

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

EXELA PHARMA SCIENCES, LLC,

Plaintiff,

v.

ETON PHARMACEUTICALS, INC.,

Defendant.

C.A. No. 20-365-MN

**CONFIDENTIAL – PURSUANT  
TO PROTECTIVE ORDER**

**EXPERT REPORT OF DENNIS ROGER JENKE, Ph.D.**

Dated: October 15, 2021

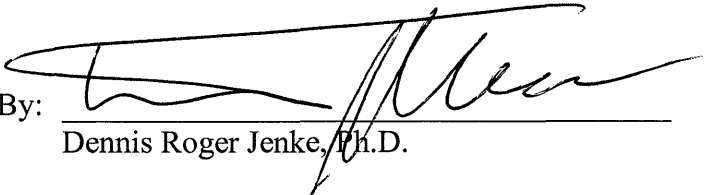
By:   
Dennis Roger Jenke, Ph.D.

**TABLE OF CONTENTS**

|       |                                                                                       |    |
|-------|---------------------------------------------------------------------------------------|----|
| I.    | QUALIFICATIONS .....                                                                  | 1  |
| II.   | FEES .....                                                                            | 2  |
| III.  | PRIOR EXPERT TESTIMONY .....                                                          | 2  |
| IV.   | MATERIALS CONSIDERED FOR THIS REPORT .....                                            | 2  |
| V.    | SUMMARY OF OPINIONS AND EXPECTED TESTIMONY .....                                      | 2  |
| VI.   | LEGAL FRAMEWORK ON WHICH MY OPINIONS ARE BASED .....                                  | 4  |
|       | A. Anticipation.....                                                                  | 5  |
|       | B. Obviousness .....                                                                  | 5  |
|       | C. Enablement .....                                                                   | 8  |
|       | D. Indefiniteness .....                                                               | 9  |
| VII.  | PERSON OF ORDINARY SKILL IN THE ART (POSA).....                                       | 9  |
| VIII. | APPLICABLE CLAIM CONSTRUCTIONS .....                                                  | 10 |
| IX.   | The Asserted Patents, file histories AND POST-GRANT REVIEW.....                       | 13 |
|       | A. The Specification of the Patents-in-Suit .....                                     | 13 |
|       | B. Prosecution of the '453 and '155 Patents .....                                     | 17 |
|       | C. Eton's Petitions for Post-Grant Review of the Patents-in-Suit<br>Were Denied ..... | 22 |
|       | D. Prosecution of the '713, '795, and '089 Patents .....                              | 23 |
| X.    | TECHNOLOGY BACKGROUND .....                                                           | 25 |
|       | A. Elemental Impurities in Pharmaceutical Products .....                              | 25 |
|       | B. Aluminum Impurities in TPN Components.....                                         | 27 |
|       | C. Factors That Influence Aluminum Contamination in TPN<br>Components .....           | 31 |
|       | D. Efforts to Reduce Aluminum Impurities in TPN Components.....                       | 38 |
|       | E. Aluminum Contamination in Cysteine Hydrochloride Products .....                    | 39 |

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

|     |                                                                                                                                                                                                                                |    |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 1.  | Cysteine Has High Affinity for Aluminum .....                                                                                                                                                                                  | 40 |
| 2.  | L-Cysteine Oxidation to Cystine .....                                                                                                                                                                                          | 40 |
| 3.  | L-Cysteine Hydrochloride is Strongly Acidic .....                                                                                                                                                                              | 43 |
| XI. | COMMENTS ON THE SCOPE AND CONTENT OF THE<br>REFERENCES FORMING THE BASIS OF DR. BAERTSCHI'S<br>INVALIDITY OPINIONS.....                                                                                                        | 43 |
| A.  | The Sandoz Product .....                                                                                                                                                                                                       | 43 |
| 1.  | The Sandoz Label .....                                                                                                                                                                                                         | 45 |
| 2.  | [REDACTED] .....                                                                                                                                                                                                               | 47 |
|     | [REDACTED] .....                                                                                                                                                                                                               | 47 |
|     | [REDACTED] .....                                                                                                                                                                                                               | 49 |
| B.  | The Hospira Aminosyn® II Product.....                                                                                                                                                                                          | 51 |
| C.  | Hernandez-Sanchez.....                                                                                                                                                                                                         | 52 |
| D.  | Aluminum in Large and Small Volume Parenteral Used in Total<br>Parenteral Nutrition, 21 C.F.R. § 201.323 (2003) .....                                                                                                          | 55 |
| E.  | U.S. Patent No. 8,415,337 Patent.....                                                                                                                                                                                          | 57 |
| F.  | Len Okabe, Studies on the Solubility of Cystine Under Various<br>Conditions, and On a New Method of Cystine Preparation, 8<br>BIOCHEM. J. 441 (1927).....                                                                      | 60 |
| G.  | S. Hofler <i>et al.</i> , Dealing With the Sulfur Part of Cysteine: Four<br>Enzymatic Steps Degrade L-cysteine to Pyruvate and<br>Thiosulfate in Arabidopsis Mitochondria, Physiologia<br>Plantarum, 157, 352-366 (2016) ..... | 62 |
| H.  | R.D. Asquith <i>et al.</i> , The Photochemical Degradation of Cystine<br>in Aqueous Solution in the Presence of Air, Biochimica et<br>Biophysica Acta, 184, 345-357 (1969) .....                                               | 63 |
| I.  | H.T. Clarke <i>et al.</i> , Some Observations on the Action of Alkali<br>Upon Cystine and Cysteine, J. BIOL. CHEM., Vol. LXXXIX,<br>No. 1, 399-419 (1930).....                                                                 | 64 |
| J.  | Ian B. Butler <i>et al.</i> , Removal of Dissolved Oxygen from Water:<br>A Comparison of Four Common Techniques, 41 TALANTA<br>211 (1994).....                                                                                 | 64 |

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

|       |                                                                                                                                                                                                              |    |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| K.    | Kenneth C. Waterman <i>et al.</i> , Stabilization of Pharmaceuticals to Oxidative Degradation, 7 PHARMACEUTICAL DEV. & TECH. 1 (2002) .....                                                                  | 66 |
| L.    | Alpaslan Yaman, Engineering Considerations in Sterile Powder Processes, in STERILE PHARMACEUTICAL PRODUCTS: PROCESS ENGINEERING APPLICATIONS (Kenneth E. Avis ed. 1995).....                                 | 69 |
| M.    | Q3D Elemental Impurities: Guidance for Industry (Sept. 2015).....                                                                                                                                            | 70 |
| N.    | Michael J Akers, Sterile Drug Products: Formulation, Packaging, Manufacturing, and Quality (2010).....                                                                                                       | 71 |
| O.    | Other Prior Art References .....                                                                                                                                                                             | 71 |
| 1.    | References That Disclose the Use of L-Cysteine Based on Patient’s Age or Condition.....                                                                                                                      | 71 |
| 2.    | References That Disclose the Amount of L-Cysteine Delivered In a Parenteral Composition.....                                                                                                                 | 72 |
| XII.  | GENERAL OBSERVATIONS REGARDING DR. BAERTSCHI’S ANTICIPATION AND OBVIOUSNESS ARGUMENTS .....                                                                                                                  | 72 |
| A.    | Dr. Baertschi Provides No Opinion That the Sandoz Product Is “Stable” .....                                                                                                                                  | 72 |
| B.    |  .....                                                                                                                   | 75 |
| C.    | Dr. Baertschi’s Opinions on the Scope of “About” Are Unsupported.....                                                                                                                                        | 78 |
| D.    | Dr. Baertschi Provides No Evidence That the Sandoz Product or Any Alleged Combination Meets The Headspace and Dissolved Oxygen Limitations .....                                                             | 83 |
| E.    | Dr. Baertschi Treats Each Claim Limitation Independently Rather Than Addressing Whether a POSA Would Have Had a Reasonable Expectation of Success in Achieving the <i>Claimed</i> Invention as a Whole ..... | 84 |
| XIII. | OPINIONS REGARDING the VALIDITY OF THE ASSERTED PATENTS.....                                                                                                                                                 | 87 |
| A.    | Objective Indicia .....                                                                                                                                                                                      | 87 |

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

|    |                                                                                                                                                                                     |     |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 1. | Long Felt and Unmet Need.....                                                                                                                                                       | 87  |
| 2. | Unexpected Results.....                                                                                                                                                             | 88  |
| 3. | Commercial Success .....                                                                                                                                                            | 92  |
| B. | The '453 Patent .....                                                                                                                                                               | 93  |
| 1. | Dr. Baertschi Has Not Demonstrated Claims 1-7, 9, 10,<br>14 and 22 of the '453 Patent Are Anticipated by the<br>Sandoz Product .....                                                | 93  |
| 2. | Dr. Baertschi Has Not Demonstrated that Claims 1-7, 9,<br>10, 14 and 22 of the '453 Patent Are Obvious Over the<br>Sandoz Product in Combination with Any Other<br>References ..... | 101 |
| a. | Claim 1 .....                                                                                                                                                                       | 101 |
| b. | Claims 2, 9-10, and 14 .....                                                                                                                                                        | 108 |
| c. | Claims 3-7 .....                                                                                                                                                                    | 109 |
| d. | Claim 22.....                                                                                                                                                                       | 110 |
| C. | The '155 Patent .....                                                                                                                                                               | 111 |
| 1. | Dr. Baertschi Has Not Demonstrated Claims 1-8 and 10-<br>29 of the '155 Patent Are Anticipated by the Sandoz<br>Product .....                                                       | 111 |
| 2. | Dr. Baertschi Has Not Demonstrated Claims 1-8 and 10-<br>29 of the '155 Patent Are Obvious .....                                                                                    | 117 |
| a. | Claim 1 .....                                                                                                                                                                       | 117 |
| b. | Claims 2-3 .....                                                                                                                                                                    | 119 |
| c. | Claims 4-8, 10-21, 23-25 .....                                                                                                                                                      | 120 |
| d. | Claim 27.....                                                                                                                                                                       | 121 |
| e. | Claim 28.....                                                                                                                                                                       | 122 |
| f. | Claim 29.....                                                                                                                                                                       | 123 |
| D. | The '713 Patent .....                                                                                                                                                               | 124 |

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

|    |                                                                                                                                   |     |
|----|-----------------------------------------------------------------------------------------------------------------------------------|-----|
| 1. | Dr. Baertschi Has Not Demonstrated Claims 1, 11, 15<br>and 16 of the '713 Patent Are Anticipated by the Sandoz<br>Product .....   | 124 |
| 2. | Dr. Baertschi Has Not Demonstrated Claims 1, 11, 15,<br>and 16 of the '713 Patent Are Obvious.....                                | 127 |
| a. | Claim 1 .....                                                                                                                     | 127 |
| b. | Claim 11 .....                                                                                                                    | 131 |
| c. | Claim 15 and 16 .....                                                                                                             | 132 |
| E. | The '795 Patent .....                                                                                                             | 132 |
| 1. | Dr. Baertschi Has Not Demonstrated Claims 1, 11, 19,<br>and 27 of the '795 Patent Are Anticipated by the Sandoz<br>Product .....  | 132 |
| 2. | Dr. Baertschi Has Not Demonstrated Claims 1, 11, 19,<br>and 27 of the '795 Patent Are Obvious.....                                | 137 |
| a. | Claim 1 .....                                                                                                                     | 137 |
| b. | Claims 19 and 27 .....                                                                                                            | 140 |
| c. | Claim 11 .....                                                                                                                    | 141 |
| F. | The '089 Patent .....                                                                                                             | 142 |
| 1. | Dr. Baertschi Has Not Demonstrated Claims 1, 2, 7, 8,<br>and 14 of the '089 Patent Are Anticipated by the Sandoz<br>Product ..... | 142 |
| 2. | Dr. Baertschi Has Not Demonstrated Claims 1, 2, 7, 8,<br>and 14 of the '089 Patent Are Obvious.....                               | 146 |
| a. | Claim 1 .....                                                                                                                     | 146 |
| b. | Claim 2.....                                                                                                                      | 148 |
| c. | Claim 7 .....                                                                                                                     | 148 |
| d. | Claim 8.....                                                                                                                      | 149 |
| e. | Claim 14.....                                                                                                                     | 150 |

**I. QUALIFICATIONS**

1. My educational background, career history, publications, and other relevant qualifications provided here are only a summary. My full curriculum vitae is attached as Exhibit 1 to this Report.

2. I received a B.A. in Chemistry, Mathematics, and Physics from Illinois College in 1975. I received a Master's degree in Geochemistry from the Montana College of Mineral Science and Technology in 1978. In 1983, I received a Ph.D. in Analytical Chemistry from Montana State University. I also received a Master's in Business Administration from the Keller School of Management in 1992.

3. I am currently the Chief Executive Scientist of Triad Scientific Solutions LLC, a consulting firm that provides science-based solutions to plastic/product compatibility challenges associated with packaging, manufacturing equipment and delivery devices in the pharmaceutical, cosmetic, food and related industries. I founded Triad Scientific Solutions in 2017.

4. Previously, I was employed by Baxter Healthcare Corporation, and was appointed to the position of Baxter Distinguished Scientist in Baxter's Analytical Center of Excellence prior to my retirement. Over my 33 year career at Baxter, my responsibilities included leading the corporate function charged with establishing material/product compatibility, specifically with respect to establishing the suitability for use of packaging systems, manufacturing systems and administration devices for pharmaceutical products including extractables/leachables and product ingredient binding.

5. In addition to my work experience, I serve as the Chair of the Chemistry Working Group, Product Quality Research Institute (PQRI) Extractables and Leachables Taskforce for Parenteral and Ophthalmic Drug Products (PODP). I am also a Member of the United States

## **CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

Pharmacopeia (USP) Packaging and Distribution Expert Committee and Chair of the USP Expert Panels on Polymers Used in Pharmaceutical Packaging and Plastic Components used in Pharmaceutical and Biopharmaceutical Manufacturing. I am also the USP's Alternate Member to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Taskforce for developing ICH Q3E: Guideline for Extractables and Leachables (E&L). I am a member of Working Group BE/WG12, Allowable Limits for Leachable Substances, International Standards Organization (ISO). I was also the past Chair and member of the Board of Directors of the Extractables & Leachables Safety Information Exchange (ELSIE).

### **II. FEES**

6. I have been retained by Fish & Richardson P.C. as an expert for Plaintiff Exela Pharma Sciences, LLC in this litigation. I am being compensated for the services I render in this case at an hourly rate of \$450 plus expenses. My compensation is in no way based on the outcome of the litigation.

### **III. PRIOR EXPERT TESTIMONY**

7. In the last four years, I have not testified as an expert at trial or by deposition.

### **IV. MATERIALS CONSIDERED FOR THIS REPORT**

8. In formulating my opinions and writing this report, I have reviewed portions of the materials listed in Exhibit 2. I reserve the right to rely on additional materials produced in this litigation after the submission of my report.

9. My opinions expressed in this report are based on those materials as well as my general knowledge, education, and experience.

### **V. SUMMARY OF OPINIONS AND EXPECTED TESTIMONY**

10. If called as a witness, I expect to provide the opinions contained in this report regarding invalidity. In summary, I expect to testify that:

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

- a. Claims 1-7, 9-10, 14, and 22 of the '453 Patent are not anticipated or obvious;
- b. Claims 1-8, 10-21, 23-25, and 27-29 of the '155 patent are not anticipated or obvious
- c. Claims 1, 11, 19, and 27 of the '795 Patent are not anticipated or obvious
- d. Claims 1 and 15-16 of the '713 Patent are not anticipated or obvious
- e. Claims 1, 2, 7, 8, 14 and 15 of the '089 Patent are not anticipated or obvious
- f. The claim term “pharmaceutically acceptable amount of cystine” is not indefinite; and
- g. The claim term “about” is not indefinite.

11. I note that although Exela is asserting claims 8-10 of the '713 Patent, Dr. Baertschi offered no opinions or analysis of claim 8-10 of the '713 Patent. Dr. Baertschi provided a partial analysis of claim 11 in Exhibit D, but provided no analysis of claims 9 and 10 from which claim 11 ultimately depend. I also note that although Exela is asserting claim 15 of the '089 Patent, Dr. Baertschi provided no opinions or analysis regarding claim 15. I reserve the right to offer opinions as to these claims should Dr. Baertschi be permitted to do so.

12. In addition to my opinions that the Asserted Claims are not obvious or anticipated, I expect to testify on the level of a person of ordinary skill in the art, the file histories of the Asserted Patents, contents and scope of the prior art, and technological background related to the Asserted Patents. At trial, I expect to provide exhibits or other demonstratives to illustrate the ideas and opinions conveyed in this report.

13. I reserve the right to supplement or amend this report as necessary.

**VI. LEGAL FRAMEWORK ON WHICH MY OPINIONS ARE BASED**

14. I am neither an attorney nor a legal expert. The legal standards I applied in reaching the opinions I present throughout this report were provided to me by counsel for Exela. In preparing my expert report, I have tried to faithfully apply these legal standards to the matters that I address. I do not intend to offer opinions on the law. Below, I will describe the law I applied in considering whether the Asserted Claims of the Patents-in-Suit have been shown by Eton/Dr. Baertschi to be invalid.

15. I understand that issued patents, like the Patents-in-Suit, are presumed valid and that in deference to work performed by the U.S. Patent and Trademark Office (USPTO), Defendant Eton must prove by clear and convincing evidence that each asserted claim of the Patents-in-Suit is invalid.

16. I understand that “clear and convincing evidence” is evidence that produces an abiding conviction that the truth of a factual contention is highly probable. I understand that “clear and convincing evidence” is a higher burden of proof than “preponderance of the evidence,” which is the burden by which Exela must prove infringement of the Asserted Claims by Eton’s proposed generic product, and a lower burden of proof than the “beyond a reasonable doubt” standard applied in criminal prosecutions.

17. I understand that USPTO Examiners are assumed to have expertise in interpreting the prior art and to be familiar with the level of skill in the art. I further understand that Examiners, as persons of scientific competence in the fields in which they work, are informed by their scientific knowledge as to the meaning of prior art references to persons of ordinary skill in the art and the likely motivation of such persons as influenced by prior art references or by the typical training of a person with ordinary skill in the art.

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

**A. Anticipation**

18. I understand that a patent claim is anticipated by a prior art reference if the reference would disclose to one of ordinary skill in the art, either expressly or inherently, each of the limitations of the claim.

19. I have been informed that a claim limitation/requirement not expressly found in a reference may nonetheless be inherent if the subject matter described in the prior art reference necessarily functions in accordance with, or includes, the claimed limitations/requirement. I understand that it is not enough that the missing limitation/requirement merely be probable or obvious. I further understand that where Eton/Dr. Baertschi allege a limitation/requirement is inherently present, it must be present in every single application/use of the claims. In other words, it is not enough for a limitation/requirement to be satisfied only part of the time.

20. In order to anticipate a claim, the prior art reference must not only disclose all limitations/requirements of the claim, but must also disclose those limitations/requirements arranged as in the claim.

21. I also understand that in order to find a patent invalid on anticipation grounds, the anticipating reference must enable one of ordinary skill in the art in the field of the invention to practice the invention without undue experimentation. My understanding of the enablement requirement is described below.

**B. Obviousness**

22. I understand that a claim may be found invalid as obvious “if the differences between the subject matter sought to be patented and the prior art are such that the claimed subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.”

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

23. I understand that an obviousness inquiry requires consideration of the following factors: (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 pertinent art; and (4) the objective indicia of nonobviousness.

