IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CADENCE PHARMACEUTICALS, INC. and SCR PHARMATOP,	:	
Plaintiffs,	:	
v.	:	C.A. No. 11-733-LPS
EXELA PHARMA SCIENCES, LLC, EXELA PHARMSCI, INC., and EXELA HOLDINGS, INC.,	:	UNSEALED ON NOVEMBER 22, 2013
Defendants.	:	

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MEMORANDUM OPINION

November 14, 2013
Wilmington, Delaware

STARK, U.S. District Judge:

Plaintiffs Cadence Pharmaceuticals, Inc. and SCR Pharmatop (collectively, "Plaintiffs") allege that Defendants Exela Pharma Sciences, LLC, Exela Pharmsci, Inc., and Exela Holdings, Inc. (collectively, "Defendants" or "Exela") infringe U.S. Patent Nos. 6,028,222 ("the '222 patent") and 6,992,218 ("the '218 patent") (collectively, the "patents-in-suit").[1] The patents-in-suit relate to formulations and methods for making liquid acetaminophen compositions. The '222 patent addresses an oxygenation problem by including "a buffering agent" and a free radical scavenger/antagonist in the chemical composition of liquid acetaminophen. (*See* PTX-001 at col. 18, ll. 50-55) The '218 patent relates to an "extreme, and possibly complete" deoxygenation process, which reduces the oxygen content of the drug during the manufacturing process and potentially removes all oxygen from the chemical formulation. (*See* PTX-002 at col. 4, ll. 1-14, col. 6, ll. 50-56)

In August 2012, the Court construed the disputed terms of the patents-in-suit. (D.I. 188, 189) The Court conducted a seven-day bench trial in this matter in May and July of 2013. (*See* D.I. 405-410, 450) (hereinafter "Tr.")[2] The parties completed post-trial briefing on July 26,

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[1]Defendants Perrigo Company, Paddock Laboratories, Inc., and Paddock Laboratories, LLC were dismissed from the suit by a joint stipulation of the parties. (D.I. 276, 277)

[2]On August 21, 2013, Defendants filed a request to redact portions of the trial transcript. (D.I. 456) Plaintiffs oppose the motion. (D.I. 457) The Court will deny the motion. The trial was open to the public. *See generally Mosaic Techs., Inc. v. LSI Corp.*, 878 F. Supp. 2d 503, 507 (D. Del. 2012) ("[T]here is a strong presumption in favor of public access to all judicial records and documents, including transcripts, evidence, pleadings, and other materials submitted by litigants") (internal quotation marks omitted). Moreover, by the time Defendants filed their motion, the trial transcript had been available for purchase from the court reporter or viewing at a public terminal for two months (for all trial days except the last, which had been available for more than six weeks). It appears that third parties have already obtained copies of the underacted transcripts. (*See* D.I. 457 n.1) Defendants missed the July 12, 2013 deadline for requesting redactions to the May trial transcripts and do not propose any redactions to the July transcript. While Defendants "assum[ed] that redactions to all trial transcripts would be due after the final

2013. (D.I. 414, 417, 436, 437, 440, 442, 444, 445) In connection with the briefing, the parties submitted proposed findings of fact and conclusions of law. (D.I. 415, 416, 418, 441, 443)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) Plaintiffs have proven by a preponderance of the evidence that Exela infringes claims 1, 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent; (2) Plaintiffs have proven by a preponderance of the evidence that Exela infringes claims 1, 3, 4, and 19 of the '218 patent; (3) Exela has failed to prove by clear and convincing evidence that claims 1, 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent are invalid; and (4) Exela has failed to prove by clear and convincing evidence that claims 1, 3, 4, and 19 of the '218 patent are invalid. The Court's findings of fact and conclusions of law are set forth in detail below.

I. FINDINGS OF FACT

This section contains the Court's findings of fact for issues raised by the parties during trial. Certain findings of fact are also provided in connection with the Court's conclusions of law.

A. The Parties

1. Plaintiff Cadence is a Delaware corporation, having a principal place of business at 12481 High Bluff Drive, Suite 200, San Diego, California, 92130. (D.I. 416 (Statement of Uncontested Facts ("SUF")) ¶ 1)

2. Plaintiff Pharmatop is a French civil law partnership, having its headquarters at 10, Square St. Florentin, 78150 Le Chesnay, France. (*Id.* at ¶ 2)

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day of trial, rather than piecemeal" (D.I. 455 n.1), they provide no basis for this assumption.

3. Exela Pharma Sciences, LLC is a Delaware corporation having a principal place of business at 1325 William White Place, Lenoir, North Carolina, 28645. (*Id.* at ¶ 4)

4. Exela PharmSci, Inc. is a Virginia corporation having its headquarters at 19978 Palmer Classic Parkway, Reston, Virginia, 20147. (*Id.* at ¶ 5)

5. Exela Pharma Sciences, LLC is a wholly-owned subsidiary of Exela PharmSci, Inc. (*Id.* at ¶ 6)

6. Exela Holdings, Inc. is a Delaware corporation having its headquarters at 19978 Palmer Classic Parkway, Reston, Virginia, 20147. (*Id.* at ¶ 7)

7. Exela PharmSci, Inc. is a wholly-owned subsidiary of Exela Holdings, Inc. (*Id.* at ¶ 8)

8. Pharmatop owns the '222 and the '218 patents. (SUF at ¶ 153; Tr. at 159, 180) Cadence has an exclusive license to the '222 and '218 patents. (PTX-243; Tr. at 110-14)

B. U.S. Patent No. 6,028,222

9. The '222 patent, entitled "Stable Liquid Paracetamol Compositions, and Method for Preparing Same," issued on February 22, 2000 and expires on August 5, 2017. (PTX-001; SUF at ¶¶ 11, 12)

10. The '222 patent issued from U.S. Patent Application No. 09/051,246, filed on June 5, 1998, as the commencement of the national stage under 35 U.S.C. § 371 of PCT/FR97/01452, filed on August 5, 1997, and claims priority to French Application No. 96/09858, filed on August 5, 1996. (SUF at ¶ 13) The named inventors of the '222 patent are Francois Dietlin and Daniele Fredj. (*Id.* at ¶ 15)

11. The '222 patent contains a certificate of correction, which states, *inter alia*,

"Column 2, lines 26-27, 'alca-nol' should read – alka-nol –." (PTX-001 at 12; PTX-003 at 591; SUF at ¶ 45)

12. Plaintiffs assert that Exela's proposed generic product and/or manufacturing process infringe claims 1, 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent. Claim 1 is the only independent claim. The asserted claims are reproduced below:

> 1. A stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing a buffering agent and at least one member of the group consisting of a free radical scavenger and a radical antagonist.
>
> 3. The formulation of claim 1 wherein the aqueous medium is buffered at a pH of 4 to 8.
>
> 4. The formulation of claim 3 wherein the aqueous medium is buffered at a pH of 5.5 to 6.
>
> 5. The formulation of claim 1 containing a free radical antagonist selected from the group consisting of ascorbic acid ascorbic acid derivatives, organic compounds having at least one thiol and a alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds.
>
> 9. The formulation of claim 1 wherein the free radical scavenger is an aliphatic polyhydroxy alkanol of 2 to 10 carbon atoms.
>
> 10. The formulation of claim 9 wherein the polyhydroxy alkanol is a cyclic glucitol or a straight chain glucitol of 6 to 10 carbon atoms.
>
> 12. The formulation of claim 10 wherein the cyclic glucitol is selected from the group consisting of mannitol, sorbitol, inositol, glucose and levulose.
>
> 16. The formulation of claim 14 diluted to a concentration of 2 to 50 mg/ml.
>
> 17. The formulation of claim 1 also containing an isotonizing

agent in an amount to obtain isotonicity.

18. The formulation of claim 1 sterilized by heat treatment.

13. The '222 patent explains, "It has been known for many years and notably from a paper of FAIRBROTHER J. E. entitled: Acetaminophen, published in Analytical Profiles of Drug Substances (1974), volume 3, pp. 1-109, that paracetamol in the presence of moisture, and all the more in aqueous solution, may be hydrolysed to yield p-aminophenol, which compound may itself be broken down into quinone-imine." (PTX-001 at col. 1, ll. 16-22) The '222 patent states that "paracetamol in aqueous solution is unstable, a fact which primarily correlates with hydrolysis both in acidic and basic environment." (*Id.* at col. 1, ll. 30-32)

14. Paracetamol is another name for acetaminophen. (SUF at ¶ 80)

15. The '222 patent teaches that "removal of oxygen dissolved in the carrier" is one of the variables that has an impact on stability, and further that "Removal of dissolved oxygen is readily accomplished by bubbling an inert gas and preferably by bubbling nitrogen." (PTX-001 at col. 2, ll. 31-37)

C. U.S. Patent No. 6,992,218

16. The '218 patent, entitled "Method for Obtaining Aqueous Formulations of Oxidation-Sensitive Active Principles," issued on January 31, 2006 and expires on June 6, 2021. (PTX-002; SUF at ¶¶ 46, 47)

17. The '218 patent issued from U.S. Patent Application No. 10/332,060, filed on August 4, 2003 as the commencement of the national stage under 35 U.S.C. § 371 of PCT/FR01/01749, filed on June 6, 2001, and claims priority to French Application No.

00/07231, filed on June 6, 2000. (SUF at ¶ 48) The named inventors of the '218 patent are Francois Dietlin and Daniele Fredj. (*Id.* at ¶ 50)

18. Plaintiffs assert that Exela's proposed generic product and/or manufacturing process infringe claims 1, 3, 4, and 19 of the '218 patent. Claim 1 is the only independent claim. The asserted claims are reproduced below:

> 1. A method for preparing an aqueous solution with an active principle of phenolic nature susceptible to oxidation, which is paracetamol, while preserving for a prolonged period, comprising deoxygenation of the solution by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm, and optionally the aforementioned aqueous solution with an active principle is topped with an inert gas atmosphere heavier than air and placed in a closed container in which the prevailing pressure is 65,000 Pa maximum, and the oxygen content of the aqueous solution is below 2 ppm, and optionally the deoxygenation of the solution is completed by addition of an antioxidant.
>
> 3. The method for preparing a formulation of claim 1 wherein the residual oxygen content of the aqueous solution is below 1 ppm.
>
> 4. The method for preparing a formulation of claim 1 wherein the residual oxygen content in the aqueous solution is equal to 0.5 ppm or below.
>
> 19. An injectable aqueous solutions containing, as an active ingredient, a principle of phenolic nature susceptible to oxidation, preserved by the method of claim 1.

19. According to the '218 patent, the reduction of the amount of paracetamol in the solution through degradation is a "major problem" because "it is important that the dose of active principle is precisely determined." (PTX-002 at col. 1, ll. 44-50) In addition, the inventors of the '218 patent found that "the problem of stabilization of the formulations according to the invention was appreciably more complex than anticipated." (*Id.* at col. 3, ll. 27-29)

20. The '218 patent teaches that deoxygenation "take[s] a considerable amount of time." (*Id.* at col. 2, ll. 41-43) According to the '218 patent:

> Within the framework of the industrial manufacture of injectable solutions, it has been easy to deoxygenate bulk solutions in air-tight tanks and thus to keep them away from the air. However, during subsequent bottle or bag filling and packaging operations, it is difficult to keep the solutions totally away from air. In spite of precautions that may be taken for this purpose, especially filling and packaging the bottles with the addition of inert gas, once packaged, the solutions can may once again contain, or fix, or take up significant quantities of dissolved oxygen.

(*Id.* at col. 2, l. 61 to col. 3, l. 3)

21. In "Example II" of the '218 patent, the solution was bubbled with nitrogen until the dissolved oxygen content was approximately 0.2 ppm. (*Id.* at col. 7, ll. 10-12) "After being kept at 25° C for 6 months, the solution is still colourless, there is no change in the paracetamol content, and the content of degradation products of paracetamol determined by HPLC remains lower than 0.015% of the paracetamol." (*Id.* at col. 7, ll. 14-18)

22. In "Example IV," the dissolved oxygen content was reduced to approximately 1.5 ppm. (*Id.* at col. 8, ll. 10-11) After 24 months, the solution "remained colourless," the "paracetamol content was 100% of the original value, and the degradation products of the paracetamol measured by HPLC represented less than 0.02% of the paracetamol content." (*Id.* at col. 8, ll. 11-17)

D. OFIRMEV®

23. Cadence is listed by the U.S. Food and Drug Administration ("FDA") as holding approved New Drug Application ("NDA") No. 022450 for OFIRMEV®, which is an intravenous

formulation of acetaminophen. OFIRMEV® was approved by the FDA on November 2, 2010, and is indicated for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. (SUF at ¶ 70)

24. The FDA's official publication of approved drugs, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), includes the '222 and '218 patents in the listing for Cadence's OFIRMEV® product. (*Id.* at ¶ 71)

25. The non-drug ingredients of OFIRMEV® include dibasic sodium phosphate, mannitol, cysteine hydrochloride monohydrate, sodium hydroxide, hydrochloric acid, and Water for Injection ("WFI"). (*Id.* at ¶ 72) The antioxidant in Cadence's OFIRMEV® formulation is cysteine hydrochloride. (PTX-287 at 5; Tr. at 700; SUF at ¶ 73)

26. Cadence sought Priority Review status for OFIRMEV®. (PTX-776 at 1-3; Tr. at 124-25) On July 13, 2009, the FDA granted the request for Priority Review for Cadence's NDA. (PTX-775; Tr. at 130-31) Cadence's NDA was "granted a priority review because this product fulfills an unmet medical need for the treatment of fever and acute pain with an intravenous formulation in hospitalized adults and pediatric patients." (PTX-659 at 17; *see also* PTX-1010 at 4 (FDA stating that "Ofirmev™ was granted a priority review because this product fulfilled an unmet medical need for the treatment of fever and acute pain with an intravenous formulation"))

27. The FDA label for OFIRMEV® states that "no clinical benefit" was demonstrated for the decrease in opioid consumption. (PTX-653 at 9)

E. Perfalgan

28. OFIRMEV® is sold outside the United States under the name Perfalgan. (Tr. at 112-13) The OFIRMEV® and Perfalgan formulations are identical. (*Id.* at 1382) The processes

used to make OFIRMEV® and Perfalgan are substantially identical. (*Id.* at 1383-84)

29. OFIRMEV® and the vial version of Perfalgan contain the following ingredients: paracetamol, mannitol, cysteine hydrochloride monohydrate, dibasic sodium phosphate, sodium hydroxide, hydrochloric acid, and WFI. (SUF at ¶ 79)

F. Exela's ANDA No. 203092 and ANDA Product

30. Exela filed ANDA No. 203092 seeking regulatory approval to engage in the commercial manufacture, use, sale, or offer for sale, and/or importation of its generic Acetaminophen Injection product (10 mg/mL, 100 mL vial) ("Exela's ANDA product"), prior to the expiration of the '222 and '218 patents. (*Id.* at ¶ 82)

31. By letter dated July 12, 2011, Exela notified Cadence that it had filed its ANDA. (*Id.* at ¶ 83) Exela likewise notified Pharmatop that it had filed an ANDA application. (*Id.* at ¶ 84)

32. Exela was aware of the '222 and '218 patents at the time it submitted its ANDA No. 203092 to the FDA with a certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) ("Paragraph IV certification") seeking approval prior to expiration of the '222 and '218 patents. (*Id.* at ¶ 85)

