

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEXUS PHARMACEUTICALS, LLC,
Petitioner

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner

Case PGR2020-00064
Patent No. 11,642,370

DECLARATION OF DR. DENNIS R. JENKE, Ph.D.

EXELA 2001
Nexus Pharmaceuticals v. Exela Pharma Sciences
PGR2024-00016

I, Dr. Dennis R. Jenke, declare as follows:

1. My name is Dennis R. Jenke. I am over the age of twenty-one (21) years, and I am competent to testify to the matters stated herein.

2. I have been asked by Fish & Richardson, P.C. on behalf of Exela Pharma Sciences, LLC (“Exela”) to provide this declaration in the matter of the Post Grant Review of U.S. Patent No. 11,642,370 (the “’370 patent”).

3. I am being compensated for my work in connection with this PGR proceeding at a rate of \$550/hour for preparation of my declaration. My compensation is not in any way contingent on the substance of my opinions or the outcome of these proceedings.

I. ASSIGNMENT

4. I have been asked by counsel for Exela to review U.S. Patent No. 11,642,370 (the “’370 patent”) and Nexus’ Petition for Post Grant Review (PGR2024-00016). I have been asked to comment on my previous opinions regarding the non-obviousness of patents related to the ’370 patent provided in *Exela Pharma Sciences, LLC v. Eton Pharmaceuticals, Inc.* (D. Del. C.A. No. 20-365-MN). I have also been asked to comment on the ability of a person of

ordinary skill in the art (POSA) to practice the claims of '370 patent based on the disclosure in the specification.

5. This declaration sets forth the basis and reasons for my opinions from the perspective of a Ph.D. Analytical Chemist with 40 years of experience developing and characterizing aqueous drug formulations and their associated container-closure systems.

II. EXPERIENCE AND QUALIFICATIONS

6. I received a Bachelor of Arts 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.

7. 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.

8. 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.

9. In addition to my work experience, I served 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 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).

10. A more complete recitation of my professional background and expertise is provided in my curriculum vitae, attached here as **Exhibit A**.

III. PERSON OF ORDINARY SKILL IN THE ART

11. From my reading of the '370 Patent, one of ordinary skill in the art would have attained a Pharm.D. or M.S. or Ph.D. in chemistry, chemical engineering, pharmaceutical sciences, or a related field, and have three or more years of experience in developing and commercializing aqueous drug formulations. Practical experience, either in industry or academia, can be substituted for a M.S., Ph.D. or Pharm.D. degree, and additional education can compensate for less practical experience.

12. Under this definition, I consider myself to meet and/or exceed the qualifications of both a person of skill in the art and a collaborator of those skilled in the art as of 2023-2024.

13. I understand that Dr. Confalone has defined a POSA broadly as someone who would have had education and work experience in the fields of pharmaceutical drug product formulation and development.

14. Based on my 40 years of experience in the pharmaceutical industry, drug product development, registration, and commercialization (and drug product discovery) are typically conducted by a team of individuals, each with complementary skills, knowledge, and roles. These multi-disciplinary drug

development teams commonly include members with expertise in drug formulation, organic chemistry, analytical chemistry, process chemistry, packaging, extractables and leachables (E&L), toxicology, regulatory affairs, manufacturing operations, and marketing and business development. As it is likely the case that no single team member has a mastery of all disciplines involved in developing, registering, and commercializing a drug product, the business reality is that drug product development is rarely accomplished by a single individual working independently.

15. From my perspective, this collaborative and multi-disciplinary aspect should be reflected in the description of the person of ordinary skill in the art for the '370 patent.

IV. Technical Background

A. Aluminum Contamination of Parenteral Drugs

16. 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. 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 drug products containing all of a patient's nutrients, including amino acids, electrolytes, carbohydrates, and lipids. I provided

an overview the history of aluminum contamination in parenteral drugs and the factors that influence aluminum contamination in my previous expert report.¹

B. Aluminum Contamination in Cysteine Hydrochloride Products

17. Cysteine-hydrochloride injection products are TPN components that were identified long ago as a major contributor to aluminum contamination of TPN solutions.² Prior to the invention of the Asserted Patents, my understanding is that the only cysteine hydrochloride injection 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.

18. Cysteine hydrochloride injection products have several features that in my opinion make them especially susceptible to aluminum contamination.

a. Cysteine Has High Affinity for Aluminum.

19. The active ingredient in L-cysteine hydrochloride injection products is cysteine hydrochloride monohydrate, a salt of the sulfur-containing amino acid cysteine. (Ex. 1001 ('370 Patent) at 6:36-46.)