24. I understand that objective indicia evidence may be the “most probative evidence of nonobviousness,” and that a fact finder must consider such evidence before making an obvious determination. A non-exhaustive list of such objective indicia includes: (1) a long-felt but unresolved need that was satisfied by the claimed invention; (2) the failure of others to develop or practice the claimed invention; (3) unexpected or surprising results from the claimed invention; (4) skepticism of the claimed invention by those in the relevant field; (5) copying of the claimed invention by others; (6) acceptance of the claimed invention, as shown, for example, by praise from others in the industry, adoption of the claimed invention, or licensing of the claimed invention; (7) the commercial success of the patented invention; and (8) teaching away from the claimed invention.

25. I understand that to establish objective indicia of non-obviousness, the patentee must show a “nexus” between the objective indicia and the claimed invention. For example, there must be a nexus between the claimed invention and its commercial success, i.e., the commercial success must be due to the inventive aspects of the claimed invention. I understand the nexus requirement is satisfied if, for example, the patentee shows that the thing that is commercially successful is the invention disclosed and claimed in the patent.

26. I understand that prior art references are to be looked at from the viewpoint of a person of ordinary skill in the art. I also understand that a prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention.

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

27. I understand that obviousness is analyzed from the perspective of one skilled in the art at the time the invention was made. In other words, the use of hindsight is not permitted.

28. I understand that considering the claimed subject matter as a whole is an important aspect of an obviousness analysis, and that it is improper to consider the invention as only the differences between the claimed invention and the prior art. I understand that distilling an invention down to the “gist” or “thrust” or advantages disregards the requirement of analyzing the subject matter as a whole. In addition, a patent claim composed of several elements or steps is not proved obvious merely by demonstrating that each of its steps was, independently, known in the prior art. I also understand that a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified, and that this inquiry is part of analyzing the subject matter as a whole. Finally, I understand that, in identifying the invention as a whole, I must look at both the subject matter that is literally recited in the claim and also those properties of the subject matter that are inherent in the claimed subject matter and also those disclosed in the specification.

29. I understand Eton/Dr. Baertschi must show that there was a reason or motivation to combine the prior art references to arrive at the claimed invention. Conclusory assertions that a combination of prior art would have been “common sense” or “intuitive” are insufficient to support a finding of a motivation to combine. I further understand Eton/Dr. Baertschi must show there was a reasonable expectation of success in combining the prior art references to achieve the claimed invention.

30. I understand that, while previously there was a “teaching, suggestion, or motivation” test for determining whether prior art references are properly combined in an obvious analysis, that test is no longer rigidly applied but continues to capture a helpful insight. I

## **CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

understand that when the patented invention is a combination of known elements, the fact finder must determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. In making such a determination, the fact finder may consider the teachings of prior art references, the effects of demands known to people working in the field or present in the marketplace, and the background knowledge possessed by persons having ordinary skill in the art. I understand that Eton/Dr. Baertschi must present specific reasons why the patent elements would have been combined, because inventions in many instances rely upon building blocks long since uncovered and discoveries almost of necessity will be combinations of what, in some sense, is already known.

31. Finally, I understand that the obviousness analysis should not be framed as an inquiry into whether a person of skill, with only the references in Eton's/Dr. Baertschi's proposed combinations sitting in front of him or her, would have been motivated to combine those references in a way that renders the claimed invention obvious. Instead, the question is whether that skilled artisan would have been motivated to select the specific references in Eton's/Dr. Baertschi's proposed combinations out of the sea of prior art in order to combine their elements in such a way that would address a particular need present and appreciated in the field at that time.

### **C. Enablement**

32. I understand that every issued patent claimed is presumed to comply with the enablement requirement and that a party challenging this presumption must establish by clear and convincing evidence that the requirement was not met.

33. I understand that a patent must disclose sufficient information to enable those skilled in the art to make and use the full scope of the claimed inventions without undue experimentation.

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

34. I understand that one determines whether any experimentation is undue by weighing the following set of factors: (1) the quantity of experimentation necessary to make or use the invention; (2) the amount of direction or guidance the patent provides; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the skill level possessed by a person of ordinary skill in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

35. It is my further understanding that the claims are valid if one of ordinary skill in the art would have to conduct some experimentation, as long as it is not undue. In particular, the patent need not disclose what is already well-known to those of ordinary skill in the art.

**D. Indefiniteness**

36. I understand that every issued patent claim is presumed to comply with the definiteness requirement and that a party challenging this presumption must establish by clear and convincing evidence that the requirement was not met.

37. I understand that a claim is invalid as indefinite if, when read in light of the specification delineating the patent, and the prosecution history, it fails to inform with reasonable certainty those of ordinary skill in the art about the scope of the invention.

38. On June 30, 2021, I submitted a declaration in the parties' claim construction proceedings, opining that a person of skill in the art could reasonably understand the scope of the term "pharmaceutically acceptable amount of cystine," which appears in Asserted Claims of the '713 and '089 Patents, and that the term is not indefinite. I maintain that opinion and incorporate my June 30, 2021 declaration here.

**VII. PERSON OF ORDINARY SKILL IN THE ART (POSA)**

39. I understand that Exela has proposed that a person of ordinary skill in the art is someone who has attained a Pharm. D., or M.S. or Ph.D. in chemistry, chemical engineering, or

## **CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

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.

40. Based on my review of the Asserted Patents, I agree with this definition.

41. Based on this definition, I met the definition of a person of ordinary skill in the art well before January 15, 2019, the effective filing date of the Asserted Patents.

42. I understand that Eton has proposed that a person of ordinary skill in the art “would hold a bachelor’s degree in pharmacy or a related field, along with five years of practical experience in drug formulation or a related field. In addition, a person of ordinary skill may have a graduate degree in pharmacy or a related field and three years of practical experience in drug formulation or a related field.”

43. It appears that Eton’s description is similar to Exela’s, but in my opinion Eton’s person of ordinary skill is under-qualified to perform such roles as the project technical lead for a the development of a commercially significant drug product. However, these differences would not change my opinions about the plain meaning of the claim terms that I have reached. Nor would my opinions on validity of the Asserted Patents change under either definition.

### **VIII. APPLICABLE CLAIM CONSTRUCTIONS**

44. The terms for which the parties have agreed on claim constructions are below. I have applied these agreed constructions in reaching my opinions on validity.

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

| <b>Claim Term</b>                                                                                        | <b>Agreed Upon Construction</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| “time of manufacture”<br>(’453 Patent, claim 1; ’719 Patent, claims 12-15, 18-21)                        | Plain and ordinary meaning, i.e., conclusion/completion of manufacturing the product                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| “total parenteral nutrition regimen”<br>(’453 Patent, claim 22)                                          | Plain and ordinary meaning, i.e., total parenteral nutrition provided as part of a daily dosing regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| “parenteral nutrition composition”<br>(’795 Patent, claims 1, 19, and 27; ’089 Patent, claims 1 and 2) ) | Plain and ordinary meaning, i.e., a nutritional composition for intravenous administration to a subject                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| “total parenteral nutrition composition”<br>(’155 Patent, claim 28)                                      | “a nutritional composition for intravenous administration to a subject, the composition being capable of providing all the subject’s nutrition”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| “stable L-cysteine composition”<br>(’453 Patent, claim 1; ’155 Patent, claims 1-3, 27, 28)               | “A 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.” |
| “safe”<br>(’795 Patent, claims 1, 9, 10, 19, 27; ’089 Patent, claim 2)                                   | “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.”                                                                                                                                                                                                                                                                                                                                                                                                                |

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

| <b>Claim Term</b>                                                                                                                                                                                                                                                                  | <b>Agreed Upon Construction</b>                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| “wherein for at least 12 months from the time of manufacture of the solution, the solution will remain:<br>substantially free of visually detectable matter,<br>at a pH from about 1.0 to about 2.5, and<br>containing no more than 150 ppb of aluminum”<br>(’795 Patent, claim 1) | No construction is necessary, and the parties agree that “at least 12 months from the time of manufacture of the solution” applies to the recited limitations regarding visually detectable matter, pH, and aluminum |

45. The terms for which the parties dispute the claim construction are below. I have applied Exela’s proposed constructions in reaching my opinions on validity since Eton did not propose a competing construction.

| <b>Claim Term</b>                                 | <b>Plaintiff’s Proposed Construction</b>                                                                                                                                                                               | <b>Defendant’s Proposed Construction</b> |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| “about”                                           | Plain and ordinary meaning, i.e., “approximately”                                                                                                                                                                      | Indefinite                               |
| “a pharmaceutically acceptable amount of cystine” | Plain and ordinary meaning, i.e., an amount of cystine that is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the mammal being treated therewith <sup>1</sup> | Indefinite                               |

46. I understand that in his Opening Report, Dr. Baertschi has applied a previously undisclosed construction for the term “about” in the ’453 and ’155 Patents, that “a numerical

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<sup>1</sup> As set forth above in Section VI.D, I incorporate herein my claim construction declaration, submitted June 30, 2021, which addresses the construction of “pharmaceutically acceptable amount of cystine.”

value or range is intended to be understood as encompassing a range of plus or minus 20%, whether or not the term ‘about’ is explicitly recited.” (*See* Baertschi Op. Rep., ¶¶ 165-177, 225-237.) Dr. Baertschi explicitly applies this construction to the aluminum limitations in Claims 1 and 22 of the ’453 Patent and Claim 1 and 28 of the ’155 Patent. (*See id.* at ¶¶ 175, 235.) He also suggests this construction should apply to the aluminum and length of time limitations of the ’713, ’795 and ’089 Patent claims (*see id.* at ¶¶ 120, 128, 134), but he does not appear to actually apply this construction in his invalidity analysis. In my opinion, Dr. Baertschi’s construction of “about” is incorrect for the reasons discussed below in Section XII.C. I have nonetheless provided an analysis of the validity of the claims under Dr. Baertschi’s construction.

47. I reserve the right to respond to any arguments Eton’s experts make regarding the proposed constructions of these or other terms. I also reserve the right to update my opinions after the Court issues its opinion on claim construction, if needed.

48. Where the parties have not provided a construction of a claim term or phrase, I use the meaning that I believe a hypothetical person of ordinary skill in the art would understand to be the plain and ordinary meaning of the term.

## **IX. THE ASSERTED PATENTS, FILE HISTORIES AND POST-GRANT REVIEW**

### **A. The Specification of the Patents-in-Suit**

49. All five Asserted Patents share the same specification. For convenience, I will cite only to the specification of the ’453 Patent, but the same disclosure appears in each of the Asserted Patents. The Asserted Patents generally relate to stable, highly pure L-cysteine compositions for use in total parenteral nutrition (TPN). Specifically, the Patents explain that they disclose “compositions for parenteral administration comprising L-cysteine that are stable and have desirable safety attributes for extended periods of time.” (’453 Patent at 1:7-10.)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

50. L-cysteine is an essential amino acid that is often used in TPN solutions that are administered to patients, such as vulnerable preterm infants or critically ill adults, requiring nutritional supplementation. (*See* Opening Report of Dr. Robert Kuhn at Section VII.C.)

51. A known problem in prior L-cysteine products used in TPN solutions was that they contained high enough levels of aluminum that aluminum posed a health and safety threat to the vulnerable and health-compromised patients to whom the products were administered. The specification discusses this problem as follows: “L-cysteine for injection is a marketed product used as a component of a nutritional supplement regimen referred to as total parenteral nutrition (TPN). The Aluminum content in known L-cysteine compositions for injection is higher than desired.” (’453 Patent at 5:62-66.) The specification further notes that products with the aluminum content in previous L-cysteine products “would likely be deemed unsafe by the FDA.” (*Id.* at 4:16-58.)

52. Thus, the inventors initially focused their efforts on “identifying the sources of Aluminum in the product and attempting to minimize it in the product.” (*Id.*) The specification explains that the “focus of the subject matter described herein is in minimizing the Aluminum levels coming from L-Cysteine compositions so that when admixed with other ingredients of TPN admixtures, the overall Aluminum levels could be reduced while minimizing introduction of undesirable materials such as heavy metals, anions, and particulates.” (*Id.* at 6:10-17.)

53. While working on the aluminum problem, the inventors discovered that “the problems of safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace as well as certain heavy metals and certain ions that may leach or be extracted

out of the container closure.” (*Id.* at 4:38-43.) The specification discusses the various challenges posed by these “intertwined” and inter-related variables.

54. The specification explains several potential solutions that the inventors used in their attempts to address the aluminum problem and the unexpected challenges they faced as they tried to make product, manufacturing, and packaging changes to address the aluminum issue. For example, the inventors tried to use plastic vials for their L-cysteine compositions because of concerns with the aluminum contribution from glass vials. (*Id.* at 4:48-52.) But the use of plastic vials failed to produce an acceptable drug product, as the inventors made “the unexpected discovery that simply removing a source of Aluminum by replacing glass with plastic did not result in a product having the desired properties. Additional efforts to identify the root cause for the product failure led to the finding that the product likely failed because oxygen entered the plastic container and into the product at a rate higher than previously expected or predicted.” (*Id.* at 4:55-63.) The product failed in plastic because of unacceptably high particulate counts. (*Id.* (citing Example 3).)

55. Cystine is “an oxidation product of L-cysteine” that “can increase over time.” (*Id.* at 6:49-56.) “In the presence of oxygen, two L-Cysteine residues will form a disulfide covalent bond forming L-Cystine.” (*See id.* at 57:25-27.) The specification explains that “it may be desirable to maintain the amount of cystine within predetermined levels over time.” (*Id.*)

56. It is important to control oxygen and cystine levels because, as the specification teaches, higher levels of cystine can lead to precipitation problems and “undissolved cystine may be visually detected as particulate matter in solution.” (*Id.* at 16:59-60; *see also id.* at 57:21-29.) These “[p]articulates are dangerous in injectable compositions and create a safety concern, in addition to the stability issue of the product.” (*Id.* at 5:1-3.)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

57. The specification also explains that “[p]yruvic acid is another undesirable compound that can be found in L-cysteine compositions known in the art. It is possible that the amount of pyruvic acid in these compositions can increase over time. Thus, it may be desirable to maintain the amount of pyruvic acid within predetermined levels over time.” (*Id.* at 6:57-63.)

58. The specification discusses issues seen with these degradation products, particularly with cystine. For example, “[i]ncreased oxygen levels in the product led to unacceptable levels of oxidation products, such as cystine, which precipitated and caused particulates in the product.” (*Id.* at 4:65–5:1.) The inventors hypothesized that reducing the aluminum levels in the formulation appeared to exacerbate those precipitation problems. The specification explains that “precipitation may have been exacerbated by reduction in Aluminum since Aluminum in solution may have a stabilizing effect. Consequently, removing Aluminum may have the unintended consequence of increased precipitation and product failure in the presence of even small amounts of oxygen in the container. This was unexpected.” (*Id.* at 5:4-9.)

59. Because of the issues that arose with the impurities in the product, the specification explains that “it has been found that the desirable attributes of L-cysteine compositions for infusion can be obtained without the characteristic impurity profile that is known in the art. Such impurity profile makes the product less safe to be used by patients, in particular, preterm and term infants and pediatric patients of 1 month to 1 year as well as critically ill adults.” (*Id.* at 4:15-25.) It goes on to explain that the prior art did not address the inter-related issues of aluminum and the other impurities that the inventors faced. (*Id.*)

60. Thus, the compositions of the invention focus on having an impurity profile that is safer than that of prior products. The specification explains that these compositions

“unexpectedly” contain low levels of aluminum and certain other impurities. “As a result, the present compositions and methods of using said compositions are safer to the intended subject compared to the currently available compositions and methods.” (*Id.* at 4:28-32.)

61. Importantly, the inventors were ultimately able to achieve a formulation with substantially reduced aluminum levels compared to prior products that remains stable over the shelf life of the product. The specification explains that “what has now been achieved is an unexpected and substantial reduction in Aluminum content of an L-Cysteine composition that permits exposure to less than or equal to 4-5 micrograms per kilogram per day ( $\mu\text{g/kg/d}$ ) to avoid or minimize Aluminum toxicity while still providing therapeutically effective L-cysteine in a stable composition.” (*Id.* at 7:19-25.)

**B. Prosecution of the '453 and '155 Patents**

62. During the prosecution of the '453 Patent, the examiner initially rejected the claims as (a) not enabled, and (b) obvious over the combination of the Sigma-Aldrich product information for L-cysteine hydrochloride monohydrate (dated May 2006) and Whiting et al. (Journal of Food Protection, Vol. 55, No. 1, Pages 23-27, January 1992.)

63. On the obviousness rejection, according to the examiner, Sigma-Aldrich discloses that “L-cysteine is soluble in water at 100 mg/mL,” and Whiting discloses that “it was known that oxygen in the headspace can allow outgrowth and toxin production.” (ExelaCYS00000215, ExelaCYS00005805.) The examiner thus initially concluded that it would have been obvious “to store the solution of Sigma-Aldrich in an oxygen reduced atmosphere to reduce the chances of undesired reactions causing side products.” (*Id.*) The examiner recognized that the references did not disclose the claimed side products (impurities) and their levels but found that it was “reasonably expected that the impurity content is below the claimed amount where the disclosures above suggest the impurities come from combination products.” (*Id.*)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

64. On the enablement rejection, the examiner noted that the art was “unpredictable,” a point with which I agree, and cited to “Lima-Rogel et al ((2016), Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico. *Journal of Parenteral and Enteral Nutrition*, 40: 1014-1020) and Hintz, et al ((2008), Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation. *JPEN J Parenter Enteral Nutr*, 32: 242-246) which disclose while aluminum contamination is a known problem, it is unknown how to reduce the aluminum content of formulations.” (*Id.* at ExelaCYS00005803.)

65. The examiner found that “[b]ecause of the known unpredictability of the art, and in the absence of experimental evidence,” skilled artisans would not believe that the claimed components would work as recited in the claim and described in the specification. (*Id.*)

66. In response to the office action, Exela addressed both the enablement and obviousness rejections. On enablement, Exela responded by explaining that the specification “describe[s] to the person of ordinary skill how to make the claimed compositions as well as how unexpected technical issues and product failures were overcome,” citing to specific examples. (ExelaCYS00000215, ExelaCYS00005861.) Exela also cited back to its discussion of the problems that the inventors faced at an interview with the examiner: “In this aspect, during the interview, Applicant discussed with Examiner Packard that the cited art reports on the problem at hand, which after many years was still unsolved prior to the present inventors’ solution as described in the present application. However, turning to the text throughout the present specification, it sets forth that the present inventors addressed many variables and describes the factors that the present inventors used to overcome the Aluminum safety issues at hand....” (*Id.*)

67. In response to the obviousness rejection, Exela also cited to its discussion of the problems the inventors had faced and explained that “there is no evidence that prior to the

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

present application, the person of ordinary skill would have looked at the Office Action's combination of references to achieve the claimed invention described, let alone, with a reasonable expectation of success. As discussed above in Section II, and for brevity not repeated entirely here, it was only after the present inventors addressed and overcame the problem of Aluminum that they were confronted with the problems of stability and precipitate formation. Put another way, the art did not know about the additional problems." (*Id.* at ExelaCYS00005862.) The inventors, though, were able to overcome those inter-related problems in developing the claimed inventions.

68. The file history also contains a summary of an interview between the examiner and Exela. That summary further emphasizes the importance of the aluminum reduction and the unexpected issues that the inventors encountered as they went about reducing the aluminum levels, stating that "[w]e discussed the criticality of the aluminum impurity and what was required to lower the amount to the claimed range. We also discussed which steps were expected to reduce the contaminate, yet didn't, leading to unpredictability in the art." (ExelaCYS00000215, ExelaCYS00005875.)