33. The active pharmaceutical ingredient of Exela's ANDA product is acetaminophen. (PTX-009 at 2; SUF at ¶ 87)

34. Mannitol is present in the Exela ANDA product in a concentration of 38.5 mg/mL. (PTX-009 at 2; SUF at ¶ 88)

35. Sodium ascorbate is present in the Exela ANDA product in a concentration of 0.5 mg/mL. (PTX-009 at 2; SUF at ¶ 89) Sodium ascorbate is the sodium salt of ascorbic acid. (SUF at ¶ 102) Another name for ascorbic acid is vitamin C. (*Id.* at ¶ 103)

36. On February 8, 2013, Exela amended its ANDA "to provide updated stability data for the ANDA submission batch. The updated stability data includes six (6) months stability data at accelerated (40°C ± 2°C, 75 ± 5% RH) conditions and 24 month real time data at labeled storage (25° C [±] 2° C, 60% [±] 5% RH) conditions in support of a twenty-four (24) month expiration date." (PTX-037 at 1; SUF at ¶ 91) The stability study states that "based on the totality of the accelerated and real-time stability data, the pH specification is tightened from 4.5-6.5 to 5.3-6.3, the total % impurities is tightened from NMT 0.5% to NMT 0.3%, Hunter Color attribute b is shifted from 0-3.5 to 0.5-4.0 without widening the range, and the Hunter Color attribute L is tightened from NLT +90 to NLT +95." (PTX-802 at 5; SUF at ¶ 100)

G. The Expert Witnesses at Trial

37. Dr. Kinam Park testified as an expert "in pharmaceutical formulations, including the utilization of techniques for analyzing the levels of constituents in formulations," on behalf of Plaintiffs. (Tr. at 239)

38. Dr. Martin A. Schoonen testified as a "chemistry expert and particularly in the field of deoxygenation techniques and analysis," on behalf of Plaintiffs. (*Id.* at 314)

39. Dr. Yoon Yeo testified as an expert "in the chemistry of pH titration experiments," on behalf of Plaintiffs. (*Id.* at 449)

40. Dr. Robert J. Orr testified as an expert "in the field of pharmaceutical development, pharmaceutical formulations and pharmaceutical design, including the design of parenteral formulation[s],"[3] on behalf of Plaintiffs. (*Id.* at 613)

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[3]The parties use the word "parenteral" interchangeably with the word "injectable." (Tr. at 130, 164, 871)

41. Dr. Edmund Elder testified as "an expert in the field of pharmaceutical formulations, including parenteral formulations, as well as formulation development and design," on behalf of Plaintiffs. (*Id.* at 1212)

42. Dr. Asokumar Buvanendran testified as "an expert in the management of acute pain, including the use and development of multimodal analgesia," on behalf of Plaintiffs. (*Id.* at 1453)

43. Dr. Gregory Bell testified as "an expert with respect to commercial success as a secondary indicator of nonobviousness," on behalf of Plaintiffs. (*Id.* at 1518)

44. Dr. Anthony Palmieri testified as an expert "in the field of pharmaceutical formulation," on behalf of Exela. (*Id.* at 837)

45. Dr. Timothy R. Deer testified as "an expert in anesthesiology in pain medicine, including the treatment of acute and chronic pain," on behalf of Exela. (*Id.* at 1596)

46. Mr. Harry C. Boghigian testified as "an expert on marketing, promotion and commercial size of a pharmaceutical product and the commercial success in the context of secondary considerations of nonobviousness," on behalf of Exela. (*Id.* at 1657)

H. Person Having Ordinary Skill in the Art

47. The Court has determined that a person of ordinary skill in the art relating to the inventions claimed by the patents-in-suit, at the time that the claimed inventions were made, would have at least a bachelor's degree in chemistry, pharmacy, or a related field, and two to five years of experience in formulating pharmaceuticals, or equivalent experience. (D.I. 188 at 7 n.4; SUF at ¶ 109)

I. Facts Relating to Infringement of the '222 Patent

48. The Court has construed the term "stable," as it appears in the '222 patent, to mean, "The active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life." (D.I. 188 at 5-9) Exela has submitted testing showing that under ambient storage conditions, its ANDA product is stable for two years. (PTX-037 at 1; Tr. at 618-19) Exela has not disputed that its product satisfies the "stable" limitation of the asserted claims of the '222 patent.

49. The Court has construed the term "aqueous medium," as it appears in the '222 patent, to mean, "A solution of acetaminophen dissolved in a medium containing water or aqueous mixtures of water and a polyhydric compound and/or a water soluble alcohol." (D.I. 188 at 9-12) The solvent in the Exela ANDA product is WFI, which meets the Court's construction. (PTX-009 at 2; Tr. at 619-20) Exela has not disputed that its product satisfies the "aqueous medium" limitation of the asserted claims of the '222 patent.

50. The Court has construed the term "a buffering agent," as it appears in the '222 patent, to mean, "An agent that helps the formulation resist change in pH." (D.I. 188 at 12-13) Sodium ascorbate has been identified as a "buffering agent" in scientific literature. For example, "The Titration Curve and Dissociation Constants of Vitamin C" includes titration curves showing that ascorbic acid (sodium ascorbate's conjugate acid) resists change in pH from about pH 2 to 6. (PTX-279 at 5; Tr. at 629-33) "Buffers - pH Control within Pharmaceutical Systems," by Gordon Flynn (hereinafter "the Flynn article"), also lists ascorbic acid as a buffering agent. (PTX-336 at 16; Tr. at 971-74) Exela disputes Plaintiffs' allegation that the sodium ascorbate in its ANDA product satisfies the "buffering agent" limitation of the '222

patent.

51. The Flynn article defines buffer capacity as "the ability of a buffer to resist pH change." (PTX-336 at 9) According to the Flynn article, buffer capacity can be calculated using the Van Slyke equation, which is reproduced below:

$$\beta = 2.303 * C_T * \frac{K_a[H^+]}{(K_a+[H^+])^2}$$

52. In the Van Slyke equation, C_T represents the total buffer concentration (sum of the concentrations of the species participating in the equilibrium defined by Ka). (*Id.* at 10) When calculating the "maximum buffer capacity," the equation may be simplified to $\beta = 0.576\ C_T$. However, Flynn also teaches that "buffers, like all other adjuvants, are exogenous chemicals and the safest, practical amount to use is the minimum amount which gets the buffering job done." (*Id.* at 21)

53. The Flynn article further teaches:

> It has been shown that the maximum buffer capacity is at the pKa of a compound, . . . At ± 1 unit of pH away from the pKa the buffer capacity is about one-third of its maximum and this is generally taken as the useful limit of application. . . .
>
> How much buffer capacity is needed is the next question of the formulator. The answer to this question depends on the system at hand, but a rough rule of thumb can be formulated. In previous discussion it was shown that a reasonable estimate of the amount of acid or base produced via a hydrolytic decomposition might be on the order of about 0.005 moles/liter over the shelf-life of a product. Effective buffering would be obtained, providing one was near the pKa, with ten times as much buffer or about 0.05 molar buffer.

(*Id.* at 19) According to the Flynn article, the pKa of sodium ascorbate is 4.17. (*Id.* at 16) Thus, the approximate buffering range of sodium ascorbate is between pH 3.2 and 5.2. (*Id.*)

54. Plaintiffs' expert, Dr. Yoon Yeo, performed titration experiments on the Exela ANDA product. Titration experiments measure pH while adding known increments of a strong acid or base to a solution. (Tr. at 448-49) Titration experiments can be used to determine if an excipient acts as a "buffering agent" by testing a formulation with and without the excipient in question. (*Id.* at 451, 856) The experiment begins by lowering the pH and then gradually adding basic titrant, measuring the pH after each addition. (*Id.* at 451, 856-57)

55. Dr. Yeo performed three titration experiments. In the first two experiments, Dr. Yeo tested Exela's ANDA product prepared with and without sodium ascorbate according to the list of ingredients specified in Exela's ANDA (PTX-013). (Tr. at 452-53) Each titration was performed in triplicate to ensure consistency and reproducibility. (PTX-013; Tr. at 454) Dr. Yeo's third titration experiment evaluated samples of Exela's ANDA product manufactured on November 23, 2010. (Tr. at 458-61)

56. The Exela ANDA product is adjusted to pH 5.6 during manufacture and has a release specification of pH 5.5. (PTX-009 at 2; PTX-010 at 3; Tr. at 639-40)

57. The Court has construed the term "free radical scavenger/antagonist," as it appears in the '222 patent, to mean, "Substance that functions in the formulation as an antioxidant." (D.I. 188 at 13-14) Exela's ANDA product contains mannitol. (Tr. at 641) Exela disputes Plaintiffs' allegation that the mannitol in its ANDA product satisfies the "free radical scavenger/antagonist" limitation of the '222 patent.

58. The '222 patent identifies mannitol as a preferred free radical scavenger and

includes data showing that mannitol is effective at 20 mg/mL, about half the concentration in the Exela ANDA product. (PTX-001 at col. 2, ll. 54-57, col. 13, l. 36 to col. 14, l. 40; PTX-009 at 2; Tr. at 620-23) Mannitol is from the group of "alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds." (PTX-001 at col. 2, ll. 54-57, col. 13, l. 36 to col. 14, l. 40; PTX-009 at 2; Tr. at 620-23, 640-41)

59. References known to those of ordinary skill in the art identify mannitol among excipients which contribute to a formulation's tonicity, indicating its use as an isotonizing agent. (PTX-281 at 13; Tr. at 644-46)

60. The Exela ANDA product contains 10 mg/mL acetaminophen. (PTX-009 at 2; Tr. at 643-44)

61. The Exela ANDA product is terminally sterilized in an autoclave. (PTX-008 at 12; Tr. at 647-48)

J. Facts Relating to Infringement of the '218 Patent

62. Exela's ANDA describes an injectable aqueous acetaminophen solution. (Tr. at 684-85) Exela's ANDA further includes two batch records: a submission batch record (XLNL1021) and a proposed commercial batch record. (PTX-008 at 4-12; Tr. at 764) The manufacturing process for Exela's ANDA formulation is described in PTX-008 and is displayed in a flow diagram shown there. (PTX-008 at 5; Tr. at 763-64)

63. Exela's commercial manufacturing process ("Exela's ANDA process") uses a disposable system comprising a mixer, and inside the mixer is a polymeric bag, and inside the bag is a polymer mix blade which serves as an agitator. (Tr. at 765) Water for injection is added into the plastic bag, the agitator is turned on, and bubbling with nitrogen gas is begun. (PTX-008

at 38; Tr. at 765) Exela's ANDA process bubbles water for injection with nitrogen gas until the dissolved oxygen content is above 2 ppm but below 3 ppm. (PTX-008 at 8, 9, 38; Tr. at 765-66)

64. Once the dissolved oxygen content in the water for injection has reached a level that is above 2 ppm but below 3 ppm, the nitrogen bubbling is stopped and the nitrogen tank and tube are removed from the mixing bag to prevent any more bubbling or introduction of nitrogen into the system. (PTX-008 at 39; Tr. at 766) After the nitrogen bubbling of the water for injection is ceased, an argon blanket is added to the top of the mixing bag. The argon input tube does not come in contact with the surface of the water. (PTX-008 at 9; Tr. at 766)

65. "Positive argon blanketing" means that the argon flows from a pressurized tank. (DTX-225; Tr. at 1128) Dr. Palmieri agreed that blanketing with argon will deoxygenate an aqueous medium. (Tr. at 1028)

66. After blanketing the top of the water for injection and the head space with argon, Exela adds mannitol and then mixes until the mannitol is dissolved in the water. (PTX-008 at 9, 39; Tr. at 767) The sodium ascorbate antioxidant is then added to the mixing bag and agitated until also dissolved in the water. (PTX-008 at 9, 40; Tr. at 767) Next, acetaminophen is added to the formulation, the mixing bag is sealed, and the solution is stirred until the acetaminophen is dissolved. The stirring occurs without continuing argon blanketing. (PTX-008 at 10, 40; Tr. at 767) The pH of the solution is then measured, and – depending on the pH of the solution – the pH is adjusted with sodium hydroxide and/or hydrochloric acid solution. (PTX-008 at 41; Tr. at 767-68) Argon blanketing is resumed, the pH is adjusted, and additional water is added to make 500 liters of solution. (PTX-008 at 10, 42; Tr. at 768) The final dissolved oxygen of Exela's ANDA process is below 0.5 ppm. (PTX-306 at 22; Tr. at 245-46, 683-84)

67. PTX-810 is Exela's Batch II Record prepared for Exela's expert Dr. Palmieri; the handwriting on the document is Mr. Sterling's. (Tr. at 779, 802-03) PTX-811 is the Batch III Record, or "Exhibit" Batch Record, which Exela prepared during the Plaintiffs' site inspection on April 2, 2013. (PTX-811; Tr. at 781, 803)

68. Exela's ANDA product contains WFI as a solvent and acetaminophen as an active principle. (PTX-009 at 2; Tr. at 619-20, 653)

69. Exela has requested a 24-month shelf life for its ANDA product, which constitutes a prolonged pharmaceutically-acceptable shelf life. (PTX-009 at 12; Tr. at 653-54) Exela has also submitted testing showing that its ANDA product is stable for two years under ambient storage conditions (PTX-037) – the same stability period disclosed in the '218 patent's Example IV, made according to the method of claim 1. (PTX-002 at col. 8, ll. 3-17; Tr. at 655)

K. Facts Relating to Validity of the '222 Patent

70. PTX-765 is a certified translation of Greek Patent Publication No. 870101510 ("GR510"), published on December 7, 1987. GR510 is prior art to the '222 patent.

71. GR510 discloses "[s]table water-based solutions of Paracetamol for injection, for therapeutic purposes." (PTX-765 at 1) According to GR510, the "solutions have excellent chemical stability and are especially suitable for parenteral use." (*Id.*) "The pH of the solution [in GR510] caries [sic] between 5 and 6.5." (*Id.*)

72. The solution of GR510 also contains sodium metabisulfite, which is an antioxidant. (PTX-765 at 7; Tr. at 879, 1282)

73. The buffer in the GR510 solution is disodium dibasic phosphate. (PTX-765 at 7; Tr. at 879)

74. GR510 discloses a paracetamol concentration of 0.15 mg/mL and a paracetamol concentration of 150mg/ml. (PTX-765 at 5, 6)

75. Glycerol formal is a water soluble alcohol. (Tr. at 877-78)

76. Exela did not perform any stability tests for the GR510 formulation. (*Id.* at 1033-40)

77. The Merck Index entry for fructose (levulose) shows that the structure of fructose (levulose) has an oxygen in the ring structure. (DTX-262 at 3; Tr. at 1301)

78. "Chemical Stability of Pharmaceuticals," by Kenneth A. Connors ("Connors"), discloses sorbitol as a chelating agent. (DTX-438 at 16)

79. A chelating agent is a type of free radical scavenger. (Tr. at 889)

80. PTX-789 is a certified translation of Korean Patent Publication No. 1993-0011994 ("KR994"), published on December 23, 1993. KR994 is prior art to the '222 patent.