¹ Ex. 2019 (Jenke Reb. Rpt.), ¶¶ 84-114.

² See, e.g., Ex. 2022 (Driscoll, M; Driscoll, D.F., Calculating aluminum content in total parenteral nutrition admixtures. Am. J. Health-Syst. Pharm. 2005:62:312-5); Ex. 1006 (Hernandez-Sanchez) at 231.

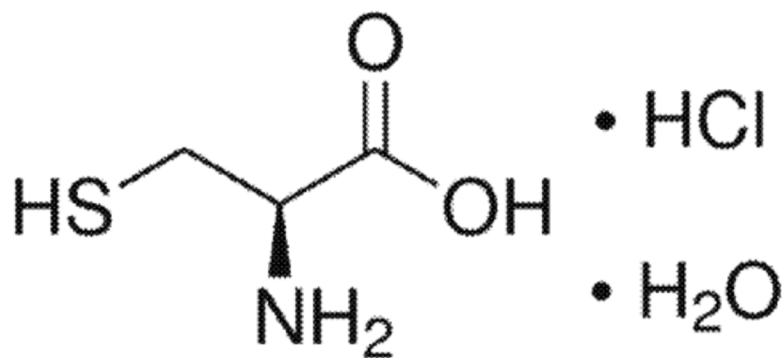


Figure 1. Cysteine Hydrochloride Monohydrate

20. Previous research by Bohrer identified cysteine as one of several amino acids that leach aluminum from glass.³ She estimated that cysteine's affinity for aluminum was comparable to well-known complexing agents such as citrate and oxalate,⁴ and noted that cysteine was one of only two amino acids whose affinity for aluminum was so great that it continued to extract aluminum over the entire study period without reaching equilibrium.⁵

b. L-Cysteine Oxidation to Cystine

21. Cysteine is an oxygen sensitive molecule that can be oxidized to form the disulfide molecule cystine (Figure 2.) Cystine is thus a degradation-related

³ Ex. 1008 (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.))

⁴ See Ex. 2019 (Jenke Reb. Rpt.) at Section X.C, Figure 2.)

⁵ Ex. 1008 (Bohrer (Part II)) at 106-107, Figure 2.

impurity observed in L-cysteine hydrochloride injection products (Ex. 1001 ('370 Patent) at 6:63-7:5.)

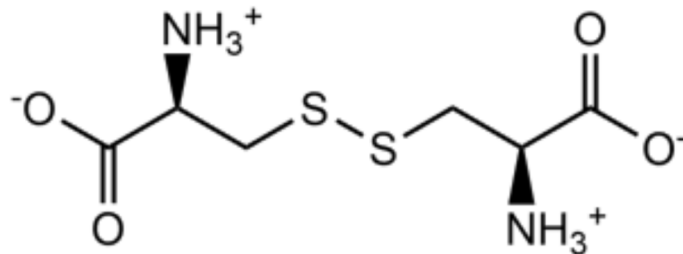


Figure 2: Cystine, An Oxidative Degradation Product of Cysteine

22. Cystine was also identified by Bohrer as an amino acid that leaches aluminum from glass.⁶ In 2006, Bohrer conducted additional studies on the affinity of cysteine and cystine for binding aluminum and demonstrated that

⁶ Ex. 1008 (Bohrer (Part II)) at 106-107, Figure 2.

