–15).

60. Drs. Schoneich, Jenke, and Baertschi all meet the minimum qualifications of a POSA under both proposals. (*Supra* ¶¶ 12, 13, 15).

G. Facts Relevant to Infringement

1. The '713 and '795 Patents

61. The parties stipulated that Eton's ANDA product, as described in ANDA No. 214082, meets all of the limitations of claims 1, 19, and 27 of the '795 patent and claims 8, 9, and 10 of the '713 patent, and thus infringes those claims under 35 U.S.C. § 271(e)(2). (D.I. 199).

2. Claim 27 of the '155 Patent

62. The parties agreed that Eton's ANDA product described in ANDA No. 214082 meets all of the limitations of claim 27 of the '155 patent except one: "per Liter of said stable L-cysteine composition, ... pyruvic acid relative to L-cysteine no more than about 2.0 wt %." ("the pyruvic acid limitation"). (D.I. 201). [7]

63. The parties also agreed that, if the Court finds that the ANDA product described in ANDA No. 214082 meets the pyruvic acid limitation, then that product together with Eton's proposed labeling described in ANDA No. 214082, infringes claim 27 of the '155 patent under 35 U.S.C. § 271(e)(2). (*Id.*).

***123** 64. The parties further agreed that, if the ANDA product described in ANDA No. 214082 meets the pyruvic acid limitation, then the ANDA product induces infringement of claim 27 under 35. U.S.C. § 271(b) and contributes to the infringement of claim 27 under 35 U.S.C. § 271(c) based on the act of direct infringement found pursuant to 35 U.S.C. § 271(e)(2). (*Id.*).

65. The dispute about the pyruvic acid limitation is whether the claim covers a product containing no pyruvic acid.

66. There is no real dispute that Eton's ANDA product meets the limitation if zero pyruvic acid is included. Eton asserts that its product has not been proven to include any pyruvic acid. (D.I. 220 at 1–3, D.I. 212 at 28 ("Eton does not believe that any pyruvic acid exists in its proposed ANDA product")). Exela points out that the acceptance criteria in the finished product stability specification for Eton's ANDA product requires that the ANDA product contain "total impurities" of ≤2.0%. (JTX-14.11951, Tr. 247:1–9). Exela asserts that as pyruvic acid is an impurity, if the total amount of impurities cannot exceed 2.0%, then the amount of one impurity (pyruvic acid) can certainly not exceed 2.0%. (Tr. 250:6–16).

67. Based on the Court's construction of "pyruvic acid relative to L-cysteine not more than about 2.0 wt %" (*infra*, § III.A), which includes a composition having no pyruvic acid, Eton's ANDA product contains no more than about 2.0 wt % of pyruvic acid relative to L-cysteine.

68. Eton's ANDA product, thus, meets all of the limitations of claim 27.

H. Facts Relevant to Invalidity

1. The Prior Art

a. The Sandoz Product

69. Allergy Labs manufactured an L-cysteine product for Sandoz ("the Sandoz product") on a contract basis from 2003

to 2016. (Tr. 293:13–24). Throughout that time, Allergy Labs followed the same manufacturing process and specification. (Tr. 378:3–9).

70. The Sandoz product contained three ingredients: cysteine hydrochloride (the active ingredient), water and a pH adjuster, such as hydrochloric acid and/or sodium hydroxide, if needed. (DTX 54.19-20, Tr. 161:3–6, 161:17–20, 296:17–23).

71. The Sandoz product was sold from 2003 to 2016. (Tr. 293:13–24, 378:3–9, 301:1–3).

72. The Sandoz product was not FDA approved. (PTX-191.6, Tr. 105:11–12, 296:3–8). It was nevertheless sold because the FDA permits the making and selling of unapproved products that are in short supply. (Tr. 159:1–4).

73. The label for the Sandoz product states that it contains no more than 5,000 mcg/L of aluminum and contains a warning that "[t]his product contains aluminum that may be toxic." (PTX-191.2, .5).

74. One of ordinary skill would understand that the Sandoz product could contain as much as 5,000 ppb of aluminum at product expiration, and that it would put patients at risk to assume a lower level of aluminum. (Tr. 505:21–506:2, *see also* Tr. 95:16-96:13 (pharmacists use the maximum concentration of aluminum at expiry because it is the only number they have)).

75. A product containing 5,000 ppb of aluminum would result in aluminum exposure of 14 mcg/kg per day, more than twice the limit set by the FDA. (Tr. 106:6–107:1).

76. The aluminum levels in the Sandoz product, as demonstrated by certificates of analysis, increased over time. For example, ***124** a certificate of analysis for a 50 mL vial showed a value of 48 ppb aluminum near the time of manufacture and values of 407 and 362 ppb about 24 months from manufacture. (DTX-124.001–003, Tr. 570:6–571:20).

77. Moreover, the aluminum levels varied across lots of the Sandoz product. (PTX-194 (summary of Allergy Labs certificates of analysis), PTX-195 (summary of Sandoz Canada certificates of analysis), Tr. 148:22-149:7, 506:10-16). For example, at seven months after the date of manufacture, one lot shows aluminum levels of 580 ppb and another lot shows aluminum levels of 213 ppb. (PTX-195.3).

78. Aluminum levels also varied within the same lot. For example, measurements from two vials in the same lot twenty-four months after manufacture (362 ppb and 407 ppb of aluminum) show that "the aluminum content on a vial-to-vial basis is somewhat variable." (DTX-124.2–.3, Tr. 571:5–10).

79. Despite the fact that the Sandoz product contained high levels of aluminum, doctors used it because they had no other option. (Tr. 107:22–109:5).

80. None of the Allergy Labs certificates of analysis for the Sandoz product reference amounts of cystine, pyruvic acid, lead or mercury, but no certificate of analysis in the record discloses total impurity levels greater than 2%. (DTX-123, DTX-124, DTX-125, PTX-194, PTX-195, Tr. 462:25–463:3).

81. Allergy Labs's manufacture of the Sandoz product is reflected in batch records, only one of which was introduced at trial as part of DTX-54A (hereafter "the Sandoz Product Batch Record"). (Tr. 297:5–298:8). [8]

82. Page 46 of DTX-54, entitled "Filled Vial Labelling Record" appears to depict the label included with the package. That label states that it is a "Pharmacy Bulk Package" configuration, a 50 mL size product. (DTX-54.046).

83. The Sandoz Product Batch Record does not identify the supplier of the cysteine hydrochloride or the amount of aluminum in that cysteine hydrochloride. (*See* DTX-54).

84. Allergy Labs's process for making the Sandoz product begins with Step 1 on DTX-54.022, and concludes with Step 19 on DTX-54.025. (Tr. 318:18–319:25).

85. Allergy Labs 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. (Tr. 320:1–10).

86. Allergy Labs did not terminally sterilize the Sandoz product. (Tr. 320:13–15, DTX-54.029–.033).

87. There is no indication which glass vial Allergy Labs used to contain the Sandoz product. The Sandoz Product Batch Record does not identify the container used other than noting it was a 50 mL 20mm Clear Glass Vial. (DTX-54.026).

88. Around July 20, 2016, there was a recall of the Sandoz product (manufactured by Allergy Labs), resulting in Sandoz being unable to supply the market. As a result of the recall, Sandoz began importing product manufactured in Canada. (Tr. 160:10–16, JTX-13.11224). No evidence about the Canadian-made product's manufacturing process is in the record.

***125** 89. In 2016, Sandoz sought (but did not obtain) FDA approval for a cysteine product by filing an ANDA. (PTX-308.1–2, Tr. 507:23–25).

90. In May 2019, Sandoz reached out to Exela and asked for, but did not receive, a license to market an L-cysteine product. (Tr. 200:18–202:11, 508:5–13, PTX-490).

b. The Abbott Product

91. Dr. Hoffstetter testified that when he worked at Abbott in the early 1990s, he worked on an L-cysteine injectable product. (Tr. 290:7–291:1). He recalled that the product ingredients were "just the L-cysteine drug, the API, and ... water for injection" and it was contained in a Type I U.S.D class vial. (Tr. 292:2–11). There was, however, no meaningful detail provided about the specific method of manufacturing the product, the amount of aluminum contained at any given time, or the amounts of other impurities or precipitates.

c. Bohrer Papers (PTX-227, PTX-228, PTX-271)

92. Dr. Denise Bohrer and colleagues published several papers addressing aluminum leaching in TPN products. (PTX-227, PTX-228, PTX-271). These papers illustrate that a number of different variables, including affinity for aluminum, time, temperature, pH, and oxygen affect the amount of aluminum leaching.

93. In *Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part II: Amino acids for parenteral nutrition*, published in volume 15 of the Journal of Trace Elements in Medicine and Biology in 2001 ("Bohrer 2001"), Dr. Bohrer measured the amount of aluminum leached from glass containers with solutions of amino acids typically found in parenteral products. (PTX-227).

94. Bohrer 2001 found that cysteine had the highest affinity for aluminum of the amino acids tested. (PTX-227.4 (Figure 2)). Cystine, a degradation product of cysteine, had the next highest affinity for aluminum. (*Id.*). Lysine, another amino acid not found in L-cysteine products, was found to have the lowest affinity for aluminum. (*Id.*).

