UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ACCORD HEALTHCARE, INC.
Petitioner

v.

HELSINN HEALTHCARE S.A. and
ROCHE PALO ALTO LLC
Patent Owners

_____

Case PGR _____
U.S. Patent No. 8,598,219
Issue Date: December 3, 2013

Title: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

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PETITION FOR POST GRANT REVIEW
OF U.S. PATENT NO. 8,598,219 UNDER
35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.200 ET SEQ.

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EXHIBIT LIST

Exhibit 1001	U.S. Patent No. 8,598,219 ("the '219 patent");
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Exhibit 1003	Letter entitled "Identification of Continuation-In-Part Claim Support Required Under 37 C.F.R. § 1.78(d)(3) and Choice of Law" filed May 23, 2013 in application 13/901,437 ('219 patent):
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Exhibit 1006	ALOXI® Product Label (revision 05/2014);
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Exhibit 1008	Handbook of Pharmaceutical Excipients (2nd Ed., 1994, pp.176-179 and pp. 294-298);
Exhibit 1009	Declaration of Daniele Bonadeo, M. Chem. Pharm. filed April 6, 2009 in application 11/186,311 ("Bonadeo Declaration") (U.S. Patent No. 7,947,724);
Exhibit 1010	Appeal Brief filed May 24, 2010 in application 11/186,311; (U.S. Patent No. 7,947,724);
Exhibit 1011	Appeal Brief filed November 13, 2009 in application 11/388,270; (U.S. Patent No. 7,960,424).
Exhibit 1012	Supplemental Amendment filed September 16, 2010 in application 11/388,270; (U.S. Patent No. 7,960,424).
Exhibit 1013	Amendment filed December 15, 2009 in application 11/388,268; (U.S. Patent No. 7,947,725).

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Exhibit 1015	Declaration of Arnold J. Repta, Ph.D.
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I. INTRODUCTION

On behalf of Accord Healthcare, Inc. ("Accord" or "Petitioner") and in accordance with 35 U.S.C. §§ 310-329 and 37 C.F.R. § 42.200 *et seq*., post grant review is respectfully requested for claims 1-5 and 8 of U.S. Patent No. 8,598,219 ("the '219 patent") (Ex. 1001), which is jointly assigned to Helsinn Healthcare S.A. ("Helsinn") and Roche Palo Alto, LLC ("Roche"). This Petition establishes that it is more likely than not that at least one of the Challenged Claims of the '219 patent is unpatentable.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Accord is the real party-in-interest for the instant Petition.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

(1) *Helsinn Healthcare S.A. et al v. Dr. Reddy's Laboratories, Ltd. et al*, USDC NJ 3:12-cv-02867, filed May 11, 2012;

(2) *Helsinn Healthcare S.A. et al v. Dr. Reddy's Laboratories, Ltd. et al*, USDC NJ 3:11-cv-03962, filed July 8, 2011;

(3) *Helsinn Healthcare S.A. et al v. Accord Healthcare Inc. et al*; USDC DEL 1:13-cv-2101, filed on December 27, 2013;

(4) *Helsinn Healthcare S.A. et al v. Cipla Ltd. et al*; USDC DEL 1:14-cv-427; filed on April 7, 2014; and

(5) *Helsinn Healthcare SA et al v. Mylan Inc. et al*; USDC DEL 1:14-cv-709; filed on June 4, 2014, are pending.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner's designation of counsel: Lead counsel is Michael J. Fink (Reg. No. 31,827) and back-up counsel is Paul A. Braier (Reg. No. 42,357). Per 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition.

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Papers concerning this matter should be served on the following:

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Petitioner consents to electronic service by email at the above email addresses.

III. PAYMENT OF FEES

Payment of $30,000.00 for the fees set forth in 37 C.F.R. § 42.15(a)(1-4) for this Petition for Post Grant Review accompanies this request by way of credit card payment. The undersigned authorizes payment for any additional fees due in connection with this Petition to be charged to Deposit Account No. 19-0089.