cystine is a stronger aluminum-complexing agent than cysteine (Figure 3.)⁷

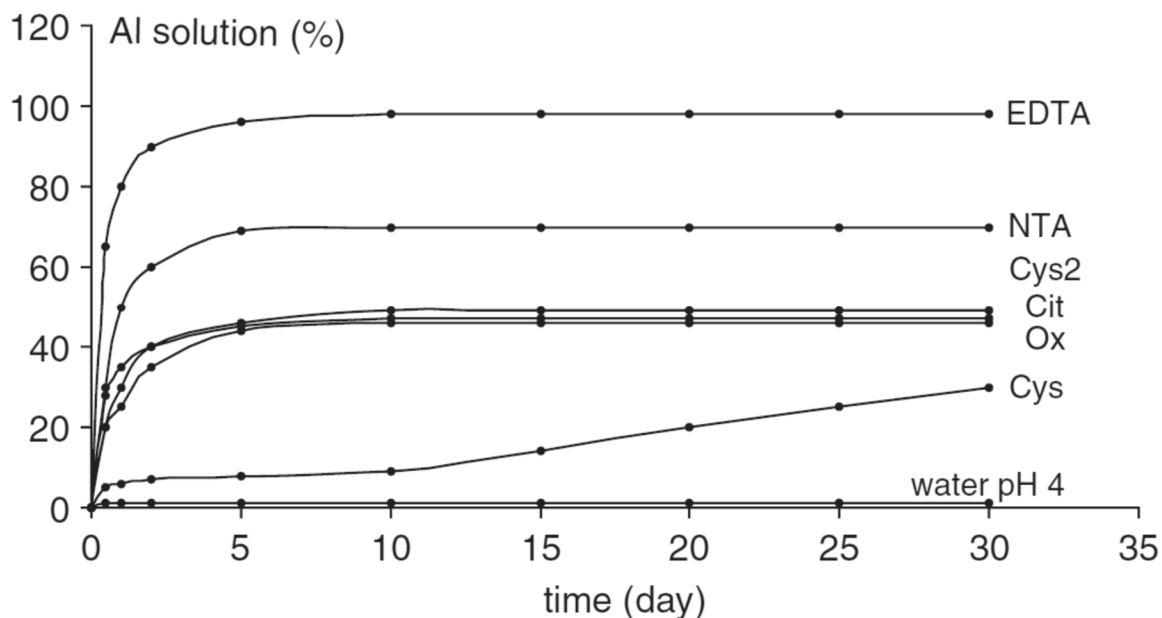


Figure 3. Aluminum extracted from an Al^{3+} -form cation exchanger by the action of ligands as a function of the time. Cys2 is cystine and CYS is cysteine.

23. Bohrer also studied the effects of oxygen on the aluminum leaching abilities of cysteine (Figure AA.)⁸ In the absence of oxygen, aluminum leaching into the cysteine solution stopped increasing after 7 days, as it did for solutions containing other ligands. In the presence of oxygen, however, aluminum levels continued to increase in the cysteine solution up to 100 days (or more). Bohrer

⁷ Ex. 1011 (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.))

⁸ *Id.* (Bohrer (2006)) at 997, Supplemental Figure B.

attributed the increased amount of leached aluminum to the oxidation of cysteine into cystine, a stronger complexing agent than cysteine.

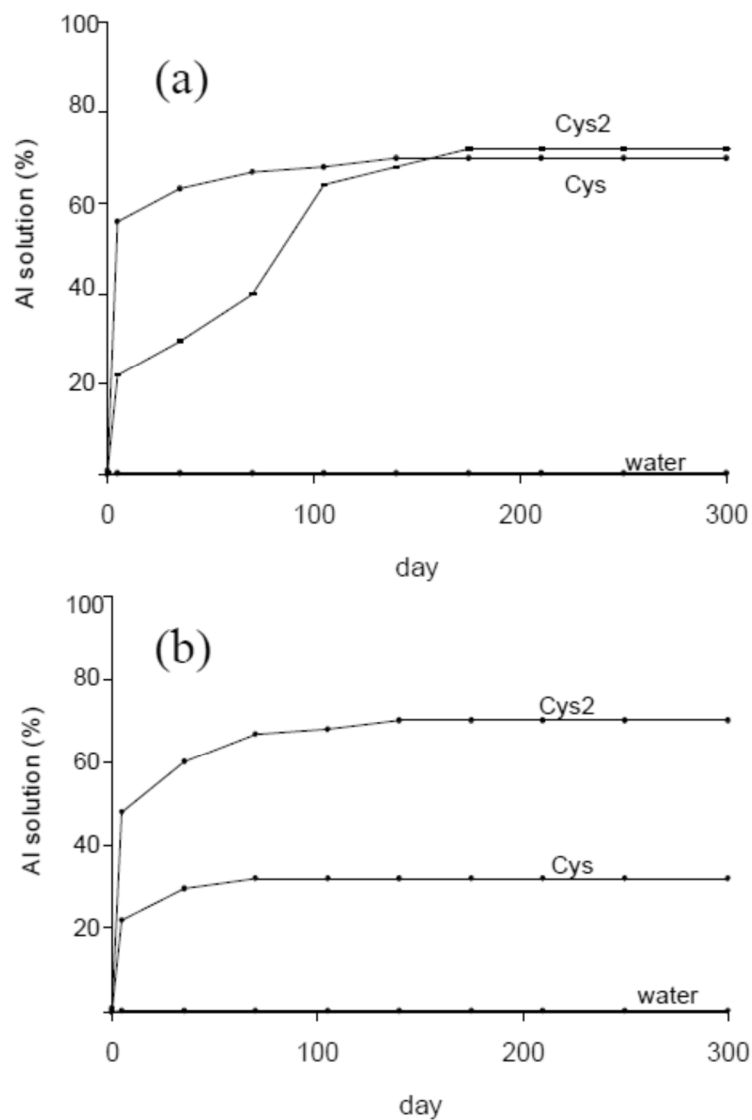


Figure AA. Aluminum extracted from an Al³⁺-form cation exchanger by action of cysteine (Cys) and cystine (Cys2) solutions in the presence (a) and absence (b) of oxygen.