95. Bohrer 2001 further demonstrated that the aluminum leaching continues to increase over time, and, even after almost a year, it continues to rise. (PTX-227.4 (Figure 2)). Thus, the time that amino acid solutions are in contact with glass affects how much aluminum is leached.

96. In *Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part III: Interaction container-chemicals during the heating for sterilization*, published in the Journal of Trace Elements in Medicine and Biology in 2003 ("Bohrer 2003"), Dr. Bohrer found that temperature influences the amount of aluminum leaching.

97. Bohrer 2003 found that sterilization by heat increases the ability of all amino acids to leach aluminum "dramatically." (PTX-228.5, Tr. 590:4–590:19). Of the amino acids tested, Bohrer 2003 found that sterilization by heat most increases cysteine and cystine's capacity to leach. (*Id.*).

98. Another Bohrer paper, *Ion-Exchange and potentiometric characterization of Al-cystine and Alcysteine complexes*, discloses that aluminum leaching persists longer if it is exposed to oxygen than if it is not exposed to oxygen. (PTX-271). Specifically, Bohrer looked at two formulations of cysteine that differed only in the amount of oxygen present and found that aluminum leaching behavior persisted longer when oxygen was present than when it was not. (PTX-271.4; Tr. 593:2–20). The record does not indicate when this paper was published.

***126 d. Hernandez-Sanchez (PTX-152/DTX-409)**

99. In *Aluminum in parenteral nutrition: a systematic review*, published in the European Journal of Clinical Nutrition in 2013 ("Hernandez-Sanchez"), Dr. Hernandez-Sanchez and co-authors gathered and reported information related to aluminum in parenteral nutrition products. (PTX-152).

100. Hernandez-Sanchez reports in the abstract that the "Aluminium (Al) toxicity problem in parenteral nutrition solutions (PNS) is decades old and is still unresolved." (PTX-152.1).

101. Hernandez-Sanchez identified cysteine hydrochloride as one of the three largest contributors of aluminum to TPN solutions. (PTX-152.2, Tr. 101:25–102:9).

102. Hernandez-Sanchez recommended that, to reduce aluminum in TPN solutions, manufacturers should improve manufacturing techniques, and healthcare providers should do their best to try minimizing aluminum exposure in TPN solutions by selecting products with the least amount of aluminum contamination. (PTX-152.8, Tr. 102:24–103:12). Hernandez-Sanchez did not, however, recommend how manufacturers should improve their manufacturing techniques to provide low aluminum products. (PTX-152.8, Tr. 103:13–16).

103. Hernandez-Sanchez explains, as Bohrer 2001 did, that one source of aluminum is glass and instructs that parenteral products "should be stored in containers that do not interact physically or chemically with the preparations." (PTX-152.2).

104. Hernandez-Sanchez teaches away from using glass vials, reporting that "repackaging CaGluc from glass containers to polyethylene vials reduces the mean Al concentration from 5000 to 195 mg/l (a 96% decrease)." (*Id.*).

105. Hernandez-Sanchez also discloses "high lot-to-lot variation" in aluminum content in TPN products. (PTX-152.1).

e. U.S. Patent No. 8,415,337 ("the '337 patent") (DTX-523)

106. The '337 patent, entitled "Ibuprofen Compositions and Methods Of Making Same," issued April 9, 2013. (DTX-523). The '337 patent relates to pharmaceutical compositions of alkylammonium salts of ibuprofen, such as ibuprofen lysinate and processes for making them.

107. The '337 patent addresses the problem of aluminum and lysine combining to form a precipitate. (Tr. 608:16–21). To deal with this problem, the '337 patent recommends the use of vials like the Schott Type I Plus vial, which it specifically names. (DTX-523 at 5:15–20).

108. Precipitation of aluminum is not an issue with cysteine solutions. (Tr. 609:1–3).

109. Lysine also differs from cysteine in terms of aluminum affinity. As discussed *supra* ¶ 94, Bohrer 2001 found that of the eight amino acids tested, cysteine has the most affinity for aluminum and lysine has the least affinity for aluminum. (PTX-227.4).

110. The pH of the lysine mixture in the '337 patent is about 7.0. (DTX-523 at 3:36–37, 5:61–62). This is markedly different than the pH of the cysteine formulation of the asserted claims, which is 1–2.5. (Tr. 590:20–592:22).

f. Schott Type I Plus Brochure (JTX-13.11804–11811)

111. The Schott Type I Plus vial, described in its brochure at JTX-13N at JTX-13.11804–11811 ("the Schott brochure"), has been on the market since the early 2000s. (Tr. 498:2–7, 190:11–13).

112. The Schott brochure advertises the Schott Type I Plus coated glass vial for the purposes of reducing aluminum leaching. ***127** (JTX-13N.11805 ("Barrier layer prevents depletion of glass container by drug formulation"; "Thanks to our patented coating technology, a very high barrier improvement factor against ion leaching is achieved")).

113. The brochure reports an "improvement factor" of more than 45 in terms of aluminum leaching. (JTX-13N. 11804).

114. The Schott brochure does not contain any information specific to cysteine products and suggests individually testing a given product's fit for the vial. (JTX-13N.11806 ("These individual interactions have to be investigated typically during stability studies for the specific pharmaceutical products in the frame of the registration procedure.")).

2. Anticipation of Claim 27 of the '155 Patent Based on the Sandoz Product

115. Eton offers two reasons why the Sandoz product anticipates claim 27 of the '155 patent. First, Eton argues that the Sandoz product is the same as the Eton product and, therefore, anticipates claim 27 if Eton's product infringes that claim. Second, Eton asserts that it has proven on an element-by-element basis that the prior art Sandoz product met all limitations of claim 27.

a. Differences Between the ANDA Product and Sandoz Product

116. Eton contends that its ANDA product is the same as the Sandoz product manufactured by Allergy Labs. (D.I. 212 at 7–14).

117. When Sandoz opted not to continue selling a cysteine product, Allergy Labs, the manufacturer of the Sandoz product, sought to market its own product. (Tr. 377:10–16). To that end, it created AL Pharma and filed an NDA for a cysteine product ("the AL Pharma product"). (Tr. 306:11–20). When the NDA was not approved, AL Pharma converted the application to an ANDA and filed in Eton's name, *i.e.*, the ANDA that is the subject of this suit. (Tr. 308:2–309:12).

118. A cysteine "product is the [ ] solution ... in a container, manufactured by a process[.]" (Tr. 583:12–15).

119. The ingredients, container, and manufacturing process differ between the Sandoz product and the ANDA product. As is demonstrated below, altering the source of ingredients, container of a solution, or certain steps in the manufacturing process can alter the cysteine product.

i. Differences in the Manufacturing Process

120. The manufacturing process for the Sandoz product differs from the manufacturing process to make the AL Pharma product and the ANDA product.

121. The Sandoz product was manufactured by Allergy Labs. (Tr. 293:21–24, 378:3–6). The ANDA product is manufactured by Grand River Aseptic Manufacturing ("GRAM"). (D.I. 177, Ex. 1 ¶¶ 73, 74, JTX-14.201).

122. The process used to make Eton's ANDA product uses terminal sterilization. (DTX-568.024–025, 041–42, Tr. 304:8–24, 305:15–22, JTX-14.194–95, 212–13). The process used to make the Sandoz product did not use terminal sterilization. (Tr. 320:13–15, DTX-54.029–.033).

123. Terminal sterilization uses heat to sterilize a product. (Tr. 304:25–305:3). As described above in ¶¶ 96-97, heat increases the rate aluminum leaches from glass vials as well as cysteine's capacity for leaching aluminum. (PTX-228.5, Tr. 590:4–590:19). Terminal sterilization also increases degradation products like pyruvic acid. (Tr. 493:17-19, 511:21–512:9).

124. Additionally, Allergy Labs did not use oxygen controls in making the Sandoz ***128** product. (Tr. 320:5–9). The process used to make Eton's ANDA product, however, employs various manufacturing controls to limit the amount of oxygen exposed to the solution. These include nitrogen sparging, using a nitrogen blanket during manufacturing and filling, and requiring that the dissolved oxygen in the water both not exceed 1 ppm before cysteine is added and be below 5 ppm at the conclusion of the mixing step, and requires headspace oxygen in the vial to be not more than 5.0%. (DTX-568.016, JTX-14.194, .10344, .10369, Tr. 328:2–329:5, 334:23–335:16).

125. Oxygen controls affect the formation of precipitates. When aluminum is reduced to very low levels in a cysteine product, small amounts of oxygen in the container can increase precipitation and lead to product failure. (Tr. 197:5–198:15, 199:7–200:16, *supra* ¶¶ 51, 52). Moreover, aluminum leaching will persist longer in the presence of oxygen. (PTX-271).

ii. Other Differences

126. The supplier of the active ingredient, cysteine hydrochloride, differs between the Sandoz product and the ANDA product. Allergy Labs used cysteine hydrochloride from Kyowa Hakko Bio to make the Sandoz product.[9] (PTX-653.605, Tr. 307:7–16). The ANDA product cysteine hydrochloride is supplied by Nippon Protein. (JTX-14.186).