81. KR994 discloses various formulations of acetaminophen, including tablets, capsules, ointments, oral solutions, injections, rectal capsules, and parenteral formulations. (PTX-789 at 1-2)

82. KR994 lists a number of buffers that could be added to paracetamol formulations. (*Id.* at 2) These buffers include, for example, Sorenson's Buffer. (*Id.*)

83. KR994 states: "The method in accordance with the present invention can produce various types of paracetamol preparations with conventional processes by adding one or more additives of: the excipients normally used in the manufacture of injections, powder, tablets, capsules, syrups, or suppositories, e.g., lactose, various kinds of starch, sugar, mannitol, sorbitol, or inorganic salts (e.g., calcium phosphate, aluminum, silicate, calcium sulfate, etc.); binders,

e.g., sucrose, glucose, starch, gelatin, carboxymethyl cellulose, methyl cellulose, gum arabic, ethyl cellulose, hydroxypropyl methyl cellulose, or polyvinyl pyrrolidone; lubricants, e.g., cornstarch, talc, magnesium stearate, calcium stearate, or waxes; moisturizers, e.g., glycerin or sorbitol etc.; solvents, e.g., water; buffers, e.g., Gifford's buffer, Farley's buffer, Hind-Goyan's buffer, or Sorenson's buffer, etc.; isotonic agents, e.g., sodium chloride, etc. . . ." (*Id.* at 2)

84. KR994 provides stability data for its disclosed embodiments 2 and 5 of the injectable paracetamol formulations. (*Id.* at 4-5) This stability test data shows that the formulations made according to embodiments 2 and 5 were clear and colorless: after two years of storage at room temperature; in accelerated testing conditions (40° C); and upon exposure to light. (*Id.* at 4-5) The tested formulations also had levels of the para-aminophenol impurity that were within 1% after 24 months. (*Id.*) KR994 states that in the stability tests of embodiments 2 and 5, "[t]he para-aminophenol, which is the main product of decomposition of paracetamol, was less than 1%, proving that the products are stable through administration period." (*Id.* at 4)

85. Embodiments 2 and 5 do not contain any of the specific buffering agents listed in KR994. (*Id.* at 4-5)

86. Claim 3 of KR994 reads: "An injection containing the paracetamol composition of Claim 1 or Claim 2 as the main ingredient, wherein the paracetamol composition is prepared by adding supplements selected from the water, antioxidant, pain relieving agent, solubilizing agent, or pH control agent, etc. that are commonly used in injections, and then sterilizing." (*Id.* at 10)

87. According to an FDA publication regarding stability testing, "Stability studies should include testing of those attributes of the drug product that are susceptible to change during

storage and are likely to influence quality, safety, and/or efficacy." (PTX-950 at 12)

88. In the Federal Register, Vol. 61, No. 3, Thursday, January 4, 1996, the FDA published a guideline "intended to provide guidance to applicants for drug marketing registration on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a country, region, or member State." (PTX-787 at 1) Qualification of impurities "is the process of acquiring and evaluating data which establishes the biological safety of an individual impurity or a given impurity profile at the level specified." (PTX-787 at 3; *see also* SUF at ¶ 143)

89. The FDA "Guidelines on Impurities in New Drug Substances" provide the following table to illustrate the impurity threshold guidelines for registration of new drug substances:

Maximum daily dose	Qualification threshold
≤ 2 grams (g)/day	0.1 percent or 1 milligram per day intake (whichever is lower)
> 2 g/day	0.05 percent

(PTX-787 at 3) As shown above, the FDA threshold is 0.1% for drugs for which the maximum daily dose is less than or equal to 2 grams/day, and is 0.05% for drugs for which the maximum daily dose is more than 2 grams/day. (*Id.*)

90. The Guidelines set forth in PTX-787 were approved not only by the FDA, but also by regulatory agencies from the European Union and Japan. (*Id.* at 1) Specifically, the

"guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)." (*Id.*) In addition, the following regulatory and industry representatives provided comments relating to development of the Guidelines: the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, the FDA, and the Pharmaceutical Research and Manufacturers of America. (*Id.*) Representatives from the International Federation of Pharmaceutical Manufacturers Associations, the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area also were involved. (*Id.*)

91. The standard dose of acetaminophen is 325-1,000 mg, with a maximum daily intake of 4,000 mg. (PTX-328 at 18; PTX-653 at 1; Tr. at 1239-40)

92. Exela limits the maximum para-aminophenol content in its ANDA product to no more than 0.1%. (PTX-045 at 42; Tr. at 798, 1176)

93. Mr. Sterling, Exela's primary ANDA formulator, stated that Exela selected the 0.1% para-aminophenol threshold "[b]ased on a review of the current FDA, EP, and USP" guidelines. (PTX-075 at 1; Tr. at 1177-78)

94. DTX-113 is U.S. Patent No. 5,270,050 (hereinafter "the '050 patent"). The '050 patent was issued on December 14, 1993 and is prior art to the '222 patent. (DTX-113) The '050 patent is entitled "Paracetamol-based Pharmaceutical Composition" and discloses a composition "in the form of an ophthalmic solution containing an aqueous solution, paracetamol and a buffer and, optionally, an antioxidant and a preservative." (*Id.* at col. 1, ll. 28-32)

95. There is no discussion of stability in the '050 patent. Exela did not address stability of the '050 patent formulation in its Paragraph IV letter. (*See* DTX-225 at 33-40) Dr. Koneru did not address stability in his trial testimony. (*See* Tr. at 1147-53)

L. Facts Relating to Validity of the '218 Patent

96. The '222 patent is prior art to the '218 patent. (SUF at ¶ 110) During prosecution of the '218 patent, the U.S. Patent and Trademark Office ("PTO") Examiner stated that "[t]he difference between the ['222 patent] and herein claimed method is that the ['222 patent] does not mention the level of oxygen and the pressure . . . [and] it was well within ordinary skill in the art to work out [the oxygen content] parameters to achieve maximum stabilization." (PTX-004 at 392) In allowing the '218 patent, the Examiner stated that "after nitrogen is bubbled, the oxygen content is below 2 ppm, which results in unexpected stabilization of the paracetamol, see for example, pages 16 and 17, wherein it is clearly demonstrated that because of oxygen being less than 2.0 ppm, the stability of the paracetamol is unexpectedly achieved for much longer time." (*Id.* at 427)

97. In 1978, Dr. Palmieri published an article in the *Journal of Pharmaceutical Sciences* directed to the "effect of dissolved oxygen levels on oxidative degradation of pyrogallol." (PTX-338 at 1) Dr. Palmieri chose pyrogallol for his study because of its "rapidity of oxidation." (*Id.* at 2) Dr. Palmieri's article states that reducing oxidative degradation is "[a]n important factor in drug stabilization," and that "[t]here is a rank-order correlation of dissolved oxygen and degradation rates." (*Id.*) According to Dr. Palmieri, "even systems of less than 1 ppm dissolved oxygen exhibited degradation. This result is explainable since pyrogallol may degrade by a nonoxidative process. Many chemicals having primarily oxidative pathways for

degradation also degrade by other means." (*Id.*) Dr. Palmieri's article also states that "it is difficult to alter the oxygen concentration with present equipment." (*Id.*)

98. Oxidation is the primary degradation pathway for pyrogallol. (*Id.* at 2)

99. Oxidation does not cause paracetamol to degrade. (Tr. at 1575)

100. According to Connors, the "major route of degradation contributing to the instability of [paracetamol] is its hydrolysis." (DTX-438 at 18-19) Hydrolysis is not the same as oxidation. (Tr. at 1041)

101. Reducing the oxygen content of a formulation would not stop hydrolytic degradation. (*Id.* at 1045, 1049)

102. Deoxygenation by bubbling can "risk physical damage to sensitive molecules" as a result of "extended contact with the oxygen impurities present in nitrogen gas." (*Id.* at 1052)

M. Facts Relating to Secondary Considerations of Nonobviousness

103. Before 1976, the only parenteral antipyretic available in the U.S. was Dipyrone, which was associated with severe incidents of agranulocytosis, leading to withdrawal of the product's FDA approval in 1976. (PTX-776 at 16; Tr. at 126-28, 1481) Since that time, the FDA has been "anxious" to have a "safe[] parenteral antipyretic available," observing that it would be "advantageous to develop a parenteral form of a known safe and effective antipyretic agent." (PTX-776 at 1)

104. The FDA has previously described efforts to develop an injectable formulation of acetaminophen as "challenging" and further noted that "33 years after the [FDA] expressed the need for another parenteral antipyretic agent, no such product is available." (PTX-776 at 1; *see also* PTX-1011 at 2; Tr. at 128, 1629)

105. InjectApap was an injectable acetaminophen-containing product developed by Ortho-McNeil and approved by the FDA in March 1986. (DTX-742; PTX-242 at 3; Tr. at 127, 1507, 1598-99, 1681-82) However, InjectApap was never brought to market (Tr. at 1631) and was known to "produce tissue irritation and necrosis" (PTX-776 at 17-18).

106. DTX-108 is a 1987 article that purports to disclose an injectable stable paracetamol formulation. DTX-109 is German Patent No. 279,405, which relates to parenteral acetaminophen solutions that can be used to treat pain and fever and can be ready to use. DTX-175 is U.S. Patent No. 6,423,749, directed to an injectable paracetamol formulation.

107. Prodafalgan was an injectable acetaminophen containing product developed by UPSA Laboratories ("UPSA").[4] (Tr. at 1443) Prodafalgan had to be reconstituted shortly before administration. (PTX-348 at 1-2; PTX-1011 at 2; Tr. at 1404, 1478-79) Reconstitution of formulations increases the risk of microbial contamination. (PTX-886 at 6; Tr. at 158) Prodafalgan also caused pain at the injection site and posed a risk of contact dermatitis to healthcare providers. (PTX-270 at 2; PTX-886 at 1; PTX-1011 at 2; Tr. at 1404, 1479-80) UPSA was not able to successfully develop a "ready-to-use" injectable acetaminophen formulation. (Tr. at 1401, 1403-05) Prodafalgan was never marketed in the U.S. (Tr. at 1479)

108. Mr. Jehan-Yves Drouin is Vice President for Market Access in France for BMS (formerly UPSA). (Tr. at 1400) Mr. Drouin was in charge of business development for Prodafalgan in Europe and subsequently was responsible for the sales and marketing of Perfalgan, including its launch, until 2004. (Tr. at 1399-1401, 1434, 1440-41)

109. Perfalgan has generated $1.7 billion in sales between 2003 and 2011. (Tr. at

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[4] Bristol-Myers Squibb Co. ("BMS") acquired UPSA Laboratories in 1995. (Tr. at 185, 1400)

1531-32) Shortly after launch, Perfalgan became the top selling non-opioid IV analgesic in each of the "Big Five" European markets. (PTX-872; PTX-1009; Tr. at 188-89, 1527-29) In three of the five countries, Perfalgan became the number one selling IV non-opioid in terms of unit sales, and in the other two it was the second highest-selling product. (PTX-872; PTX-1009; Tr. at 1529-30)

110. OFIRMEV® is Cadence's sole product. (Tr. at 1327, 1546) Since its launch in January 2011, OFIRMEV® has become the highest selling non-opioid IV analgesic by revenue. (PTX-872; PTX-1009; Tr. at 1534-36) In the first quarter of 2013, OFIRMEV® sales had already reached half of Cadence's total sales for all of 2012. (PTX-872; PTX-972 at 16; DTX-711 at 4; Tr. at 1536) Cadence has raised the price of OFIRMEV® several times, with no disruption in volume growth of sales. (Tr. at 1347) However, sales of OFIRMEV® did not meet Cadence's pre-launch projections for 2011 or 2012, and Cadence has never made a profit. (PTX-098 at 1; Tr. at 138-39, 1342, 1352-54, 1360, 1661-62, 1674-75)

111. Cadence's SEC filings and internal marketing documents show that Cadence spent significant amounts on sales and marketing. (PTX-893 at 57; PTX-261 at 1; Tr. at 1343, 1354-59) Cadence did not have a sales force prior to launching OFIRMEV®. (Tr. at 1337)

112. Exela has estimated that the market for a first-to-file generic product would "exceed $300mm in revenue." (PTX-063 at 3; Tr. at 1163)

II. INFRINGEMENT

A. Legal Standards

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly construed claims with the accused infringing product. *See id.* If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Id.* at 1552.

A patent owner may prove infringement under two theories: literal infringement or the doctrine of equivalents. The patent owner has the burden of proving infringement under either theory by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). Literal infringement occurs where "every limitation in a patent claim is found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). Infringement under the doctrine of equivalents occurs where the accused product embodies every element of a claim either literally or by an equivalent. *See id.* This doctrine "allows the patentee to claim insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002).

A patentee may invoke the doctrine of equivalents where the accused device "performs substantially the same function in substantially the same way to obtain the same result." *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950); *see also Brilliant Instruments, Inc. v. GuideTech, LLC*, 707 F.3d 1342, 1346-47 (Fed. Cir. 2013). A patentee may be prevented from invoking the doctrine of equivalents, however, by prosecution history estoppel. Prosecution history estoppel requires that the claims of a patent be interpreted in light of the proceedings in the PTO during the application process. *See Festo*, 535 U.S. at 734. Estoppel arises when an amendment is made to secure a patent and that amendment narrows the patent's scope. *See id.* at 736. In such cases, the "amendment may be presumed to be a general disclaimer of the territory between the original claim and the amended claim," and the patentee bears the burden of showing that the amendment does not surrender the particular equivalent in question. *Id.* at 740. Applicability of prosecution history estoppel is a question of law. *See Panduit Corp. v. HellermannTyton Corp.*, 451 F.3d 819, 826 (Fed. Cir. 2006).

B. Exela's ANDA Product Infringes Each Asserted Claim of the '222 Patent

Plaintiffs assert that Exela's ANDA product infringes claims 1, 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent. At trial, the parties' dispute focused on two issues: (1) whether the sodium ascorbate in Exela's ANDA product functions as a "buffering agent;" and (2) whether the mannitol in Exela's ANDA product functions as an antioxidant.

1. Sodium ascorbate acts as a buffering agent in Exela's ANDA product

Claim 1 of the '222 patent requires an "aqueous medium" that contains "a buffering agent." The Court has construed the term "a buffering agent" as "[a]n agent that helps the formulation resist change in pH." (D.I. 188 at 12-13) Plaintiffs contend that the sodium

ascorbate in Exela's ANDA product is the claimed "buffering agent." Exela responds that sodium ascorbate is not a buffering agent because it does not sufficiently "help" Exela's ANDA product resist change in pH. The Court has previously rejected Exela's argument and now does so again.

During claim construction, Exela proposed to construe the term "buffering agent" to require "an ***effective*** concentration to resist ***material*** changes in pH." (D.I. 146 at 14-16) (emphasis added) Exela argued that Plaintiffs' proposed construction – which did not include the "effective concentration" requirement – was incorrect because it "broadly encompasses any compound that may resist pH changes in the formulation, ***even if its effect is negligible.***" (*Id.* at 16) (emphasis added) Exela further argued that "Plaintiffs' definition of 'buffering agent' could include substances that have no material effect on the formulation, contrary to the stated purpose for the buffering agent." (D.I. 163 at 9) The Court disagreed with Exela and adopted Plaintiffs' proposed construction. Thus, to the extent Exela argues that the buffering effect of sodium ascorbate in Exela's ANDA product is too negligible to be considered "helpful," this argument is not persuasive.

Under the Court's claim construction, any excipient that helps a formulation resist change in pH is a "buffering agent" within the scope of the claims. As discussed below, Plaintiffs presented credible evidence, including expert testimony, showing that sodium ascorbate helps Exela's ANDA product resist changes in pH. The evidence and arguments offered by Exela were not persuasive. Plaintiffs have met their burden to prove infringement under the preponderance of the evidence standard.

a. Dr. Yeo's titration experiments

Plaintiffs' expert, Dr. Yoon Yeo, performed titration experiments on the Exela ANDA product and testified persuasively that the results support a conclusion that Exela's ANDA product resists change in pH. (Tr. at 452) Titration experiments are accepted in the pharmaceutical art as a standard method to determine whether an excipient acts as a "buffering agent." (*Id.* at 955-56)

Dr. Yeo preformed several experiments. First, Dr. Yeo prepared two batches of Exela's ANDA product according to the list of ingredients specified in Exela's ANDA. (*Id.* at 453) The only difference between the batches was that one batch contained sodium ascorbate and one batch did not. (*Id.*) Dr. Yeo also evaluated samples from a batch of Exela's ANDA product that was manufactured and provided by Exela. (*Id.* at 290, 458-59) The results of the titration tests on all three batches showed that Exela's ANDA product with sodium ascorbate resists change in pH until at least about pH 5.5. (PTX-314; PTX-316; Tr. at 452-60, 634-36) By contrast, the product without sodium ascorbate does not resist change in pH, but instead demonstrates a quick rise in pH when a titrant is added. (PTX-316; Tr. at 452-60, 634-36) Based on these results, the Court concludes that sodium ascorbate in Exela's ANDA product helps that product resist change in pH.