IV. REQUIREMENTS FOR POST GRANT REVIEW - 37 C.F.R. § 42.204

A. Grounds for Standing Under 37 C.F.R. § 42.204(a)

Petitioner hereby certifies that the Petitioner is not barred or estopped from requesting post grant review challenging the claims of the '219 patent for any reason, including any reason under 37 C.F.R. § 42.201. This Petition is filed within nine months of the December 3, 2013 issue date of the '219 patent. Petitioner has not filed a civil action challenging validity of a claim of the '219 patent.

Petitioner hereby certifies that the '219 patent is available for post grant review. Continuation-in-part application 13/901,437, which issued as the '219 patent, was filed on May 23, 2013, with an Application Data Sheet ("ADS") identifying the application as an AIA application. Ex. 1002, p. 5.

Moreover, Applicants filed a letter on May 23, 2013, entitled "Identification of Continuation-In-Part Claim Support Required Under 37 C.F.R. § 1.78(d)(3) and Choice of Law" in which Applicants asserted that the application is subject to AIA. Ex. 1003, pp. 2-8. The letter stated that claim 9 only has support in newly-added Example 8 of the continuation-in-part application. Ex. 1003, pp. 7-8. After the Examiner mistakenly characterized the application as pre-AIA (Ex. 1004, p. 2), Applicants held an interview with the Examiner. In the Interview Summary (Ex. 1005), the Examiner indicated that the Applicants successfully argued that the

application is an AIA application because a) it is a CIP application: b) the ADS indicates that it is a CIP application; and c) the ADS designates the application as an AIA application. Ex. 1005, p. 2.

B. Identification of Challenge Under 37 C.F.R. § 42.204(b)

1. Claims for Which Post Grant Review is Requested Under 37 C.F.R. § 42.204(b)(1)

Petitioner requests post grant review of claims 1-5 and 8 of the '219 patent ("the Challenged Claims"). Petitioner does not request review of claims 6 or 7.

2. The Specific Art and Statutory Ground(s) on Which the Challenge is Based Under 37 C.F.R. § 42.204(b)(2)

Ground 1: Claims 1-5 and 8 of the '219 patent are unpatentable under 35 U.S.C. §112(a) for lack of written description of the claimed subject matter being stable at 18 or 24 months when stored at room temperature.

Ground 2: Claims 1-5 and 8 of the '219 patent are unpatentable under 35 U.S.C. §112(a) because the specification does not enable the broadly claimed subject matter outside a pH range of 4 to 6.

Ground 3: Claims 1-5 and 8 of the '219 patent are unpatentable under 35 U.S.C. §112(b) because the claims do not particularly point out and distinctly claim the subject matter which the inventors regard as the invention.

Ground 4: Claims 1-5 and 8 of the '219 patent are unpatentable under 35 U.S.C. §112(a) for lack of written description of the claimed subject matter which omits a pH range of 4 to 6.

3. Supporting Evidence Under 37 C.F.R. § 42.204(b)(5)

A list of supporting evidence is provided in the Exhibit List beginning on page vi. A copy of each exhibit is submitted herewith. This Petition is additionally supported by the testimony set forth in the expert declaration of Arnold J. Repta, Ph.D. ("Repta Dec.")(Ex. 1015).

4. A Person Of Ordinary Skill In The Art

A person of ordinary skill in the relevant art ("POSA") would have the equivalent of at least a master's degree in pharmacy or a related discipline, and an additional five years of experience developing parenteral formulations, including substantial experience with developing intravenous formulations. Repta Dec. (Ex. 1015) ¶¶ 21-24.

A POSA would understand that formulations are not simply lists of separate and independent ingredients. A POSA would understand that all ingredients in a formulation, including the drug (more commonly referred to as Active Pharmaceutical Ingredient, or API) and excipients (pharmacologically inactive ingredients) can all potentially interact with each other in unpredictable ways. A POSA would also understand that other properties of an injectable solution, such as pH, concentrations, etc., can have profound impact on the properties of the formulation. A POSA would understand that changing one aspect of a formulation, such as an excipient or pH, can have substantial effects on the

formulation's properties including but not limited to such things as stability, solubility and injection site issues. Repta Dec. (Ex. 1015) ¶¶ 25, 36. A POSA has the point of view of a scientist. Repta Dec. (Ex. 1015) ¶ 34.