127. The active pharmaceutical ingredient can impact the end product because the raw materials used to make the product are a source of impurities. (Tr. 354:18–355:2). For example, to lower aluminum content during development of ELCYS, Exela switched suppliers of cysteine hydrochloride to a supplier that offered the product with lower aluminum content than its previous source. (Tr. 204:8–17).

128. There is scant evidence in the record about the aluminum content of the cysteine supplied by Kyowa compared to that of Nippon Protein, or whether any such differences matter in terms of whether claim limitations are met. (Tr. 307:7–308:1).

129. The glass vial used as a container also differs between the Sandoz product and the ANDA product. (DTX-166

("the glass vial sources are different for Allergy Labs and GRAM"), JTX-14.197–198, JTX-14.10387, Tr. 369:5–370:21). As evidenced by Exela's development of ELCYS, the vial can impact how much aluminum is leached and thus the aluminum content of the product. (Tr. 146:23–147:6, 358:1–9, 584:24–585:5; PTX-1.1656–.1663, *supra*, ¶ 52).

130. Finally, there is a difference between the Sandoz product and the ANDA product in terms of the aluminum content over time. There was no evidence that any Sandoz product met the claimed limitation requiring less than 150 ppb (mcg) over a 12 month or more time period. (Tr. 472:14–18, 506:7–21, 577:9–14). Eton has stipulated that its product meets that limitation. (D.I. 199).

* * *

131. The ANDA product and the Sandoz product are made by different manufacturing techniques, use different vials, and source their active pharmaceutical ingredients from different suppliers.

132. Not only are the individual differences between the Sandoz product and the ANDA significant, but they also have the capacity to interact and affect the product ***129** in unpredictable ways. As Dr. Jenke explained, "the impact or the mechanism by which time and temperature influences leaching is different than the mechanism by which the solution impacts leaching, but the combined effect, the effect that dictates how much aluminum is actually in the product is caused by the interacting phenomenon of both the solution and time and temperature." (Tr. 586:7–21).

133. The ANDA product is not the same as the Sandoz product.

b. Eton Has Not Proven that Any Prior Art Sandoz Product Had Aluminum Below 150 ppb at Three Months

134. The parties agreed that the Sandoz product met all but the following limitations of claim 27 of the '155 patent: (1) stable L-cysteine composition, (2) per liter of L-cysteine composition, not more than 150 mcg of aluminum, (3) cystine not more than about 2.0 wt %, and (4) pyruvic acid not more than about 2.0 wt %. (Tr. 452:13–18, 456:20–457:7, 467:1–17).

135. The "stable" limitation requires that the product "contain the specified levels of all components for sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting." The "specified levels" are described in the claim limitations (*e.g.*, not more than 150 ppb of aluminum) and the "sufficient period of time" is three months. (*See infra §* III.A (Claim Construction)).

136. Of the certificates of analysis in evidence (DTX-123, DTX-124, DTX-125, DTX-486, PTX-194 (summary), PTX-195 (summary)), only one, DTX-486 ("the Sandoz Canada certificate"), suggests a product that contained less than 150 ppb aluminum at the three-month mark.[10] The Sandoz Canada certificate shows a level of 150 ppb aluminum at seven months from the manufacturing date and reports that Sandoz Canada Inc. manufactured the tested product.

137. The Sandoz Canada certificate is not itself prior art. (D.I. 212 at 3 (Eton explaining that "[t]he documents describing the Sandoz product, such as the Certificates of Analyses and Sandoz New Drug Application [ ] filing, are not themselves the prior art reference, but merely describe the product itself that was publicly sold from 2003 through 2016.")).

138. Eton offered no evidence that the lot tested in the Sandoz Canada certificate was ever sold, offered for sale, imported, in public use or otherwise available to the public in the United States (or elsewhere).[11] No testimonial or documentary ***130** evidence supports that the lot tested in the Sandoz Canada certificate was ever in the prior art.

3. Obviousness of All Claims Based on the Prior Art Sandoz Product in View of the Knowledge of a POSA

139. Eton asserts that each of claim 27 of the '155 patent, claims 8, 9, and 10 of the '713 patent, and claims 1, 19, and 27 of the '795 patent are obvious in light of the combination of the Sandoz product with the knowledge of one of skill in the art regarding leaching of aluminum and coated vials.

140. Each of the asserted claims requires an L-cysteine solution or composition in which the amount of aluminum is not more than 150 ppb[12] for a period of time (*e.g.*, 3 months, 12 months, 24 months).

141. Each of the asserted claims requires an L-cysteine solution or composition with a limited amount of impurities or precipitates. [13]

a. The Sandoz Product

142. As discussed in section I.H.2.a, *supra*, the Sandoz product is not the same as the ANDA product. The differences in the source of the ingredients, manufacturing process and container render it inappropriate to use the ANDA product to determine the amounts of aluminum and other impurities (such as cystine and pyruvic acid) in the Sandoz product over time.

143. The evidence about the properties of the Sandoz product consists of three Allergy Labs certificates of analysis. (DTX-123, DTX-124, DTX-125). Dr. Hofstetter testified that Allergy Labs only prepared commercial batches for Sandoz. (Tr. 300:22–301:3). The certificates of analysis for three of those batches indicate that the Sandoz product had less than 150 ppb aluminum after 1 month but exceeded 150 ppb at the 24-month mark. The certificates indicate that the product contained less than 2% impurities at both the 1-month and 24-month mark, but do not indicate whether the product contained any mercury or lead. (Tr. 573:9–14).

144. The Sandoz product was stored in a 50 mL 20mm Clear Glass Vial, but the record does not identify anything else about the vial, including its supplier. (DTX-54.026).

b. The Complex Nature of Aluminum Leaching

145. The asserted claims cover a low-aluminum product with a limited amount of impurities such as cystine and pyruvic acid. The evidence shows that the levels of aluminum are not independent of the ***131** amounts of impurities in a cysteine product.

146. For example, when Exela reduced the aluminum levels in its cysteine product to very low levels, its product failed. One month into stability testing, the plastic-vial batches unexpectedly failed because the product contained visible particulate matter. (JTX-13.11801, Tr. 184:15–24). "Exela analyzed the particulates and found that it [was] L-Cystine, a [degradant and] result of oxidation of L-Cysteine." (JTX-13.11801).

147. Similarly, the experience of non-party Avadel Legacy Pharmaceuticals, LLC ("Avadel") illustrates the relationship between aluminum levels and impurities in a cysteine product.

148. Avadel prepared six batches of its cysteine formulation that were identical except for the vial used. (Tr. 594:11–595:5). Half of the batches were contained in Schott Type I Plus vials, which are lined, and the other half were contained in normal Type I vials, which are unlined. (Tr. 597:6–598:5).

149. Avadel manufactured these batches using certain oxygen controls (nitrogen overlay and headspace flush) but omitting other oxygen control steps (nitrogen sparging). (Tr. 601:7–24, 602:13–15). Avadel did not employ nitrogen sparging because it believed "the difference in cystine levels between bench-scale batches made using sparged vs. non-sparged WFI were insignificant." (PTX-1.1657, Tr. 601:7–602:7).

150. The use of different vials affected the aluminum levels in each vial. The lined Schott Type I Plus vials showed aluminum at less than 5 ppb through 24 months, and aluminum levels in the unlined Type I vials measured from about 45 ppb at manufacture and 102 ppb at 3 months, up to 221 ppb at 12 months. (PTX-1.1505-07, 1661, 1640).

151. The lined vials (with extremely low levels of aluminum) unexpectedly generated precipitates that Avadel later determined to be cystine precipitates, resulting in product failure. (PTX-1.1664, 1683).

152. That the same formulation was stored in two different containers, with only the low-aluminum solution experiencing notable precipitation, is evidence that aluminum acts as a stabilizing force on cysteine in the presence of oxygen.

153. Avadel responded to this observation by adding two nitrogen sparging steps that it had believed were unnecessary. (PTX-1.1640, 1675). This step improved the stability of the product. (PTX-1.1675, 1657, Tr. 600:8–602:22).

154. Avadel's experience led it to comment that "the apparent kinetics and equilibrium chemistry of the various cysteine and cystine species is complicated and not always predictable in a practical setting." (PTX-1.1674–1675).

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c. The Prior Art Did Not Teach How To Reduce Aluminum in a Cysteine Product

155. The prior art did not provide a pathway to lowering the amount of aluminum in the Sandoz product.

156. Eton asserts that Hernandez-Sanchez's teaching that parenteral products "should be stored in containers that do not interact physically or chemically with the preparations" would lead one of skill in the art to the Schott Type I Plus vial. (D.I. 212 at 25 (citing PTX-152.2)). Hernandez-Sanchez, however, merely identifies the problem and does not offer a solution. Indeed, the 2013 review paper states that "Aluminium (Al) toxicity problem in parenteral nutrition solutions (PNS) is decades old and is still unresolved." (PTX-152.1).

***132** 157. Hernandez-Sanchez teaches away from storing TPN products in glass vials, explaining that "repackaging CaGluc from glass containers to polyethylene vials reduces the mean Al concentration from 5000 to 195 mg/l (a 96% decrease)." (PTX-152.2).