69. After the interview and office action response, the examiner allowed the claims that issued in the '453 Patent. In the notice of allowance, the examiner first found that, "[a]s noted by Applicants, while compositions with L-cysteine have been known in the art, the contaminant of aluminum hinders the further use of the product, especially for certain patient populations where the contaminant is beyond what is allowable for FDA approval." (ExelaCYS00000215, ExelaCYS00005873.) The examiner went on to refer to the unmet need in the field that was filled by the invention, explaining that "Applicants have used multiple means disclosed in the specification and in the claims to achieve a composition which is far below the

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

FDA demand, filling an unmet need which has been present for quite a number of years.” (*Id.*) The examiner concluded that “[b]ecause each step taken independently did not demonstrate the desired result and there was no obvious reason to combine the steps actually taken, the product as claimed cannot be viewed as obvious. Instead the unexpected result is due to the Applicants unexpected findings resulting from testing combinations of theories with no expectation of success.” (*Id.*) For the reasons I explain throughout this report, I agree with the examiner’s reasoning and believe that it is an accurate reflection of how a person skilled in the art would have viewed the prior art in the context of the claimed invention.<sup>2</sup>

70. I reviewed Dr. Baertschi’s summary of the file history, and, in my opinion, it is incomplete and does not fully credit the reasons for allowance. Dr. Baertschi appears to suggest that the examiner would not have allowed the claims if he had been aware of the Waterman reference or certain statements in the Hernandez-Sanchez article relied on by Dr. Baertschi. I disagree.

71. Dr. Baertschi alleges that Waterman both establishes that cysteine is known to oxidize under normal storage conditions and provides proposals to address that issue. (Baertschi Op. Rep., ¶ 103.) I disagree. Waterman is a review article about stabilizing pharmaceuticals against oxidative degradation, and does nothing to suggest the complexity of the problems that the inventors faced. As discussed in detail below in Section XI.K, Waterman generally teaches that oxidation is one of the main modes of degradation for many pharmaceuticals, but Waterman says nothing specifically about the oxidation of L-cysteine in a formulation for use in a TPN solution, and, more importantly, how to specifically control L-cysteine oxidation. Moreover, Waterman does nothing to connect the oxidation of cysteine to any of the other problems

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<sup>2</sup> The ’155 Patent was allowed without any substantive prosecution.

addressed by the claims, including the reduction of aluminum in an L-cysteine formulation for TPN.

72. With respect to solving the problem of cysteine oxidation, Dr. Baertschi alleges that “Waterman makes a number of proposals, including optimizing the formulation pH and reducing headspace oxygen including by replacing headspace oxygen with nitrogen.” Waterman contains over thirty pages of recommendations of how to prevent oxidative degradation in various types of drugs products, none of which is an L-cysteine solution, and Dr. Baertschi provides no reason why a POSA would select any of the individual general recommendations specifically for L-cysteine solutions for use in TPN. Waterman says nothing about aluminum reduction, let alone anything about aluminum reduction causing other stability issues in an L-cysteine formulation for use in a TPN solution.

73. I disagree with Dr. Baertschi’s suggestion that Waterman taught or suggested the problems of stability and precipitate formulation that the inventors encountered. (Baertschi Op. Rep., ¶ 102.) Waterman simply reiterates that cysteine could oxidize, which is already noted in the specification of the Patents-in-Suit. When the Exela inventors started trying to reduce aluminum, they encountered additional and unexpected stability problems, as explained in the specification, which were due, at least in part, to effects that Waterman (or any prior art reference Dr. Baertschi relies on, for that matter) says nothing about (specifically the link between aluminum levels and particulate formation). Thus, the inventors’ statements to the examiner that “it was only after the present inventors addressed and overcame the problem of Aluminum that they were confronted with the problem of stability and precipitate formation,” and “[p]ut another way, the art did not know about the additional problems,” were correct—the art did not know about the sum total of the problems that could be caused in the cysteine

formulation by taking steps to deal with the high aluminum content, and so certainly the art could not have taught how to avoid or overcome those problems.

74. With respect to Hernandez-Sanchez, that reference was disclosed to the examiner in prosecution, and is listed on page 3 of the Patent's "References cited" list, so I understand from counsel that the examiner is presumed to have been aware of it. And although Hernandez-Sanchez recognizes the problem of high aluminum content in TPN formulations and suggests that it should be reduced, it does nothing to suggest taking any of the specific steps that led to the invention, as discussed in more detail below at Section XI.C. Indeed, the problem of high aluminum in L-cysteine TPN formulations persisted in the art long after Hernandez-Sanchez. And Hernandez-Sanchez says nothing about the other problems in the formulation that may arise if the aluminum is reduced.

75. For these reasons, and as discussed in more detail below, I disagree with Dr. Baertschi's suggestions that Waterman and Hernandez-Sanchez would have or should have prevented the claims from issuing or render them obvious.

**C. Eton's Petitions for Post-Grant Review of the Patents-in-Suit Were Denied**

76. I note that Dr. Baertschi does not mention in his report that Eton filed petitions for post-grant review on two of the Patents-in-Suit, the '453 and the '155 Patents. The PTAB denied institution on both of them, concluding that Eton had failed to show that it was more likely than not that any of the challenged claims were invalid as obvious. (ExelaCYS00069310 and ExelaCYS00072178.) I understand from counsel that the PTAB also denied Eton's follow-up requests for reconsideration. In both of the petitions, Eton's main reference was a Sandoz product label like the one that Dr. Baertschi relies on here. In addition, Eton cited the Waterman reference (among others) to the PTAB as teaching the reduction of oxygen for oxygen-sensitive compounds in liquid formulations. (Eton Petition at 29-20.) Eton argued that "Waterman

discloses that “[a]n oxygen level between 3 and 8% in the headspace is generally attainable at most manufacturing sites.” (*Id.* at 48.)

77. The PTAB thus considered arguments similar to those that Dr. Baertschi makes in his report and nonetheless determined, after seeing Eton’s arguments on the Sandoz label/product, Waterman, Hernandez Sanchez, and numerous other references, that “[o]n this record, we agree with Patent Owner that Petitioner has not provided a sufficient evidentiary basis from which to conclude that there is a reasonable expectation for making L-cysteine containing solutions having the requisite aluminum content as recited in claim 1 of the ’453 Patent.” (ExelaCYS00069310, ExelaCYS00069331.)

**D. Prosecution of the ’713, ’795, and ’089 Patents**

78. Three of the Patents-in-Suit, the ’713, ’089, and ’795 Patents, issued after Eton filed its PGR petitions and after the PTAB denied institution. It is my understanding from counsel that the examiner was presented with the entire PGR petition, including the references that Eton relied on. During the prosecution of the ’713 Patent, the examiner at one point rejected the claims as obvious over a Sandoz product label and Hernandez-Sanchez, along with several other references including Waterman. (ExelaCYS00272661, at ExelaCYS00273733.) In response, Exela agreed that, based on Hernandez-Sanchez and what was known in the art, “[w]ithout question, manufacturers of parenteral products would have been highly motivated to develop an L-cysteine product with substantially reduced aluminum levels that remain low over time. Yet, the cited art shows that the problem went unsolved for decades until Applicant’s invention.” (*Id.* at ExelaCYS00275145.) Exela cited to the Sandoz product as an example of a product that *failed* to solve the problem. (*Id.*)

79. Exela also explained the problems of the interrelated variables that the inventors faced when focusing on reducing the aluminum content in the formulation: “Reducing

aluminum levels in L-cysteine parenteral solutions proved to be a surprisingly complex undertaking because of the chemistry of L-cysteine. The present inventors discovered in solving the problem that one has to consider and balance multiple variables, including interactions of the active, its concentration, trace components, the excipients, the solvents, the packaging, the pH, and the manufacturing among other things. The art did not predict and could not have predicted how those variables would interact under the specific conditions of the presently claimed L-cysteine parenteral solution, let alone how changing one variable would affect the other variables.” (*Id.* at ExelaCYS00275146.) I agree with this discussion of the unforeseen (and unforeseeable) problems faced by the inventors as they attempted to lower the aluminum levels and arrive at the stable, low impurity L-cysteine compositions of the invention.

80. In allowing the claims, the examiner noted that the “Board of Appeals held it would not be obvious to reduce the aluminum content of the prior art to the claimed range and that the reduction is not a matter of routine optimization,” essentially relying on the reasoning of the PTAB, which had addressed the Sandoz product and the Waterman reference that Eton relies on here. (*Id.* at ExelaCYS00275189.)

81. [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED] But more fundamentally, in my opinion, nothing that Dr. Baertschi points to suggests that the examiner was somehow incorrect or unaware of key information in allowing the claims of the Patents-in-Suit. To the contrary, the examiner was aware of much of

the same information that Eton relies on here and still allowed the claims of the '713, '089, and '795 Patents.<sup>3</sup>

## X. TECHNOLOGY BACKGROUND

### A. Elemental Impurities in Pharmaceutical Products<sup>4</sup>

82. An impurity in a drug product is an extraneous entity that is not the drug substance or an excipient in the drug product.<sup>5</sup> Because impurities do not provide a therapeutic benefit to the user of the drug product and because they could adversely impact the safety and/or efficacy of the drug product, they are expected to be identified and rigorously managed. One set of impurities that presents a potentially high risk in terms of reactivity and safety impact are those impurities, organic or inorganic, whose chemical formulas include elements from the following series in the periodic table: transition metals, metalloids, other metals, and lanthanides and actinides. Impurities that contain such elements have been termed *elemental impurities*. As is the case with all impurities, elemental impurities should be managed so that their levels in drug products are known and low. To this end, standards-setting organizations such as ICH and the USP have developed guidelines and recommendations that address the management of elemental impurities in drug products.<sup>6</sup>

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<sup>3</sup> The Examiner's rejections and Exela's responses are the same for all three patents.

<sup>4</sup> Adapted from Jenke, R.J., Stults, C.L.M., Paskiet, D.M. Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A Literature Review *PDA J Pharm Sci and Tech* **69**: 1-48 (2015); *see also* Jenke, R.J. Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: An Updated Literature Review *PDA J Pharm Sci and Tech* **74**: 324-347 (2020)

<sup>5</sup> International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Impurities in New Drug Products. Q3B(R2). Current Step 4 Version, June 2, 2006.

<sup>6</sup> *See, for example*, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for Elemental Impurities. Q3D(R1). Current Version, March 22, 2019; 232 Elemental Impurities—Limits. In *The United States Pharmacopeia, USP 35–NF30, Supplement No. 2*; United States Pharmacopeial Convention,

83. Elemental impurities in drug products can arise from a number of different sources and via a number of different mechanisms. One potential source of elemental impurities is the materials that are used in the drug product's manufacturing or packaging systems. Elemental entities that are present in these materials of construction, such as glass, stainless steel, and polymers, may leach into the drug products during the time that the drug product (or its precursors) is in contact with the materials, and these leached elemental entities become elemental impurities in the drug product. In fact, the product quality impact of the leaching of elemental entities from packaging systems is well documented.<sup>7</sup> Thus, knowledge about the presence, level, and "leachability" of elemental entities in materials used in manufacturing and packaging systems is relevant to understanding how manufacturing and packaging systems contribute to a drug product's total elemental impurity burden. Such an understanding may be instrumental in terms of evaluating the relative risk associated with element entities in materials and packaging systems and the establishment of appropriate elemental impurity controls and specifications.

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Inc.: Rockville, MD, 2012; pp 5633, 5634; ICH. ICH Harmonised Tripartite Guideline. Pharmaceutical Development. Q8(R2). Current Step 4 Version, August, 2009; ICH. ICH Harmonised Tripartite Guideline. Quality Risk Management. Q9. Current Step 4 Version, November 9, 2005; ICH. ICH Harmonised Tripartite Guideline. Pharmaceutical Development. Q10. Current Step 4 Version, June 4, 2008.

<sup>7</sup> See, for example, Markovic, I. Risk management strategies for safety qualification of extractable and leachables substances in therapeutic biologic protein products. *Am. Pharm. Rev.* **2009**, 12 (4), 96, 98 –101; Nashed-Samuel, Y.; Liu, D.; Fujimori, K.; Preez, L.; Lee, H. Extractable and leachable implications on biological products in prefilled syringes. *Am. Pharm. Rev.* **2011**, 14 (1), 74, 76, 78 – 80; Christensen, S.; Moellar, E. H.; Bonde, C.; Lilleoere, A. Preliminary studies on the physical stability of a glucagon-like peptide-1 derivate in the presence of metal ions. *Eur. J. Pharm. Biopharm.* **2007**, 66 (3), 366 –371; Liu, W.; Swift, R.; Torraca, G.; Nashed-Samuel, Y.; Wen, Z.; Vance, A.; Mire-Sluis, A.; Freund, E. Davis, J.; Narhi, L. Root cause analysis of tungsten-induced protein aggregation in pre-filled syringes. *PDA J. Pharm. Sci. Technol.* **2010**, 64 (1), 11–19; Castner, J.; Williams, N.; Bresnick, M. Leachables found in parenteral drug products. *Am. Pharm. Rev.* **2004**, 7 (2), 70, 72–75.

**B. Aluminum Impurities in TPN Components**

84. Aluminum is an elemental impurity that can be a safety risk for patients being treated with pharmaceutical drug products. I understand that aluminum has the potential to produce toxicity to the brain, skeletal system, liver and erythropoietic system.<sup>8</sup> Due to its toxicity, aluminum contamination has been a long-standing concern for total parenteral nutrition (TPN), which I understand to be the intravenous administration of all of a patient's nutrients, including amino acids, electrolytes, carbohydrates, and lipids.<sup>9</sup>

85. In 2013, Hernandez-Sanchez observed "[a]luminum (Al) toxicity in parenteral nutrition solutions (PNS) has been a problem for decades and is still unresolved."<sup>10</sup> Hernandez-Sanchez further observed that "a high Al content in PNS (parenteral nutrition solutions) is largely the result of three PDP (parenteral drug products): calcium gluconate (up to 81%), inorganic phosphates (especially potassium) and cysteine hydrochloride."<sup>11</sup> Others have noted that "aluminum contamination of parenteral nutrition solutions has been a documented problem for 3 decades."<sup>12</sup> For instance, the link between aluminum exposure and disorders associated with chronic renal failure was established in the middle 1970s<sup>13,14</sup>, with the link between

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<sup>8</sup> Kuhn Opening Report at ¶ 51.

<sup>9</sup> Kuhn Opening Report at ¶ 36, 51.

<sup>10</sup> Hernandez-Sanchez, A.; Tejada-Gonzalez, P.; Arteta-Jimenez, M. Aluminum in parenteral nutrition: a systematic review. *Eur J Clin Nutr.* **67**: 230-238 (2013) (ExelaCYS00069980.)

<sup>11</sup> Hernandez-Sanchez at ExelaCYS00069981.

<sup>12</sup> Yokel, R.A.; Unrine, J.M. Aluminum and phthalates in Calcium Gluconate: Contribution From Glass and Plastic Packaging. *JPGN.* **64(1)**: 109-114 (2017.)

<sup>13</sup> Alfrey, A.C.; LeGendre, G.R.; Kaehny, W.D. The dialysis encephalopathy syndrome: Possible aluminum intoxication. *N Eng J Med.* **294**: 184-188 (1976.)

<sup>14</sup> Ward, M.K.; Feest, T.G.; Ellis, H.A.; et al. Osteomalacic dialysis osteodystrophy: Evidence for a water-borne aetiological agent, probably aluminum. *Lancet.* **1**: 841-845 (1978.)

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aluminum toxicity and intravenous therapy in general—and parenteral nutrition in particular—being established shortly thereafter.<sup>15,16,17</sup>

86. In response to the increasing evidence of aluminum toxicity associated with parenteral nutrition, Koo noted in 1986 that, “although it is known that certain components of parenteral nutrition solutions such as calcium and phosphate may be contaminated with aluminum, there are no systematic data to document the extent of aluminum contamination from various components of parenteral nutrition solution and whether ‘low’ aluminum containing alternates are available”.<sup>18</sup> Chemical analysis of commercially available parenteral products for their aluminum content prompted these authors to conclude that “aluminum contamination of nutrient products is widespread.”<sup>19</sup> However, Broadbent and Pybus note in a letter the same year to the New Zealand Medical Journal that “it should be feasible to make intravenous products without significant aluminum contamination.”<sup>20</sup>

87. In 1986, the FDA also began to take action regarding the problem of aluminum toxicity in parenteral products.<sup>21</sup> In 1990, the FDA published a notice of intent to label parenteral

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<sup>15</sup> Ott, S.M.; Maloney, N.A.; Klein, G.L.; et al. Aluminum is associated with low bone marrow formation in patients receiving chronic parenteral nutrition. *Ann Intern Med.* **98**: 910 – 914 (1983.)

<sup>16</sup> Sedman, A.B.; Klein, G.L.; Merritt, R.J.; et al. Evidence of aluminum loading in infants receiving intravenous therapy. *N Eng J Med.* **312**: 1337 – 1343 (1985) (ExelaCYS00039698.)

<sup>17</sup> Koo, W.W.; Kaplan, L.A.; Bendon, R.; et al. Response to aluminum in parenteral nutrition during infancy. *J. Pediatr.* **10**: 877 – 883 (1986.)

<sup>18</sup> Koo W.K.; Kaplan, L.A.; et al. Aluminum in Parenteral Nutrition Solution – Sources and Possible Alternatives. *J Pare Ent Nut.* **10(6)**: 591 – 595 (1986) (ExelaCYS00070139.)

<sup>19</sup> Koo (1986.)

<sup>20</sup> Broadbent, R.; Pybus, J. Aluminum contamination of intravenous fluids in neonates. *N Zeal Med J.* 166-167 (1986.)

<sup>21</sup> See, e.g., Klein GL. The aluminum content of parenteral solutions: current status. *Nutr Rev.* 1991; 49(3):74-79 (ExelaCYS00293444); US Food and Drug Administration. Aluminum content of parenteral products. Public Workshop, Division of Metabolism and Endocrine Drug Products, Center for Drugs and Biologics; November 6, 1986; Bethesda, MD. (ExelaCYS00293254.)

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products for aluminum content.<sup>22</sup> This date is noteworthy because the FDA observed that it “has become increasingly concerned about aluminum content in parenteral drug products, including aluminum present as a contaminant.” In 1998, the FDA proposed a rule, “Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition,” to amend its labeling requirement for these drug products.<sup>23</sup> The rule set an upper limit of 25 mcg/L of aluminum in Large Volume Parenterals (“LVPs”) used in TPN solutions, and required a statement of the maximum aluminum concentration in Small Volume Parenterals (“SVPs”) at expiry. The rule also required that the maximum aluminum concentration in SVPs be stated as the highest of: (1) the highest level for the batches produced during the last 3 years; (2) the highest level for the latest five batches; or (3) the maximum historical level, but only until completion of production of the first five batches after the rule took effect. The final rule was not implemented until July 26, 2004.<sup>24</sup> The delays were due to concerns expressed by manufacturers that they had inadequate time for final rule implementation and requests that they be given three years to bring products that required reformulation and/or repackaging into compliance.<sup>25</sup>

88. Concurrently, research turned to identifying the possible sources of aluminum in these solutions. Historically, TPN components were commercially available packaged in

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<sup>22</sup> See US Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral nutrition. *Fed Regist.* 1998;63(2):176-185. <http://www.gpo.gov/fdsys/pkg/FR-1998-01-05/html/98-76.htm> (ExelaCYS00293508.)

<sup>23</sup> *Id.*

<sup>24</sup> US Food and Drug Administration. Code of Federal Regulations Title 21: aluminum in large and small volume parenterals used in total parenteral nutrition. §201.323 (ExelaCYS00293508.) <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.323>.