c. L-Cysteine Hydrochloride Injection Products are Strongly Acidic

24. Cysteine hydrochloride injection products are strongly acidic, with a pH range of 1.0 to 2.5.⁹ 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.¹⁰ For perspective, a cysteine hydrochloride solution with a pH of 1.0 is 1,000,000 times stronger as an acid than is a neutral solution of pH 7.0. Acidic solutions are understood to leach aluminum from glass via ion exchange, but there is a lack of data on the aluminum leaching behavior of solutions at pH less than 6, let alone at strongly acidic pHs between 1.0 and 2.5.¹¹

25. In addition, Bohrer determined that formation of aluminum complexes of cysteine and cystine are pH-dependent.¹² However, Bohrer only studied the formation of those complexes at pH values of approximately 3 to 11.

C. Reducing Al in Cysteine Hydrochloride Product Was Multidimensional Problem

26. As I explained during my trial testimony in Exela's previous litigation against Eton Pharmaceuticals, "the problem of developing a stable L-

⁹ See, e.g., Ex. 2004 (ELCYS® Label)

¹⁰ See, e.g., Ex. 2023 (Roethlisberger, D.; Mahler, H.C.; Altenburger, U. Pappenburger, A. If Euhydric and Isotonic Do Not Work, What Are Acceptable pH and Osmolality for Parenteral Drug Dosage Forms? *Journal of Pharmaceutical Sciences* 106: 446-456 (2017)) at Table 2 (identifying SVPs with pH values of 2.55 to 4.75 as "extreme".)

¹¹ See Ex. 2019 (Jenke Reb. Rpt.) at ¶ 113.

¹² Ex. 1011 (Bohrer (2006)) at 996-997.

cysteine formulation is a multidimensional problem where several of the dimensions are interconnected.”¹³

27. As discussed in my previous expert report, 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.

28. In addition, a POSA would understand that oxidation of cysteine to cystine may affect the amount of aluminum leached from the container.¹⁴ 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

¹³ Ex. 2020 (Day 3 Trial Tr.) at 582:13-16.

¹⁴ See Ex. 1011 (Bohrer (2006)).

precipitation and product failure.¹⁵ 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, low in pH, and substantially free from particulates.

29. Further, “the impact or the mechanism by which time and temperature influences leaching is different than the mechanism by which the solution impacts leaching, but the combined effect, the effect that dictates how much aluminum is actually in the product is caused by the interacting phenomenon of both the solution and time and temperature.”¹⁶

30. In the prosecution history of related U.S. Patent No. 10,933,089, 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

¹⁵ See, e.g., Ex. 1001 (’370 Patent) at 5:20-25.

¹⁶ Paper 1 at 34 (citing Jenke trial testimony, Ex. 2020 (Day 3 Trial Tr.) at 586:7-21.

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.”¹⁷ 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.

31. I note that this assessment is looking at the problem *prospectively* based on the knowledge of the POSA at the time of the invention without the help of the patentee’s insights, which is much different than looking at the problem from the point of view of the POSA *after* the invention and with the patent in hand to use as a roadmap to practice the invention. It is a much different exercise for a POSA to solve the problem of Al contamination *a priori* without Exela’s experimental work to determine which variables are important and how those variables interact than for a POSA to figure out if specific combinations of values

¹⁷ Ex. 1023 (’089 File History) at 304.

within the claimed ranges of the already identified variables would result in a solution that maintains the claimed features over the claimed time frame.

V. The '370 Patent Provides Sufficient Information for a POSA to Practice The Claims

32. I understand that Nexus alleges in its Petition that “because the Patent Owner defeated obviousness by asserting aluminum and oxygen criticality, but the patent specification does not show what ranges of these components work or do not work (especially when combined with other variables), the patent claims are not enabled or described to their full scope.”¹⁸

33. In my opinion, the '370 Patent provides sufficient support for the claimed ranges over the claimed time frame both individually and when considered as a whole.