158. Eton suggests the Hernandez-Sanchez paper would lead a POSA to coated glass vials disclosed by the '337 patent. As described *supra* in ¶¶ 106 to 110, the problem addressed in the '337 patent is materially different than the problem facing one trying to make a low-aluminum cysteine product that is low in particulate matter because lysine has a low affinity for aluminum and a markedly different pH value than cysteine. Therefore, an artisan would not have a reasonable expectation of success in developing a low-aluminum L-cysteine product based on what the '337 patent discloses.

159. Although the Schott Type I Plus vial brochure advertises itself as being ideal for limiting aluminum leaching, it contains no information specific to cysteine formulations. (*See* JTX-13.11804–11811).

160. The Schott Type I Plus vial was on the market for more than a decade before Exela's invention, during which time practitioners and the FDA were focusing on the aluminum problem in TPN products. (*Supra* ¶ 54, *infra* ¶¶ 168–174).

161. Aluminum leaching was a persistent problem in TPN products and the prior art did not provide a roadmap to Exela's invention.

4. Objective Indicia of Non-Obviousness

162. Aluminum toxicity had been known to be a problem with TPN compositions since the 1980s. (Tr. 82:10–14). Side effects of aluminum toxicity include neurotoxicity, changes in neurodevelopment over time, or weakening of bones. (Tr. 80:18–81:15).

163. In 1985, Sedman and co-authors published *Evidence of Aluminum Loading in Infants Receiving Intravenous Therapy* in the New England Journal of Medicine, addressing aluminum exposure in infants receiving parenteral therapy and demonstrating that aluminum loading in neonatal TPM patients was occurring. (PTX-190).

164. Sedman's article led the FDA to hold a workshop on aluminum in TPN products in 1986. (PTX-171, Tr. 84:23–85:7). The workshop recognized the need to solve the aluminum problem in TPN products and, in the interim, to disclose aluminum content on labels. (Tr. 85:24–86:11).

165. In 1989, Klein and co-authors published *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* in the Journal of Pediatric Gastroenterology and Nutrition. (PTX-162). Klein reported on an eight-month old infant receiving TPN who had demonstrated osteopenic bone disease (*i.e.*, poor formation of the bone) and reported unsuccessful attempts to treat the patient. (PTX-162.1, Tr. 87:6–88:5). [14] Klein taught that once aluminum deposition occurred, there was not much that could be done about it, so the focus on the field should be prevention. (Tr. 88:10–14).

166. In 1997, Bishop and others published their study of the effects of high-aluminum TPN solutions on mental development in premature infants in the article *Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions* appearing in the New England Journal of Medicine. (PTX-181.1, Tr. 89:4–90:2). ***133** Bishop compared infants with a daily aluminum exposure of 45 mcg/kg per day (the standard, high-aluminum TPN solution) with those exposed to 4 to 5 mcg/kg per day using an aluminum-depleted TPN solution. (PTX-181.2, Tr. 90:15–22). Bishop observed that patients receiving the standard, high-aluminum TPN solution scored ten points lower on the Bayley Score of Infant Development (a 100 point scale that is often used to assess how well a child is moving along with milestones

of neurological function) than those receiving the aluminum-depleted TPN solutions. (PTX-181.3, Tr. 89:4–90:14, 90:23–91:13). In addition, Bishop observed a two-fold difference in the percentage of patients scoring below an 85 on the Bayley Score (a score associated with significant mental delay) between those receiving the standard, high-aluminum TPN solution and those receiving the aluminum-depleted TPN solution (38% v. 17%). (PTX-181.3, Tr. 90:23–91:13).

167. Bishop concluded that the Bayley Score of the children receiving the standard, high-aluminum TPN solution went down one point for every day of exposure. (PTX-181.5, Tr. 91:14–92:12).

168. In 2000, the FDA promulgated a rule titled "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition," [15] which required the maximum aluminum level at the expiration or end of shelf life to be stated on the container for small volume parenterals. (PTX-243, Tr. 93:12–20, 94:9–95:5). This FDA rule also required labels for small and large volume parenterals to include warning language that the product contains aluminum that can be toxic, and that a daily aluminum exposure of 4 to 5 mcg/kg per day can lead to aluminum accumulation associated with neurotoxicity and bone toxicity. (PTX-243.2-3, Tr. 95:6–15, 96:25–97:8). The FDA rule was implemented in July 2004. (Tr. 96:14–17).

169. Dr. Kuhn testified that, at the time of the FDA rule's implementation, he was unable to meet the daily exposure target because the aluminum content of all of the ingredients added together was much higher than 5 mcg/kg. (Tr. 96:25–97:8).

170. In 2005, Driscoll et al. published commentary in the American Journal of Health-System Pharmacy, titled *Calculating aluminum content in total parenteral nutrition admixtures*, which calculated aluminum exposure from a number of simulated TPN solutions for an adult and for an infant based on the labeling requirements from the FDA regulation. (PTX-189.1, Tr. 97:10–98:7). Driscoll identified cysteine hydrochloride as one of the three biggest sources of aluminum in TPN solutions. (PTX-189.1, Tr. 98:8–17). Driscoll concluded that limiting the aluminum exposure for TPN patients to less than 5 mcg/kg per day would not be possible for most patients. (PTX-189.3-.4, Tr. 98:18–99:5).

171. In 2008, Poole et al. published *Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation* in the Journal of Parenteral and Enteral Nutrition. (PTX-156). Poole calculated the aluminum exposure from one hundred TPN solutions administered to their pediatric patients based on the labeled aluminum levels. (PTX-156.2, Tr. 99:6–100:8). Poole found that, for babies, every TPN solution exceeded the 4–5 mcg/kg per day target set by the FDA. (PTX-156.3; Tr. 100:9–25).

172. As already noted, in 2013, Hernandez-Sanchez (*supra* ¶ 100), stated that aluminum toxicity in TPN solutions "has been a problem for decades and is still unresolved" (PTX-152.1) and concluded that it ***134** was virtually impossible to comply with the FDA's guidance of less than 5 mcg/kg per day of aluminum exposure. (PTX-152.7). Hernandez-Sanchez identified cysteine hydrochloride as one of the major contributors of aluminum. (PTX-152.1-2, Tr. 102:10–19).

173. In 2016, Lima-Rogel published *Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico* in the Journal of Parenteral and Enteral Nutrition. (PTX-153). Lima-Rogel stated that "[a]luminum contamination from intravenous solutions still represents an unsolved clinical and biochemical problem." (PTX-153.1).

174. The Sandoz product was sold from 2003 to 2016, during which time contemporary publications noted the still unresolved problem with aluminum levels in TPN compositions. (Tr. 293:13–24, 378:3–9, 301:1–3, PTX-152).

175. Moreover, as noted above (*supra* ¶¶ 89, 90), in 2016, Sandoz sought (but did not obtain) FDA approval for a cysteine product by filing an ANDA and then in May 2019, reached out to Exela seeking a license to market an L-cysteine product. (Tr. 200:18–202:11, Tr. 508:5-13, PTX-490).

176. Before Exela received approval for ELCYS in April 2019, no FDA-approved cysteine product had been on the market since 2005. [16]

177. To date, the only FDA-approved cysteine products are ELCYS and Avadel's product (which is now owned by a third-party). [17]

178. ELCYS is an embodiment of all asserted claims. (*See supra* ¶¶ 36-41). And the Avadel product has been granted a license under the patents at issue in this case. (Tr. 230:17-21).

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179. Dr. Kuhn testified that he uses ELCYS every day in the TPN solutions compounded in his pharmacy, and now his patients who receive TPN solutions meet the FDA daily aluminum guidance. (Tr. 110:7-9, 113:10–13). The introduction of ELCYS also allowed Dr. Kuhn to use cysteine in the TPN solutions of older pediatric patients who previously would not have received cysteine, which in turn allowed those patients to receive increased amounts of calcium and phosphorus. (Tr. 110:22–111:8).

II. LEGAL STANDARDS

A. Claim Construction

[1] **[2]** **[3]** **[4]** "[T]he ultimate question of the proper construction of the patent [is] a question of law," although subsidiary fact-finding is sometimes necessary. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 135 S. Ct. 831, 837-38, 190 L.Ed.2d 719 (2015). "[T]he words of a claim are generally given their ordinary and customary meaning [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (internal citations and quotation marks omitted). Although "the claims themselves provide substantial guidance as to the meaning of particular claim terms," the context of the surrounding words of the claim also must be considered. *Id.* at 1314. "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after ***135** reading the entire patent." *Id.* at 1321 (internal quotation marks omitted).

[5] **[6]** **[7]** The patent specification "is always highly relevant to the claim construction analysis ... [as] it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). It is also possible that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. "Even when the specification describes only a single embodiment, [however,] the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks omitted) (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004)).

[8] **[9]** **[10]** In addition to the specification, a court "should also consider the patent's prosecution history, if it is in evidence." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). The prosecution history, which is "intrinsic evidence, ... consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

[11] **[12]** **[13]** **[14]** In some cases, courts "will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." *Teva*, 135 S. Ct. at 841. Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Expert testimony can be useful "to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Phillips*, 415 F.3d at 1318. Nonetheless, courts must not lose sight of the fact that "expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Overall, although extrinsic evidence "may be useful to the court," it is "less reliable" than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See*

Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

B. Infringement

[15] **[16]** A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States ... during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making ***136** an infringement determination. *See Markman*, 52 F.3d at 976. First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly-construed claims to the accused infringing product. *See id.* Literal infringement occurs where "every limitation in a patent claim is found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995).