<sup>25</sup> US Food and Drug Administration. Minutes of an FDA meeting with Health Industries Manufacturers Association representatives; June 1, 2000. <http://www.fda.gov/ohrms/dockets/dailys/00/jun00/062700/mm00001.pdf> (ExelaCYS00293499.)

pharmaceutical grade glass vials and bottles, depending on the volume. Several authors established that leaching of aluminum from the product's glass containers was the major source of the aluminum present in these parenteral nutrition solutions,<sup>26,27,28,29</sup> with Baumann noting that “75 – 90% of the aluminum found in calcium gluconate, sodium phosphate or sodium acetate stems from glass.”<sup>30</sup> These findings supported the recommendation that “use of products packaged in glass containers with rubber stoppers should be avoided<sup>31</sup> and the observation that “finding ways to produce calcium gluconate in non-glass containers ... would likely decrease the current level of Al contamination.”<sup>32</sup>

89. Around the same time as that research, Driscoll observed that “[a] high aluminum content in TPN admixtures is largely the result of three parenteral nutrient additives: calcium gluconate, inorganic phosphate injection (sodium or potassium), and cysteine hydrochloride.”<sup>33</sup>

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<sup>26</sup> Bohrer, D. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part I: Salts, glucose, heparin and albumin. *J Trace Elem Med Biol.* **15**: 95 – 101 (2001.)

<sup>27</sup> Bohrer, D.N. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part II: Amino acids for parenteral nutrition. *J Trace Elem Med Biol.* **15**: 103 – 108 (2001) (ExelaCYS00069995.)

<sup>28</sup> Bohrer, D.N. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part III: Interaction container-chemicals during the heating for sterilization. *J Trace Elem Med Biol.* **17**: 107 – 115 (2003) (ExelaCYS00070034.)

<sup>29</sup> Bohrer, D.; do Nascimento, P.; Binotto, R.; et al. Contribution of the raw material to aluminum contamination in parenterals. *JPEN.* **26**: 382 – 388 (2002.)

<sup>30</sup> Baumann, L. Glas ist de Aluminium-Kontaminationsquelle fur Parenteralia. *Krankenhauspharmazie.* **19**: 71 – 74 (1998.)

<sup>31</sup> Mirtallo, J.M. Aluminum Contamination of Parenteral Nutrition Fluids. *JPEN.* **34(3)**: 346 – 347 (2010) (ExelaCYS00071673.)

<sup>32</sup> Poole, R.L.; Schiff, L.; Hintz, S.R.; et al. Aluminum Content of Parenteral Nutrition in Neonates: Measured Versus Calculated Values. *JPGN.* **50(2)**: 208 – 211 (2010) (ExelaCYS00293223.)

<sup>33</sup> Driscoll, M; Driscoll, D.F., Calculating aluminum content in total parenteral nutrition admixtures. *Am. J. Health-Syst. Pharm.* 2005;62:312-5.

**C. Factors That Influence Aluminum Contamination in TPN Components**

90. In order for aluminum contamination of TPN components to occur, the aluminum must enter the drug product from various sources. As discussed in Section X.A above, a contributor to aluminum contamination of TPN components can be the packaging material, specifically glass containers. The level of aluminum contamination in a specific TPN component will depend on its ability to leach aluminum from the packaging material, which is influenced by several different but inter-related factors.

91. **Accessibility of Aluminum.** In general, an element such as aluminum can be leached from a pharmaceutical package only if the element is present in the packaging in the first place. Aluminum leaching is a frequently observed phenomenon in glass packaging because glass is an aluminosilicate – that is, glass is intrinsically an aluminum-containing material. This is not true of plastics, which are composed of organic polymers that do not themselves contain aluminum. Although plastics may contain small amounts of intentional additive, such as antioxidants, processing aids, colorants and flame-retardants, or unintentional additives, such as manufacturing process residuals, that contain aluminum compounds, plastics are generally not formulated to intentionally contain as large quantities of aluminum as glass. Data I and my co-authors collected from studies on the total pool of elemental entities in materials available for use in packaging and/or manufacturing systems confirms that aluminum is typically present in glass containers in much larger amounts (1.2-1.6%) than in plastics containers.<sup>34</sup>

92. Beyond the mere presence of the aluminum in the packaging material, the amount of aluminum that can contaminate a TPN component solution is also dependent on the amount of aluminum that can be leached or removed from the packaging material by the TPN component

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<sup>34</sup> Jenke (2015) at Table 1.

solution. Data collected from several studies on the amounts of elemental impurities extracted from various packaging or manufacturing shows that the amount of aluminum extracted from any particular type of glass package is dependent upon the specific extraction conditions.<sup>35</sup> For example, one study of Type I glass vials filled with water for injection and autoclaved at 121° C for 1h found 14-144 µg/L of Al was extracted (Ref. 12), while another study of Type I glass vials filled with water and stored at 40° C for 24 weeks found that 2000 µg/L of Al was extracted (Ref.16.)<sup>36</sup>

93. **Affinity of the Drug Product for Aluminum.** If a specific chemical component or ingredient of a TPN solution has a chemical affinity for metal ions, then that component would demonstrate increased metal leaching. For example, if the component is a metal complexing agent, *i.e.*, a compound that bonds with a metal to form a chemical complex, then this would increase metal leaching. The more stable the complex formed between the component and the metal is, the stronger the affinity the component has for that metal and the greater the effect the component will have on aluminum leaching.

94. In 2001, Bohrer studied the ability of various amino acids used in TPN to leach aluminum from glass containers and determined that cysteine, cystine, aspartic acid, and glutamic acid are able to leach aluminum from glass to a far greater extent than other amino acids.<sup>37</sup> (Figure 1.)

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<sup>35</sup> Jenke (2020) at Table 2.

<sup>36</sup> *Id.*

<sup>37</sup> Bohrer, D.N. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part II: Amino acids for parenteral nutrition. *J Trace Elem Med Biol.* **15**: 103 – 108 (2001) (ExelaCYS00069995.)

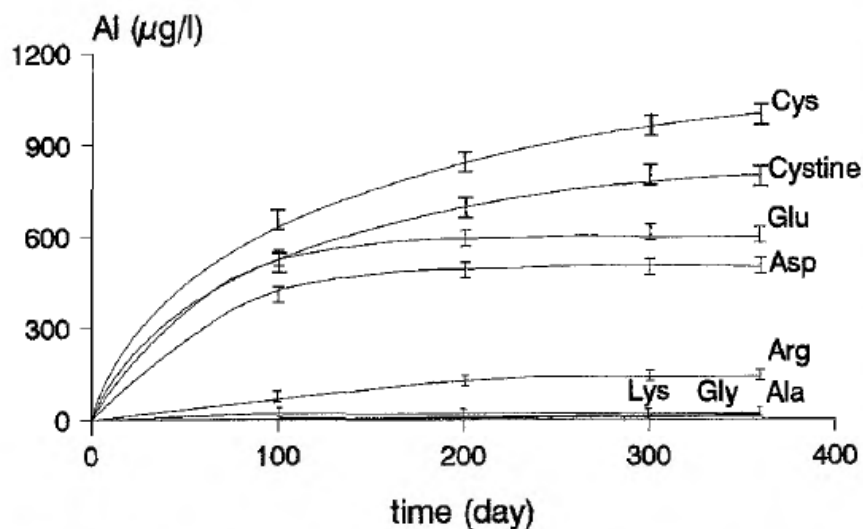


**Figure 1. Aluminum leached from glass containers by amino acids as function of time at room temperature.**

95. When those amino acids were compared to well-known aluminum complexing agents, they were found to extract similar amounts of aluminum under similar extraction conditions. (Figure 2.) Bohrer attributed this ability to leach aluminum to those four amino acids having an affinity for aluminum comparable to the studied complexing agents. The study noted that a relationship between the stability constant of the aluminum complexes and the aluminum released from glass was observed; that is, the higher the stability constant, the higher the amount of aluminum released.

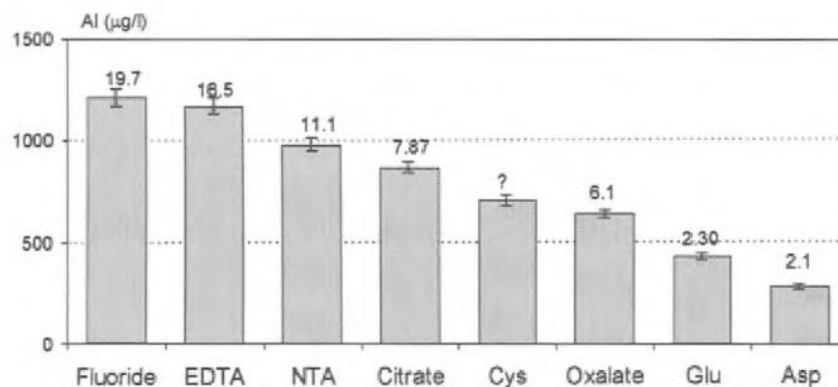


**Figure 2. Aluminum released from PN glass bottles by action of 0.017 mol/l solution of amino acids and complexing agents after 60 days storage at room temperature.<sup>38</sup>**

96. Bohrer also reported that when polyethylene (plastic) containers were used in place of glass, no increase in the aluminum concentration was observed over the same time period.<sup>39</sup>

97. **pH.** The pH of a drug product is another factor that may affect the leaching of metal impurities, including aluminum, from the packaging materials. pH is a measure of the concentration of hydronium ( $H^+$ ) molecules in a solution, and it is reported on a negative log scale, such that a difference of 1.0 in pH corresponds to factor of 10 difference in  $H^+$  concentration.

98. The pH of the solution plays an important role in metal impurity extraction, particularly in glass containers. Drug product solutions can degrade the surface of glass packaging, but the mechanism of that attack differs depending on the pH of the solution. Low (acidic) pH tends to favor the exchange of metal ions from glass, whereas high (alkaline) pH solutions tends to promote the dissolution of the glass surface itself.<sup>40</sup> At alkaline pH, it is well known that hydroxyl ions present in the solution react with the silica and aluminum oxide in the glass structure to dissolve the glass and release aluminum ions into the solution.<sup>41</sup> The mechanism of glass degradation at low pH is not well understood. There is a paucity of data on

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<sup>38</sup> The numbers above the bars are the stability constants (log K) of the aluminum complexes.

<sup>39</sup> Bohrer (Part II) at 107.

<sup>40</sup> Hernandez-Sanchez at 231; *see also* Bohrer, D.N. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part III: Interaction container-chemicals during the heating for sterilization. *J Trace Elem Med Biol.* 17: 107 – 115 (2003) (ExelaCYS00070034); Biavanti, A., Poncini, M., Ferrarini, A. Complexing Agents and pH Influence on Chemical Durability of Type I Molded Glass Containers. *PDA J. Pharm. Sci. and Tech.* 71 306-316 (2017.)

<sup>41</sup> *See, e.g.,* Bohrer (Part III) at 113.

how glass dissolves at pH less than about 6, but what data is available shows an increase of dissolution at low pH.<sup>42</sup> This may be the result of increased ion exchange between hydronium ions and the alkali in the glass, increased catalytic activity of the hydronium ion with decreasing pH, or the interplay of both.<sup>43</sup> At neutral pH, these effects are largely muted.<sup>44</sup>

99. These changing interactions with glass over different pH ranges can affect the leaching of aluminum from glass containers. For example, Ogawa studied the effects of pH on aluminum leaching from Type I glass vials by four common buffer solutions – phosphate, citrate, acetate, and histidine buffers. The study found that the aluminum concentration in each of the buffer systems increased as the pH was increased from pH 4. (Figure 3.) Further experiments varying heat, time and pH led to the conclusion that each buffer system has its own eluting ability from glass containers depending on temperature, time and its concentration.<sup>45</sup>

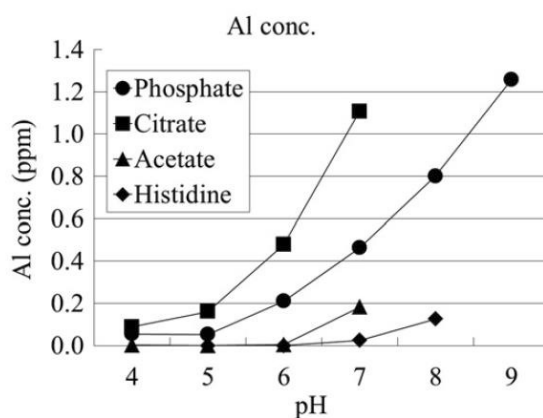


**Figure 3. Aluminum concentrations in phosphate, citrate, acetate and histidine buffer solutions (50mM) in glass vials heated at 105° C for 240 minutes.**

<sup>42</sup> Strachan, D. Glass dissolution as a function of pH and its implications for understanding mechanisms and future experiments. *Geochimica et Cosmochimica Acta* 219: 111-123 (2017) at 116, 119-120.

<sup>43</sup> Strachan 2019

<sup>44</sup> Biavanti 2017

<sup>45</sup> Ogawa at 316-318.

100. **Time of Contact with Packaging.** The longer a drug product is in contact with packaging material from which it can leach aluminum, the greater the level of aluminum contamination. Bohrer observed this phenomenon in a study of aluminum leaching from glass containers by different amino acid solutions as a function of time of storage at room temperature.<sup>46</sup> She observed that aluminum concentrations in solutions of certain amino acids increased over time, with some eventually reaching an equilibrium (arginine, lysine, aspartic and glutamic acid) and others continuing to increase over the entire study period (cysteine and cystine).<sup>47</sup> She noted that the contamination of amino acid parenteral solutions attributable to their storage in glass containers is “the most troubling because it is on-going until the product is used; over many months of storage, the aluminum contributions of the glass container predominates.”<sup>48</sup>

101. **Temperature.** Temperature is also a factor in the contamination of drug products, with aluminum leaching increasing upon exposure to heat. This factor is especially important for TPN components, as they must be sterilized for parenteral administration, and because that sterilization is often performed as terminal sterilization with steam. In 2003, Bohrer studied the effects of heat sterilization on various solutions in glass, plastic, and rubber packaging materials.<sup>49</sup> She observed that even water is capable of extracting aluminum from glass packaging after being heated to a sterilization temperature of 121° C for 30 minutes.<sup>50</sup> (Figure 4.)

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<sup>46</sup> Bohrer (Part II) at 106-107, Figure 2.

<sup>47</sup> Bohrer (Part II) at 106-107, Figure 2.

<sup>48</sup> Bohrer (Part II) at 107.

<sup>49</sup> Bohrer (Part III.)

<sup>50</sup> Bohrer (Part III) at 110.

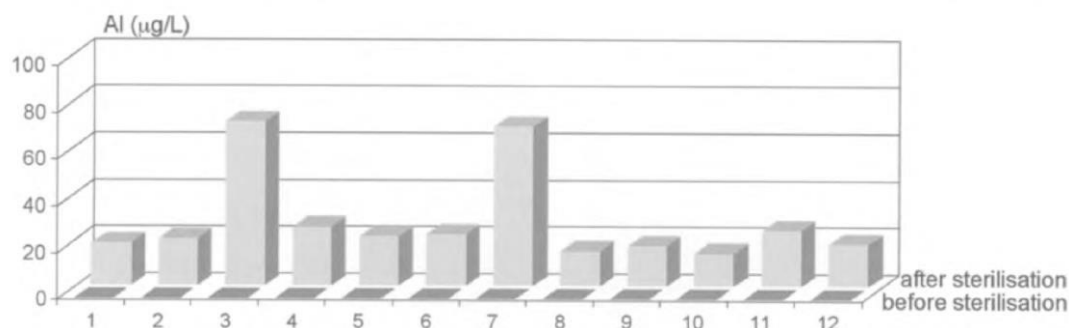


Fig. 1. Aluminium extracted from glass ampoules during sterilisation at 121 °C for 30 min by action of pure water.

**Figure 4. Aluminum extracted from glass ampoules during sterilization at 121° C for 30 minutes by action of pure water.**

102. Importantly, these factors do not operate independently of each other. For example, Bohrer also studied the effects of heat sterilization on aluminum contamination in various amino acids solutions. While heat sterilization increased the aluminum level in almost all of the amino acid solutions, the effect was most dramatic for those amino acids that demonstrated an affinity for binding aluminum, such as cysteine and cystine.<sup>51</sup> (Figure 5.)

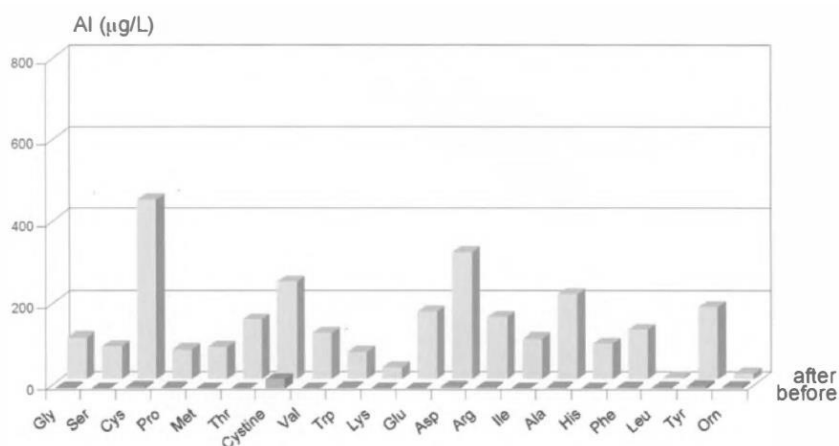


**Figure 5. Aluminum extracted from glass ampoules during sterilization at 121° C for 30 minutes by action of solutions of different amino acids at a concentration of 0.5% (m/v).<sup>52</sup>**

<sup>51</sup> Bohrer (III) at 110-111, Figure 2.

<sup>52</sup> Results are a mean of three replicates. After = after sterilization, before = before sterilization.

**D. Efforts to Reduce Aluminum Impurities in TPN Components**

103. While the problem of aluminum toxicity in TPN components has not been fully resolved, some progress has been made in reducing the aluminum content in certain components. Such is the case with calcium gluconate.

104. Several of the factors discussed in Section X.B above demonstrate why calcium gluconate is susceptible to aluminum contamination. Gluconate is an example of a compound that has a particular affinity for aluminum, as it is a very good metal chelating agent. Thus, a drug product containing calcium gluconate would aggressively leach aluminum from packaging that contains aluminum.<sup>53</sup> This is especially true for calcium gluconate injection products because this is the active ingredient in the drug product and it is formulated in the drug product in relatively high amounts (weight percent levels).<sup>54</sup>

105. For calcium gluconate, switching from glass to plastic vials proved to be successful in decreasing the level of aluminum contamination. This was verified in a study by Frey, who reported a 96% percent reduction in aluminum leaching in calcium gluconate packaged in polyethylene versus glass containers,<sup>55</sup> and additional authors.<sup>56,57</sup> Commercial

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<sup>53</sup> Yokel, R.A.; Unrine, J.M. Aluminum and phthalates in Calcium Gluconate: Contribution From Glass and Plastic Packaging. *JPGN*. 64(1): 109-114 (2017.)

<sup>54</sup> *Id.* at 11 (discussing calcium gluconate injection products that contain ~7-10% calcium gluconate.)

<sup>55</sup> Frey, O.R. Polyethylene vials of calcium gluconate reduce aluminum contamination of TPN. *Ann Pharmacother*. 34: 811-2 (2000.)