For the purposes of this Request for Post Grant Review, it is assumed that the effective date for the '219 patent is January 30, 2003, the filing date of the provisional application to which the '219 patent claims priority. Repta Dec. (Ex. 1015) ¶ 26. However, the arguments and opinions herein do not depend on the exact date, and would remain the same even if another date, such as January 30, 2002 (one year prior to the provisional filing date); January 30, 2004 (which is the filing date of PCT EP2004/000888); or May 23, 2013 (which is the filing date of the '219 patent itself), were to be used. Repta Dec. (Ex. 1015) ¶ 27.

V. Background

Palonosetron is a drug used to treat or prevent nausea and vomiting that may occur as a side effect of chemotherapy. It is currently sold in the United States exclusively by Helsinn under the trade name ALOXI®. Ex. 1006, pp. 1, 2, 9.

The '219 patent is part of a family of at least seven patents, four pending applications, a broadening reissue application, and two abandoned applications. A demonstrative chart illustrating the relationship between the various family members is provided in Ex. 1007. The patent owners, Helsinn and Roche, allege that the patents in this family cover the FDA-approved drug product ALOXI®.

Independent claims 1 and 8 are reproduced below:

1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

from 0.005 mg/mL to 1.0 mg/mL EDTA; and

from 10 mg/mL to 80 mg/mL mannitol,

wherein said formulation is stable at 24 months when stored at room temperature.

8. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

from 0.005 mg/mL to 1.0 mg/mL EDTA; and

from 10 mg/mL to 80 mg/mL mannitol,

wherein said formulation is stable at 18 months when stored at room temperature.

As such, the claimed subject matter in both claims 1 and 8 recite (1) a 5 mL sterile aqueous isotonic solution; (2) palonosetron hydrochloride; (3) EDTA; (4) mannitol; and, (5) a period of stability when stored at room temperature, *i.e.,* 24 months and 18 months respectively.

Dependent claims 2 to 4 each depend upon independent claim 1 while dependent claim 5 depends upon dependent claim 4. Dependent claim 2 further defines claim 1 by reciting that the EDTA is in an amount of 0.5 mg/mL. Dependent claim 3 further defines claim 1 by reciting that the mannitol is in an amount of 41.5 mg/mL. Dependent claim 4 further defines claim 1 by reciting that the solution further comprises a citrate buffer. Dependent claim 5 further defines claim 4 by reciting that the citrate buffer is at a concentration of 20 millimolar.

VI. Statement Of Material Facts Under 37 C.F.R. § 42.22(c)

Petitioner provides the flowing statement of material facts:

1. U.S. Patent No. 8,598,219 (Ex. 1001) is jointly assigned to Helsinn Healthcare S.A. and Roche Palo Alto, LLC.

2. This Petition is filed within nine months of the December 3, 2013 issue date of the ‘219 patent.

3. Petitioner has not filed a civil action challenging validity of a claim of the ‘219 patent.

4. Continuation-in-part application 13/901,437, which issued as the '219 patent, was filed on May 23, 2013, with an Application Data Sheet identifying the application as an AIA application. Ex. 1002, p. 5.

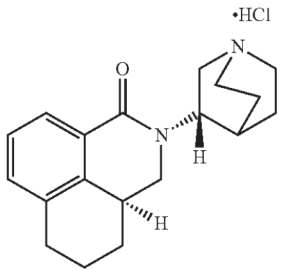
5. The Applicants of the '219 patent filed a letter on May 23, 2013, entitled "Identification of Continuation-In-Part Claim Support Required Under 37 C.F.R. § 1.78(d)(3) and Choice of Law" in which Applicants asserted that the application is subject to AIA. Ex. 1003, pp. 2-8.

6. Palonosetron is a drug that treats or prevents nausea and vomiting that may occur as a side effect of chemotherapy. It is currently sold in the United States exclusively by Helsinn under the trade name ALOXI®. Ex. 1006, pp. 1, 2, 9.