Although Exela admits that titration experiments are "routine laboratory" work, Exela did not conduct its own titration experiments to challenge Dr. Yeo's. (Tr. at 733, 953, 969-70) Rather, Exela attempts to discredit Dr. Yeo's experiments as "incomplete and flawed." (D.I. 436 at 6) Specifically, Exela contends that Dr. Yeo's conclusions should not be accepted because: (1) they are based on a subjective analysis of the titration curves; (2) Dr. Yeo did not provide any

information about the concentration of the alleged buffering agent; (3) Dr. Yeo used an overly dilute titrant concentration; (4) Dr. Yeo did not consider the effect of temperature on the pH of the ascorbic acid; (5) Dr. Yeo did not provide any evidence that her pH meter was properly calibrated; and (6) Dr. Yeo did not consider the effect of dissolved carbon dioxide in water. (D.I. 414 at 6-9) The Court will address these criticisms below.[5]

Exela accuses Dr. Yeo of merely "eyeballing" the results of her titration experiments. (D.I. 414 at 2, 7) But there is no evidence in the record that one of ordinary skill in the art would consider this evaluation method to be improper. To the contrary, Dr. Yeo credibly testified that one of ordinary skill in the art can visually evaluate the curve of a graph to identify the point at which a buffer is no longer effective. (Tr. at 457) At trial, Dr. Yeo also calculated the slope of the ascorbic acid curves in her graphs, to show more precisely where the ascorbic acid stopped helping the product resist change in pH.[6] Additionally, even a lay fact-finder can see that the resulting graphs for batches with sodium ascorbate show a different titration curve than the graphs for batches without it.

Exela's remaining criticisms are likewise unpersuasive. With respect to the concentration

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[5]At trial, Dr. Yeo testified that she performed her own buffer-capacity calculation. (Tr. at 507-09, 595) Exela asks the Court to draw the adverse inference that the results of this calculation were unfavorable to Plaintiffs because Dr. Yeo did not include the results in her expert reports. (D.I. 414 at 8 n.3; D.I. 436 at 4) The Court will not draw such an inference. At trial, Defendants did not ask Dr. Yeo what her calculation ultimately revealed, or whether it was consistent with Dr. Palmieri's calculation. (Tr. at 507-09, 595) Under the circumstances, an adverse inference is not warranted.

[6]Exela has moved to strike this portion of the testimony because Dr. Yeo's slope calculations were not part of her expert report. (D.I. 414 at 7, 25) However, all of the data associated with Dr. Yeo's testing was provided to Exela, and Exela conducted its own regression analysis of this data prior to trial. The Court denies Exela's motion.

of the alleged buffering agent, Dr. Yeo testified that she followed the manufacturing process set out in Exela's ANDA submission. (*Id.* at 453) With respect to dilution, Dr. Yeo credibly testified that she used the 0.0125 M titrant in order to increase the number of data points for evaluation. (*Id.* at 453-54) Dr. Yeo testified that she performed all of her experiments in triplicate and in the same lab. (*Id.* at 454, 605) She also testified that her lab is maintained at a constant temperature. (Tr. at 605) Accordingly, even if temperature could influence the results of a titration experiment, there is no evidence that this occurred here. With respect to calibration, Exela's only criticism is that Dr. Yeo's ***report*** does not indicate whether she calibrated her meter. (D.I. 414 at 8) But Exela never ***asked*** Dr. Yeo whether she calibrated her meter (Tr. at 515), and there is no evidence to suggest that Dr. Yeo's pH meter was not calibrated. The Court will not speculate that Dr. Yeo failed to calibrate her meter. Finally, Exela contends that Dr. Yeo did not account for the buffering effect of carbonic acid (which is present in water in small amounts) in the product. However, Dr. Yeo persuasively explained that both the "with" and the "without" products contained carbonic acid and, thus, the presence of carbonic acid could not have accounted for any difference in pH resistance between the two products. (*Id.* at 599)

b. Exela's evidence is unpersuasive

Exela asserts three principal reasons why sodium ascorbate is not a buffering agent: (1) sodium ascorbate is not recognized as a buffer in scientific literature; (2) Exela's ANDA product is outside the useful pH buffering range of sodium ascorbate; and (3) the "buffering capacity" of sodium ascorbate at the pH value of Exela's ANDA product is too small to help that product resist change in pH. (D.I. 414 at 3-6) Having considered Exela's evidence and arguments, the Court is not persuaded.

Exela's first argument is inconsistent with the evidence presented at trial. Although Exela was able to locate several scientific publications that do not identify sodium ascorbate as a buffer (*see* DTX-060; DTX-061; DTX-062; DTX-063; PTX-278), the record shows that sodium ascorbate is recognized as a buffer in the scientific community (*see* PTX-279; PTX-336). For instance, "The Titration Curve and Dissociation Constants of Vitamin C," includes titration curves showing that ascorbic acid (sodium ascorbate's conjugate acid) resists change in pH from about pH 2 to 6. (*See* PTX-279; Tr. at 629-33) Likewise, the Flynn article, which is cited heavily by Exela, lists ascorbic acid as a buffering agent. (*See* PTX-336 at 16) The Court concludes that one of ordinary skill in the art would recognize sodium ascorbate as a buffering agent in the context of the '222 patent.

Exela's next argument is that even if sodium ascorbate could be a buffer, it does not act like a buffer at the pH of Exela's ANDA product. This argument is largely based on the Flynn article (PTX-336). The Flynn article teaches that the useful range of a buffering agent is approximately ±1 pH unit from the pKa of that buffering agent. (*Id.* at 19) The pKa of sodium ascorbate is 4.17. Thus, according to Flynn, the approximate useful buffering range of sodium ascorbate is between pH 3.2 and 5.2. The pH range of Exela's ANDA product is between 5.3 and 6.3. (PTX-802 at 5) Because the pH of Exela's ANDA product is outside the buffering range of sodium ascorbate, Exela contends that sodium ascorbate does not act as a buffer in Exela's ANDA product. (D.I. 414 at 4-5) The Court disagrees.

First, the record shows that the ±1 pH range for buffering capacity is not a hard-line rule, but only a general guideline. For instance, the "Physical Pharmacy" book cited by Exela explains, "A buffer solution is useful within a range of ***about*** ± 1 pH unit about the pKa of its

acid." (DTX-065 at 17) (emphasis added) Likewise, the Flynn article teaches that at "± 1 unit of pH away from the pKa the buffer capacity is ***about one-third of its maximum*** and this is ***generally*** taken as the useful limit of application." (PTX-336 at 19) (emphasis added) With Exela's ANDA product having a pH of 5.3, the sodium ascorbate may operate at a little less than one-third of its maximum buffering capability, which is enough to help resist a change in pH. This is consistent with Dr. Yeo's titration data.

Exela's next argument concerns the "buffer capacity" of sodium ascorbate. Both parties agree that buffer capacity is "[t]he ability of a buffer to resist pH change." (PTX-336 at 9) Exela relies on the Flynn article for the proposition that "a buffer capacity of 0.01 to 0.1 . . . define[s] the useful limit[] for a buffering agent." (D.I. 436 at 3) According to Exela, "[o]utside these limits, a skilled artisan would not consider an agent to resist pH change." (*Id.*) However, contrary to Exela's arguments, Flynn does not limit the useful buffering range to 0.01 to 0.1. Rather, Flynn explains that "a buffer capacity between 0.01 and 0.1 ***appears generally adequate***." (PTX-336 at 19) (emphasis added) But Flynn also explains that the appropriate buffer capacity "depends on the system at hand," and the appropriate amount of buffer capacity is based on the amount of hydrolytic decomposition expected over the shelf life of the formulation. (*Id.* at 19-21) According to Flynn, "[e]ffective buffering would be obtained, provid[ed] one was near the pKa, with ten times as much buffer" as the amount of hydrolytic decomposition. (*Id.* at 19) Exela, however, admits that it did not calculate, or even consider, the hydrolytic decomposition of its ANDA product. (Tr. at 1013)

2. Mannitol functions as an antioxidant in Exela's ANDA product

Claim 1 of the '222 patent also requires a "free radical scavenger," which the Court has

construed to mean a "[s]ubstance that functions in the formulation as an antioxidant." (D.I. 188 at 13-14) Plaintiffs assert that mannitol is the claimed antioxidant in Exela's ANDA product. In response, Exela contends that the evidence presented at trial establishes that mannitol does not function as an antioxidant in Exela's ANDA product. The Court concludes that: (1) Exela has waived this non-infringement argument; and (2) Plaintiffs have showed by a preponderance of the evidence that mannitol functions as an antioxidant in Exela's ANDA product.

Plaintiffs contend that, prior to trial, Exela never disputed that mannitol acts as an antioxidant in its product and, accordingly, this argument should be deemed waived. (D.I. 437 at 10 n.10) At the direction of the Court, the parties submitted supplemental letter briefs to address the waiver issue. (*See* D.I. 460, 461) Having reviewed the parties' letter briefs, as well as the supporting exhibits submitted with them, the Court concludes that Exela knew that Plaintiffs had identified mannitol as the claimed antioxidant and did challenge that contention prior to trial. For instance, Dr. Orr's expert report expressly identified mannitol as the claimed "free radical scavenger/antagonist" of claim 1. (D.I. 461 Ex. C at 11) Dr. Orr also identified mannitol as satisfying the requirements of dependent claims 5, 9, 10, and 12. For example, with respect to dependent claim 5, Dr. Orr opined: "Exela's ANDA product infringes claim 5 of the '222 patent because the ANDA product is covered by claim 1 and because it contains mannitol, which is a preferred polyhydroxylated compound." (*Id.* at 17) The Court finds no indication – and Exela's letter brief identifies none – that Exela ever previously challenged Plaintiffs' contentions with respect to the function of mannitol. Exela's non-infringement contention based on mannitol comes far too late and is waived.

In any case, Plaintiffs have proven by a preponderance of the evidence that mannitol

functions as an antioxidant in Exela's ANDA product. For example, the '222 patent identifies mannitol as a preferred free radical scavenger and includes data showing that mannitol is effective at 20 mg/mL. (PTX-001 at col. 2, ll. 54-57, col. 13, l. 36 to col. 14, l. 40; Tr. at 620-23) Exela's ANDA product contains nearly twice the necessary amount of mannitol, 38.5 mg/mL. (PTX-009 at 2) Although Exela's ANDA formulator, Mr. Sterling, testified that Exela conducted tests to "evaluate the antioxidant effect of mannitol" (Tr. at 761), there is insufficient evidence in the record to persuade the Court that those tests prove that mannitol does not function as an antioxidant in Exela's product.[7]

3. Exela infringes the asserted dependent claims of the '222 patent

Plaintiffs assert that Exela's ANDA product infringes dependent claims 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent, and at trial presented evidence with respect to the additional limitations of these dependent claims. Exela did not dispute Plaintiffs' evidence, or raise any non-infringement challenges in rebuttal. Therefore, the Court concludes that Exela infringes dependent claims 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent.

C. Infringement of the '218 Patent

Plaintiffs contend that Exela's ANDA process infringes claims 1, 3, 4, and 19 of the '218 patent, either literally or under the doctrine of equivalents. Exela responds that Plaintiffs failed to prove infringement because: (1) Exela does not deoxygenate its solution by "bubbling," as that term is understood by those of ordinary skill in the art; (2) Exela adds an antioxidant to its product before the dissolved oxygen ("DO") content falls below 2.0 ppm; and (3) the DO content

[7]Exela's expert, Dr. Palmieri did not address the "antioxidant" limitation in his expert report.

of Exela's product is below 2.0 ppm prior to addition of acetaminophen.[8] (D.I. 414 at 11-16) For the reasons below, the Court concludes that Plaintiffs have proven by a preponderance of the evidence that Exela infringes the asserted claims of the '218 patent under the doctrine of equivalents.

1. Exela's process satisfies the "bubbling" limitation

Claim 1 of the '218 patent requires "deoxygenation of the solution by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm." (PTX-002) The Court construed this claim term to mean: "Either bubbling or placing under vacuum or both is carried out until the oxygen content of the solution is less than 2 ppm prior to optional addition of an antioxidant." (D.I. 188 at 23) Exela's ANDA process satisfies this limitation literally and by equivalents.

a. Literal infringement

The parties' dispute centers on the appropriate construction of the word "bubbling."[9]

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[8]Exela also contends that Plaintiffs failed to prove infringement because Dr. Schoonen's "theoretical models" only addressed Exela's stability batch process, not Exela's commercial batch process. (D.I. 414 at 11-12) The Court does not agree. As discussed below, even without Dr. Schoonen's models, Plaintiffs provided persuasive evidence in the form of test results, documents, and expert testimony establishing the presence of every element of the asserted claims either literally or under the doctrine of equivalents. Any purported differences between Exela's stability batch process and commercial batch process do not impact the Court's conclusion. In any event, Exela failed to raise any non-infringement arguments based on purported differences between its stability and commercial batch processes prior to trial, so the Court deems those arguments to be waived. (*See* D.I. 437 at 11-15; D.I. 462 at 2-3; *see also Invista North America S.a.r.l. v. M&G USA Corp.*, 2013 WL 3216109, at *5 (D. Del. June 25, 2013) (striking non-infringement defense that "alter[ed] the entire infringement and non-infringement landscape that was developed and vetted during fact and expert discovery," because that "new defense" was "untimely and highly prejudicial")).

[9]Neither party asked the Court to construe this term during claim construction.

Plaintiffs contend that any process that creates bubbles of inert gas in the solution satisfies the "bubbling" claim requirement. (D.I. 417 at 9) Exela, by contrast, contends that "bubbling" is "a term of art," referring to a specific process requiring "the use of pressure to force the inert gas into the liquid." (D.I. 415 at ¶¶ 173, 176; Tr. at 925-26, 1024)

This is a claim construction issue. The Court looks to intrinsic as well as extrinsic evidence to determine how one of ordinary skill in the art would understand the term "bubbling" in the context of the '218 patent. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). Here, the intrinsic evidence favors Plaintiffs, because nothing in the specification or the prosecution history requires "bubbling" to be limited to the specific process proposed by Exela. The only evidence offered by Exela in support of its proposed construction is extrinsic, namely the following testimony of Dr. Palmieri:

> **Q.** What does bubbling mean in the pharmaceutical industry?
>
> **Dr. Palmieri.** Bubbling is a term of art. It[] says it's the same as sparging, what we are doing is synonymous with sparging. What a person of skill in the art would know is that bubbling is a term that means you are forcing an inert gas, nitrogen, into a solution under some pressure, and that would be known as bubbling.[10]

(Tr. at 925) Exela did not introduce any evidence, other than Dr. Palmieri's opinion, to support its proposed construction. (D.I. 415 at ¶¶ 175, 176, 179) While expert testimony may be used to "establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field . . . conclusory, unsupported assertions by experts as to the definition of a claim

[10]Plaintiffs' expert, Dr. Schoonen, disagreed with Dr. Palmieri on this point. (Tr. at 318-23, 426)

term are not useful to a court." *Phillips*, 415 F.3d at 1318. Hence, the Court is not persuaded that "bubbling" should be interpreted narrowly as Exela proposes.