[17] In an infringement action brought pursuant to 35 U.S.C. § 271(e)(2)(A) – the statutory provision under which Plaintiffs have sued Defendant here – the infringement inquiry is "whether, if a particular drug were put on the market, it would infringe the relevant patent." *Acorda Therapeutics Inc. v. Mylan Pharm. Inc.*, 817 F.3d 755, 760 (Fed. Cir. 2016).

C. Validity

[18] **[19]** **[20]** An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. To invalidate a patent, the party seeking invalidation must carry its burden of proof by "clear and convincing evidence." *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original).

1. Anticipation

[21] **[22]** **[23]** **[24]** Anticipation is a question of fact. *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017). A patent claim is anticipated if each and every limitation is found, either expressly or inherently, in a single prior art reference. *See In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *Moba, B.V v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321-22 (Fed. Cir. 2003). This test mirrors, to some extent, the test for infringement, and "it is axiomatic that that which would literally infringe if later anticipates if earlier." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001). In order to anticipate, however, a reference must "show all of the limitations of the claims arranged or combined in the same way as recited in the claims." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008).

[25] **[26]** **[27]** Pursuant to 35 U.S.C. § 102(a), a patent may be found invalid if "the invention was known or used by others in this country" before the invention by the applicant. "If the invention was known to or used by others in this country before the date of the patentee's invention, the later inventor has not contributed to the store of knowledge, and has no entitlement to a patent." *Woodland Tr. v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998). "For prior art to anticipate because it has been 'used,' the use must be accessible to the public." *Minnesota Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002); *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1305-06 (Fed. Cir. 2006). "The prior knowledge and use by a single person is sufficient." *Coffin v. Ogden*, 85 U.S. 120, 124, 18 Wall. 120, 21 L.Ed. 821 (1873); *see also Brush v. Condit*, 132 U.S. 39, 48, 10 S.Ct. 1, 33 L.Ed. 251 (1889).

[28] **[29]** Material not explicitly contained in a single prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document. *See Ultradent Prods., Inc. v. Life-Like Cosmetics, Inc.*, 127 F.3d 1065, 1069 (Fed. Cir. 1997). Incorporation by reference provides a ***137** method for integrating material from various documents into a host document by citing such material in a manner making clear that the material is effectively part of the host document as if it were explicitly contained therein. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

2. Obviousness

[30] **[31]** **[32]** A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art, and (4) objective considerations of nonobviousness. *See* *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012); *see also* *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). Although an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See* *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007).

[33] **[34]** The use of hindsight is not permitted when determining whether a claim would have been obvious to one of ordinary skill in the art. *See* *id.* at 421, 127 S.Ct. 1727 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon ex post reasoning"). To protect against the improper use of hindsight when assessing obviousness, the Court is required to consider objective (or "secondary") considerations (or "indicia") of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g.*, *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

III. DISCUSSION

A. Claim Construction

During the claim construction proceedings, the parties agreed to the following constructions for terms in the asserted claims:

1. "safe" means "a property of the compositions and methods relative to the art method and compositions and/or to FDA regulatory determination of the compositions and methods as part of a therapeutically or nutritionally effective regimen" ('795 Patent, claims 1, 19, 27)

2. "wherein for at least 12 months from the time of manufacture of the solution, the solution will remain: substantially free of visually detectable matter, at a pH from about 1.0 to about 2.5, and containing no more than 150 ppb of aluminum" needs no construction, and "at least 12 months from the time of manufacture of the solution" applies to the recited limitations regarding visually ***138** detectable matter, pH, and aluminum" ('795 Patent, claim 1)

[35] **[36]** **[37]** At the beginning of trial, the Court heard claim construction arguments on two disputed terms: (1) "about," in claim 27 of the '155 patent, and (2) "pharmaceutically acceptable amount of cystine," in claim 1 of the '713 patent, from which asserted claims 8, 9, and 10 depend. During the course of trial, two additional claim construction disputes emerged. The first regarded the term "stable L-cysteine composition" in claim 27 of the '155 patent, for which the parties had twice previously represented they agreed upon a definition. (D.I. 83, D.I. 179-1 at 10). The second regarded "pyruvic acid relative to L-cysteine not more than about 2.0 wt %" also in claim 27. At trial, the Court construed three of those terms as follows:

1. "about" means "approximately" and is not indefinite, as Defendant contends. ('155 patent, claim 27).

2. "pharmaceutically acceptable amount of cystine" has its plain and ordinary meaning, which is "an amount of cystine that is compatible chemically and/or toxicology with the other ingredients comprising a formulation and/or the mammal being treated therewith." The term is not indefinite. ('713 patent, claims 8, 9, and 10).

3. "stable L-cysteine composition" mean "an L-cysteine composition that has the component profiles described herein, for example, Aluminum, L-Cystine, and pyruvic acid, at the levels described and for the amount of

> time identified. In other words, a stable composition will contain the specified levels of all components for sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting. In general, products are considered stable if the period of time is three months, or three to six months, or three to 12 months, or three to 15 months, or three to 18 months or three to 24 months." [18] ('155 patent, claim 27).

The Court explained its reasoning for its constructions of the above terms at trial. (*See* Tr. 543:16–548:24).

As to "pyruvic acid relative to L-cysteine not more than about 2.0 wt %" in claim 27 of the '155 patent, the parties dispute whether this term requires the presence of pyruvic acid, or whether it can be met by the absence of pyruvic acid. Plaintiff contends that this limitation "set[s] only a ceiling [ ] and not a floor [ ] on the amount of pyruvic acid the formulation may contain." (D.I. 209 at 6). Defendant argued at trial that this limitation requires the presence of at least some pyruvic acid, otherwise the limitation would be superfluous (Tr. 280:14–281:20), but Defendant did not advance a claim construction position in its post-trial briefs.

The Court agrees with Plaintiff. "[P]yruvic acid relative to L-cysteine not more than about 2.0 wt %" does not require the presence of pyruvic acid in the formulation. As an initial matter, the plain and ordinary language of this term does not set a lower boundary for the amount of pyruvic acid or indicate that it must be present. In contrast, unasserted claim 28 of the '155 patent requires "pyruvic acid in an amount from about 0.001 wt % to about 2.0 wt % relative to L-cysteine." (JTX-2 at 4:43–44). This suggests that the patentee ***139** knew how to set a lower bound on the amount of pyruvic acid relative to L-cysteine, but chose not to do so in claim 27.

Moreover, the specification offers further support for the Court's construction, as it contemplates compositions that may contain no pyruvic acid. At column 25, lines 51–55 of the '155 patent, the specification states:

> Advantageously, in certain embodiments, the compositions maintain pyruvic acid levels for extended periods, and/or are substantially free or essentially free of pyruvic acid. ***When present***, pyruvic acid is typically present in a relatively small amount compared to L-cysteine."

(JTX-2 at 21:51–55) (emphasis added).

[38] For the above reasons, the Court construes "pyruvic acid relative to L-cysteine not more than about 2.0 wt %" to have its plain and ordinary meaning, which sets a limit to the amount of pyruvic acid when present, but does not require the presence of pyruvic acid.

B. Infringement

Prior to trial, the parties stipulated to infringement of all asserted claims of the '713 and '795 patents, leaving only claim 27 of the '155 patent contested. (D.I. 199). With respect to claim 27, the parties agreed that Eton's ANDA product meets all limitations except one: "pyruvic acid relative to L-cysteine not more than about 2.0 wt %." (D.I. 201). The parties agreed that if the Court found that the ANDA product met this limitation, then Eton infringes claim 27 under 35 U.S.C. § 271(e)(2), contributes to the infringement of claim 27 under 35 U.S.C. § 271(c), and induces infringement of claim 27 under 35 U.S.C. § 271(b). (D.I. 201 ¶¶ 2–4).

[39] Defendant's non-infringement position is that Exela did not prove that its product contains any pyruvic acid. (D.I. 220 at 1-3, D.I. 212 at 28 ("Eton does not believe that any pyruvic acid exists in its proposed ANDA product")). The Court, however, construed "pyruvic acid relative to L-cysteine not more than about 2.0 wt %" to require only that the amount not exceed the maximum stated in the claim. The claim does not set a minimum amount of pyruvic acid, and the claim as construed does not require that any pyruvic acid be present.

[40] "What a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement." *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013). Defendant seeks to market an L-cysteine product that contains no more than 2.0% impurities total. (*Supra* ¶ 66). Thus, the level of one of those impurities, pyruvic acid, must be less than 2.0%. [19] Because Eton's ANDA product contains less than 2.0% pyruvic acid relative to L-cysteine, it meets the only disputed limitation

of claim 27. Thus, Exela has proven that Eton directly infringes claim 27 of the '155 patent, and based on the parties' stipulation (D.I. 201), Eton contributorily infringes and induces infringement of claim 27 as well.