<sup>56</sup> Beaney, A.M.; Smeaton, I. Aluminum Levels in Parenteral Nutrition – time to change to plastic ampoules of Calcium Gluconate? Presented at the 15th Congress of the European Association of Hospital Pharmacists. Nice, France, 2010.  
[http://www.wales.nhs.uk/sites3/documents/828/Aluminium%20levels%20in%20Parenteral%20Nutrition%20-%20time%20to%20change%20to%20plastic%20ampoules%20of%20Calcium%20Gluconate\\_.pdf](http://www.wales.nhs.uk/sites3/documents/828/Aluminium%20levels%20in%20Parenteral%20Nutrition%20-%20time%20to%20change%20to%20plastic%20ampoules%20of%20Calcium%20Gluconate_.pdf)

<sup>57</sup> Raspaud, B.; Venet, A.; Jourand, A.; et al. Contamination of calcium gluconate by aluminum: which consequences for parenteral nutrition in neonatology?

products containing calcium gluconate in plastic vials were introduced into the European market in July of 1999<sup>58</sup> and in the United States in 2017.<sup>59</sup>

106. More recently, calcium gluconate in sodium chloride injection became commercially available in ready-to-use non-PVC plastic bags (NDA Approval, NDA 210906, William Chong, Center for Drug Evaluation and Research, Food and Drug Administration, 10/29/2018.) This product, marketed by WG Critical Care LLC (Paramus, New Jersey), is packaged in a plastic bag inside a foil overpouch and is marketed as the “first and only single-dose bag formulation indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia.”<sup>60</sup>

**E. Aluminum Contamination in Cysteine Hydrochloride Products**

107. Cysteine hydrochloride is another TPN component that was identified long ago as a major contributor to aluminum contamination of TPN solutions.<sup>61</sup> Prior to the invention of the Asserted Patents, my understanding, including based on Dr. Baertschi’s report, is that the only cysteine hydrochloride product available in the U.S. was an unapproved product from Sandoz that was labeled as containing no more than 5,000 mcg/L of aluminum. Applying the factors listed above in Section X.C, cysteine hydrochloride has several features that in my opinion make it especially susceptible to aluminum contamination.

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<http://www.gerpac.eu/contamination-of-calcium-gluconate-solutions-by-aluminum-which-consequences-for-parenteral-nutrition-in-neonatology>

<sup>58</sup> Calcium Braun 10%/20% Mini-Plasco, B. Braun Melsungen AG, polyethylene vial

<sup>59</sup> NDC 63323-360-61, Calcium Gluconate, NDA 208418, Fresenius Kabi USA, polypropylene vial; Letter to Customers, Pavon Kolli, Production manager, Critical Care, Fresenius Kabi, USA, April 30, 2015; NDA Approval, NDA 208418, Jean-Marc Guettier, Center for Drug Evaluation and Research, Food and Drug Administration, 06/15/2017

<sup>60</sup> <https://www.prnewswire.com/news-releases/wg-critical-care-wgcc-expands-portfolio-with-unique-product-300778820.html>

<sup>61</sup> See, e.g., Driscoll, M; Driscoll, D.F., Calculating aluminum content in total parenteral nutrition admixtures. Am. J. Health-Syst. Pharm. 2005;62:312-5; Hernandez-Sanchez at 231.

## 1. Cysteine Has High Affinity for Aluminum

108. The active ingredient in L-cysteine hydrochloride injection products is cysteine hydrochloride monohydrate, a salt of the sulfur-containing amino acid cysteine. (*See, e.g.,* ExelaCYS00018776 at 783; ETON-CYST00009635 at 9645-46.)

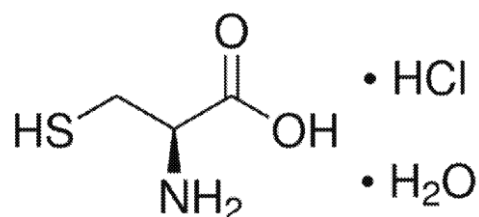


**Figure 1. Cysteine Hydrochloride Monohydrate**

109. As discussed in Section X.C above, Bohrer identified cysteine as one of the amino acids that are able to leach aluminum from glass.<sup>62</sup> (*See also* Figure 1.) She estimated that cysteine's affinity for aluminum was comparable to well-known complexing agents such as citrate and oxalate. (*See* Section X.C, Figure 2.) Even within the group of aluminum binding amino acids, cysteine proved to be unique in that it was one of only two amino acids that continued to extract aluminum over the entire study period without reaching equilibrium.<sup>63</sup>

## 2. L-Cysteine Oxidation to Cystine

110. Cysteine is an oxygen sensitive molecule that can be oxidized to form the disulfide molecule cystine (Figure 2.) Cystine is a degradation impurity observed in L-cysteine hydrochloride products. (*See, e.g.,* ExelaCYS00020970 at 975-977; ETON-CYST00021681 at 687)

<sup>62</sup> Bohrer, D.N. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part II: Amino acids for parenteral nutrition. *J Trace Elem Med Biol.* **15**: 103 – 108 (2001.)

<sup>63</sup> Bohrer (Part II) at 106-107, Figure 2.

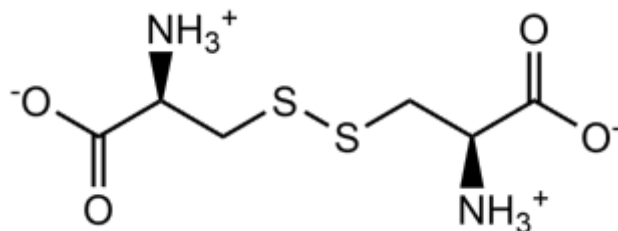


**Figure 2. Cystine, An Oxidative Degradation Product of Cysteine**

111. Cystine was also identified by Bohrer as an amino acid that is able to leach aluminum from glass.<sup>64</sup> In 2006, Bohrer conducted additional studies on the affinity of cysteine and cystine for binding aluminum. She demonstrated, through use of an ion exchange resin, that cystine is a stronger aluminum-complexing agent than cysteine (Figure 3).<sup>65</sup> Bohrer hypothesized that formation of the cystine dimer creates a molecule with four N/O binding sites for aluminum, as opposed to two such binding sites, which may explain cystine's greater affinity for aluminum.

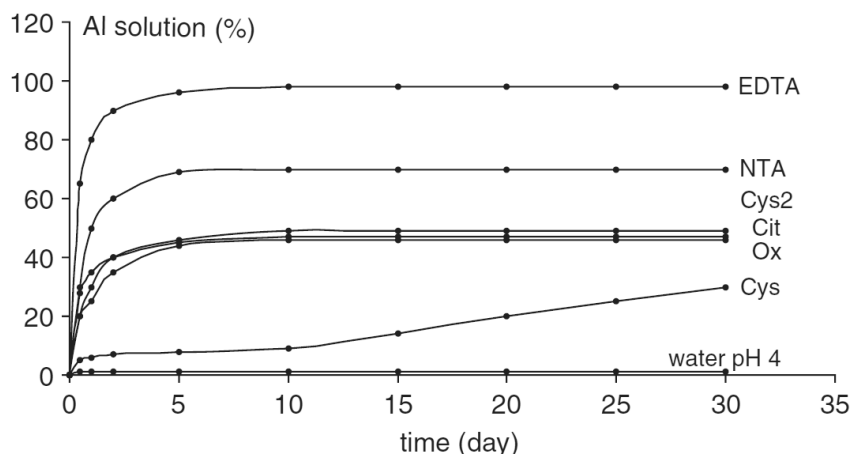


**Figure 3. Aluminum extracted from an Al<sup>3+</sup>-form cation exchanger by the action of ligands as a function of the time. Cys2 is cystine and CYS is cysteine.**

<sup>64</sup> Bohrer (Part II) at 106-107, Figure 2.

<sup>65</sup> Bohrer, D.N., Polli, V.G., Nascimento, P.C., Mendonca, J.K.A., de Carvalho, L.M., Pomblum, S.G. Ion-exchange and potentiometric characterization of Al-cystine and Al-cysteine complexes. *J. Biol Inorg Chem* 11:991-998 (2006.)

112. Bohrer also studied the effects of oxygen exposure on the aluminum leaching abilities of cysteine (Figure AA.)<sup>66</sup> In the absence of oxygen, aluminum extraction in the cysteine solution stopped increasing after 7 days, as it did for solutions containing the other ligands. In the presence of oxygen, however, aluminum levels continued to increase in the cysteine solution up to 100 days (or more). Bohrer attributed the increased amount of aluminum extraction to the oxidation of cysteine into cystine, which she reported as being a stronger complexing agent than cysteine.

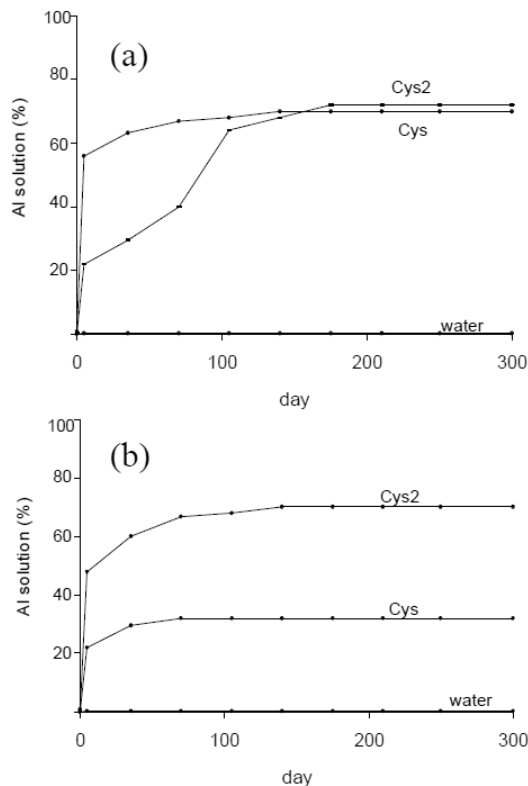


**Figure AA. Aluminum extracted from an Al<sup>3+</sup>-form cation exchanger by action of cysteine and cystine solutions in the presence (a) and absence (b) of oxygen.**

<sup>66</sup> Bohrer (2006) at 997, Supplemental Figure B.

**3. L-Cysteine Hydrochloride is Strongly Acidic**

113. Cysteine hydrochloride products are strongly acidic, with a pH range of 1.0 to 2.5.<sup>67</sup> I understand that this is uncommon amongst parenteral drugs, as most drugs that are intended for injection into the blood stream are closer to neutral pH.<sup>68</sup> For perspective, a cysteine hydrochloride solution with a pH of 1.0 has roughly a 10,000,000 times greater concentration of H<sup>+</sup> than a neutral solution of pH 7.0. As discussed above in Section X.C, acidic solutions are understood to leach aluminum from glass via ion exchange, but there is a lack of data on the behavior of solutions at pH less than 6, let alone at strongly acidic pHs between 1.0 and 2.5.

114. In addition, Bohrer determined that formation of aluminum complexes of cysteine and cystine are pH-dependent.<sup>69</sup> However, Bohrer only studied the formation of those complexes at pH values of approximately 3 to 11.

**XI. COMMENTS ON THE SCOPE AND CONTENT OF THE REFERENCES FORMING THE BASIS OF DR. BAERTSCHI'S INVALIDITY OPINIONS**

**A. The Sandoz Product**

115. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

<sup>67</sup> See, e.g., ELCYS® Label (ExelaCYS00018776 at 18783.)

<sup>68</sup> See, e.g., Roethlisberger, D.; Mahler, H.C.; Altenburger, U. Pappenburger, A. If Euhydric and Isotonic Do Not Work, What Are Acceptable pH and Osmolality for Parenteral Drug Dosage Forms? *Journal of Pharmaceutical Sciences* 106: 446-456 (2017) at Table 2 (identifying SVPs with pH values of 2.55 to 4.75 as “extreme”).

<sup>69</sup> Bohrer (2006) at 996-997.

[REDACTED]

[REDACTED]

[REDACTED]

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**1. The Sandoz Label**

117. I have reviewed the Sandoz Label Dr. Baertschi cites. (ExelaCYS00109346-352.) This label relates to a “Pharmacy Bulk Package” form of a 50 mg/mL L-cysteine hydrochloride injection, USP that is manufactured for Sandoz in 50 mL vials. It contains instructions for use and a mock-up of part of the packaging. It bears a revision date of November 2009 (ExelaCYS00109350), and appears to have been downloaded from the internet in May 2015 based on the information displayed in the document’s header and footer. The Sandoz Label says that a 10 mL product is also available (ExelaCYS00109349), but does not include mock-up of the packaging for the 10 mL product.

118. The Sandoz Label describes the product as follows:

**DESCRIPTION**

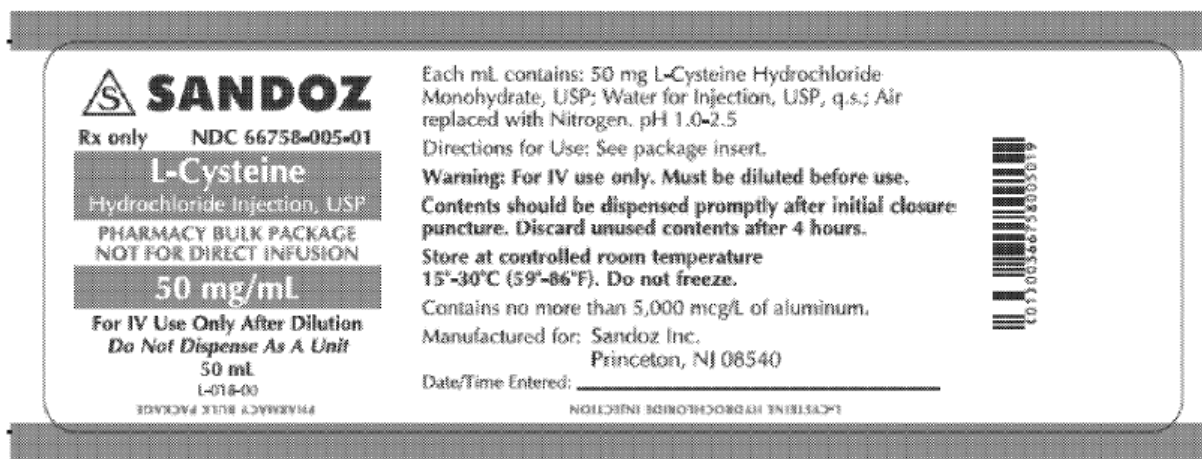
L-Cysteine Hydrochloride Injection, USP, 50 mg/mL, is a sterile, nonpyrogenic solution. Each mL contains: 50 mg of L-Cysteine Hydrochloride Monohydrate USP; Water for Injection, USP q.s.; Air replaced with Nitrogen. pH 1.0-2.5

(ExelaCYS000109346.)

119. Dr. Baertschi has correctly quoted what the Sandoz Label says about the product’s use: “for use only after dilution as an additive to Crystalline Amino Acid Injection to meet the intravenous amino acid nutritional requirements of infants receiving total parenteral nutrition.” (*Id.* ¶ 54; ExelaCYS000109346.) The Sandoz Label also contains Dosage and Administration instructions, which instruct admixing the Sandoz cysteine product with crystalline amino acid injection and dextrose. (ExelaCYS00109348.)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

120. The Sandoz Label includes the following information about aluminum content, as reflected on the packaging mock up for the 50 mL vial configuration: “Contains no more than 5,000 mcg/L of aluminum.”



(ExelaCYS000106350.) No information on aluminum content for the 10 mL vial configuration is provided within the Sandoz Label.

121. The instructions section of the Sandoz Label contains a Warning about aluminum:

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

*Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration*

(ExelaCYS000109347.)

122. The Sandoz Label lacks information about the following, which are aspects of the product that are relevant to the Asserted Claims:

- a. The amount of cystine present in the product at any time point;
- b. The amount of pyruvic acid present in the product at any time point;
- c. The amount of headspace oxygen present in the product at any time point;

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

- d. The amount of dissolved oxygen present in the product at any time point;
- e. The exact amount of aluminum present in the product at any time point.

I understand Dr. Baertschi contends that the absence of an antioxidant in the Sandoz product, as reflected in the Sandoz Label, “suggests that other methods for removing or reducing oxygen content were utilized in the production and packaging of the Sandoz Product.” (Baertschi Op. Rep. ¶ 56.) I do not believe that inference is required, as the label states “Air replaced with Nitrogen.” (ExelaCYS000109346.)

2. [REDACTED]

123. [REDACTED]

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**B. The Hospira Aminosyn® II Product**

140. I understand that the Hospira Aminosyn® II Product refers to the amino acid injection with electrolytes in dextrose injection with calcium described in label produced at ExelaCYS00034700 (“Hospira Label”). The Hospira Label describes a crystalline amino acid solution labeled Aminosyn® II, which includes the following amino acids: isoleucine, leucine,

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, arginine, histidine, proline, serine, tyrosine, and glycine. (Hospira Label at 1-2.)

141. The Hospira Aminosyn® II Product label was disclosed to the examiner in prosecution of the '453, '155, '713, '795, and '089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

142. I also understand that Eton relied on a 2007 version of the Hospira label in its PGR petitions against the '453 and '155 Patents, and that it was disclosed to the examiner in prosecution of the '713, '795, and '089 Patents. It is listed in the “References Cited” list for those three patents, and I understand from counsel that the examiner is therefore presumed to have been aware of it.

**C. Hernandez-Sanchez**

143. I understand that Dr. Baertschi relies on the article “Aluminum in Parenteral Nutrition: A Systematic Review,” Alfredo Hernández-Sánchez et al., *Eur. J. Clin. Nutr.* 67: 230-238 (2013), produced as (ETON-CYST00021128-136), to establish the knowledge of a POSA prior to the earliest priority date of the Asserted Patents. (Baertschi Op. Rep., ¶ 64.) Hernandez-Sanchez is a review article summarizing literature published on aluminum in parenteral nutrition up through November 2012. The article covers topics including the sources of aluminum contamination in TPN/PNS components, patient risks and manifestations of aluminum toxicity, diagnostics and treatment of aluminum toxicity, and aluminum regulations.

144. I understand that Eton relied on Hernandez-Sanchez in its PGR petitions against the '453 and '155 Patents. Hernandez-Sanchez was also disclosed to the examiner in prosecution of all five of the Asserted Patents. It is listed in the “References Cited” list for each

of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

145. In the very first sentence, Hernandez-Sanchez recognizes that “[a]luminum (Al) toxicity problems in parenteral nutrition solutions (PNS) is decades old and is still unresolved.” Hernández-Sánchez also provides an overview of the sources of aluminum contamination in TPN/PNS solutions, noting that “[a] high Al content in PNS is largely the result of three PDP: calcium gluconate (CaGluc; up to 81%), inorganic phosphates (especially potassium) and cysteine hydrochloride.” (pg. 231) The article also suggests that aluminum contamination can be reduced by repackaging in plastic vials, noting that “replacing CaGluc from glass containers to polyethylene vials reduces the mean Al concentration from 5000 to 195 ug/L (a 96% decrease).” (pg. 231) Hernandez-Sanchez notably does not suggest the use of the Schott Type I+ vials, even though those had been available since at least the early 2000’s.<sup>70</sup>

146. Dr. Baertschi points to Hernandez-Sanchez as support for his assertion that “the label for parenteral products lists only the maximum, rather than the actual aluminum content, making it difficult to estimate the actual aluminum content and that actual measured aluminum exposure levels were significantly less than the aluminum content listed on the manufacturer’s label.” (Baertschi Op. Rep., ¶ 104.) Dr. Baertschi seems to assume, incorrectly, that the measured aluminum contents identified in Hernandez-Sanchez for certain products somehow establish that those products will always be significantly lower than the labeled amounts. Dr. Baertschi fails to appreciate that the “actual” aluminum content of a TPN component is not

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<sup>70</sup> See, e.g. Akers, M.J. Parenteral Preparations in Remington: The Science and Practice of Pharmacy, 810 (David B. Troy et al. eds., 21st ed. 2006) (ExelaCYS00070128 at 70135) (discussing Schott Type I glass vials coated with silicon dioxide); Schott Type I Plus Trademark Registration ([https://tmsearch.uspto.gov/bin/gate.exe?f=login&p\\_lang=english&p\\_d=trmk](https://tmsearch.uspto.gov/bin/gate.exe?f=login&p_lang=english&p_d=trmk)) (first use in commerce was 1997.)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

static. As discussed above in Section X, leaching of aluminum from packaging materials is a time-dependent process and the longer the product remains in contact with the packaging material, the more aluminum it may leach. The “actual” aluminum content of a TPN component may depend on, among other things, when it is used. Especially for those components packaged in glass vials, a POSA would expect the product to contain lower aluminum levels closer to time of manufacture and higher levels closer to expiry. Thus, in my opinion a POSA would not assume that the measured aluminum levels presented in Hernandez-Sanchez are indicative of the actual amount of aluminum in the product throughout its shelf-life, nor would a POSA conclude “that actual measured aluminum exposure levels were significantly less than the aluminum content listed on the manufacturer’s label,” as Dr. Baertschi asserts. (Baertschi Op. Rep., ¶ 104.) I do, however, agree that a POSA would find it “difficult to estimate the actual aluminum content” of any particular product (*id.*), which is precisely the reason FDA regulations require SVP manufacturers to state on the product’s label the maximum aluminum level on expiry as measured by one of three specific methods. (*See* Section X above.)