Based on the Court's construction, Exela's ANDA process satisfies the "bubbling" limitation. Dr. Schoonen testified that Exela's ANDA process includes an "argon blanketing" step, which creates bubbles of argon in the solution. (Tr. at 323-25; *see also* PTX-008 at 5) According to Dr. Schoonen, "the net result is argon is going into solution, oxygen is leaving the solution." (Tr. at 325) Dr. Palmieri confirmed that bubbles were formed during the "argon blanketing" step in Exela's ANDA process, disputing only whether "argon blanketing" can be considered bubbling. (*Id.* at 1021) Therefore, the Court concludes that Exela's ANDA process literally satisfies this limitation of the '218 patent.

b. Doctrine of equivalents

With respect to the doctrine of equivalents, the parties dispute whether the claimed step of "bubbling with at least one inert gas and/or placing under vacuum"[11] is equivalent to blanketing the solution with argon, as occurs in the Exela process. To find infringement under the doctrine of equivalents, the Court must determine whether these two processes "perform[] substantially the same function in substantially the same way to obtain the same result." *Graver Tank*, 339 U.S. at 608. Having considered the evidence presented at trial, the Court concludes that any differences between the two processes are insubstantial and they are, therefore, equivalent.

First, the claim language equates two different processes for deoxygenation: "bubbling

[11]For purposes of analyzing the doctrine of equivalents, the Court will apply Exela's proposed definition of "bubbling" as a process that requires "the use of pressure to force the inert gas into the liquid." (D.I. 415 at ¶¶ 173, 176; Tr. at 925-26, 1024)

with at least one inert gas" and "placing under vacuum." According to the claim, these processes may be used alone "and/or" together to deoxygenate the solution to below 2.0 ppm. (PTX-002) The claim, thus, suggests that the two processes are interchangeable, and that the principles underlying the two processes are equivalent.

There is no dispute that "argon blanketing" performs the same "function" as "bubbling" or "placing under a vacuum," as Dr. Palmieri testified that "argon blanketing can deoxygenate water."[12] (Tr. at 1028) The "way" the three processes deoxygenate the solution is also substantially the same. At trial, Dr. Schoonen explained that applying an argon blanket "create[s] a disequilibrium" in the system. (*Id.* at 324) To reestablish equilibrium, oxygen in the solution will transfer from the aqueous phase into the gas phase, and "will partition into th[e] head space." (*Id.* at 325) "The net result is argon is going into solution, oxygen is leaving the solution." (*Id.*) Dr. Schoonen testified that "placing the solution under a vacuum" functions the same way: the vacuum creates a disequilibrium and "oxygen will transfer from the aqueous phase trying to establish, reestablish equilibrium." (*Id.* at 355-56) Dr. Schoonen also testified that "bubbling," as Exela interprets this term, deoxygenates in substantially the same way: by creating a pressure differential which removes oxygen from the solution. (*Id.* at 354) With respect to the "results," the evidence showed that all three methods can be used to deoxygenate a solution to below 2.0 ppm. Specifically, Exela Batch II (PTX-810) and Batch III (PTX-811) results showed that using an argon blanket can reduce the DO content of the solution to below 2.0 ppm. (*See*

[12]Notably, Exela previously denied "that positive argon blanketing used in its manufacturing process 'decreases the dissolved oxygen content' by any appreciable level." (PTX-56 at 5)

PTX-810 at 8-10 (2.5 ppm to 0.1 ppm); PTX-811 at 6-8 (2.4 to 0.1))[13]

Exela responds that "Plaintiffs did not identify a single reference that equates bubbling with mixing under an argon blanket." (D.I. 436 at 12) Given the detailed, technical, and credible testimony of Dr. Schoonen, this argument is unpersuasive. So, too, was Dr. Palmieri's largely conclusive testimony on this point. (Tr. at 928-29) For instance, when asked whether "blanketing a liquid with an inert gas and mixing [is] equivalent to placing the liquid under a vacuum," Dr. Palmieri answered "No." (*Id.*) When asked to explain, Dr. Palmieri simply answered: "Because they're very different. There is not a vacuum. You have got, again, a layer of material above the solution. And it's not placing it under a vacuum." (Tr. at 929)

2. Exela's addition of an antioxidant is irrelevant

Claim 1 of the '218 patent includes a step of optionally completing the deoxygenation of the solution "by addition of an antioxidant." (PTX-002) Exela recognizes that this step is optional, but contends that "if the antioxidant is added, it must be added ***after*** the aqueous acetaminophen solution has been deoxygenated until its oxygen content is below 2 ppm." (D.I. 380 at 3) (emphasis added) In other words, according to Exela, although the step of adding an antioxidant is optional, if the step is performed, it must be performed according to the order of steps recited in the claim.[14] (*Id.*) Applying this logic, Exela contends that it cannot infringe because it "adds an antioxidant prior to the addition of acetaminophen and prior to the dissolved

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[13]Exela's request to strike portions of Dr. Schoonen's testimony (D.I. 14 at 14 n.4) is denied.

[14]This argument is based on the Court's statement that, "Consistent with the claim language and the specification, the process implicitly requires that the steps listed in claim 1 be performed in the stated order. Thus, the Court's constructions clarify that the first step must produce a solution with an oxygen content of 2 ppm prior to performing a later step." (D.I. 188 at 25)

oxygen content being reduced to below the level required by the claims." (D.I. 436 at 15) The Court does not agree.

There are two optional steps in the claimed process of the '218 patent.[15] During claim construction, the Court stated that "consistent with the plain meaning of the term 'optionally,' the steps recited in these [two] clauses do not necessarily have to be performed in order to practice the claimed method." (D.I. 188 at 23-24) Because the step of adding an antioxidant is optional, it makes no difference when that step is performed. For purposes of claim scope, it is as if the optional step does not exist. *See In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006) ("[O]ptional elements do not narrow the claim because they can always be omitted."); *see also* Manual of Patent Examining Procedure § 2111.04.

Exela cannot convert an optional claim step into a mandatory one by simply performing that step. Instead, the Court concludes that Exela's addition of an antioxidant during its manufacturing process is immaterial to the infringement analysis.

3. Exela deoxygenates "the solution" to below 2.0 ppm

Claim 1 of the '218 patent requires "deoxygenation of the solution by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm." (PTX-002) The parties dispute whether the '218 patent requires forming "the solution" ***prior to*** reducing the dissolved oxygen content below 2.0 ppm.

The Court has construed the term "aqueous solution" to mean "[a] composition containing water as a solvent and an active ingredient susceptible to oxidation." (D.I. 188 at 18)

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[15]Claim 1 of the '218 patent also includes the transitional phrase "comprising," which presumptively renders the claim open-ended. *See Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376 (Fed. Cir. 2004).

The "active ingredient susceptible to oxidation" in Exela's ANDA product is acetaminophen.[16] (D.I. 418 at ¶ 76) Based on the Court's construction, Exela contends that an "aqueous solution" is formed only ***after*** the addition of acetaminophen. Pursuant to Exela's ANDA process, however, the dissolved oxygen content is reduced below the critical 2.0 ppm threshold ***before*** adding acetaminophen. (D.I. 414 at 13) For this reason, Exela believes that it does not deoxygenate "the solution" to below 2.0 ppm and, thus, does not infringe any claim of the '218 patent. (*Id.*) Plaintiffs respond with evidence they believe shows this claim limitation is met both literally and under the doctrine of equivalents.

a. Literal infringement

Plaintiffs contend that Exela's ANDA process literally infringes the '218 patent because: "(1) the Court's claim construction does not require that the dissolved oxygen start above 2.0 ppm; (2) Exela's ANDA process comprises a single deoxygenation stage; and (3) Dr. Schoonen's theoretical model predicts that the dissolved oxygen level will drop below 2.0 ppm after addition of acetaminophen." (D.I. 437 at 17) The Court is not persuaded.

Plaintiffs contend that the Court's claim construction does not require that the dissolved oxygen content of the solution start above 2.0 ppm. According to Plaintiffs, all that is required is that "the oxygen content must be below 2.0 ppm after the bubbling/vacuuming" step. (D.I. 188 at 23) But, claim 1 of the '218 patent requires "deoxygenation of the solution . . . ***until*** the oxygen content is below 2 ppm." (PTX-002) (emphasis added) The plain meaning of the word "until" in this limitation requires "the solution" to have a dissolved oxygen content of greater than 2.0 ppm prior to the deoxygenation step. Other than the conclusory testimony of its expert,

[16]Paracetamol is another name for acetaminophen. (SUF at ¶ 80)

Dr. Orr, Plaintiffs have offered no evidence to the contrary. (D.I. 418 at ¶ 77; Tr. at 673-74)

Plaintiffs' second and third arguments are also unpersuasive. The plain language of the claim requires the solution to be formed before deoxygenation begins. The evidence presented at trial established that the dissolved oxygen level of Exela's ANDA product is below 2.0 ppm prior to the addition of acetaminophen. (*See* PTX-810 at 8-10; PTX-811 at 6-8) Given that the results of Dr. Schoonen's theoretical model are directly contradicted by the undisputed measurements taken during Exela's ANDA process, the Court does not find Dr. Schoonen's opinion persuasive.

The Court concludes that Plaintiffs have failed to prove literal infringement of this claim limitation.

b. Doctrine of equivalents

Plaintiffs contend that Exela's ANDA process satisfies the claim limitation requiring bubbling "the solution" until it is below 2.0 ppm under the doctrine of equivalents. According to Plaintiffs, "[t]here is no evidence in the specification that the [timing for adding] acetaminophen matters, the extrinsic evidence confirms that it does not, and the prior art did not necessitate claiming a particular order" of adding ingredients to the solution. (D.I. 437 at 17) The Court agrees.

At trial, the evidence showed no substantial differences between a process in which acetaminophen is added before reducing the oxygen content of the formulation to below 2.0 ppm and a process in which acetaminophen is added after reducing the oxygen content to below 2.0 ppm. Exela's formulation scientist, Mr. Sterling, testified that tests conducted by Exela during development of its ANDA product showed no differences based on the timing of adding acetaminophen relative to reducing the oxygen content of the formulation. (Tr. at 811-17) The

same conclusions are set forth in Exela's patent application for the accused ANDA process. (*See, e.g.*, PTX-067 at 61 (compare Example 15 with Example 16)) Plaintiffs' expert, Dr. Orr, further testified that adding acetaminophen before or after the deoxygenation step would have no impact on the stability of the final product. (Tr. at 679-80) Because the differences between the claim limitation and Exela's ANDA process are insubstantial, Exela's ANDA process infringes under the doctrine of equivalents. *See Brilliant Instruments*, 707 F.3d at 1346 (explaining that to "find infringement under the doctrine of equivalents, any differences between the claimed invention and the accused product must be insubstantial").

Exela has not disputed the accuracy of the evidence offered by Plaintiffs. Rather, Exela contends that Plaintiffs cannot show infringement under the doctrine of equivalents because: (1) Plaintiffs' arguments would vitiate the "bubbling . . . , until the oxygen content is below 2 ppm" limitation from the claim; and (2) Plaintiffs should be estopped from asserting infringement under the doctrine of equivalents as a result of arguments made during prosecution of the '218 patent. (D.I. 436 at 14) Neither argument is persuasive.

With respect to vitiation, the Federal Circuit has recently explained that:

> The vitiation test cannot be satisfied merely by noting that the equivalent substitute is outside the claimed limitation's literal scope. Rather, vitiation applies when one of skill in the art would understand that the literal and substitute limitations are not interchangeable, not insubstantially different, and when they do not perform substantially the same function in substantially the same way, to accomplish substantially the same result.

Brilliant Instruments, 707 F.3d at 1347. As explained above, based on the evidence presented at trial, the Court has concluded that the two processes are essentially interchangeable. Indeed,

regardless of when acetaminophen is added to the formulation, the result is the same – the "solution resulting from either bubbling or placing under vacuum or both [will have] an oxygen content of less than 2 ppm." (D.I. 188 at 24) For this reason, finding infringement under the doctrine of equivalents does not vitiate the bubbling limitation of the claim.

With respect to Exela's prosecution history argument, there is no dispute that the patent applicants did not amend the "bubbling" limitation during prosecution of the '218 patent. (PTX-004 at 398) Rather, the applicants distinguished the prior art, by explaining that the prior art failed to teach "the oxygen content [being] below 2 ppm [which] results in a stable solution as can be seen from the data in the examples." (PTX-004 at 404) Neither the Examiner's rejection, nor the applicants' response, concerned the timing for adding the "active ingredient susceptible to oxidation" to create "the solution." Rather, the arguments focused on whether the prior art disclosed the specific oxygen content threshold (below 2.0 ppm). Accordingly, prosecution history estoppel does not apply, and Plaintiffs are not precluded from seeking a determination of infringement under the doctrine of equivalents. *See Riles v. Shell Exploration & Prod. Co.*, 298 F.3d 1302, 1310 (Fed. Cir. 2002) (stating that prosecution history estoppel applies only to subject matter "unmistakabl[y] surrender[ed]" through statements made during prosecution).

4. Exela infringes the asserted dependent claims of the '218 patent

Plaintiffs assert that Exela's ANDA product/process infringes dependent claims 3, 4, and 19 of the '218 patent, and at trial presented evidence with respect to the additional limitations of these dependent claims. Exela did not dispute Plaintiffs' evidence, or raise any non-infringement challenges in rebuttal. Therefore, the Court concludes that Exela infringes dependent claims 3, 4, and 19 of the '218 patent.

III. VALIDITY

Exela contends that both the '222 and the '218 patent are invalid. The Court addresses each asserted basis for invalidity below.

A. Legal Standards

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (anticipation); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (obviousness). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted). In connection with the presumption of validity, the Federal Circuit has explained that:

> When no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008).

1. Anticipation

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373,

1377 (Fed. Cir. 2003). Inherent anticipation, which is the theory Exela asserts here, requires that every element of the claim must "necessarily and inevitably" be present in the anticipating reference, even though those elements are not expressly disclosed. *See id.* at 1378. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Bettcher Indus. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011).

2. Obviousness

A patent may not issue "if the differences between the subject matter sought to be patented and the prior art are such that the 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." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *Procter & Gamble*, 566 F.3d at 994; *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry

must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007). In addition, the use of hindsight is not permitted when determining whether a claim would have been obvious to one of ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning").

B. Validity of the '222 Patent

Exela contends that the asserted claims of the '222 patent are either anticipated or obvious over three prior art references: (1) Greek Patent Application No. 870101510 ("GR510"); (2) Korean Patent No. 1993-0011994 ("KR994"); and (3) U.S. Patent No. 5,270,050 ("the '050 patent").