C. Validity

[41] Eton contends that claim 27 of the '155 patent is anticipated by the Sandoz product and that all asserted claims are obvious in view of the Sandoz product and the knowledge of one of skill in the art ***140** regarding leaching and use of coated vials.[20] The Court addresses each defense in turn.

1. Anticipation

Eton asserts two bases on which claim 27 of the '155 patent is anticipated by the Sandoz product: (1) the Sandoz product is the same as the ANDA product and (2) the Sandoz product sold commercially possessed all limitations of claim 27.

a. Eton Has Not Proven that the Sandoz and ANDA Products Are the Same

[42] Eton argues that the Sandoz product is the same as the ANDA product, and thus, if the ANDA product infringes, the Sandoz product must anticipate because "[t]hat which infringes, if later, would anticipate, if earlier." *Peters v. Active Mfg. Co.*, 129 U.S. 530, 537, 9 S.Ct. 389, 32 L.Ed. 738 (1889). Eton submits that ingredients of the products are the same and the manufacturing process for the two products is similar, with the only difference being that the ANDA product has an additional step of terminal sterilization, which is immaterial. (DTX-568.024–025, 041–42, Tr. 304:8–24, 305:15–22, 623:16–21). The evidence, however, points to differences between the two products, including differences that can impact the amount of aluminum, cystine, and pyruvic acid in the composition referenced.

First, it is apparent that the Sandoz product and Eton's ANDA Product are not the same, as they differ as to amount of aluminum over time. (*Supra* ¶ 130). Eton's expert Dr. Baertschi acknowledged that the Sandoz product would not have met Eton's specifications for aluminum over the shelf life of its ANDA product.[21] (*Id.*). And there was no evidence that the Sandoz product maintained aluminum levels below 150 ppb for 3 months from manufacture, let alone 12, 18, or 24 months. (*Id.*).

Moreover, as Exela points out, the added terminal sterilization step involves heat. The prior art taught that heat impacts the amount of leaching of aluminum as well as the degradation and impurity content of cysteine products. (*Supra* ¶¶ 96-97, Tr. 305:19–22). Specifically, higher heat increases the amount of leaching of these products "dramatically." (*Id.*). Moreover, the additional sterilization step is not the only difference in the manufacturing process. Eton also added oxygen controls that were not part of the process to make the Sandoz product. (*Supra* ¶ 124). As Bohrer taught, the amount of oxygen present impacts aluminum leaching in a cysteine formulation, *i.e.*, that leaching behavior persisted longer when oxygen was present than when it was not. (*Supra* ¶ 98).

The differences are not limited to manufacturing. The Sandoz product used a different vial than the ANDA product and Eton offered no evidence that the change to the vial was not substantial. (*Supra* ¶ 129). Although this may seem a minor adjustment, the evidence shows that the vial used can affect how much aluminum is leached. Indeed, this is evident from the real-life experience of companies in the field. For example, non-party Avadel put the same formulation into lined and unlined vials, with the result that the formulation ***141** in the lined vials had low levels of aluminum and later precipitates formed, but the unlined vial had a higher aluminum level and no problem with precipitates. (*Supra* ¶¶ 148–152). Similarly, during Exela's development process it switched from glass to plastic vials, which substantially lowered the aluminum levels but later caused precipitates to form. (*Supra* ¶¶ 51–52).

Further, the two products are made with cysteine hydrochloride sourced from different companies. (*Supra* ¶ 126). As Exela argues, this is meaningful because different suppliers sell products with different impurity profiles. Again, the impact of this is evidenced by real world facts. Indeed, Exela lowered the amount of aluminum in its product in part by sourcing its active pharmaceutical ingredient from its supplier who offered the ingredient with a lower aluminum level than its previous source. (Tr. 204:8–17, *supra* ¶ 51). And again, Eton offered no evidence as to the immateriality of the specific change.

Each of the differences between the two products has the potential to impact the end product with respect to aluminum content and impurities. Moreover, the evidence demonstrates

that the factors in the process are interconnected, such that a change in one factor, like aluminum levels, can alter another factor, like the level of cystine. (Tr. 582:7–16). Thus, the differences between the products preclude a finding that the Sandoz product is the same as the ANDA product. And Defendant has not proven anticipation by clear and convincing evidence on that ground.

b. Eton Has Not Proven that the Sandoz Product Contains Each and Every Element of Claim 27

As noted above (*supra* ¶ 134), the parties agreed that the Sandoz product met all but four limitations of claim 27 of the '155 patent: (1) stable L-cysteine composition, (2) per liter of L-cysteine composition, not more than 150 mcg of aluminum, (3) cystine not more than about 2.0 wt %, and (4) pyruvic acid not more than about 2.0 wt %.

[43] Eton's asserted proof that the Sandoz product was a stable composition having not more than 150 mcg of aluminum relies on a single certificate of analysis, the Sandoz Canada certificate, that reports an aluminum level of 150 ppb seven months after the date of manufacture. (DTX-486). Eton does not assert that the Sandoz Canada certificate is prior art, but states that it describes the Sandoz product that was in public use. (D.I. 212 at 3 ("The documents describing the Sandoz product, such as the Certificates of Analyses and Sandoz New Drug Application [ ] filing, are not themselves the prior art reference, but merely describe the product itself that was publicly sold from 2003 through 2016."), D.I. 211 ¶ 9). There is, however, insufficient evidence that the Sandoz Canada certificate describes a lot that was in public use, on sale, or otherwise available to the public in the United States (or elsewhere).

Eton argues that the certificates of analysis it submitted describe products that were on sale because Dr. Hofstetter testified that Allergy Labs only prepared commercial batches for Sandoz. Even crediting that testimony, however, the Sandoz Canada certificate lists "Sandoz Canada Inc." as its manufacturer, not "Allergy Labs." (DTX-486). And although there is some evidence that lots that Sandoz Canada Inc. manufactured may have been on sale or in public use or otherwise available to the public (*supra* ¶ 88), there is no evidence as to the properties of the products in those lots, let alone the properties of those lots as relevant to the specific limitations of claim 27. (*Supra* ¶ 138). Given the variability seen in terms of aluminum levels (*see* ***142** *supra* ¶¶ 76-78) and the fact that only one of the many certificates of analysis reviewed met the aluminum limit claimed, the Court cannot conclude that any Sandoz product sold possessed all claimed limitations of claim 27 of the '155 patent. Eton has thus failed to prove that claim 27 is anticipated by the Sandoz product.

2. Obviousness

Eton contends that all asserted claims are obvious in view of the Sandoz product and the knowledge of one of skill in the art. (D.I. 212 at 29–37). The obviousness argument is generally the same as to all claims. The parties addressed the claims collectively, and the Court will do so as well. [22]

a. Eton Has Not Demonstrated That Putting the Sandoz Product In a Schott Type I Plus Vial Would Result in the Claimed Inventions

[44] Eton's obviousness arguments are, like its anticipation arguments, based on the Sandoz product. More specifically, Eton contends that the Sandoz product contained all asserted claim limitations other than those limiting the level of aluminum over the time specified in the claims (3, 12, or 24 months) and that it was obvious to use Schott Type I Plus vials to reduce the aluminum to acceptable levels. Even assuming Eton were correct as to the properties of the Sandoz product, its argument fails to look at the invention "as a whole, not separate pieces of the claim." *Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1282 (Fed. Cir. 2011) (quoting *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)). Indeed, all of the asserted claims require not only a stable L-cysteine solution (or composition) containing no more than 150 ppb of aluminum, but also impose limits either on the amounts of certain impurities or that the solution be substantially free of visually detectable particulate matter. (*Supra* ¶¶ 140–141).

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

illustrated in the real world experiences of Exela and Avadel in developing their cysteine products. During development, Exela lowered the aluminum levels to very low levels using oxygen controls and placed the product in plastic vials. (*Supra* ¶¶ 52–53). Those batches, however, generated particulates and failed. (*Id.*). Avadel faced similar challenges. When Avadel put its L-cysteine product into Schott Type I Plus vials without sufficient oxygen controls, its product produced cystine precipitates and also failed. (*Supra* ¶ 151). Avadel's difficulties in development led it to comment on the "complex" chemistry of cysteine and how it is "not always predictable in a practical setting." (*Supra* ¶ 158).