A. Specification Provides Sufficient Support for Aluminum Limitations

34. The specification provides data on the aluminum levels measured in batches of the claimed L-cysteine hydrochloride solution while stored under various stability conditions. Table 22 reports the measured elemental leachables levels, including aluminum, in three batches of the L-cysteine hydrochloride product (XMHJ1705, XMHJ1706, and XMHJ1707) stored for 1, 3, 6, 9 and 12 months under standard conditions (25° C/60% relative humidity (RH)) and 6

¹⁸ Paper 1 at 3.

months under accelerated conditions (40° C/75% RH).¹⁹

35. According to FDA guidelines, 6 months of accelerated data along with 12 months of long-term data can be used to extrapolate 24-month stability for the purposes of establishing a product's shelf life.²⁰

36. The results reported in Table 22 show aluminum measured below the quantitation limit (“<QL”) under most conditions, including the 6 month accelerated data. One batch did exhibit measurable amounts of aluminum at 12 months under standard storage conditions, with the following reported levels: 4 ppb, 19 ppb, 5 ppb, 5 ppb, 6 ppb, 1 ppb, 5 ppb, 26 ppb, and 39 ppb.²¹ With 39 ppb being the highest after 12 months, the invention falls well below the no more than 250 and 150 ppb criteria provided in the claim language.

37. Thus, a POSA reviewing the testing data provided in the specification would understand that the aluminum levels in the L-cysteine hydrochloride product stayed below the claimed 250 and 150 ppb levels for 24 months.

¹⁹ Ex. 1001 ('370 Patent) at Example 9 and Table 22.

²⁰ Guidance for Industry ANDAs: Stability Testing of Drug Substances and Production Questions and Answers, at 4. (May 2014) <https://www.fda.gov/media/87051/download> (“Data from the three ANDA submission batches (i.e., 6 months), accelerated data meeting all criteria (without significant change per ICH Q1A(R2)), and 12 months long-term data without variability will not need statistical evaluation, and with appropriate post approval stability commitments, can be used to support extrapolation to a 24 months shelf life.”)

²¹ Ex. 1001 ('370 Patent) at Table 22.

38. While Table 22 does not disclose aluminum levels in the upper limits of the claimed ranges, in my opinion, this is not necessary to show that a POSA could practice the claims without undue experimentation. A POSA would understand that the goal of the invention is to reduce the aluminum level as much as possible to avoid aluminum toxicity to the patient.²² Moreover, a POSA would understand from the pre-existing L-cysteine hydrochloride products and the chemistry underlying the interaction of L-cysteine with glass that aluminum levels in these products increase over time.²³ Thus, the specification demonstrates that Exela was able to produce L-cysteine hydrochloride products with aluminum levels at the most desirable levels that, unlike the previously available products, stayed within the claimed ranges for the claimed period of time.

B. Specification Provides Sufficient Support for Oxygen Limitations

39. The specification describes two processes used to lower the levels of dissolved oxygen and headspace oxygen in the formulated cysteine hydrochloride injection product – headspace oxygen reduction and argon overlay (Example 4) and use of a high-speed filler (Example 5).²⁴ Using these methods, the headspace oxygen can be reduced from an ambient level of approximately 20% to below

²² Ex. 1001 ('370 Patent) at 7:12-19.

²³ Ex. 2019 (Jenke Reb. Rpt.) at ¶¶ 94, 109.

²⁴ Ex. 1001 ('370 Patent) at 44:1-49:50.

approximately 2.3 %²⁵ and dissolved oxygen levels can be reduced from approximately 10 ppm to below approximately 0.6 ppm in the sealed vial.²⁶

40. I agree with Nexus's expert that there is an equilibrium between the headspace and dissolved oxygen levels, and that changing one will change the other.²⁷ I also agree that the amount of oxygen in the headspace is much larger than the dissolved amount,²⁸ so the headspace oxygen would approximate the total oxygen in these products.

41. Using the techniques for oxygen removal described in the specification, a POSA would be able to produce a packaged vial of cysteine hydrochloride injection product whose initial total oxygen level meets the claimed value of below 5%.²⁹

42. Data in the specification further demonstrates that oxygen levels would decrease over the shelf life of the product. Data for batches XMHJ1705, XMHJ1706, and XMHJ1707 demonstrated initial headspace oxygen levels of approximately 1.9-2.3%.³⁰ Data collected for those same batches after nine months of storage at 25° C/60% RH showed headspace oxygen levels of approximately

²⁵ Ex. 1001 ('370 Patent) at Tables 12-16.

²⁶ Ex. 1001 ('370 Patent) at Table 12.

²⁷ Ex. 1003 (Confalone Decl.) at ¶ 95.

²⁸ *Id.*

²⁹ Example 1001 ('370 Patent) at Example 4; Example 5.

³⁰ *Id.* at 49:19-30, Tables 13 and 16.