1. GR510[17]

Exela argues that GR510 anticipates claims 1, 3, and 4 of the '222 patent, and that claims 5, 9, 10, 12, 17, and 18 are obvious over GR510 in view of additional prior art references. Exela also contends that GR510 anticipates or renders obvious claim 16. (D.I. 414 at 18-21)

a. Independent claim 1

With respect to anticipation of claim 1, Plaintiffs argue that: (1) Exela failed to establish that GR510 is "stable;" and (2) GR510 does not satisfy the "aqueous medium" limitation. (D.I. 417 at 17-19)

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[17]Plaintiffs contend that Exela has failed to prove that GR510 was publicly available before the priority date of the '222 patent, precluding the Court from considering GR510 as a prior art reference. (D.I. 417 at 17) The Court does not agree. The cover page of GR510 contains a "publication date" of December 7, 1987. (PTX-765 at 1) Plaintiffs have provided no basis to believe that GR510 was not published by the Greek Patent Office on that date.

i. "stable"

Claim 1 of the '222 patent requires a "stable, liquid formulation." (PTX-001) The Court construed "stable" to mean that "[t]he active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life." (D.I. 188 at 5) According to Plaintiffs, Exela has failed to establish that GR510 has a pharmaceutically acceptable shelf life. (D.I. 417 at 17-18) On this point, Exela relies primarily on the testimony of Dr. Palmieri, who pointed to GR510's characterization of its formulation as "stable," and opined that a commercial embodiment of GR510 (Apotel) has been sold in Greece for more than 20 years, which strongly suggests that the embodiment is stable. (D.I. 414 at 18-19)

In the Court's view, the disclosure of GR510 does not show that GR510 uses the word "stable" in the same way as the '222 patent, to mean that "[t]he active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life." Dr. Palmieri did not address this issue. (Tr. at 871) Exela's only response to this deficiency is that "GR510 provides no data to indicate that there is a color change that would indicate an unstable product." (D.I. 436 at 19) But that argument improperly attempts to shift the burden of proving validity to Plaintiffs. Instead, Exela bears the burden to prove that the GR510 formulation is stable, as part of its burden to invalidate the '222 patent. Additionally, as Dr. Palmieri testified, "[t]here is no technical reason" that Exela could not have performed a stability study on the GR510 formulation (Tr. at 1040), but Exela did not produce evidence of any such test. Moreover, even if a person of ordinary skill in the art could look at the disclosure of GR510 and conclude that its formulation is "most likely" stable, as Dr. Palmieri opined (Tr. at 1038), that does not rise to the level of an abiding conviction as to the truth, so it falls well short

of Exela's clear and convincing burden.

The evidence presented with respect to Apotel is also unpersuasive. Exela contends that Apotel has been on the Greek market for 20 years, but the only evidence on this point is the testimony of Dr. Palmieri, who admitted that he had no personal knowledge of any facts related to Apotel. (Tr. at 1031-32) In particular, Dr. Palmieri had no personal knowledge regarding the process used to make Apotel, or the amount of ingredients used in the Apotel formulation. (*Id.* at 1031-32) The only document Dr. Palmieri cited as "disclosing the formulation of the Apotel product" (DTX-429) did not provide sufficient details from which the Court could conclude that Apotel satisfies the stability limitation of the '222 patent. (Tr. at 1031-32) Moreover, DTX-429 is dated "02/10/1998," which is after the critical date of the '222 patent. (DTX-429 at 2) Given this record, the Court is unable to conclude that Apotel is the commercial embodiment of GR510 and does not find clear and convincing evidence that GR510 satisfies the "stable" limitation of the '222 patent.[18]

ii. "aqueous medium"

Claim 1 of the '222 patent also requires an "aqueous medium." (PTX-001) The Court has previously construed this term to mean "a medium containing water or aqueous mixtures of water and a polyhydric compound and/or a water soluble ***alcohol***." (D.I. 188 at 10) (emphasis

[18]Plaintiffs additionally argue that GR510 fails to satisfy the "stable" limitation because it is not "pharmaceutically acceptable, as required by the Court's construction." (D.I. 417 at 18) According to Plaintiffs, the glycerol formal in the GR510 formulation is toxic, and administering a therapeutic dose of the GR510 formulation would contain "an amount of glycerol formal that is far in excess of the daily intake limit" to be considered pharmaceutically acceptable. (*Id.*) However, the Court's construction does not require the claimed formulation to be "pharmaceutically acceptable," only that the formulation have a "pharmaceutically acceptable ***shelf life***." (*See* D.I. 188 at 5) (emphasis added)

added) Plaintiffs contend that GR510 fails to satisfy this limitation because "glycerol formal is neither a polyhydric compound nor a water soluble ***alkanol***." (D.I. 417 at 18) (emphasis in original) Of course, the Court's construction uses the word "alcohol," not "alkanol." Plaintiffs ask the Court to replace "alcohol" with "alkanol."[19] Plaintiffs also ask the Court to further construe the word "alkanol" to mean an "aliphatic alcohol that consists only of hydrogen and carbon atoms other than a hydroxyl group." (D.I. 437 at 20)

According to Plaintiffs, the Court's original claim construction was based entirely on a single paragraph in the '222 patent specification (col. 2, ll. 22-27), which was later modified by a certificate of correction. (D.I. 417 at 18) (citing D.I. 188 at 10-11) Plaintiffs contend that the certificate of correction requires the Court to reevaluate its construction. (*Id.*) This argument is not persuasive. The certificate of correction did not change the substance of the '222 patent disclosure; it simply corrected a spelling error by replacing "alcanol" with the correctly spelled "alkanol." (PTX-001)

Moreover, even if the Court replaced the word "alcohol" in its construction with the word "alkanol," as Plaintiffs propose, the Court would not adopt Plaintiffs' proposed definition of "alkanol," as it is not consistent with the disclosure of the specification. For instance, claims 9-12 of the '222 patent define "aliphatic polyhydroxy ***alkanol***" to include glucose, but glucose falls outside of Plaintiffs' proposed construction. (Tr. at 1301) For this additional reason, the Court rejects Plaintiffs' position and concludes that GR510 satisfies the "aqueous medium" limitation of the '222 patent.

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[19]Prior to trial, the parties submitted supplemental claim construction briefs addressing the appropriate construction of the term "alkanol." (*See* D.I. 347, 350, 357, 359) At that time, the Court declined to further construe this term. (Tr. at 68)

b. Dependent claims 3 and 4

Dependent claims 3 and 4 are directed to specific pH ranges for buffering the aqueous medium. (PTX-001) Exela contends that claims 3 and 4 are anticipated by GR510. Having concluded that GR510 does not anticipate independent claim 1, the Court also concludes that GR510 cannot anticipate dependent claims 3 and 4. *See Synqor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013) (explaining that court "need not consider Defendants' arguments that certain dependent claim limitations would have been obvious where the base claim has not been proven invalid"); *Hartness Int'l Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108 (Fed. Cir. 1987) (finding independent claim 1 was valid and adding that, *a fortiori*, "dependent claim 3 was nonobvious (and novel) because it contained all the limitations of claim 1 plus a further limitation").

c. Dependent claims 5, 9, 10, and 12

Dependent claims 5, 9, 10, and 12 further define the specific antioxidants that may be used in the claimed formulation. (PTX-001) Exela contends that these claims are obvious over GR510 in combination with Connors (DTX-428). (D.I. 414 at 20)[20] Specifically, although GR510 discloses using a specific antioxidant – sodium metabisulfite – Exela believes that it would have been obvious for one of ordinary skill in the art to replace that antioxidant with one or more compounds listed in Connors. (*Id.*) At trial, Exela introduced evidence identifying the drawbacks of using sodium metabisulfite as an antioxidant, including FDA regulations that

[20] Exela's brief actually references KR994, not GR510 (D.I. 414 at 20), but the Court believes (as does, apparently, Cadence) that Exela meant GR510 here, for reasons including the heading, "The Asserted Claims Are Anticipated Or Rendered Obvious By GR510 Alone Or In Combination With Other Prior Art" (*id.* at 18).

require a warning label to be placed on products containing sodium metabisulfite. (*See* 21 C.F.R. § 201.22 (1982); *see also* DTX-438 at 16) Exela also showed that Connors identifies a small number of potential substitutes for sodium metabisulfite. (DTX-438 at 16) Based on this information, Exela contends that one of ordinary skill in the art would have had a reasonable expectation of success in substituting any of the listed antioxidants for the sodium metabisulfite in GR510. *See Procter & Gamble*, 566 F.3d at 994.

Given that claims 5, 9, 10, and 12 each depend from valid independent claim 1, and because Connors does not cure the deficient disclosure of GR510 with respect to the limitations found in claim 1 and incorporated into dependent claims 5, 9, 10, and 12, these dependent claims, too, are valid. *See Synqor*, 709 F.3d at 1375; *Hartness*, 819 F.2d at 1108.

d. Dependent claim 16

Exela contends that GR510 anticipates or renders obvious claim 16, which claims an acetaminophen concentration of 2-50 mg/mL. (D.I. 414 at 20) GR510 discloses acetaminophen concentrations of 0.15 mg/mL and 150 mg/mL. (PTX-765 at 5, 6) Neither concentration falls within the claimed range; thus, there is no anticipation. However, Exela also contends that, based on the disclosure of GR510, it would have been obvious for one of ordinary skill in the art to have tried any concentration between 0.15 mg/mL and 150 mg/mL and to have had a reasonable expectation of success, including for a range of 2-50 mg/mL.[21] However, because the

[21]Plaintiffs have moved to strike "Dr. Palmieri's testimony that claim 16 is invalid because one allegedly could dilute a solution containing 150 mg/mL to a solution containing 2-50 mg/mL, because it was never disclosed in any of Dr. Palmieri's export reports or in deposition." (D.I. 417 at 19 n.11) Plaintiffs have further moved to strike Dr. Palmieri's testimony that "sodium metabisulfite becomes sodium bisulfite when dissolved in water[,] . . . which was never disclosed in any expert report or at deposition." (*Id.* at n.12) Because the Court has not relied on the objected-to testimony of Dr. Palmieri, the Court will deny Plaintiffs' motion.

Court has already concluded that GR510 does not teach the "stable" limitation of claim 1, GR510 cannot render claim 16 obvious even if it would have been obvious for one of ordinary skill in the art to use a concentration between 2-50 mg/mL.

e. Dependent claims 17 and 18

Claim 17 requires adding an isotonizing agent to obtain isotonicity. (PTX-001) Exela contends that this claim is obvious over GR510 in combination with "prior knowledge" in the art. (D.I. 414 at 21) Claim 17 depends from independent claim 1. Because the "prior knowledge" identified by Exela does not cure the deficiencies of GR510 with respect to independent claim 1, claim 17 is valid.

Claim 18 requires sterilizing the formulation by heat treatment. (PTX-001) Exela contends that this claim is invalid over the combination of GR510 and U.S. Pat. No. 3,161,310 ("the '310 patent"). Exela relies on the '310 patent for its purported disclosure of using heat as the preferred method of sterilization. (D.I. 414 at 21) Claim 18 depends from independent claim 1. Because the '310 patent does not cure the deficient disclosure of GR510 with respect to claim 1, the Court concludes that claim 18 is also valid.

2. KR994

Exela argues that KR994 anticipates claims 1 and 3 of the '222 patent, and that claims 4, 5, 9, 10, 12, 17, and 18 are obvious over KR994 in view of additional prior art references. (D.I. 414 at 21-23)

a. Independent claim 1

Plaintiffs dispute that KR994 anticipates claim 1, arguing that: (1) Exela failed to establish that KR994 is "stable;" and (2) KR994 does not include a "buffering agent." (D.I. 417

at 21-22)

i. "stable"

Claim 1 of the '222 patent requires a "stable, liquid formulation." (PTX-001) As explained above, the Court construed the word "stable" to mean that "[t]he active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life." (D.I. 188 at 5) The "active pharmaceutical ingredient" in the '222 patent is paracetamol, also known as acetaminophen. (PTX-001 at col. 1, ll. 9-12; SUF at ¶ 80) When exposed to water, paracetamol degrades to para-aminophenol, which is toxic. (PTX-0001 at col. 1, ll. 39-48; Tr. at 162, 229, 1041) Measuring the amount of para-aminophenol in a formulation after a set time period is one way to determine whether the formulation is stable. (*See* PTX-950 at 4) ("Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.") Thus, if a formulation contains an excess amount of para-aminophenol, that is evidence that the formulation does not have "a pharmaceutically acceptable shelf life."

According to Exela, KR994 discloses paracetamol formulations that are stable for up to two years. (D.I. 414 at 21) As evidence, Exela points to data from "stability tests" disclosed in KR994. (PTX-789 at 4-5) This stability test data shows that formulations made according to embodiments 2 and 5 of KR994 were clear and colorless after two years storage at room temperature, in accelerated testing conditions (40° C), and upon exposure to light. (*Id.*) The KR994 inventors considered a formulation stable if it had less than 1% concentration of para-aminophenol after 24 months – and their tested formulations were reported to have met this standard. (*Id.* at 4-5) Exela contends that the stability data provided in KR994 proves that the

KR994 formulation has a pharmaceutically acceptable shelf life. (D.I. 415 at ¶ 228)

Plaintiffs do not dispute that KR994 includes "stability tests" data, or that the inventors of KR994 considered their formulation "stable" based on those tests. Plaintiffs instead contend that the Court's claim construction requires a different, more demanding standard. According to Plaintiffs, the KR994 formulation would not be considered stable under the threshold established by the Court's construction. (D.I. 417 at 21) The Court agrees with Plaintiffs.

Exela has failed to prove that a formulation with a 1% concentration of para-aminophenol, as in KR994, would have "a pharmaceutically acceptable shelf life" under well-accepted U.S. standards. The FDA's "Guidelines on Impurities in New Drug Substances" set a 0.05% to 0.1% threshold for toxic impurities such as para-aminophenol – limits that are ten to twenty times lower than the KR994 application.[22] (PTX-787 at 3) Although published by the FDA, these "Guidelines" were approved by regulatory agencies from the European Union and Japan, and were based on input from regulatory and industry representatives from all over the world. (*See* PTX-787 at 1) Exela follows these guidelines as well, limiting the maximum para-aminophenol content in its ANDA product to no more than 0.1%. (PTX-045 at 42; Tr. at 798, 1176-77) As explained by Mr. Sterling, Exela's primary ANDA formulator, Exela selected the 0.1% para-aminophenol threshold "[b]ased on a review of the current FDA, EP, and USP" guidelines. (PTX-075 at 1) Accordingly, as Dr. Elder testified, one of skill in the art would not find the KR994 formulation to be "stable" as that term is used in the '222 patent. (Tr. at 1261-

[22]The FDA threshold is 0.1% for drugs when the maximum daily dose is less than or equal to 2 grams/day, and is 0.05% when the maximum daily dose is more than 2 grams/day. (PTX-787 at 3) The standard dose of acetaminophen is 325-1,000 mg, with a maximum daily intake of 4,000 mg. (PTX-328 at 18; PTX-653 at 1; Tr. at 1239-40)

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Exela argues that it is not proper to "tie patentability to FDA approval," and contends that the FDA Guidelines are irrelevant because they were issued "much later." (D.I. 436 at 23) These arguments are not persuasive. The FDA Guidelines cited by Plaintiffs were published in January 1996, eight months prior to the critical date of the '222 patent. (PTX-787) Those FDA Guidelines are the only unbiased, objective evidence in the record indicating what one of ordinary skill in the art at the time of the invention would understand to be an acceptable toxic impurity threshold for a new drug to be registered in the U.S. Exela has offered no evidence that one of ordinary skill in the art would consider a formulation with twenty times the maximum amount of para-aminophenol allowed under FDA Guidelines to be stable. Additionally, Plaintiffs correctly note that the data provided in the KR994 "stability test" is limited to embodiments 2 and 5, which do not contain any of the specific buffering agents listed in KR994. (PTX-789 at 4-5) There is no evidence in the record to support a conclusion that adding buffer to the formulations of embodiments 2 and 5 of KR994 results in the same (or even similar) stability profiles. To the contrary, Dr. Elder testified that adding excipients to a formulation can cause the active ingredient to precipitate. (Tr. at 1265) This casts further doubt on the stability study results in KR994.

ii. "buffering agent"

Plaintiffs contend that Exela has failed to establish that KR994 contains a buffering agent. (D.I. 417 at 22) Plaintiffs admit that KR994 discloses a "list of buffers in a general description of the invention," but contend that this disclosure is not sufficient because "[n]one of these buffers are disclosed in embodiments 1-5." (*Id.*) The Court is not persuaded by Plaintiffs.