There is simply no evidence that combination of the Sandoz product in the Schott Type I Plus vials would have achieved the claimed inventions. Indeed, to the extent that the Sandoz product, like the Avadel product that failed, was made without oxygen controls, that suggests that the Sandoz ***143** product in the Schott Type I Plus vial (as the Avadel product was) would also have produced unacceptable cystine precipitates and taken it outside of the claimed inventions.

b. Eton Has Failed To Show a Reason to Combine the Sandoz Product and the Schott Type I Plus Vial

[45] Eton has not shown that a POSA would have chosen the Schott Type I Plus vials to reduce aluminum levels with cysteine products. To the contrary, the evidence shows that a POSA would not have had a reason to put the Sandoz product in a Schott Type I Plus vial. Indeed, Sandoz sold its product from 2003 to 2016. (*Supra* ¶ 71). The Schott Type I Plus vials had been available since the early 2000s. (*Supra* ¶ 54). From 2003 to 2016, the problem of aluminum leaching was known and remained unresolved. (*Supra* ¶ 174). Yet it was apparently not obvious to Sandoz to put its product in Schott Type I Plus vials. Moreover, "[t]he elapsed time between the prior art and the [ ] patent's filing date evinces that the [ ] patent's claimed invention was not obvious to try." *Leo Pharms.*, 726 F.3d at 1356. Such a "considerable time lapse suggests instead" that Eton "only traverses the obstacles to this inventive enterprise with a resort to hindsight." *Id.*

Indeed, it is only through hindsight – knowing what Exela did and claimed and then looking at the prior art through that lens – that Eton argues obviousness. For example, Eton argues that Hernandez-Sanchez suggests the use of a coated vial (D.I. 212 at 25), but not even its expert, Dr. Baertschi, connected any disclosure in Hernandez-Sanchez to coated vials, let alone the Schott Type I Plus vial. Hernandez-Sanchez recognizes the well-known problem of high aluminum in glass, but it provides no actionable solutions. *See* *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008) (explaining that "knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references"). To the extent Hernandez-Sanchez points to anything, it is to polyethylene (plastic) containers, not coated glass vials. [23] (*Supra* ¶ 104).

Similarly, Eton points to the '337 patent as motivating a POSA to put the Sandoz product in coated vials. That patent, however, addressed a different aluminum problem (aluminum precipitation) for a different pharmaceutical formulation (ibuprofen lysine) that had a much different pH and a minimal ability to leach aluminum from glass. (*Supra* ¶¶ 106–110). A POSA would not have extrapolated the '337 patent to cysteine formulations particularly given the differences between cysteine and lysine noted by Bohrer 2001 in terms of affinity for aluminum. *See* *Intendis GMBH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355, 1366 (Fed. Cir. 2016) (finding no clear error with district court's determination that "swapping ingredients in complex chemical formulations is anything but 'routine.' "). The '337 patent teaches nothing about making or achieving the claimed inventions.

[46] Eton's hindsight-infected arguments fail to make the proper obviousness analysis, which "requires a form of amnesia that 'forgets' the invention and analyzes the prior art and understanding of the problem at the date of invention." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012).

c. Eton Has Failed to Show a Reasonable Expectation of Success

[47] **[48]** **[49]** Eton's arguments as to reasonable expectation of success are similarly ***144** tainted by hindsight. Indeed, Eton's primary argument is that "Exela's own expressed 'expectation' that using the Schott Type I Plus glass vial would resolve the leaching problem was 'reasonable.' " (D.I. 212 at 24). The use, however, of the "inventor's own path itself never leads to a conclusion of obviousness; that is hindsight." *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017). [24] Rather,

"[w]hat matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art." *Id.* And here, Eton's arguments as to the path a POSA would follow are belied by reality, particularly in that no one (not even Sandoz) did it in the face of an undisputed strong motivation to reduce aluminum in cysteine compositions. This is especially noteworthy against the backdrop of Avadel's experience and the fact that the individual components of Eton's proffered solution were each known for years.

d. Objective Indicia – Long Felt Need

i. ELCYS Filled The Need for a Low-Aluminum Cysteine Product That Had Existed For Decades

[50] For more than two decades before Exela's inventions, the clinical community widely recognized that aluminum contamination of TPN components, including cysteine, was a long-standing problem. Numerous papers discussed the issue, expressly characterizing the problem as "decades old and ... still unresolved," and emphasizing the need for a solution. (PTX-152.1). Even the FDA stepped in to push companies to reduce aluminum content, implementing in 2004 regulations requiring labels to report the maximum aluminum content that had been observed in the product and to contain an aluminum toxicity warning not to exceed 4-5 mcg/kg per day of aluminum. (*Supra* ¶ 168). Relying on that art, and the fact that the only product available to him – the Sandoz product – was labeled as containing up to 5,000 ppb aluminum, thereby precluding compliance with FDA's recommended daily aluminum maximum, Dr. Kuhn explained that there was a long-felt need for a stable, low-aluminum cysteine product for TPN. (Tr. 109:14–17). Dr. Jenke agreed based on his own review of all the art, and no Eton fact or expert witness disputed the need. (Tr. 672:10–15).

ELCYS filled that need. ELCYS provided, for the first time, a stable, low-aluminum cysteine composition that allowed clinicians to administer TPN solutions without exceeding the FDA's recommended daily maximum aluminum amount. Because ELCYS is an embodiment of the Asserted Claims, a nexus is presumed. *Alcon Research, Ltd. v. Watson Labs., Inc.*, No. 15-1159-GMS, 2018 WL 1115090, at *25 (D. Del. Mar. 1, 2018). A nexus is also clear as a factual matter, given that the Asserted Claims provide just what the art was calling for – a stable, low-aluminum cysteine composition for use in TPN, including for up to two years after manufacture.

ii. The Sandoz Product Had Not Already Fulfilled the Need

[51] Eton asserts that the Sandoz product has already met any need because the Sandoz product had far less aluminum ***145** than the label stated. Eton's argument, however, is based largely on attorney argument. Indeed, the evidence is to the contrary. First, the fact that clinicians and researchers consistently acknowledged and called for a solution to the problem of high aluminum in TPN solutions over a period of many years during which the Sandoz product was on the market suggests that the Sandoz product was, in fact, part of the problem – not that it contained the solution.

Second, the Sandoz product was not a stable, low-aluminum cysteine composition for use in TPN. The label for the Sandoz product states that it had no more than 5,000 ppb of aluminum, which is more than twice the FDA limit, and it also contained a warning that "[t]his product contains aluminum that may be toxic." (DTX-514). As Exela's experts explained, it is important to calculate the potential aluminum exposure from the Sandoz product by using the amount stated on the label because that is the only information available to clinicians and to assume a lower level would be risky. [25] (Tr. 105:13–107:21). The labeled amount is set based on the FDA's regulations, which require that label reflect the "highest level" of aluminum observed in specified batches.

Moreover, even if the Court were to look to the certificates of analysis from Allergy Labs and Sandoz Canada, it is apparent that the Sandoz product did not fulfill the long-felt need. The certificates of analysis show aluminum levels under 5,000 ppb, but the levels at the relevant times are still high, and still highly variable. (PTX-194 (summary table)). Many of the certificates show high levels of aluminum measured relatively early in the product's shelf life, for example, 580 ppb at 7 months, and there is no dispute that aluminum levels tend to rise over time. (*Id.*, Tr. 148:25–149:7, 506:10–15, 624:3–15). With that much variability in aluminum levels, there would be no way, even taking all the certificates of analysis into account, for clinicians to know if they would be administering a product with acceptably low aluminum levels at the time they used the product in a clinical setting, or a product with levels much closer to the labeled maximum amount. (Tr. 505:21–506:2).

e. Avadel's Simultaneous Invention is of Little Persuasive Value

[52] Eton asserts that a third-party, Avadel, simultaneously invented a stable L-cysteine product with low-aluminum and little to no particulate matter. Avadel's achievement, Eton contends, demonstrates that the claimed invention is obvious. The Court is not persuaded.

[53] As an initial matter, "a single instance of simultaneous invention cannot alone support a finding of obviousness[.]" *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d 366, 408 (D.N.J. 2019), *aff'd*, 964 F.3d 1049 (Fed. Cir. 2020). Indeed, in *Regents of University of California v. Broad Institute, Inc.*, the Federal Circuit relied on strong evidence of the invention's novelty to discount evidence of six simultaneous inventions. 903 F.3d 1286, 1291, 1295–96 (Fed. Cir. 2018). Similarly, the Court finds that Avadel's experience, detailed above, demonstrates that the invention Exela claimed was unexpected and complicated. Therefore, it is of little weight that Avadel later achieved the same solution after much experimentation and effort.

f. Post-Grant Proceedings

Eton petitioned for post-grant review of the '453 patent, to which the asserted patents ***146** claim priority, as well as post-grant review of the '155 patent. The Patent Trial and Appeal Board denied institution of post-grant review for both patents. (PTX-226, PTX-231). Eton contends that the Board never evaluated the prior art Sandoz product in any meaningful way, and in fact erred in its analysis of the Sandoz product. (D.I. 212 at 35–37). Exela claims that Eton misunderstands Exela's trial examination based on the post-grant reviews.

The Court has independently examined each of Eton's invalidity claims without reference to the post-grant review proceedings and has found that Eton had not proven by clear and convincing evidence that any asserted claim is invalid as being anticipated or obvious. Therefore, the Court need not scrutinize the Board's reasoning or the accuracy of its findings.

g. Eton Has Not Proven the Asserted Claims Obvious

[54] As explained, Eton has failed to meet its burden of proving (1) that its obviousness combination – putting the Sandoz product in a Schott Type I Plus vial – would have even yielded the claimed inventions; (2) a reason to combine the Sandoz product with a Schott Type I Plus vial; and (3) a POSA would have had a reasonable expectation of success in achieving the claimed inventions. This applies to each patent-in-suit and, in particular, with respect to the specific aluminum-over-time and cystine-over-time claim limitations of each asserted claim, which encompass periods of time sufficient for the product to be administered in a clinical setting ('155 patent, claim 27), 12 months ('713 patent, claims 8-10, '795 patent, claim 1), and 18 or 24 months ('795 patent, claims 19 and 27).