0.16 to 0.89%.³¹ Similarly, initial dissolved oxygen levels for those batches were approximately 0.4-1.6 ppm,³² while dissolved oxygen levels reported at nine months for those batches were approximately 0.12-0.14 ppm.³³

43. While the specification does not provide oxygen data beyond nine months, in my opinion, a POSA would not expect the oxygen content to increase at any point after that period. As explained above, cysteine reacts with (consumes) oxygen to form the oxidation product cystine. As there is no viable process by which oxygen would be generated and oxygen will not permeate through a properly sealed vial, the oxygen levels in the vial would only decrease over time.

44. Thus, by using the disclosed manufacturing techniques to reduce the initial total oxygen level below 5%, the inventors demonstrated that they were capable of manufacturing L-cysteine hydrochloride products with total oxygen levels that would not exceed 5% total oxygen over the claimed 24-month period.

C. Cystine Was Known to Have Increased Solubility at pH 1.0 to 2.5

45. The pH of the L-cysteine hydrochloride solution is important because the solubility of cystine, the product of the oxidation of cysteine, is pH-dependent.³⁴ Precipitation occurs when cystine is present in the drug product in an

³¹ *Id.* at 49:62-67, Table 18.

³² *Id.* at 49:19-30, Tables 13 and 16.

³³ *Id.* at 49:62-67, Table 18.

³⁴ Ex. 1061(Okabe, L.; Studies on the Solubility of Cystine under Various

amount above its solubility limit, the level at which particulates would begin to form.

46. Cystine has low solubility at a pH in the range of approximately pH of 3 to 11, so even low amounts of cystine (< 0.2 mg/mL) would risk formation of precipitates at those pH levels. In contrast, the solubility of cystine significantly increases over the pH range of approximately 1.0 to 2.5, with the solubility at pH 1.0 being more than a factor of ten greater than the solubility at pH 3.0.³⁵

47. As a result, a POSA would know that cystine would have increased solubility in a solution of pH 1.0 to 2.5.

D. Any Combination of Claimed Values Would Yield Product That Meets Claimed Limitations for Claimed Time Period

48. Based on the disclosures in the '370 patent and the POSA's understanding of the solubility of cystine at pH 1.0 to 2.5, it is my opinion that a POSA would expect that, for an L-cysteine hydrochloride product where total oxygen is kept below 5%, aluminum is kept below 250 ppb, and pH in the range of from 1.0 to 2.5, the claimed L-cysteine solution will maintain those values within the claimed ranges and remain free of visually detectable particulate matter for

Conditions, and on a New Method of Cystine Preparation, *J. of Biochemistry*, 1927, Vol. 8, No. 2); Ex. 2024 (Carta, L.; Tola, G.; Solubilities of L-Cystine, L-Tyrosine, L-Leucine, and Glycine in Aqueous Solutions at Various pHs and NaCl Concentrations, *J. Chem. Eng. Data* 1996, 41, 414-417).

³⁵ Ex. 2024 (Carta).

twenty-four months.

E. ***Undue Experimentation Is Not Required to Determine that a Product Produced by the Processes Described in the Patent Maintains the Claimed Properties for the Claimed Time Period***

49. The Petition misunderstands my previous opinions regarding the complexity of reducing aluminum levels in L-cysteine hydrochloride products. Predicting *a priori* which variables would be important to control and how those variables would interact with each other, as Exela discovered when it made the invention claimed in the '370 patent, is not the same as selecting specific values within the claimed ranges once they have been identified.

50. As the specification explains, “[u]p to now, there has been no guidance with regard to the compatibility of L-cysteine with coated glass vials or that any vials could be used to provide L-cysteine compositions having low levels of Aluminum.”³⁶ The guidance contained in the specification of the '370 provides a detailed roadmap for a POSA to understand what variables need to be controlled and what ranges for those variables would produce a L-cysteine hydrochloride product that meets the Claims.

51. Once Exela identified the variables and demonstrated that controlling their values within a certain range resulted in stable L-cysteine hydrochloride products, determining whether products made with specific values within those

³⁶ Ex. 1001 ('370 Patent) at 22:64-67.

ranges would be stable over the claimed time period requires only stability study-type experimentation that a POSA would consider routinely necessary. With the '370 Patent specification as a roadmap, the POSA would be able to determine if a given L-cysteine hydrochloride product would remain within the claimed ranges for the claimed amount time without the need for undue experimentation.

52. I disagree with Dr. Confalone's assertion that a POSA would need to perform 7,680 experiments to figure out if combinations of values within the claimed ranges would result in stable products.³⁷ Dr. Confalone has divided each range into discreet, arbitrarily chosen, values and assumed that each of those discreet values must be tested against each and every other discreet value in the other ranges.