147. Contrary to Dr. Baertschi’s assertion, Hernandez-Sanchez provides no specific instructions on how to reduce aluminum in an L-cysteine hydrochloride product. Rather, it provides a list of general recommendations for manufactures and healthcare providers involved in the provision of PNS, including: (1) “[m]anufacturers should improve manufacturing techniques, approved by FDA, in order to provide a wide range of low-Al-content PNS alternatives that make it feasible to meet the requirements”; (2) “[a]ll healthcare providers should ensure that ingredients with the lowest amount of Al[uminum] are used in the preparation of PNS”; and (3) “pharmacists should identify manufacturers whose products result in less Al[uminum] contamination than those of others.” (pg. 237.)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

148. With respect to recommendation two and three, I disagree with Dr. Baertschi's assertion that "[w]hile these proposals were made in the context of healthcare providers, they are obviously applicable and easily implemented by manufacturers of L-Cysteine products." (Baertschi Op. Rep., ¶ 105.) A POSA would understand that a healthcare provider purchasing a commercial product with the least amount of aluminum contamination is an entirely different endeavor from a manufacturer selecting packaging as one of many variables that go into the manufacturing of an L-Cysteine product.

149. Moreover, a POSA would understand that changing the manufacturing process for a parenteral drug product and gaining FDA approval is a complicated process that can take years to complete. (*See* Section X above.) As discussed in Section X.A and X.B above, the aluminum content of the packaging material is only one of many factors that can contribute to the amount of aluminum contamination in a TPN component such as L-cysteine hydrochloride. The interplay of those factors makes it difficult to predict how a change of packaging material will affect the aluminum level in the drug product, and impossible to know what other aspects of the product may be affected. For example, following the general recommendations of Hernandez-Sanchez would have meant changing the L-cysteine hydrochloride product packaging to that packaging material containing the lowest amount of available aluminum, which would be plastic vials. As discovered by the Exela researchers, so doing did not produce a viable product; instead, it introduced unanticipated product stability problems including cysteine oxidation and cystine precipitation.

**D. Aluminum in Large and Small Volume Parenteral Used in Total Parenteral Nutrition, 21 C.F.R. § 201.323 (2003)**

150. I understand that 21 C.F.R. § 201.323 is an FDA regulation titled "Aluminum in large and small volume parenterals used in total parenteral nutrition", which was implemented in

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

2004. (See Section X.B above.) I understand that Eton relied on 21 C.F.R. § 201.322 in its PGR petitions against the '453 and '155 Patents. 21 C.F.R. § 201.323 was also disclosed to the examiner in prosecution of the '713, '795, and '089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

151. Contrary to Dr. Baertschi assertion, the regulation does not “require[] the aluminum in parenteral drug products used in total parenteral nutrition therapy to be less than 25 ppb.” (See, e.g., Baertschi Op. Rep., Ex. B pg. 7.) 21 C.F.R. § 201.323(a) requires that “[t]he aluminum content of **large volume parenteral (LVP)** drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter ([micro]g/L)” (emphasis added.) This section of the regulation does not apply to L-cysteine because L-cysteine is a **small volume parenteral (SVP)**.

152. For SVP’s, 21 C.F.R. § 201.323(c) requires that “the maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content of SVPs must be stated as follows: ‘Contains no more than \_\_\_ [micro]g/L of aluminum.’” As described above in Section X.B, §201.323(c)(1-3) requires that the aluminum content be stated as the highest of three categories of aluminum measurements.

153. 21 C.F.R. § 201.323(e) also requires that the package insert for all SVPs used in TPN contain a warning statement regarding aluminum:

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

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

[micro]g/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration

**E. U.S. Patent No. 8,415,337 Patent**

154. U.S. Patent No. 8,415,337 (“the ’337 Patent”), titled “Ibuprofen Compositions and Methods of Making Same” (ETON-CYST00020457-471), discloses “an improved ibuprofen lysine pharmaceutical composition and a process for preparing the same.” (’337 Patent at Abstract.) The ’337 Patent describes a problem with the formation of ibuprofen aluminum salt precipitates in alkylammonium salt ibuprofen compositions. (*Id.* at 1:48-58.) The described invention relates to pharmaceutical compositions of alkylammonium salts of ibuprofen capable of complexing with aluminum that is substantially free of ibuprofen aluminum salt precipitate. (*See, e.g.*, 2:8-3:42.)

155. I understand that Eton relied on the ’337 Patent in its PGR petition against the ’453 and ’155 Patents. The ’337 Patent was also disclosed to the examiner in prosecution of the ’713, 795 and ’089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

156. I see no reason why—and Dr. Baertschi provides no reason—for a POSA to have looked to the ’337 Patent for ways to make stable, low-aluminum L-cysteine compositions for injection. The ’337 Patent does not discuss cysteine in any form, let alone parenteral formulations of cysteine for use in TPN solutions. Rather, it focuses on alkylammonium salts of ibuprofen, and in particular, ibuprofen lysine. Chemically and structurally, L-cysteine hydrochloride and ibuprofen lysine are very different and a POSA would have had no reason to expect their interaction with glass--and specifically their propensity to leach aluminum--to be similar. As Bohrer had previously established, while L-cysteine and its oxidative degradation product cystine chelate aluminum, enabling L-cysteine solutions to aggressively leach aluminum

from glass packaging, lysine, on the other hand, does not chelate aluminum and does not extract aluminum from glass.<sup>71</sup>

157. In addition, solutions of ibuprofen lysine and L-cysteine hydrochloride for injection have very different pH values. A POSA would have understood the pH of ibuprofen lysine to be around 7 based on labeling of commercially available ibuprofen lysine injection products<sup>72</sup> and consistent with the '337 Patent disclosure of a method of preparing an ibuprofen lysine solution in which the pH of the solution is adjusted to about 7.0. (*See, e.g., '337 Patent at 2:45-68.*) A neutral pH of 7 is notably different from the acidic pH of the L-cysteine hydrochloride solution (pH 1.0 to 2.5), which would indicate to a POSA that the ibuprofen lysine and L-cysteine hydrochloride solutions could interact very differently with glass containers, specifically with respect to aluminum leaching. (*See Section X above.*)

158. The '337 Patent also suggests to a POSA that ibuprofen lysine leaches aluminum from Type I glass at a very different rate than L-cysteine hydrochloride. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] As reported in the '337 Patent, batches of ibuprofen lysine solution in Type I glass vials were found to contain only up to 141 mcg/L of aluminum over 65 months storage at 25° C and 60% relative humidity. ('337 Patent at 6:65-7:3, Table 1.) The ICP-MS technique measured the total aluminum present in the vial, i.e. soluble and

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<sup>71</sup> Bohrer (Part II) at 105-106.

<sup>72</sup> 2013 Ibuprofen Lysine injection product package insert available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/202402Orig1s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202402Orig1s000lbl.pdf)

insoluble. (*Id.* at 7:5-7.) From these differences in the aluminum leaching rate, a POSA would understand that ibuprofen lysine and L-cysteine hydrochloride interact differently with Type I glass and the aluminum contained therein.

159. To solve the problem of ibuprofen aluminum salt precipitates in alkylammonium salt ibuprofen compositions, the '337 Patent proposes various alternative containers, including packaging the ibuprofen lysine solution in a glass vial with one of several coatings disposed on the inner wall, including silicon dioxide, Teflon®, or an inert polymer. (*Id.* at 5:1-23, Claims 1, 6 and 7.) Another proposal taught by the '337 Patent is to package the ibuprofen lysine solution in a vial composed of an inert polymeric material, *i.e.* plastic. (*Id.* at 5:24-29.) As an example, the specification identifies the Dalkyo Crystal Zenith® vial, which is comprised of a proprietary cyclic olefin polymer material. (*Id.*)

160. Dr. Baertschi asserts that the '337 Patent “teaches Schott coated glass vials to prevent aluminum leaching into ibuprofen solutions; <9 ppb Al,” citing Example 5 of the '337 Patent. (*See, e.g.,* Baertschi Op. Rep., Ex. B, pg. 1.) I disagree. Example 5 actually provides data on aluminum amounts extracted by rinsing Wheaton Type I, Schott Type I+, and Dalkyo Crystal Zenith (cyclic olefin polymer) vials with three 3 mL aliquots of 10% v/v hydrochloric acid, not ibuprofen solutions. (11:19-30, Table 6.) As discussed above in Section X, this is a general method for testing aluminum extraction from a container; it does not establish the amount of aluminum leached by a specific pharmaceutical composition, let alone over the product's shelf life. Moreover, the difference in the amount of aluminum extracted from the Type I vials and the other vials is very small (0.1-0.2 µg v. 0.0 µg), (Table 6), and such a small difference would not have suggested to a POSA that the Schott Type I+ vial is markedly superior to the Wheaton (unlined) vial.

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

161. Moreover, given the significant differences in pH of L-cysteine hydrochloride and ibuprofen lysine, and the aluminum chelating ability of L-cysteine and cystine as compared to lysine, the '337 Patent would not have provided a POSA a reasonable expectation of succeeding in reducing the aluminum level in the L-cysteine hydrochloride product to the levels recited in the Asserted Patent claims simply by using the Schott Type I+ vial, let alone reducing the aluminum levels while also solving the other stability problems with l-cysteine solutions encountered by the inventors (which the '337 Patent does not address whatsoever).

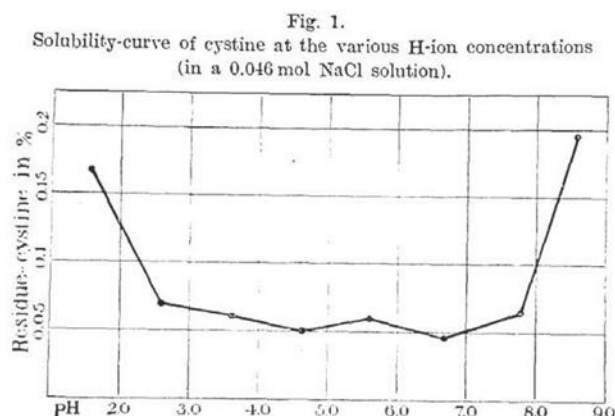
162. Dr. Baertschi also cites to Table 13 of the '337 Patent. (*See, e.g.,* Baertschi Op. Rep., Ex. B, pg. 1.) This table describes the results of testing ibuprofen lysine solutions stored in Schott Type I+ vials for 12 months at 25° C and 60% relative humidity for the formation of ibuprofen aluminum particulates. The formation of precipitates only accounts for the insoluble aluminum (not the total aluminum in the ibuprofen solution) and thus gives an incomplete picture of the total amount of aluminum extracted by the ibuprofen lysine solutions in the Schott Type I+ vials. A POSA would not view testing results for insoluble aluminum as applicable to the problem the inventors faced, since cysteine hydrochloride does not form insoluble salts with aluminum under the conditions described in the Asserted Patents.

**F. Len Okabe, Studies on the Solubility of Cystine Under Various Conditions, and On a New Method of Cystine Preparation, 8 BIOCHEM. J. 441 (1927)**

163. The Okabe reference is an article titled “Studies on the Solubility of Cystine Under Various Conditions, and On a New Method of Cystine Preparation” that was published in the Journal of Biochemistry in 1927. (ETON-CYST00021111-127) I understand that Eton relied on Okabe in its PGR petitions against the '453 and '155 Patents. Okabe was also disclosed to the examiner in prosecution of the '713, '795, and '089 Patents, and is listed in the

“References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

164. Okabe describes an optimized method of preparing cystine by hydrolyzing horse hair with 20% hydrochloric acid. As part of the optimization process, Okabe studied the effect of several variables on the solubility of cystine, including pH, salt concentration, alcohol addition, and temperature. With respect to pH, Okabe observed that the solubility of cystine was very low at approximately pH 3 to 8, but it increased at pH < 3 and pH > 8. (Figure 1.)



165. Dr. Baertschi cites Okabe for “the understanding of a person of ordinary skill in the art that L-cystine was a known oxidation degradation product of L-cysteine.” (*See, e.g.,* Baertschi Op. Rep. at Ex. B, pg. 3.) I agree that L-cysteine was known to oxidatively degrade to L-cystine, but the portion of Okabe Dr. Baertschi cites does not support this point. Okabe’s statement that “[a]fter the hydrolysate of proteins by hydrochloric acid is decolorized by the addition of animal charcoal, and a small amount of zinc powder is put into the liquid, the cystine is reduced to cysteine...” is the recitation of the first step in a method for quantitating cystine for an unspecified purpose and describes a process that is the opposite of the oxidation of cysteine to cystine. (Okabe at 441.) The fact that cystine can be reduced to cysteine in the presence of a

reducing agent (zinc metal) in no way supports Dr. Baertschi's statement concerning the circumstance that L-cysteine oxidatively degrades to L-cystine.

166. But even more fundamentally, a POSA would not view Okabe as being in the "same field of endeavor" as "the field of L-cysteine administration and/or pharmaceutical development," as Dr. Baertschi states. (Baertschi Op. Rep, ¶¶ 140, 145.) In my opinion, a POSA would not look to a reference about horse hair in trying to solve the problem of high aluminum in L-cysteine hydrochloride injection products for TPN.

**G. S. Hofler *et al.*, Dealing With the Sulfur Part of Cysteine: Four Enzymatic Steps Degrade L-cysteine to Pyruvate and Thiosulfate in Arabidopsis Mitochondria, *Physiologia Plantarum*, 157, 352-366 (2016)**

167. The Hofler reference is an article titled "Dealing with the sulfur part of cysteine: four enzymatic steps degrade L-cysteine to pyruvate and thiosulfate in Arabidopsis mitochondria" and published in the journal *Physiologia Plantarum* in 2016. (ETON-CYST00166522-ETON-CYST00166536) Hofler does not say anything about L-cysteine compositions for TPN. Rather, Hofler teaches that the complete oxidation of L-cysteine to pyruvic acid and thiosulfate can be accomplished via a four-step enzymatic process in the mitochondria of plant cells. (Hofler at 1.)

168. Dr. Baertschi relies on Hofler to demonstrate that "a POSA would further understand that L-cystine can degrade to pyruvic acid under certain conditions." (Baertschi Op. Rep., ¶ 156.) I disagree. Hofler teaches that *L-cysteine* can degrade to pyruvic acid under certain conditions, and it postulates that L-cystine is a potential intermediate that is formed non-enzymatically in some knock-out genetic studies. (See Hofler at 361.)

169. I also disagree that Hofler teaches that enzymes are *necessary* to oxidize L-cysteine to pyruvic acid, as Dr. Baertschi suggests.

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

170. A POSA would not view Hofler as being in the “same field of endeavor” as “the field of L-cysteine administration and/or pharmaceutical development,” as Dr. Baertschi states. (Baertschi Op. Rep., ¶¶ 140, 145.) In my opinion, a POSA would not look to a reference about enzymatic activity in plants in trying to solve the problem of high aluminum in L-cysteine hydrochloride injection products for TPN.

**H. R.D. Asquith *et al.*, The Photochemical Degradation of Cystine in Aqueous Solution in the Presence of Air, *Biochimica et Biophysica Acta*, 184, 345-357 (1969)**

171. The Asquith reference is an article titled “The Photochemical Degradation of Cystine in Aqueous Solution in the Presence of Air” published in the journal *Biochimica et Biophysica Acta* in 1969. (ETON-CYST00166488-ETON-CYST00166500) I understand that Eton relied on Asquith in its PGR petitions against the ’453 and ’155 Patents. Asquith was also disclosed to the examiner in prosecution of the ’713, ’795, and ’089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

172. Asquith does not say anything about L-cysteine compositions for TPN. Rather, Asquith studied the effects of ultraviolet radiation of cystine in air-saturated aqueous solution at pH 1 and pH 10 and confirmed the formation of a large number of products, including pyruvic acid. (See Asquith at 345, 353, Figure 7.) While Asquith confirmed that cystine can degrade to pyruvic acid under acidic conditions, a POSA would not read Asquith as suggesting that exposure to ultraviolet radiation is the only method by which cystine degrades to form pyruvic acid.

**I. H.T. Clarke *et al.*, Some Observations on the Action of Alakali Upon Cystine and Cysteine, J. BIOL. CHEM., Vol. LXXXIX, No. 1, 399-419 (1930)**

173. The Clarke reference is an article titled “Some Observations on the Action of Alkali Upon Cystine and Cysteine” published in the Journal of Biological Chemistry in 1930. (ETON-CYST00166501-ETON-CYST00166521) Clarke does not say anything about L-cysteine compositions for TPN. Rather, Clarke investigated the alkaline decomposition products of cystine and cysteine and confirmed that heating solutions of cystine and cysteine with lead acetate under alkaline conditions yields pyruvic acid as an initial product. (Clarke at 1.)

174. Dr. Baertschi asserts that Clarke “establishes that it was known in the art as early as 1930, that cystine and cysteine can break down into pyruvic acid under high pH and elevated temperature conditions.” (Baertschi Op. Rep., ¶ 75 (citing Clarke at 399).) He also asserts that “[h]igher yields of pyruvic acid are produced from cysteine in the presence of alkali.” (*Id.*) Based on those statements, Dr. Baertschi concludes that “[c]orrespondingly, the breakdown of cysteine or cystine into pyruvic acid would not be expected in an acidic composition.” (*Id.* at ¶ 76.) I disagree. A POSA would understand Clarke’s discussion of higher yields of pyruvic acid from cysteine as a comparison of the yield of pyruvic acid from cysteine versus cystine under similar alkaline conditions, not the yield of pyruvic acid from cysteine under acidic versus alkaline conditions. (*See* Clarke at 399.) Moreover, Clarke did not investigate the effect of acid or acidic pH on the formation of pyruvic acid.

**J. Ian B. Butler *et al.*, Removal of Dissolved Oxygen from Water: A Comparison of Four Common Techniques, 41 TALANTA 211 (1994)**

175. The Butler reference is an article titled “Removal of Dissolved Oxygen from Water: A Comparison of Four Common Techniques” that was published in the journal Talanta in 1994. (ETON-CYST00020300-304.) I understand that Eton relied on Butler in its PGR petitions against the ’453 and ’155 Patents. Butler was also disclosed to the examiner in

prosecution of the '713, '795, and '089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

176. Butler studied the efficacy of oxygen removal from deionized water by four common techniques—purging with nitrogen, boiling at one atmosphere, sonication under reduced pressure, and boiling under reduced pressure. Butler found that by nitrogen purging one liter of deionized water in a stoppered pyrex reaction kettle for approximately 20-40 minutes, the dissolved oxygen level could be reduced to 0.2 to 0.4 ppm. (Butler at 211.)