[55] Finally, the asserted claims of the '713 patent require the cysteine product to contain specified levels of mercury and/or lead. Claim 8 requires 1-10 ppb of lead, claim 9 requires 0.2–5.0 ppb of mercury, and claim 10 requires both 1-10 ppb of lead and 0.2-5.0 ppb of mercury. (JTX-4, 61:9–14). The only basis on which Eton argues obviousness of these claims as to these limitations is that lead and mercury must be present in the Sandoz product because it is the same as Eton's ANDA Product and, thus, Eton's stipulation to infringement means those limitations are present in the Sandoz product. The Court has already rejected that argument, and Dr. Baertschi did not address the lead and mercury limitations. Thus, for this additional reason, Eton failed to meet its burden to show obviousness of claims 8-10 of the '713 patent by clear and convincing evidence.

IV. CONCLUSION

As explained above, (1) the ANDA product infringes claims 8, 9, and 10 of the '713 patent and claims 1, 19, and 27 of the '795 patent; (2) Exela has proven that Defendant's ANDA product directly and contributorily infringes and induces infringement of claim 27 of the '155 patent; (3) Eton has failed to prove that claim 27 of the '155 patent is invalid as anticipated; and (4) Eton has failed to prove that any of claim 27 of the '155 patent, claims 8, 9, and 10 of the '713 patent and claims 1, 19, and 27 of the '795 patent is invalid for obviousness.

An appropriate order will be entered.

All Citations

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Footnotes

1 Defendant did not submit findings of fact concerning its non-infringement position.

2 On June 24, 2022, Eton sold its ANDA product to Dr. Reddy's Laboratories SA. (D.I. 241). Eton has represented that the sale "was structured to have no substantial impact on this litigation and Eton remains the sole defendant." (*Id.*).

3 The '795 patent erroneously states that Application No. 16/773,563 is a continuation-in-part of Application No. 16/773,641. The Parent Continuity Data for Application No. 16/850,726 available on https://portal.uspto.gov/pair/PublicPair reflects that Application No. 16/773,563 is a continuation of No. 16/773,641, which is consistent with the domestic priority as claimed by Exela in the file history. (D.I. 177, Ex. 1 ¶ 28 n.1).

4 The measurement units "mcg" (micrograms per liter) and "ppb" (parts per billion) are equivalent and are used interchangeably throughout this opinion. (Tr. 17:6–7, 138:4–7, 331:22–23).

5 Eton contests that ELCYS is an embodiment of claim 27 of the '155 patent based on its proposed construction of "pyruvic acid relative to L-cysteine not more than about 2.0 wt%." The pretrial order's statement of undisputed facts, however, specifies that ELCYS contains pyruvic acid in an amount of no more than 1.0 wt % relative to cysteine. (D.I. 177, Ex. 1 ¶ 61). Moreover, in light of the Court's construction of the pyruvic acid limitation (*infra* at § III.A), ELCYS meets this limitation for the same reasons that Eton's ANDA product does. Thus, ELCYS is a commercial embodiment of claim 27 of the '155 patent.

6 As Exela was apparently not confident that the Schott Type I Plus vials would work to both maintain low aluminum levels for the two-year shelf life and avoid precipitates, it considered other options as well. (*See, e.g.,* Tr. 190:14-191:9, 228.10-230:2, JTX-13.11803).

7 In its reply brief, Eton notes that it received FDA approval for its ANDA product on April 8, 2022. It then states "[i]n the event that Eton launches its products at risk, Exela cannot meet its burden to show that Eton's proposed ANDA product infringes the [asserted claims]" because it asserts that the ANDA product "does not maintain 150 ppb aluminum for 6 or 12 months following manufacture." (D.I. 220 at 1). Eton, however, has not launched its product and there is no evidence in the trial record supporting Eton's claim as to the aluminum content.

8 The Sandoz Product Batch Record includes dates between 2013 and 2016, but no explanation of the various dates was provided at trial. It is, however, not disputed that any Sandoz product sold was prior art (though the parties dispute whether Eton has established the characteristics of any Sandoz product that was actually sold).

9 At some point, Kyowa apparently failed an FDA inspection and AL Pharma switched to Ajinomoto for the AL Pharma product. (Tr. 307:7–16). When that happened is not clear from the record. But neither the Sandoz product nor the AL Pharma product used the cysteine supplied by Nippon Protein for the ANDA Product.

10 In its papers, Eton expressed uncertainty about whether claim 27 of the '155 patent requires aluminum at or below 150 ppb for a full three months from the date of manufacture, and Eton offered three certificates of

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analysis (DTX-123, 124, 125) that show aluminum below 150 ppb at one month from the date of manufacture. (*See* D.I. 212 at 16). The Court's construction, however, requires that the composition maintain the specified levels for at least three months. Eton does not argue that the aluminum levels at one month from the date of manufacture are indicative of the aluminum levels in those products two months later.

11 Although Dr. Hofstetter testified that Allergy Labs only prepared commercial batches for Sandoz (Tr. 300:22–301:3), the Sandoz Canada certificate was for a batch not manufactured by Allergy Labs. Moreover, the Court cannot extrapolate from one Certificate of Analysis that there must have been at least one commercial batch that met the limitation. As Dr. Baertschi agreed, the aluminum levels in the Sandoz product "varied quite a bit." (Tr. 506:10–13). And, as already noted, of the certificates of analysis marked as exhibits or summarized only one met the claim limitation. In general, the Sandoz Canada certificates of analysis showed that "there was variability in the assay results" for aluminum. (Tr. 677:6–678:1).

12 The asserted claims of the '713 and '795 patents refer to the solution having "no more than" or "less than" 150 ppb of aluminum. (JTX-4 at cl. 8, 9, 10; JTX-5 at cl. 1, 19, 27). Claim 27 of the '155 patent includes a composition containing "not more than 150 mcg of Aluminum" in a liter. (JTX-2 at cl. 27).

13 Claim 27 of the '155 patent claims a method of administering a composition that has "cystine relative to L-cysteine not more than about 2.0 wt %; and, pyruvic acid relative to L-cysteine not more than about 2.0 wt %." (JTX-2 at cl. 27). The asserted claims of the '795 patent require that the solution be "substantially free of visually detectable particulate matter, at a pH from about 1.0 to 2.5" for either 12 months (claim 1) or 24 months (claims 19 and 27). (JTX-5 at cl. 1, 19, 27). The asserted claims of the '713 patent all require "a pharmaceutically acceptable amount of cystine for at least about 12 months from the time of manufacture of the solution," asserted claim 8 requires "lead in an amount from about 1 ppb to about 10 ppb," asserted claim 9 requires "mercury in an amount from about 0.2 ppb to about 5.0 ppb," and claim 10 requires both "lead in an amount from about 1 ppb to about 10 ppb" and "mercury in an amount from about 0.2 ppb to about 5.0 ppb." (JTX-4 at cl. 8, 9, 10).

14 The osteopenia observed by Klein was consistent with the bone disorder Dr. Kuhn observed in his own neonatal unit at a UK Hospital. (Tr. 88:6-9).

15 Cysteine products for TPN are small volume parenterals. (Tr. 93:22–94:5).

16 The company that had that approval was Hospira, which had obtained approval in the 1980s. (Tr. 159:12–21, PTX-308.8).

17 Avadel received approval for a low-aluminum cysteine product after the FDA approved ELCYS. (Tr. 594:4–595:16, 230:3–12).

18 This construction is the construction that the parties agreed to prior to trial. (D.I. 83, D.I. 179-1 at 10).

19 The product contains only L-cysteine, water, and a pH adjuster if necessary. There was no dispute that the reference to 2.0% total impurities also means 2.0% relative to L-cysteine.

20 In Eton's Responsive Post-Trial Brief concerning the parties' infringement dispute, Eton for the first time argued that if the "not more than" limitation in claim 27 of the '155 patent can mean zero, the patent claim is invalid. (D.I. 220 at 3–4). This argument was not presented at trial or in the pre-trial order and is therefore waived. *See* *Allergan, Inc. v. Barr Labs., Inc.*, 808 F. Supp. 2d 715, 735 (D. Del. 2011) (refusing to address argument raised for the first time in a post-trial brief).

21 Dr. Baertschi notably did not opine that the two products were the same.

22 This is true with one exception. Claims 8-10 of the ’713 patent specify ranges for the amounts of lead or mercury or both. The additional arguments made regarding the obviousness of these claims are addressed separately.

23 Exela tried plastic vials, but those led to product failure. (*Supra* ¶¶ 52–53).

24 That Exela's expert, Dr. Jenke, acknowledged that “everything [Exela] said in that letter with respect to aluminum leaching is reasonable” (Tr. 667:10–13) does not change the result. Dr. Jenke also explained how the complexity of the art shows a lack of reasonable expectation of success. He explained how the various factors impacting aluminum leaching set up a multi-dimensional and complex problem in the case of cysteine, including because both cysteine and cystine are strong aluminum leachers. And he noted the experience of Avadel as support as well.

25 Eton offered no testimony from its expert on this issue. Eton's expert did, however, agree that it would be “risky” not to assume the product contained the amount stated in the label. (Tr. 505:21–506:2).

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