Contrary to their arguments, claim 3 of KR994 describes an injection containing paracetamol as the main ingredient "prepared by adding supplements selected from the water, antioxidant, pain relieving agent, solubilizing agent, or pH control agent." (PTX-789 at 10) The Court has construed the term "buffering agent" to mean an "agent that helps the formulation resist change in pH." (D.I. 188 at 12-13) The "pH control agent" in KR994 satisfies this construction.

b. Dependent claims 3, 4, 5, 9, 10, 12, 17, and 18

Exela contends that KR994 anticipates dependent claim 3 of the '222 patent. Claim 3 depends from independent claim 1. Having concluded that KR994 does not anticipate independent claim 1, the Court also concludes that KR994 does not anticipate dependent claim 3. *See Synqor*, 709 F.3d at 1375; *Hartness*, 819 F.2d at 1108.

Exela contends that dependent claims 4, 5, 9, 10, 12, 17, and 18 are obvious over KR994 in view of additional prior art references. (D.I. 414 at 22-23) These references are the same as those Exela proffered for combination with the GR510 reference. The Court has addressed these specific combinations above and reaches the same conclusions here.

3. U.S. Patent No. 5,270,050

Exela contends that claims 1, 3, 4, 16, and 17 of the '222 patent are anticipated by the '050 patent.[23] (D.I. 414 at 23) Exela relies on the disclosure of the '050 patent, its Paragraph IV letter, and Dr. Koneru's factual testimony. (D.I. 436 at 25) Exela's expert, Dr. Palmieri, did not address the '050 patent during his testimony. (Tr. at 54) Plaintiffs contend that Exela failed to

[23]Although Exela's Paragraph IV letter asserts that certain claims of the '222 patent are also obvious over the combination of the '050 patent and Connors (DTX-428), Exela does not address this combination in either of its post-trial briefs. (*See* D.I. 414; D.I. 436) To the extent Exela intended to maintain these arguments, the Court rejects them.

establish invalidity by clear and convincing evidence. (D.I. 437 at 23-24) According to Plaintiffs, the '050 patent fails to meet at least the "stable" limitation of claim 1 of the '222 patent.[24] The Court agrees.

There is no discussion of stability in the '050 patent. (*See* DTX-113) Exela did not address stability of the '050 patent formulation in its Paragraph IV letter. (*See* DTX-225 at 33-40) Dr. Koneru did not address stability in his testimony. (*See* Tr. at 1147-53) Instead, Exela simply states that "the formulations disclosed in the '050 patent are presumed stable and thus anticipate the claims of the '222 patent." (D.I. 414 at 24) This assertion does not constitute clear and convincing ***evidence*** that any formulation disclosed in the '050 patent is "stable," as that term is used in the '222 patent. Hence, Exela has failed to prove the '050 patent anticipates any claim of the '222 patent.

4. Secondary considerations

In evaluating obviousness, courts should consider objective evidence of nonobviousness in the form of secondary considerations, as that "may often be the most probative and cogent evidence in the record" related to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Here, Plaintiffs point to unexpected results, satisfaction of an unmet need, failure of others, commercial success, successful licensing, and praise of others as objective evidence of nonobviousness. (D. I. 440 at 1-5)

a. Nexus

Exela contends that "Plaintiffs have done no testing to establish that either Ofirmev® or

[24]During the *Markman* hearing, the parties agreed that "stable" is a claim limitation even though it appears in the preamble of claim 1. (D.I. 187 at 76)

Perfalgan contain an agent that helps resist pH change," and, therefore, no nexus exists between the commercial embodiments and the claimed invention. (D.I. 414 at 24-25) Plaintiffs respond that: (1) "Exela's Notice Letter conceded that OFIRMEV had a buffer as claimed in the '222 patent;" and (2) Exela never disputed Dr. Orr's conclusion that the '222 patent covered OFIRMEV® and Perfalgan. (D.I. 440 at 1) Exela has no reply to these facts. (*See* D.I. 442, 444) The Court concludes that Plaintiffs have established that OFIRMEV® and Perfalgan are embodiments of the '222 patent. Hence, evidence relating to OFIRMEV® and Perfalgan is relevant to the obviousness analysis with respect to the asserted claims of the '222 patent.

Exela also contends that Plaintiffs have failed to establish a nexus between OFIRMEV® and Perfalgan and any novel feature of the '222 patent. (D.I. 442 at 1-2) The Court does not agree. All of the asserted claims of the '222 patent require a "stable" formulation, which, as discussed above, is a novel feature of the '222 patent. OFIRMEV® and Perfalgan are "stable" formulations within the meaning of the '222 patent. (Tr. at 687-88, 694-95)

b. Unexpected results

Plaintiffs contend that formulations covered by the claims of the '222 patent achieved unexpected results, including that: (1) the formulations remained stable for an unexpectedly long time; (2) adding an antioxidant improved stability; and (3) the formulations remained stable following heat sterilization. (D.I. 440 at 2) Exela does not dispute these unexpected results in its supplemental briefs on secondary considerations. (*See* D.I. 442, 444) Thus, the Court concludes that the unexpected results achieved by the claimed inventions of the '222 patent weigh in favor of nonobviousness. *See In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) ("[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been

obvious.").

c. Long-felt need

Plaintiffs contend that Perfalgan and OFIRMEV® satisfied a long-felt need for stable, ready-to-use, intravenous formulations of acetaminophen. (D.I. 440 at 2-4) FDA evidence offered by Plaintiffs strongly supports the conclusion that an unmet need existed in the U.S. prior to the introduction of OFIRMEV®. For example, the FDA has stated that since 1976 it has been "anxious" to have a "safe[] parenteral antipyretic available," and that it would be "advantageous to develop a parenteral form of a known safe and effective antipyretic agent." (PTX-776 at 1) The FDA also granted priority review for Plaintiffs' NDA application, stating:

> The Applicant requested and was granted a priority review because ***this product fulfills an unmet medical need for the treatment of fever and acute pain with an intravenous formulation*** in hospitalized adults and pediatric patients. Although there are many acetaminophen products currently available in the United States, there is not a previously approved intravenous formulation.

(PTX-659 at 17) (emphasis added) In a follow-up report, the FDA confirmed that "Ofirmev™ was granted a priority review ***because this product fulfilled an unmet medical need*** for the treatment of fever and acute pain with an intravenous formulation." (PTX-1010 at 4) (emphasis added)

Exela does not meaningfully rebut these points, arguing only that "[l]ong-felt unmet need" is a legal term, and that "the FDA uses the words 'unmet need' in a different context." (D.I. 444 at 3) Exela does not explain how the context renders the FDA findings immaterial. Exela also contends that there was "no long-felt need for an injectable antipyretic because

InjectApap was previously FDA approved for fever reduction." (*Id.*) But InjectApap was never brought to market (Tr. at 1631) and was known to "produce tissue irritation and necrosis" (PTX-776 at 17-18). The Court concludes that the FDA documents support a finding of long-felt need.

Exela also contends that no long-felt need existed because there was no "buzz of excitement at national meetings," other treatments for post-operative acute pain are available, and the side effects that can be avoided by using Perfalgan and OFIRMEV® can also be avoided by other methods. (D.I. 442 at 4) Even accepting Exela's contentions, however, the evidence as a whole leads the Court to find there was a long-felt need at the time of the invention.

d. Failure of others

Plaintiffs contend that the repeated failure of others to develop an injectable formulation of acetaminophen supports a conclusion of nonobviousness. *See Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991) (concluding that failure of others "to find a solution to the problem which the patent[] in question purport[s] to solve" is evidence of nonobviousness). Plaintiffs rely on the testimony of Mr. Drouin, who testified that UPSA unsuccessfully attempted to develop an injectable formulation of acetaminophen prior to taking a license from Pharmatop.[25] (Tr. at 1405, 1409-12) Plaintiffs also cite FDA documents, which describe efforts to develop an injectable formulation of acetaminophen as "challenging" and state that "33 years after the Agency expressed the need for another parenteral antipyretic agent, no such product is available." (PTX-776 at 1; *see also* PTX-1011 at 2) In response, Exela identifies InjectApap and

[25]Mr. Drouin also testified that UPSA was approached by a "Swiss company" regarding an IV acetaminophen formulation, but that its formulation was unstable. (Tr. at 1415) The Court agrees with Exela (D.I. 444 at 3) that this testimony is not sufficiently detailed or corroborated to support a conclusion that some unidentified Swiss company failed to develop an injectable formulation of acetaminophen.

Apotel as examples of stable injectable acetaminophen formulations. Exela also introduced several publications that described purportedly stable acetaminophen formulations and methods for making such formulations. (*See* DTX-108 (article); DTX-109 (German patent); DTX-175 (U.S. patent)) The Court concludes that, overall, the evidence supports a finding that others failed in their attempts to make stable acetaminophen formulations.

e. Commercial success

Commercial success is a relevant indicator of nonobviousness "because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Plaintiffs contend that both OFIRMEV® and Perfalgan are commercially successful, as demonstrated by the substantial revenue and unit sales of these drugs. (D.I. 440 at 5)

With respect to OFIRMEV®, Exela argues that: (1) Plaintiffs' OFIRMEV® sales were the result of extensive marketing and promotional efforts, not any novel claimed features; and (2) OFIRMEV® sales did not meet Plaintiffs' target goals and, thus, were a disappointment, not a success.[26] The Court does not agree.

Exela cites Plaintiffs' SEC filings and internal marketing documents to support its argument that OFIRMEV® sales are driven by aggressive marketing and promotion. (D.I. 443 at ¶ 341) (citing PTX-893 and PTX-261) In addition, Exela's expert, Dr. Boghigian, repeatedly testified that "the product is being driven by marketing and promotion." (Tr. at 1667, 1668,

[26]Exela also contends that Plaintiffs evaluated the wrong market. (D.I. 442 at 3) The Court does not find Exela's argument persuasive.

1673, 1677) There is no doubt that marketing and promotional efforts are an important part of Plaintiffs' sales strategy. However, Exela has failed to prove that this case is like *McNeil-PPC, Inc. v. L. Perrigo Co.*, on which Exela relies (D.I. 444 at 1-2) and in which the district court found that the sales were "the calculated result of an aggressive marketing campaign of ***unprecedented*** scope." 207 F. Supp. 2d 356, 372 (E.D. Pa. 2002) (emphasis added). Exela has offered no evidence that Plaintiffs' promotional efforts were any more aggressive than is typical in the pharmaceutical industry.[27] Mr. Byrd, Cadence's Senior Vice President and Chief Commercial officer, also explained that Cadence did not have any sales force prior to launching OFIRMEV®, which contributed to the increased marketing expenses. (Tr. at 1337)

Plaintiffs acknowledge that sales of OFIRMEV® are below Plaintiffs' initial projections. (Tr. 1343, 1353) But this fact is not dispositive of the commercial success inquiry. A number of unexpected factors contributed to the disparity between projected and actual sales, including delays associated with regulatory approval by hospital therapeutic committees. (Tr. at 1343) Despite not meeting initial projections, sales have increased every year, even as Plaintiffs have twice increased prices. (Tr. at 1347, 1349-51, 1536) The steady, significant growth of OFIRMEV® sales is an indicator of nonobviousness. Further indicative of OFIRMEV's® commercial success are Exela's interest in entering the market and Exela's estimate that the market for a first-to-file generic product will "exceed $300mm in revenue." (PTX-63; Tr. at 1163)

Exela contends that sales of Perfalgan are "irrelevant," due to the "salient" cultural and

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[27]It is not necessary "that the patented invention be solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence, along with other pertinent factors." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

regulatory differences between the American and European analgesia markets. (D.I. 442 at 2-3) Exela believes that as a result of these differences, opioids are "less available to treat acute pain in Europe, and their use is discouraged." (*Id.* at 2) Exela further contends that Perfalgan sales are not relevant because they "piggybacked" on the previous success of Prodafalgan. (*Id.* at 2-3) Finally, Exela suggests that foreign sales cannot support the commercial success of a U.S. patent. (*Id.* at 2) These arguments are not persuasive.

European sales are not per se "irrelevant." Plaintiffs have pointed to several examples of cases in which a U.S. court has considered sales outside the U.S. *See, e.g.*, *Continental Can*, 948 F.2d at 1273 (sales in Japan offered as evidence of nonobviousness); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 923 F. Supp. 2d 602, 677 (D. Del. 2013) (considering worldwide sales). Fundamentally, Exela has not explained why differences between the U.S. and European analgesia markets should lead the Court to discount Perfalgan's success entirely, especially as Perfalgan has generated $1.7 billion in sales between 2003 and 2011.[28] (Tr. at 1524, 1531-32) The Court agrees that the regulatory and cultural differences between the two markets are a factor to be considered in evaluating commercial success. However, it also is true that shortly after launch Perfalgan became the top selling non-opioid IV analgesic in each of the "Big Five" European markets. (PTX-872; PTX-1009; Tr. at 188-89, 1527-29) This is evidence of a commercially successful product, even accounting for market differences.

With respect to the "piggybacking" argument, Mr. Drouin testified that BMS was able to successfully enter into the market and sell Perfalgan even in countries where Prodafalgan had not

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[28]Exela began developing its ANDA product before the FDA even approved OFIRMEV® for sale in the U.S. (Tr. at 1161) It is nearly certain, then, that Exela based its own "$300mm in revenue" projection at least in part on the Perfalgan sales in Europe.

been previously offered. (Tr. at 1417) Dr. Bell's analysis confirmed Mr. Drouin's testimony. (*See* Tr. at 1533-34) Indeed, as Dr. Bell testified, it may be that sales of Perfalgan are a better indicator of nonobviousness, given that Perfalgan entered the market much closer to the filing dates of the patents-in-suit than OFIRMEV®. (Tr. at 1526)

Exela also contends that Plaintiffs have failed to establish a nexus between the sales of their commercial products and any novel feature of the '222 patent claims. "A prima facie case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010). The Court has already concluded that OFIRMEV® and Perfalgan are commercial embodiments of the '222 patent. In addition, the Court has found that stability is a novel feature of the '222 patent. Without a stable formulation, Plaintiffs could not sell their product. Hence, the Court again concludes that Plaintiffs have established a nexus between the commercial success of OFIRMEV® and Perfalgan and the novel features of the '222 patent.

f. Licensing

Plaintiffs contend that Pharmatop's successful licensing of the patents-in-suit provides additional evidence of nonobviousness. *See In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("Licenses taken under the patent in suit may constitute evidence of nonobviousness."). Exela's only response is to argue that Plaintiffs have failed to establish a nexus between the claimed invention and its commercial embodiment. Having already rejected this argument, the Court concludes that Plaintiffs' successful licensing weighs in favor of nonobviousness.

g. Praise in the industry

Plaintiffs attempted to prove "praise" through the testimony of Dr. Buvanendran as well as certain literature (PTX-237, PTX-270, PTX-886), which Plaintiffs contend supports a conclusion of nonobviousness (D.I. 440 at 4-5). Exela's response focuses on the purported lack of nexus between the praise and the novel features of the '222 patent. However, the literature identified by Plaintiffs specifically praises the "ready-to-use" nature of OFIRMEV®, which requires a stable formulation as recited in the claims. (*See, e.g.*, PTX-270 at 2; PTX-886) Hence, this factor supports a finding of nonobviousness.

5. Conclusion on validity of the '222 patent

The Court finds that Exela has not shown, by clear and convincing evidence, that any claim of the '222 patent is anticipated or obvious over the prior art references. Further, secondary considerations support a conclusion of nonobviousness. For these reasons, the Court concludes that the '222 patent is valid.