177. Dr. Baertschi cites Butler for the conclusion that purging with nitrogen is a “quick and effective method for removing dissolved oxygen” from water. (Baertschi Op. Rep., ¶ 79.) This may be true under the strict laboratory conditions employed by Butler, but in my opinion Butler is not applicable to the manufacturing setting, let alone the specific manufacturing conditions for cysteine hydrochloride, and thus is not in the “same field of endeavor” as “the field of L-cysteine administration and/or pharmaceutical development.” (Baertschi Op. Rep., ¶¶ 140, 145.) A POSA would understand that removing dissolved oxygen from a drug product in commercial scale manufacturing operations is a very different process than removing dissolved oxygen from one liter of deionized water in a sealed vessel under laboratory conditions. Even if the same level of dissolved oxygen reduction could be achieved during the compounding step, each of the subsequent steps, e.g. sterilizing and filling, present an opportunity for oxygen to reenter the solution.

178. In addition, Butler says nothing about controlling dissolved oxygen in an L-cysteine formulation for use in TPN solutions. To the contrary, Butler himself cautioned “although purging with [nitrogen] is an efficient method to remove dissolved oxygen from

deionized water, it is a poor method to preserve solutions containing redox-sensitive species.”

(Butler at 215.) Because cysteine can be oxidized to cystine, it is a redox-sensitive species, and a POSA would understand Butler teaches that using nitrogen sparging is an efficient method to remove oxygen from a cysteine formulation for use in a TPN solution.

179. Dr. Baertschi also cites Butler for the premise that “[a] person of ordinary skill would know that head space and dissolved oxygen reach an equilibrium, and thus removing head space oxygen also results in minimizing dissolved oxygen.” (*See, e.g.*, Baertschi Op. Rep., Ex. B, pg. 6.) Butler did not measure headspace oxygen, does not teach any direct methods of removing headspace oxygen, and does not address the equilibrium between headspace and dissolved oxygen, so I disagree that this reference supports Dr. Baertschi’s assertion.

180. In my opinion, a POSA would not look to Butler in trying to solve the problem of high aluminum in L-cysteine hydrochloride injection products for TPN.

**K. Kenneth C. Waterman *et al.*, Stabilization of Pharmaceuticals to Oxidative Degradation, 7 PHARMACEUTICAL DEV. & TECH. 1 (2002)**

181. The Waterman reference is a review article titled “Stabilization of Pharmaceuticals to Oxidative Degradation” that was published in the journal Pharmaceutical Development and Technology in 2002. (ETON-CYST00020259-290.) I understand that Eton relied on Waterman in its PGR petitions against the ’453 and ’155 Patents. Waterman was also disclosed to the examiner in prosecution of the ’713, ’795, and ’089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

182. Waterman provides a general overview of the problem of oxidative degradation in drug products, including discussing various remedies for different dosage forms such as traditional liquid and solid dosage forms containing small molecules, as well as formulations

containing protein and DNA-based pharmaceuticals. (Waterman at 1.) Waterman teaches multiple factors that may influence oxidation of a drug product including acidity (pH), concentration, temperature, oxygen in the headspace, photo-oxidation, metals, and packaging. (Waterman at 3.) Waterman also cautions that “each new drug presents new challenges.” (Waterman at 1.)

183. Contrary to Dr. Baertschi’s assertions, Waterman does not address the oxidation of L-cysteine hydrochloride as a small molecule, such as in a formulation for use in TPN solutions. (Baertschi Op. Rep., ¶¶ 82, 103.) Instead, Waterman discusses the oxidation of the protein-bound cysteine in the context of protein pharmaceuticals, stating that “[t]here are five naturally occurring amino acids that contain side chains with a high electron densities, which therefore tend to oxidize under practical formulation and storage conditions: histidine (His), methionine (Met), cysteine (Cys), tryptophan (Trp), and tyrosine (Tyr).” (Waterman at 17.) Waterman is speaking of cysteine present and bound in a protein and not “free” cysteine as an independent chemical entity. Moreover, Waterman does nothing to connect the oxidation of cysteine to any of the other problems addressed by the claims, including the formation of cystine particulates and the reduction of aluminum in an L-cysteine formulation for TPN.

184. Dr. Baertschi also cites Waterman’s guidelines for protein pharmaceuticals that recommend “optimizing the formulation pH and reducing the headspace oxygen by, for example, applying a nitrogen (or argon) headspace to liquid formulations.” (Baertschi Op. Rep., ¶ 84.) Contrary to Dr. Baertschi’s assertion, Waterman does not propose these steps to address the oxidation of L-cysteine “under normal storage conditions.” (Baertschi Op. Rep., ¶ 103 (citing Waterman at 19).) Rather, as Waterman points out, these are only general guidelines given for protein pharmaceuticals “[d]ue to the complexities induced by the many potential oxidation sites

present in typical pharmaceutical proteins, each of which has different intrinsic chemical properties and a different local chemical environment as well as different sensitivities to local and global protein conformation.” (Waterman at 19.) In my opinion, a POSA would not consider guidelines for protein pharmaceuticals to be applicable to a specific small molecule formulation of L-cysteine for use in TPN solutions. Moreover, nothing in Waterman suggests that those general guidelines would be successful in solving the stability problems encountered by the inventors as a result of their efforts to reduce the aluminum levels in the L-cysteine formulation.

185. With respect to headspace oxygen, Dr. Baertschi asserts that “Waterman teaches that packaging under nitrogen can reduce headspace oxygen.” (Baertschi Op. Rep., ¶ 81.) While this is generally true, Waterman does not teach what *specific level* of headspace oxygen reduction can be obtained by packaging under nitrogen, let alone what levels are required when reducing aluminum and cystine particulate formation in an L-cysteine formulation for use in TPN solutions. (Waterman at 24.) Dr. Baertschi also alleges that Waterman “discloses a procedure for reducing dissolved oxygen content through the use of a nitrogen or argon sparge” and that “headspace oxygen levels between 3-8% are generally obtainable at most mfg. sites.” (Baertschi Op. Rep., ¶ 81, Ex. B at pg. 5.) This a general recommendation for a generic manufacturing process, and Waterman does not address whether a 3-8% headspace oxygen level is (1) attainable in the specific manufacturing process for an L-cysteine formulation for use in TPN solutions or (2) sufficient to address the stability issues encountered by the inventors while reducing the aluminum levels and managing cystine precipitation in the L-cysteine product. The same is true for Waterman’s suggestion that “if these levels are not attainable, using argon (which is a heavier gas) instead of nitrogen is an option to explore.” (Waterman at 27.)

186. Waterman’s teachings regarding headspace oxygen reduction are missing an important component – the effect of time on the headspace oxygen level. For example, Claim 1 of the ’453 Patent requires that the composition comprise “headspace oxygen that is from about 0.5% v/v to 4.0% v/v from the time of manufacture to about 1 month from manufacture when stored at room temperature.” Waterman provides no guidance on how to achieve and maintain the claimed headspace oxygen levels in an L-cysteine composition over the month period after date of manufacture. Moreover, Waterman teaches nothing connecting the control of headspace oxygen levels to any of the other problems addressed by the claims, including the reduction of aluminum in those products.

**L. Alpaslan Yaman, Engineering Considerations in Sterile Powder Processes, in STERILE PHARMACEUTICAL PRODUCTS: PROCESS ENGINEERING APPLICATIONS (Kenneth E. Avis ed. 1995)**

187. The Yaman reference is a chapter titled “Engineering Considerations in Sterile Powder Processes” in the book “Sterile Pharmaceutical Products: Process Engineering Applications” in 1995. I understand that Eton relied on Yaman in its PGR petitions against the ’453 and ’155 Patents. Yaman was also disclosed to the examiner in prosecution of the ’713, ’795, and ’089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

188. Dr. Baertschi asserts that Yaman “teaches that, for oxygen sensitive drugs (like L-cysteine), blanketing a vial with nitrogen prior to filling and sealing with a stopper can reduce headspace oxygen to between 5 and 15 percent.” (Baertschi Op. Rep., ¶ 86.) He also asserts that Yaman teaches that “[f]or materials with extreme oxygen sensitivity...the final headspace can be reduced to less than 2 percent oxygen.” (*Id.*; *see also id.* at Ex. B, pg. 5.) I disagree that these points are relevant to the L-cysteine solution product. As indicated in the title, the Yaman reference discusses oxygen control for powdered drug products. It does not discuss cysteine,

liquid formulations, or liquid formulations of as L-cysteine for use in a TPN solution. Yaman's focus on powder formulations is important because a liquid formulation will have an equilibrium between dissolved oxygen in the solution and oxygen in the headspace that is different from any equilibrium that might occur between a powder and the headspace. There is nothing in Yaman to suggest that headspace oxygen levels achieved in powdered formulations would also be achieved in liquid formulation, let alone the specific liquid formulation of L-cysteine for use in a TPN solution. Yaman is not in the "same field of endeavor" as "the field of L-cysteine administration and/or pharmaceutical development," as Dr. Baertschi asserts, and in my opinion a POSA would not consult Yaman in seeking to prepare a stable, low aluminum formulation of L-cysteine for use in TPN compositions. (Baertschi Op. Rep., ¶¶ 140, 145.)

**M. Q3D Elemental Impurities: Guidance for Industry (Sept. 2015)**

189. Q3D Elemental Impurities: Guidance for Industry ("Q3D") is a September 2015 FDA guidance that was developed within the Quality Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (Q3D at pg. 4 of PDF.) I understand that Eton relied on Q3D in its PGR petitions against the '453 and '155 Patents. Q3D Elemental Impurities was also disclosed to the examiner in prosecution of the '713, '795, and '089 Patents, and is listed in the "References Cited" list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it.

190. Q3D provides guidance on (1) the evaluation of the toxicity data for potential elemental impurities; (2) the establishment of permitted daily exposure (PDE) for each element of toxicological concern; and (3) application of a risk-based approach to control elemental impurities in drug products. Q3D also provides permitted daily exposure (PDE) limits for parenteral exposure for lead, nickel, arsenic, and mercury. (Q3D at Pb (49), Ni (59), Hg (54-55),

## **CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

As (35)) Lead, arsenic, mercury and nickel are dealt with in Q3D because they are sometimes found as impurities in drug products, but Q3D does not specifically say they are known impurities in L-cysteine products. Q3D does not provide a PDE for aluminum. Q3D also teaches nothing about how to achieve any particular impurities levels that would fall within its guidance.

### **N. Michael J Akers, Sterile Drug Products: Formulation, Packaging, Manufacturing, and Quality (2010)**

191. The Akers reference is textbook titled “Sterile Drug Products: Formulations, Packaging, Manufacturing, and Quality” published in 2010. (ETON-CYST00020954-21110.) Akers was disclosed to the examiner in prosecution of the ’713, ’795, and ’089 Patents, and is listed in the “References Cited” list for each of those patents, so I understand from counsel that the examiner is presumed to have been aware of it. I agree with Dr. Baertschi that Akers “acknowledges that particulate matter in parenteral solutions has been an issue in the pharmaceutical industry since the introduction of injectable preparations” (Akers at 436) and that “parenteral drug products should be inspected for visible particulate matter.” (Baertschi Op. Rep., ¶ 90 (citing Akers at 436, 328).) Dr. Baertschi, however, does not acknowledge in his report that Akers notes with respect to particulate matter that “[t]he particle content of IV fluids in plastic containers has been repeatedly found to be lower than that of glass containers.” (Akers at 436.)

### **O. Other Prior Art References**

#### **1. References That Disclose the Use of L-Cysteine Based on Patient’s Age or Condition**

192. In ¶¶ 91-92 of his Opening Report, Dr. Baertschi provides a list of “exemplary” references that he alleges “disclose and/or teach the use of L-Cysteine based on the demographics of the patient being treated including the age of the patient and/or the condition.” Dr. Baertschi provides no analysis of the individual references, and he makes no allegation that

they teach anything about the formulation of an L-cysteine product for use in TPN solutions, including aluminum levels, impurity levels, oxygen levels, or manufacturing processes.

**2. References That Disclose the Amount of L-Cysteine Delivered In a Parenteral Composition**

193. In ¶ 93 of his Opening Report, Dr. Baertschi provides a list of “exemplary” references that he alleges “disclose the amount of L-Cysteine delivered in a parenteral composition.” Dr. Baertschi provides no analysis of the individual references, and he makes no allegation that they teach anything about the formulation of an L-cysteine product for use in TPN solutions, including aluminum levels, impurity levels, oxygen levels, or manufacturing processes.

**XII. GENERAL OBSERVATIONS REGARDING DR. BAERTSCHI’S ANTICIPATION AND OBVIOUSNESS ARGUMENTS**

**A. Dr. Baertschi Provides No Opinion That the Sandoz Product Is “Stable”**

194. Claim 1 of the ’453 Patent and its dependent claims, and claims 1-3, 27, and 28 of the ’155 Patent and their dependent claims require a “stable” L-Cysteine composition. Dr. Baertschi does not address the “stable” claim limitation in his report or make any attempt to show that the Sandoz Product met that claim limitation.

195. The Patent specification states “[a]s used herein, the term ‘stable’ refers to a 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.” (’453 Patent at 16:40-51.)

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

196. I understand that the parties have agreed that “stable” means 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.” For a composition to contain levels of components for a sufficient period of time to enable the composition to be manufactured, stored, shipped, and clinically administered, the composition must, in my opinion, contain those levels throughout its shelf life. I apply the parties’ construction in my analysis.

197. ELCYS® was approved by FDA with a shelf life of 24 months, [REDACTED]  
[REDACTED] I understand that Sandoz’s prior unapproved versions of cysteine hydrochloride injection also had a 24-month shelf life.

198. A product’s shelf life is set to ensure that the product will contain the specified levels of its components for a sufficient period of time to enable the composition to be commercially manufactured, stored, shipped, and administered in a clinical setting. The purpose of specifying a product’s shelf life is to ensure that the product has retained its characteristics and remains safe and effective when it is ultimately administered to patients.

199. Product development includes *stability* studies to demonstrate that a product will maintain its characteristics throughout its shelf life. Different types of products may have different shelf lives, with some being shorter and some being longer. Because Exela’s ELCYS® product, [REDACTED], and Sandoz’s unapproved products all have 24-month shelf

lives, a POSA would understand and expect, and would have understood and expected in January 2019, that, to be considered “stable,” the product must maintain the specified levels of its components throughout its entire shelf life.

200. If a product with a 24-month shelf life falls outside of the required specifications for any component during that shelf life, for example at nine months, that product would not be considered stable.

201. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

203. Thus, in my opinion, Dr. Baertschi has not shown that the Sandoz product (let alone one that was offered for sale and/or sold) meets the “stable” limitation of the asserted ’453 and ’155 Patent claims.

**B.** [REDACTED]

204. [REDACTED]

[REDACTED]

205. [REDACTED]

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| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
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**C. Dr. Baertschi’s Opinions on the Scope of “About” Are Unsupported**

211. The specification of the Patents-in-Suit explains that “the term ‘about’ is used to provide flexibility to a numerical range endpoint by providing that a given value may be ‘a little above’ or ‘a little below’ the endpoint.” (’453 Patent at 57:66–58:18.) It goes on to provide examples of the variation that the term “about” may encompass for different parameters, explaining that “the term ‘about,’ as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of  $\pm 20\%$ ,  $\pm 10\%$ ,  $\pm 5\%$ ,  $\pm 1\%$ ,  $\pm 0.5\%$ , or even  $\pm 0.1\%$  of the specified amount.” (*Id.* at 58:28–39.)

212. I understand that Exela proposed that the term “about” be construed to mean “approximately” and that Eton proposed no construction and argued that the term was indefinite.

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[REDACTED]

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

213. I agree that “approximately” is generally understood to be the ordinary meaning of the term “about” in this field, and I believe that a skilled artisan can reasonably understand its scope in the context of the term’s use.

214. In Dr. Baertschi’s report, he applies a range of plus or minus 20% to all claim limitations that use the term “about.” (*See, e.g.*, Baertschi Op. Rep., ¶ 172-74.)

215. Dr. Baertschi goes further and also states that he “understand[s] that, according to the specification of the Asserted Patents, a numerical value or range is intended to be understood as encompassing a range of plus or minus 20%, whether or not the term ‘about’ is explicitly recited.” (*Id.* at ¶ 173.) Thus, Dr. Baertschi concludes that “it is my understanding that whenever a measurable value is recited in the claims of the ’453 Patent, it is intended to be understood to encompass a range of plus or minus 20%.” (*Id.* at ¶ 174.) He applies the same understanding to all the Patents-in-Suit.

216. I disagree with this reading of the claims. I do not believe that a POSA would understand the scope of “about” to be plus or minus 20% of all parameters across the board. Nor do I agree that a person of skill in the art would apply such a range even to values that do not use the term “about.” I do not read the discussion of “about” in the specification to suggest that Dr. Baertschi’s reading is the correct, or even a reasonable, reading of the term within the claims.

217. In my opinion, the different potential ranges discussed in the specification for “about”—“variations of  $\pm 20\%$ ,  $\pm 10\%$ ,  $\pm 5\%$ ,  $\pm 1\%$ ,  $\pm 0.5\%$ , or even  $\pm 0.1\%$  of the specified amount” (*id.* at 58:28–39)—are simply examples of the potential scope of the term for different parameters. The variation reflected in the use of “about” is not the same for every parameter. Instead, a POSA would understand that the variation for a given parameter depends on factors such as the batch-to-batch and measurement variability of the parameter, the magnitude of the

**CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER**

parameter, and the criticality of the parameter. These types of factors help to put the variable in context for the POSA, and that context would inform the POSA's view as to the appropriate scope of the term "about" for each of the parameters in the claims.

218. I do not believe that a POSA would treat plus or minus 20% as a one-size-fits-all meaning for "about," and nothing in the specification suggests otherwise. Indeed, Dr. Baertschi's reading of the term appears to ignore all the other exemplary variations set forth in the specification. If a POSA would apply 20% variation across the board, then those other values in the specification would be meaningless.

219. Dr. Baertschi applies his  $\pm 20\%$  understanding of "about" to various limitations in the claims. For example, he opines that the limitation requiring "less than about 150 ppb of aluminum for at least about 12 months from the time of manufacture of the solution" appearing in claim 1 of the '713 Patent would "encompass a product with less than about 180 ppb (20% more than the recited 150 ppb aluminum) 9.6 months (20% less than the recited 12 months) after its date of manufacture." (Baertschi Op. Rep., ¶ 120.) I disagree with that reading.

220. For example, in my opinion, a POSA would not read "about 12 months" to encompass 9.6 months. First, time can be precisely measured, and is not affected by any batch-to-batch variation. A sample taken at 9.6 months (i.e., 9 months and 18 days, if talking about a 30-day month) may well be "about" 10 months, but would not be considered "about" 12 months in the art. Second, Dr. Baertschi's reading does not make sense in the context of FDA-regulated injectables, which a POSA would understand the claimed L-cysteine products to be. A POSA would understand that 0, 3, 6, 9, 12, 18 and 24 months are typical intervals at which product testing is done and stability data submitted to FDA. Submitting data from aluminum testing, for

example, done at 9.6 months for the 12-month stability interval would be regarded as unacceptable.