53. In my experience, this 7,680-experiment exercise would not be necessary. First, if the study Dr. Confalone envisions was necessary, then it would be performed more efficiently, *i.e.* with fewer experiments, using a Design of Experiments (DOE) approach which is common practice in formulation development.³⁸ Second, in my opinion, while the experiment that Dr. Confalone proposes produces profound knowledge about the science of L-cysteine injection

³⁷ Ex. 1003 at ¶ 112.

³⁸ Ex. 2025 (Beg, S.; Application of Design of Experiments (DoE) in Pharmaceutical Product and Process Optimization; *Pharmaceutical Quality by Design*, 2019, Ch. 3. <https://doi.org/10.1016/B978-0-12-815799-2.00003-4>.)

products, such profound knowledge is not necessary for the POSA to produce an acceptable L-cysteine injection product. This is true because Exela generated that profound knowledge and communicated that profound knowledge in the specifications within the patent.

54. Rather, my opinion is that if the POSA followed the methods described in the specifications to produce a product and then tested that product over the 24-month shelf life for the claimed attributes, the product would have the claimed values for those claimed attributes. In other words, the inventors have created the instructions, harvesting the fruit of the knowledge they gained from the experiments they performed, that allows the POSA to be successful. The POSA does not have to do experiments to gain the knowledge that the inventor gained and then communicated in the patent; rather, the POSA needs only to review the patent to gain such knowledge. With the instructions in the patent, the POSA can make a successful product without needing to know why the solution was a success. Thus, it would be a straight-forward exercise for the POSA to make a product based on the disclosures in the specification, test the stability of that product over the 24-month time period, and establish that the product meets the claims.

55. Importantly, the Petition has not identified any values within any of the claimed ranges that would result in a L-cysteine hydrochloride product that is

unstable up to 24 months. In my opinion, there is no reason to believe that any claimed embodiment would fail, let alone a significant number of claimed embodiments, and a POSA would not have to engage in undue experimentation to make and use the full range stable L-cysteine hydrochloride products claimed with the guidance of the '370 specification in hand.

56. I hereby declare that all statements made are of my own knowledge and are true. I further declare that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this proceeding.

Respectfully submitted,

Date: May 13, 2024

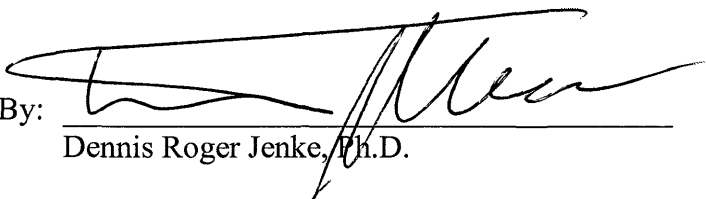
By: 
Dennis Roger Jenke, Ph.D.

EXHIBIT A

Dennis Roger Jenke, Ph.D.
Chief Executive Scientist, Triad Scientific Solutions, LLC
dennisjenke@triadscientificsolutions.com

CAREER SUMMARY

Over 30 years of direct technical experience in the pharmaceutical, environmental, mining, geoscience and chemical industries. Authored over 165 publications in related areas. Various patents related to pharmaceutical formulations (I.V. therapy). Recognized global expert in:

- Material/Solution Interactions (Extractables/Leachables, Drug Binding).
- Support of Global Product Registrations for Pharmaceutical Products.
- Computer Simulation of Industrial and Scientific Processes (migration modeling).
- Problem resolution for product/process development, implementation, and lifecycle management.
- Analytical method development/validation
- Chromatography (LC, GC, IC, TLC).
- Mass Spectrometry (MS)
- Atomic Spectroscopy (ICP, AA, GFAAS, AE).
- Instrumental Analysis (IR, NMR, UV).
- Classical and Wet Chemical Methods; Flow Injection Analysis (FIA).
- Metrology and Computerized System Validation.

PROFESSIONAL EXPERIENCE

Triad Scientific Solutions, LLC; Hawthorn Woods, IL 2016 to Present.
A provider of science-based solutions to plastic/product compatibility challenges associated with packaging, manufacturing equipment and delivery devices in the pharmaceutical, cosmetic, food and related industries

Chief Executive Scientist

Leveraging broad experience supporting product development, registration, and life-cycle management and an extensive network of experts and contract services providers, Dr. Jenke uses good science, practically applied, to address and overcome the challenges associated with managing interactions that occur between drug products and their manufacturing, packaging and delivery systems, insuring that such interactions (for example, extractables, leachables and drug binding) do not adversely affect the product's key quality attributes including safety, purity, efficacy, stability, and suitability for use.