C. Validity of the '218 patent

Exela contends that the asserted claims of the '218 patent are obvious in view of the '222 patent (PTX-001) in combination with Dr. Palmieri's 1978 *Journal of Pharmaceutical Sciences* article (PTX-338). (D.I. 414 at 16-18) According to Exela, "the only difference between the asserted claims of the '218 patent and the prior art process of the '222 patent is the DO content limitation, *i.e.*, below 2 ppm, 1 ppm, or 0.5 ppm."[29] (D.I. 414 at 17) In Exela's view, Dr.

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[29]During prosecution of the '218 patent, the PTO considered the '222 patent and rejected claim 1 for largely the same reasons as Exela now proposes. According to the Examiner, "[t]he difference between the ['222 patent] and herein claimed method is that the ['222 patent] does not mention the level of oxygen and the pressure. . . . [and] it was well within ordinary skill in the art to work out [the oxygen content] parameters to achieve maximum stabilization." (PTX-004 at

Palmieri's article provides a person of ordinary skill in the art with "strong motivation to decrease dissolved oxygen levels to as low as possible." (D.I. 436 at 17) Plaintiffs respond that Dr. Palmieri's article addresses the wrong problem and, consequently, cannot provide the requisite motivation.[30] (D.I. 418 at ¶¶ 163-68) Plaintiffs also argue that secondary considerations of nonobviousness support a finding of validity. (*See* D.I. 440, 445)

For the reasons explained below, the Court agrees with Plaintiffs that Exela has failed to establish, by clear and convincing evidence, that the claimed invention would have been obvious to a person of ordinary skill at the time the '218 patent was filed.

1. Disclosures of the cited references

The '222 patent is Exela's primary reference. As noted throughout this Opinion, the '222 patent is directed to "stable, liquid, analgesic formulations, containing paracetamol as [their] main active ingredient." (PTX-001 at col. 1, ll. 9-12) According to the '222 patent, "It has been known for many years and notably from a paper of FAIRBROTHER J. E. entitled: Acetaminophen, published in Analytical Profiles of Drug Substances (1974), volume 3, pp. 1-109, that paracetamol in the presence of moisture, and all the more in aqueous solution, may be hydrolysed to yield p-aminophenol, which compound may itself be broken down into

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392) However, the Examiner ultimately withdrew this rejection, finding that "after nitrogen is bubbled, the oxygen content is below 2 ppm, which results in unexpected stabilization of the paracetamol, see for example, pages 16 and 17, wherein it is clearly demonstrated that because of oxygen being less than 2.0 ppm, the stability of the paracetamol is unexpectedly achieved for much longer time." (*Id.* at 427) Given the Examiner's conclusion, Exela must overcome "the deference that is due to a qualified government agency presumed to have properly done its job." *PowerOasis*, 522 F.3d at 1304.

[30]Plaintiffs do not dispute the other claim limitations of the '218 patent for purposes of obviousness.

quinone-imine." (*Id.* at col. 1, ll. 16-22) The '222 patent teaches that "removal of oxygen dissolved in the carrier" is one of the variables that has an impact on stability. (*Id.* at col. 2, ll. 31-37) In this regard, the '222 patent teaches that "[r]emoval of dissolved oxygen is readily accomplished by bubbling an inert gas and preferably by bubbling nitrogen." (*Id.*)

Dr. Palmieri's article studied the "effect of dissolved oxygen levels on oxidative degradation of pyrogallol." (PTX-338 at 1) Dr. Palmieri chose pyrogallol for his study because of its "rapidity of oxidation." (*Id.* at 2) According to Dr. Palmieri's article, reducing oxidative degradation is "[a]n important factor in drug stabilization." (*Id.* at 1) From his experiments, Dr. Palmieri found that "[t]here is a rank-order correlation of dissolved oxygen and degradation rates," meaning that a reduction in the dissolved oxygen content of the solution will slow down the rate of oxidative degradation. (*Id.* at 2) Dr. Palmieri also learned that "even systems of less than 1 ppm dissolved oxygen exhibited degradation. This result is explainable since pyrogallol may degrade by a nonoxidative process. Many chemicals having primarily oxidative pathways for degradation also degrade by other means." (*Id.*)

2. Differences between the claims and the prior art

Claim 1 of the '218 patent recites: "A method for preparing an aqueous solution with an active nature susceptible to oxidation, which is paracetamol, while preserving for a prolonged period, comprising deoxygenation of the solution by bubbling with at least one inert gas and/or placing under vacuum, until the oxygen content is below 2 ppm."

Exela recognizes that the '222 patent does not disclose reducing the dissolved oxygen content to below 2.0 ppm. (D.I. 414 at 17) For this limitation, Exela relies on Dr. Palmieri's article. (*Id.*) According to Exela, Dr. Palmieri's article "not only encourages the reduction of

dissolved oxygen levels to near-zero, but shows that dissolved oxygen levels less than 0.05 ppm could be successfully achieved back in the 1970s. Thus, contrary to Plaintiffs' argument, there is more than ample motivation to combine the references and practice the teachings with a reasonable expectation of success." (D.I. 436 at 17) The Court disagrees.

The evidence presented at trial established that the degradation pathway for pyrogallol is different from the degradation pathway of paracetamol. Specifically, pyrogallol is very sensitive to oxidation, and oxidation is the primary degradation pathway for pyrogallol. (PTX-338 at 2) By contrast, oxidation does not cause paracetamol to degrade. (Tr. at 1575) The "major route of degradation contributing to the instability of [paracetamol] is its hydrolysis." (DTX-438 at 18-19) The '222 patent likewise recognizes that hydrolysis is the primary reason that "paracetamol in aqueous solution is unstable."[31] (PTX-001 at col. 1, ll. 30-32) Hydrolysis is not the same as oxidative degradation. (Tr. at 1041-42) Dr. Palmieri agreed that reducing the oxygen content of a formulation would not stop hydrolytic degradation. (*Id.* at 1045, 1049)

At the time of the invention, it was understood that deoxygenating a solution can be difficult from a manufacturing standpoint, and involves certain drawbacks. For example, deoxygenation "take[s] a considerable amount of time." (PTX-002 at col. 2, ll. 41-43) Deoxygenation also requires special equipment and precautions to keep the deoxygenized solution away from air, particularly during the filling and packaging steps.[32] (*Id.* at col. 2, l. 61 to

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[31]The '218 patent explains that degradation is a major problem in therapeutic solutions because it reduces the amount of paracetamol in the solution, yet "it is important that the dose of active principle is precisely determined." (PTX-002 at col. 1, ll. 44-50)

[32]The inventors of the '218 patent explicitly state that "the problem of stabilization of the formulations according to the invention ***was appreciably more complex than anticipated***." (PTX-002 at col. 3, ll. 27-29) (emphasis added) For this and other reasons discussed, inventor

col. 3, l. 3) Dr. Palmieri's article confirms that "it is difficult to alter the oxygen concentration with present equipment." (PTX-338 at 2) Finally, deoxygenation by bubbling can "risk physical damage to sensitive molecules" as a result of "extended contact with the oxygen impurities present in nitrogen gas." (Tr. at 1052)

Given the technical differences between the degradation pathways of the '218 patent and Dr. Palmieri's article, as well as the technical difficulties associated with deoxygenation, the Court is not persuaded that one of ordinary skill in the art would have found it obvious to reduce the oxygen concentration of a paracetamol solution to below 2.0 ppm.[33] Hence, claim 1 is valid.

Asserted dependent claims 3 and 4 of the '218 patent are directed to specific dissolved oxygen concentrations, i.e., below 1.0 ppm and below 0.5 ppm. Claim 19 is directed to an "injectable aqueous solution" preserved by the method of claim 1. Claims 3, 4, and 19 depend from claim 1. Exela does not rely on any additional references in connection with dependent claims 3, 4, and 19. Having concluded that independent claim 1 is valid over the disclosure of the '222 patent in combination with Dr. Palmieri's article, the Court concludes that claims 3, 4, and 19 also are valid.

3. Secondary considerations

Plaintiffs rely on the following secondary considerations as objective evidence of

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Dietlin's statement that – years before the filing of the '218 patent – it was known to the inventors that deoxygenating to levels below 0.5 ppm "'is a manufacturing "trick" which should only be disclosed in the pharmaceutical dossier (IIA4) with caution'" (D.I. 414 at 18) (quoting DTX402-011)), does not alter the conclusion of nonobviousness.

[33]Exela has moved to exclude testimony of Dr. Elder that "the '222 patent does not teach 'preserved for a prolonged period' (i.e., a stable formulation)." (D.I. 414 at 25) The Court has not relied on the objected-to testimony of Dr. Elder and, thus, will deny Exela's motion.

nonobviousness: unexpected results, satisfaction of an unmet need, failure of others, successful licensing, praise, and commercial success. (D. I. 440 at 1-5) Other than "unexpected results," the Court has already addressed the applicable secondary considerations in connection with the '222 patent, and the Court's conclusions there apply equally to the '218 patent. Below, the Court addresses the parties' dispute with respect to the nexus between the claims of the '218 patent and Exela's ANDA process and product, as well as the unexpected results associated with the process patented in the '218 patent.

a. Nexus

Exela contends that OFIRMEV® and Perfalgan are not manufactured using the method claimed by the '218 patent, because the dissolved oxygen content in the manufacturing processes for both products is below 2 ppm prior to formation of the aqueous solution. (D.I. 442 at 5) This is the same argument Exela posed as its basis for non-infringement of the '218 patent. In that context, the Court found that Exela's ANDA process meets the limitation requiring bubbling "the solution" until it is below 2.0 ppm under the doctrine of equivalents. For the same reasons, Exela's arguments with respect to the lack of a nexus are not persuasive. Thus, Plaintiffs have established that OFIRMEV® and Perfalgan are embodiments of the '218 patent.[34]

Exela also contends that any evidence of unmet need, commercial success, and industry praise are inapplicable, because Plaintiffs did not tie these secondary considerations to any novel feature of the '218 patent. (D.I. 444 at 1) The Court disagrees. The process claimed in the '218

[34]The OFIRMEV® and Perfalgan formulations are identical. (Tr. at 1382) The processes used to make OFIRMEV® and Perfalgan are substantially identical. (*Id.* at 1383-84)

patent results in a formulation that is "preserv[ed] for a prolonged period,"[35] as a result of bubbling the solution "until it is below 2.0 ppm." (PTX-002) No such formulation was previously available or known in the prior art. Exela's contention that Prodafalgan was a previously available "stable solution of acetaminophen equivalent" is not persuasive. (D.I. 442 at 2) Prodafalgan had to be reconstituted immediately prior to injection because it could not be "preserv[ed] for a prolonged period" in an aqueous solution. (Tr. at 1403-04, 1478-79)

b. Unexpected results

Unexpected results support nonobviousness when "the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). According to Plaintiffs, "[r]educing dissolved oxygen below 2 ppm (in the '218 patent) surprisingly achieved prolonged stability, providing the opportunity to produce a commercial product on an industrial scale." (D.I. 440 at 2) Exela responds that Plaintiffs have failed to show that this was an unexpected result of deoxygenating to below 2.0 ppm, in view of the available prior art. (D.I. 442 at 4-5) The Court agrees with Plaintiffs.

The '218 patent specification contains specific data indicating improved properties. In "Example II," the solution was bubbled with nitrogen until the dissolved oxygen content was approximately 0.2 ppm. In this experiment, "[a]fter being kept at 25° C for 6 months, the solution is still colourless, there is no change in the paracetamol content, and the content of degradation products of paracetamol determined by HPLC remains lower than 0.015% of the

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[35]The Court has construed this claim element to mean that "[t]he aqueous solution does not decompose substantially such that the formulation has a prolonged pharmaceutically acceptable shelf life." (D.I. 188 at 20)

paracetamol." (PTX-002 at col. 7, ll. 10-19) Likewise, in "Example IV," the dissolved oxygen content was reduced to approximately 1.5 ppm. (*Id.* at col. 8, ll. 10-12) After 24 months, the solution "remained colourless," the "paracetamol content was 100% of the original value, and the degradation products of the paracetamol measured by HPLC represented less than 0.02% of the paracetamol content."[36] (*Id.* at 11-17)

By contrast, the '222 patent, which is the closest prior art to the '218 patent, discloses that a paracetamol solution will degrade approximately 5% in a period of 19 months, as a result of hydrolysis. (PTX-001 at col. 1, ll. 35-39) Since reducing the oxygen content of a formulation would not stop hydrolytic degradation (Tr. at 1045, 1049), the results obtained by bubbling the solution to below 2.0 ppm, as claimed in the '218 patent, were unexpected. The Examiner of the '218 patent also agreed with this conclusion, as discussed above. (PTX-004 at 427) Hence, the Court concludes that unexpected results further support a finding of nonobviousness of the '218 patent.

4. Conclusion on validity of the '218 patent

The Court concludes that Exela has not shown, by clear and convincing evidence, that the '218 patent is obvious over the prior art references. Specifically, Exela has not proved that a person of ordinary skill in the art, at the time of invention, would have been motivated to deoxygenate an aqueous solution containing paracetamol to below 2.0 ppm. Secondary considerations also support the Court's conclusion of nonobviousness. Accordingly, the Court finds that the '218 patent is valid.

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[36]These results are reasonably commensurate with the scope of the claims. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308-09 (Fed. Cir. 2011).

IV. CONCLUSION

Plaintiffs have proven by a preponderance of the evidence that asserted claims 1, 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent and claims 1, 3, 4, and 19 of the '218 patent are infringed. By contrast, Exela has failed to prove by clear and convincing evidence that claims 1, 3, 4, 5, 9, 10, 12, 16, 17, and 18 of the '222 patent and claims 1, 3, 4, and 19 of the '218 patent are invalid. An appropriate Order will be entered.[37]

[37]Exela moved for judgment as a matter of law during trial, pursuant to Federal Rule of Civil Procedure 52(c). (Tr. at 1232-33; *see also* D.I. 380) The Court deferred ruling on the motions until after trial. (Tr. at 1233) Having now made findings of fact and reached conclusions of law on a full post-trial record, the Court denies Exela's motions for judgment as a matter of law.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CADENCE PHARMACEUTICALS, INC. and SCR PHARMATOP,	:	
Plaintiffs,	:	
v.	:	C.A. No. 11-733-LPS
EXELA PHARMA SCIENCES, LLC, EXELA PHARMSCI, INC., and EXELA HOLDINGS, INC.,	:	
Defendants.	:	

ORDER

At Wilmington this **14th** day of **November, 2013**:

For the reasons set forth in the Memorandum Opinion issued this date, IT IS HEREBY ORDERED that:

1. The parties shall meet and confer and submit, no later than **November 21st, 2013**, a proposed order consistent with the Memorandum Opinion, to enter final judgment for Plaintiffs and against Defendants, including any appropriate remedy.

2. Defendants' motion for redaction of transcript (D.I. 456) is DENIED.

3. Defendants' motion for judgment of non-infringement as a matter of law with respect to the '222 and '218 patents (D.I. 380) is DENIED.

4. Motions for judgment as a matter of law made during trial (*see* Trial Transcript at 1232-33) are DENIED.

5. Plaintiffs' motion to strike portions of Dr. Palmieri's testimony (D.I. 417 at 19 nn.11-12) is DENIED.

6. Defendants' motion to strike portions of Dr. Yeo's testimony (D.I. 414 at 7, 25) and Dr. Elder's testimony (D.I. 414 at 25) are DENIED.

7. Defendants' motion to strike portions of Dr. Schoonen's testimony (D.I. 14 at 14 n.4) is DENIED.

8. Defendants motion to strike portions of Dr. Elder's testimony (D.I. 414 at 25) is DENIED.

9. The parties shall submit a proposed redacted version of the Memorandum Opinion no later than **November 21st, 2013.**

UNITED STATES DISTRICT JUDGE