221. Moreover, the way Dr. Baertschi applies his construction of “about” stretches the meaning even beyond this mechanical application of 20%. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

222. I also disagree with Dr. Baertschi’s use of  $\pm 20\%$  with respect to aluminum. The Asserted Patents discuss in detail the importance of limiting and controlling, over time, the levels of aluminum and other undesirable and potentially unsafe impurities. In that context, a POSA would not read “about” in the aluminum limitations as permitting a high level of variation ( $\pm 20\%$ ) for the claimed aluminum ceiling—for example, “less than about 150 ppb of aluminum” extending to 180 ppb, as Dr. Baertschi contends. Rather, a POSA would apply a much lower variance to account for the criticality of aluminum in the context of the invention. Moreover, the specification of the Asserted Patents explains that the compositions of the invention contain “no more than 250 ppb, preferably about 120 ppb, or lower, of Aluminum. These compositions with no more than 120 ppb of Aluminum, and in certain embodiments, about 120 ppb, or 100 ppb, or 80 ppb, or 60 ppb, or 50 ppb, or 20 ppb, or 10 ppb or 5 ppb or 1.0 ppb, or any suitable subrange

## CONFIDENTIAL— PURSUANT TO PROTECTIVE ORDER

encompassing the specific values, *in units of 5 ppb*, permit great flexibility with respect to the amino acid supplementation for TPN preparations.” (’453 Patent at 7:50-59 (emphasis added.)) The reference to units of 5 ppb further suggests that only a small amount of variation is permitted with respect to aluminum content.

223. Further, the specification of the Asserted Patents refers to the use of “art-known methods” to “evaluate the elemental levels” of materials that may leach or be extracted into the L-cysteine product. (’453 Patent at 27:12-28.) It lists ICP-MS as one such technique, and Example 9 measures elemental leachables, including aluminum, by ICP-MS. (*Id.* at 52:36-57:15.) A POSA would understand that the general measurement variation for a technique like ICP-MS would be around 5%.<sup>74</sup>

224. Thus, in my opinion, Dr. Baertschi’s suggestion that a POSA would understand the variation permitted by “about” in conjunction with aluminum content to be  $\pm 20\%$  is not consistent with how a POSA would understand the term.

225. I also disagree with Dr. Baertschi’s suggestion that even values not containing the term “about” should be read as if they have it, and that the same variation (plus or minus 20%) should be applied. In my opinion, a POSA would understand, as the specification suggests, that the term “about” is intentionally used to provide flexibility to a specified value and allow that value to be a little above or a little below its reported magnitude, i.e., approximately rather than exact. Similarly, a POSA would understand that a value that is not intentionally preceded by the term “about” would not be governed by that same flexibility.

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<sup>74</sup> Harigaya et al., “Determination of Aluminum in Large Volume Parenteral Drug Products Used in Total Parenteral Nutrition Therapy by ICP-MS with a Dynamic Reaction Cell,” *Chem. Pharm. Bull.* 56(4) 475-479 (2008.)

**D. Dr. Baertschi Provides No Evidence That the Sandoz Product or Any Alleged Combination Meets The Headspace and Dissolved Oxygen Limitations**

226. Claims 1 of the '453 Patent and its dependent claims require (1) headspace oxygen that is from about 0.5% v/v to 4.0% v/v from the time of manufacture to about 1 month from manufacture when stored at room temperature, and (2) dissolved oxygen present in the carrier in an amount from about 0.1 parts per million (ppm) to about 5 ppm from the time of manufacture when stored at room temperature.

227. Dr. Baertschi provides no evidence that the Sandoz product had the claimed headspace and dissolved oxygen levels at the time of manufacture. With respect to headspace oxygen, Dr. Baertschi relies on the statement in the Sandoz Label that it has “[a]ir replaced with nitrogen.” (*See, e.g.* Baertschi Op. Rep., Ex. B, pg. 5.) In lieu of evidence of the headspace oxygen levels in the Sandoz Product, Dr. Baertschi points to statements in the Yaman and Waterman references as examples of headspace oxygen levels that *can* be obtained (*id.*), but these references are inapplicable for the reasons explained above in Section XI. A POSA would not combine the Sandoz Product with Yaman or Waterman to arrive at the claimed headspace oxygen level at the time of manufacture.

228. Dr. Baertschi’s attempt to demonstrate dissolved oxygen levels in the Sandoz Product at the time of manufacture is even feeble. In the absence of information about the actual dissolved oxygen levels in the Sandoz Product, Dr. Baertschi relies on the Sandoz Label statement regarding replacing air with nitrogen. He alleges that “[a] person of ordinary skill would know that head space and dissolved oxygen reach an equilibrium, and thus removing head space oxygen also results in minimizing dissolved oxygen.” (Baertschi Op. Rep., Ex. B, pg. 6.) While I agree that the headspace and dissolved oxygen levels will reach an equilibrium and that removing headspace oxygen will likely decrease dissolved oxygen levels, without knowing the

initial headspace and dissolved oxygen levels one cannot determine the headspace or dissolved oxygen levels at equilibrium. Dr. Baertschi then points to statements in the Butler reference as an example of dissolved oxygen levels that *can* be obtained, but Butler is inapplicable for the reasons explained above in Section XI.J. Dr. Baertschi does not appear to allege an obviousness combination based on Butler, but even if he did, a POSA would not have been motivated to combine the Sandoz Product with Butler to arrive at the claimed headspace oxygen level at the time of manufacture, nor would she have had any expectation of success in doing so.

229. Further, Dr. Baertschi does not even attempt to address time's effect on the headspace and dissolved oxygen level limitations. Claim 1 requires that the L-cysteine composition maintain the claimed headspace and dissolved oxygen levels "from the time of manufacture to about 1 month from manufacture." As Dr. Baertschi acknowledges, L-cysteine reacts with oxygen to form the degradation product cystine. (Baertschi Op. Rep., ¶ 74.) The sealed vial of the L-cysteine drug product has two possible sources of oxygen for the reaction – gaseous oxygen in the headspace and dissolved oxygen in the liquid phase. Over time as L-cysteine is oxidized to cystine, oxygen will be consumed and the headspace and dissolved oxygen levels will decrease. Dr. Baertschi does not acknowledge that the headspace and dissolved oxygen levels will change over time or discuss the rate at which they will change, let alone provide evidence that the headspace and oxygen levels in the Sandoz Product remained within the claimed ranges for the required time period.

**E. Dr. Baertschi Treats Each Claim Limitation Independently Rather Than Addressing Whether a POSA Would Have Had a Reasonable Expectation of Success in Achieving the *Claimed* Invention as a Whole**

230. Dr. Baertschi's opinions contain another fundamental error in that he treats each claim limitation as an independent variable that can be changed without affecting any of the other variables relevant to an L-cysteine hydrochloride composition. In my opinion, this

piecemeal approach misses the point that, in reality, the development of this product required addressing several inter-dependent variables, including aluminum levels, oxygen levels, impurity levels, particulates, and overall formulation stability. The Asserted Claims include limitations directed at multiple of these variables, with some including all of them. The specification of the Asserted Patents discusses the interplay that the inventors observed between the different variables and how addressing one led to unexpected issues with another. ('453 Patent at 4:59-5:9.) Dr. Baertschi does not account for these inter-dependent variables in reaching his opinions.

231. To illustrate his piecemeal approach, Dr. Baertschi points to Exela's representations during the prosecution of the '453 Patent that "it was only after the present inventors addressed and overcame the problem of Aluminum that they were confronted with the problem of stability and precipitate formation" and "[p]ut another way, the art did not know about the additional problems." (Baertschi Op. Rep., ¶ 102.) According to Dr. Baertschi, these representations were incorrect because "the tendency for L-cysteine to oxidatively degrade was known long before this." (*Id.*) But a POSA would understand the point of Exela's representations to the Examiner was not that they learned that L-cysteine oxidatively degrades. The point was that when the inventors reduced aluminum by using a plastic vial with previously acceptable oxygen controls, they unexpectedly introduced the problem of oxygen migration into the formulation, which ultimately led to cystine precipitation. That is, following the prior art recommendations to "use plastic", they ran into oxidation problems that caused a higher level of L-cysteine oxidation and the effect of aluminum levels on cystine precipitation, neither of which were expected. Thus, they had to deviate from the prior art's suggestions to address both the aluminum and oxidation issues simultaneously.

232. The oxygen sensitivity of L-cysteine is not the only variable that a POSA would need to consider to arrive at the claimed inventions. As discussed above in Section X, the amount of aluminum leached by a drug product from its packaging is dependent on multiple factors, including accessibility of aluminum, affinity of the drug for aluminum, pH, time of contact with packaging, and temperature. Any changes to those factors will, in turn, affect other variables in the drug product. For example, a POSA would understand that changing the pH can affect at least (1) the amount of aluminum leached from a glass container (Jenke/Biavanit/Bohrer (Part III)); (2) the reaction of L-cysteine with oxygen to form cystine; (3) the binding of aluminum by cysteine and cystine (Bohrer 2006); and (4) the solubility of cystine (Okabe.) Yet the POSA would not know how any particular change would affect the other variable until he tried it.

233. In addition, a POSA would understand that oxidation of cysteine to cystine may affect the amount of aluminum leached from the container. (Bohrer 2006.) The presence of aluminum may also have a stabilizing effect on the precipitation of cystine, as the inventors learned when they reduced the amount of aluminum in the packaging by switching to plastic vials and encountered issues with increased precipitation and product failure. (*See, e.g.*, '453 Patent at 5:4-9.) While the POSA would appreciate at a macro level that those variables are interrelated, the lack of data on the interplay between these many variables and how they would be affected at the strongly acidic pH of the L-cysteine formulation would prevent the POSA from predicting the effects at the micro level. In my opinion, there are too many competing and interrelated variables in this system to be able to reasonably predict *a priori* how to adjust all of the variables at once to arrive at a stable L-cysteine composition that is collectively low in aluminum levels, low in impurity levels and substantially free from particulates.

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234. Dr. Baertschi asserts that “because there are a finite number of identified, predictable solutions to individual aspects of the problem, a POSA would have had good reason to pursue the known options within his or her technical grasp.” (Baertschi Op. Rep., ¶ 143.) However, Dr. Baertschi is only able to identify the relevant “individual aspects of the problem” with the benefit of hindsight. Moreover, while Dr. Baertschi asserts that there are a finite number of predictable solutions for each of the independent problems faced by the inventors, there are a large number of unpredictable solutions to the multi-faceted problem, and each potential solution can have an impact on many of the variables in the formulation. Dr. Baertschi makes no attempt to link the independent solutions or show why a POSA would identify any particular combination of solutions to solve that multi-faceted problem.

### XIII. OPINIONS REGARDING THE VALIDITY OF THE ASSERTED PATENTS

#### A. Objective Indicia

235. As noted above, I understand that objective factors must be considered in assessing whether an invention would have been obvious in light of the prior art. (*See* Section VI.B.) As set forth below, the following objective factors support the nonobviousness of the Asserted Claims of the Patents-in-Suit: fulfillment of a long felt and previously unmet need by ELCYS®, which embodies the Asserted Claims, unexpected results, and commercial success of ELCYS®.

##### 1. Long Felt and Unmet Need

236. I understand that a long felt, but unresolved need for the solution offered by the invention is evidence of non-obviousness because it is reasonable to infer that the need would not have persisted had the solution been obvious.

237. I have read the Rebuttal Expert Report of Dr. Robert Kuhn and understand he has opined that Exela’s ELCYS® product, which embodies the inventions claimed in the Asserted

Patent claims (*see* Schoneich Opening Report at Section X), fulfilled a long felt, but previously unmet need for an L-cysteine component of TPN solutions with low levels of aluminum. (*See* Rebuttal Expert Report of Dr. Robert Kuhn at Section IV.) Thus, as I understand Dr. Kuhn's opinion on long-felt need, it is the characteristics that result from the inventions claimed in the Asserted Patents—namely, an L-cysteine formulation for use in TPN that has very low levels of aluminum, and maintains those low levels for the duration of the product's shelf life without introducing dangerous particulate matter or other stability problems—that has enabled the ELCYS® product to fulfill this long felt but unmet need. Based on my knowledge of the prior art and the history of high aluminum L-cysteine products for use in TPN solutions, I agree with Dr. Kuhn that ELCYS®, the first and only FDA-approved L-cysteine product that is labeled with an aluminum level of no more than 120 µg/L of aluminum, met this long felt and unmet need.

## **2. Unexpected Results**

238. I understand that evidence the claimed invention exhibits some superior property or advantage over the prior art that a POSA would have found surprising or unexpected weighs in favor of non-obviousness.

239. A POSA at the time of invention would not have predicted that successfully manufacturing a stable, low-aluminum L-cysteine product would require more rigorous controls of headspace and dissolved oxygen levels and impurity levels such as cystine, and pyruvic acid, in addition to limiting the aluminum level in the solution.

240. The inventors' goal was to create a low aluminum L-cysteine product for use in TPN solutions. Multiple prior art references suggested that the aluminum contamination in TPN components could be reduced by repackaging the component solution in plastic vials. (*See* Sections X and XI above citing, for example, Hernandez-Sanchez, Yokel, Bohrer (Part II), Frey,

Beaney, Raspaud.)<sup>75</sup> The use of TPN component solutions packaged in plastic containers has also been supported by regulatory authorities in the United States<sup>76</sup>, Canada<sup>77</sup> and the UK.<sup>78</sup>

241. However, when the inventors attempted to store L-cysteine compositions in plastic vials, although the initial aluminum levels were low, the composition failed because of stability issues, including the unanticipated formation of cystine precipitates. These stability issues would have been especially surprising because a POSA would know that “[t]he particle content of IV fluids in plastic containers has been repeatedly found to be lower than that of glass containers.” (Akers at 436.) As a result, the inventors discovered that “the problems of safety, purity and stability are results not simply or directly from the level of Aluminum, but are also intertwined with dissolved oxygen levels in the composition and oxygen in the headspace as well as certain heavy metals and certain ions that may leach or be extracted out of the container

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<sup>75</sup> See also Quagliaro, V.A. et al. Aluminum in Albumin for Injection. *Parent. Sci. Technol.* 1988, 42 (6), 187-190. (Quagliaro also demonstrated that that the use of polyethylene vials resulted in no aluminum accumulation.); Lima-Rogel V et al., Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico. *J. Parenter. Enter. Nutr.* 2016;40(7):1014 (ExelaCYS00070668.)

<sup>76</sup> Federal Register: Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition. 65(17): 4103-4111 Jan. 26, 2000 (“A manufacturer can reduce toxicity by several routes, including using containers made of different materials”).

<sup>77</sup> Pharmaceutical Partners of Canada: Dear Healthcare Professional Letter; Calcium Gluconate Injection – 10% - Important Information Concerning the Presence of Aluminum – For Health Professionals. July 20, 2011. [https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc\\_sc/2011/14639a-eng.php](https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc_sc/2011/14639a-eng.php) (“To address the issue of aluminum toxicity, PPC is investigating alternate processes and alternate container materials, such as plastic vials, to determine if they will reduce the amount of aluminum present in the product”)

<sup>78</sup> Drug Safety Update; Calcium gluconate injection in small-volume glass containers: new contraindications due to aluminum exposure risk. Published 11 December 2014. (“To limit the exposure of patients to aluminum, especially those with impaired renal function and in children, calcium gluconate injection in small-volume glass containers is also contraindicated in the preparation of total parenteral nutrition (TPN) solutions. The Group noted that calcium gluconate injection packaged in plastic containers is not likely to present a similar risk as the containers do not contain high levels of aluminum,” 2014) <https://www.gov.uk/drug-safety-update/calcium-gluconate-injection-in-small-volume-glass-containers-new-contraindications-due-to-aluminium-exposure-risk>

closure.” (’453 Patent at 4:38-43.) They further hypothesized that “precipitation may have been exacerbated by reduction in Aluminum since Aluminum in solution may have a stabilizing effect. Consequently, removing Aluminum may have the unintended consequence of increased precipitation and product failure in the presence of even small amounts of oxygen in the container.” (*Id.* at 5:4-9.)

242. This intertwined nature of the aluminum, headspace and dissolved oxygen levels, and cystine particulates was serendipitously confirmed by independent researchers at Avadel Pharmaceuticals. According to Avadel’s NDA, it manufactured engineering/feasibility/GMP scale batches of L-cysteine hydrochloride solution under oxygen controls that called for blanketing with nitrogen but no nitrogen sparge or monitoring of dissolved oxygen levels. (ExelaCYS00036346 at 36367-68, 36372, and 36374.) Avadel’s manufacturing process called for packaging the GMP batches in Schott Type I+ vials, but because of a supply issue, the batches were manufactured in a combination of Type I and Type I+ vials. (*Id.*, *see also* Table 19.) The batches manufactured in Type I+ vials met specification of no more than the 145 ppb aluminum after 12 months of long term storage (5 ppb or less), but those manufactured in the Type I vials exceeded the specification (221-274 ppb). (ExelaCYS00036165 at 36199-202, 36215-219.) However, during visual inspection of the Type I+ batches, Avadel observed that a large number of vials exhibited visible particulates, which were not observed in the Type I batches. The presence of these particulates lead to product failure and high rejection rates in the Type I+ batches. (ExelaCYS00036346 at 36375-76; ExelaCYS00036165 at 199-208; ExelaCYS00036346 at 36375; Table 23.) Avadel investigated the particulates and identified them as cystine free base dimer. (ExelaCYS00036346 at 36381-82.) Avadel also determined that the formation of these particulates was influenced by both the pH of the L-cysteine solution

and the oxygen controls imposed during the manufacturing process. (ExelaCYS00036346 at 36383-86.) From this investigation, Avadel concluded that “the apparent kinetics and equilibrium chemistry of the various cysteine and cystine species is complicated and not always predictable in a practical setting.” (ExelaCYS00036346 at 385-86.)

243. In my opinion, the inventors’ results were unexpected because the prior art did not teach or suggest how aluminum reduction in L-cysteine products would affect the other variables in the product. For example, the prior art did not connect reducing the aluminum level in the product with the precipitation of cystine in the product. (See Section XI.) Moreover, as discussed above in Section XII.E, the POSA would appreciate at a macro level that the total variables are interrelated, but the lack of data on how these many variables would be affected at the strongly acidic pH of the L-cysteine formulation would prevent the POSA from predicting the magnitude of any of those effects at the micro level. In my opinion, there are too many competing and interrelated forces in this system to be able to predict *a priori* how to adjust all of the variables in tandem to arrive at a low aluminum, stable L-cysteine composition with low levels of impurities. Instead, attempting to develop a stable, low aluminum-containing cysteine product would have been a trial-and-error proposition with no reasonable expectation of success with any particular approach.

244. For at least these reasons, in my opinion Exela’s invention of the stable, low aluminum L-cysteine product that is claimed in the Asserted Patents and commercially sold as ELCYS® constitutes unexpected results. It is also my opinion that those unexpected results can be attributed to the inventive aspects of the claimed invention—namely, an L-cysteine formulation for use in TPN that has very low levels of aluminum, and maintains those low levels

for the duration of the product's shelf-life without introducing dangerous particulate matter or other stability problems.

245. I understand Exela's ELCYS® product, which is labeled as containing no more than 120 ppb of aluminum, is labeled as being free of visible particulate matter, and has a 24-month shelf life, embodies the inventions claimed in each of the Asserted Patent claims. (*See Schoneich Opening Report at Section X.*)

### **3. Commercial Success**

246. I understand that commercial success is evidence of non-obviousness because it is reasonable to infer that commercial success is an indicator of a demand that was not met by pre-existing products. That is, the fact that a product can generate significant sales and capture market share is an indication that the product offers characteristics or features that are valued by consumers and not present in other products.

247. I have read the Expert Report of Dr. Robert Maness, and understand has opined that Exela's ELCYS® product, which embodies the inventions claimed in the Asserted Patents, experienced commercial success. (*See Rebuttal Expert Report of Dr. Robert Maness at Section VI; see also Schoneich Opening Report at Section X.*) Thus, as I understand Dr. Maness's opinion on commercial success, it is the characteristics that result from the inventions claimed in the Asserted Patents—namely, an L-cysteine formulation for use in TPN that has very low levels of aluminum, and maintains those low levels for the duration of the product's shelf life without introducing dangerous particulate matter or other stability problems—that has enabled the ELCYS® product to achieve this commercial success.