Baxter Healthcare Corporation; Round Lake, IL 1983 to 2016 (retired).
A Fortune 75 company developing, manufacturing and marketing diversified medical care products and services.

Baxter Distinguished Scientist, Baxter Analytical Center of Excellence (ACoE)

Dr. Jenke was a Distinguished Scientist at Baxter Healthcare Corporation where for more than three decades he led 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 (for example, extractables/leachables and product ingredient binding). In this role, Dr. Jenke prepared, reviewed and defended product registration submissions. Dr. Jenke created and shaped domestic and global policies in the areas of product characterization, thereby developing, optimizing, and implementing Corporate-wide strategies for material/solution compatibility assessment. As a Distinguished Scientist and a highly published, globally recognized expert in the field of chemical evaluation of material/solution interactions, Dr. Jenke has driven international efforts to generate standards for material/solution compatibility assessments.

AWARDS AND AFFILIATIONS

Dr. Jenke's memberships in industry-wide organizations responsible for the development of global standards and best practices addressing material/solution compatibility include:

- Chair, Chemistry Working Group, Product Quality Research Institute (PQRI) Extractables and Leachables Taskforce for Parenteral and Ophthalmic Drug Products (PODP).
- Member, United States Pharmacopeia (USP) Packaging and Distribution Expert Committee; including:
 - Chair, Expert Panel for USP Chapters on Polymers Used in Pharmaceutical Packaging <661>, <661.1>, <661.2>, >1661>
 - Chair, Expert Panel for USP Chapters on Polymers used in Manufacturing Components and Systems <665>, <1665>
 - Member, Expert Panel for USP Chapters on Elastomeric Closures, <381>, <382>, <1381>, <1382>
- Adjunct Member, United States Pharmacopeia (USP) Combined Pharmaceutical Waters Expert Panel.
- Association for the Advancement of Medical Instrumentation (AAMI), Biological Evaluation Committee:
 - BE/WG02, Degradation Aspects Related to Biological Testing, Committee Alternate
 - BE/WG12, Allowable Limits for Leachable Substances, Committee Member
 - BE/WG12, Sample Preparation and Reference Standards, Committee Member
 - BE/WG14, Material Characterization, Committee Member
- Expert Member, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Q3E: Guideline for Extractables and Leachables (E&L)

Dr. Jenke was a Past President, Chicago Chromatography Discussion Group and the past Chair, Board of Directors, and current Scientific Advisor to the Extractables & Leachables Safety Information Exchange (ELSIE).

Dr. Jenke is an expert Reviewer for numerous technical journals including Analytical Chemistry, PDA Journal of Pharmaceutical Science and Technology, Journal of Chromatographic Science, Journal of Chromatography, Journal of Applied Polymer Science, Pharmaceutical Research, International Journal of Pharmaceutics. He is an Associate Editor for the Journal of Chromatographic Science and an Editorial Board member for Pharmaceutical Outsourcing.

External recognition received by Dr. Jenke includes:

- Received the 2005 Frederick D. Simon Award for Best Technical Manuscript published in the PDA Journal of Pharmaceutical Science and Technology (2005).
- Received the USP Award for an Innovative Response to a Public Health Challenge for “outstanding dedication and service in evolving the breadth and scope of standards for pharmaceutical packaging”.
- Received Leadership (2014) and Chair (2015) Awards from the Extractables and Leachables Safety Information Exchange (ELSIE), for outstanding service and contributions to that organization.
- Recognized as a member of the Pharmaceutical Power List by Medicine Maker Magazine (2015).
- Received “Expert Certification” from the Chinese National Pharmaceutical Packaging Association (CNPPA, 2016) as an invited Technical Consultant.
- Received the 2020 AAMI Standards Developer Award from the Association for the Advancement of medical Instrumentation for ISO standard 10993:18, Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process.

EDUCATION

Masters in Business Administration (with distinction); Keller Graduate School of Management, 1992; Course work emphasis in strategic, personnel and general business management.

Ph.D. in Analytical Chemistry; Montana State University, 1983; Theoretical and practical studies of ion chromatography, modeling of separation processes and optimization of the methodology in practical applications.

M.S in Geochemistry; Montana College of Mineral Science and Technology, 1978; Chemical characterization and modeling of an industrial wastewater treatment process.

B.A. in Chemistry, Mathematics, Physics; Illinois College, 1975; Second “triple major” in College’s 160-year history; varsity letters in tennis and football; member, Phi Alpha Literary Society.