7. The '219 patent is part of a family of at least seven patents, four pending applications, a broadening re-issue application, and two abandoned applications. Ex. 1001, p. 1; Ex. 1007.

8. The patent owners, Helsinn and Roche, allege that the patents in this family cover the FDA-approved drug product ALOXI®.

9. Palonosetron hydrochloride is a drug having the structural formula:



(Ex. 1001, col. 3, lines 48-65; Repta Dec. (Ex. 1015) ¶ 30).

10. EDTA is a chelating agent also known as ethylenediaminetetraacetic acid or edetic acid, and has the chemical formula:

$$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$$

Ex. 1001, col. 5, line 62; Ex. 1008, p. 3, Repta Dec. (Ex. 1015) ¶ 31.

11. Mannitol is a sugar alcohol having empirical formula $C_6H_{14}O_6$. Ex. 1008, pp. 7-8; Repta Dec. (Ex. 1015) ¶ 32. Mannitol is used as a tonicifying agent for injectable formulas of the '219 patent. Ex. 1001, col. 6, lines 4-16 and col. 7, line 37; Repta Dec. (Ex. 1015) ¶ 32.

12. The specification of the '219 patent does not describe a pharmaceutical single-use, unit-dose formulations for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting that is stable at 18 or 24 months when stored at room temperature. Ex. 1001.

13. The '219 patent discloses a multitude of formulations that have a goal of being shelf stable for periods greater than 24 months at room temperature. Ex. 1001, col. 2, lines 56-59.

14. The specification of the '219 patent does not disclose a formulation that would achieve either the recited "stable at 24 months when stored at room

temperature" (claim 1) or the recited "stable at 18 months when stored at room temperature" (claim 8). Ex. 1001, cols. 9-10.

15. Provisional Application No. 60/444,352, from which the '219 patent claims priority, does not disclose shelf stability for a period of 24 months at room temperature. Ex. 1016

16. The Provisional Application No. 60/444,352 discloses "shelf stable for periods greater than 18 months at room temperature." Ex. 1016, p. 5, ¶ 1.

17. There is no disclosure in the '219 patent of any changes to the formulations in the provisional application that would increase the alleged 18 month stability to 24 month stability. Ex. 1001, col. 2, lines 56-57; Ex. 1016, p. 5, ¶ 1.

18. There is no disclosure of achieving 24 month stability when stored at room temperature for any formulation in the '219 patent. Ex. 1001.

19. There is no disclosure of achieving 18 month stability when stored at room temperature for any formulation in the '219 patent. Ex. 1001

20. Examples 6 and 7 of the '219 patent show stability for 48 hours at 23° C, and up to 14 days (apparently in the dark) at 4° C. Ex. 1001, col. 8, lines 15 *et seq.*

21. The only Examples of the ‘219 patent which disclose formulations containing both mannitol and EDTA are Examples 4 and 5. Ex. 1001, col. 7, line 40 - col. 8, line 13.

22. The concentration of mannitol in Example 5 of the ‘219 patent is 150 mg/ml, which is not within the range recited in the claims of the ‘219 patent. Ex. 1015, ¶ 41.

23. The Examples of the ‘219 patent do not provide any evidence that any formulation is stable at 18 months when stored at room temperature. Ex. 1015, ¶¶ 84, 85, 88, 90, 91.

24. The Examples of the ‘219 patent do not provide any evidence that any formulation is stable at 24 months when stored at room temperature. Ex. 1015, ¶¶ 84, 85, 88, 90, 91.

25. Examples 4 and 5 in the ‘219 patent are prophetic examples illustrating possible representative pharmaceutical formulations that demonstrate a need for adjustment of the pH of the representative formulations to a pH of approximately 5.0 (pH 5.0 ± .05 or 4.8 ± .05) by addition of sodium hydroxide solution or hydrochloric acid solution. Ex. 1015, ¶ 44

26. The specification discloses that “the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations,” (Ex. 1001,

col. 3, lines 19-21; col. 5, lines 48-50), but there is no disclosure that this increase is to 18 or 24 months. Ex. 1015, ¶¶ 81, 82.

27. During prosecution of the first-filed non-provisional application in the '219 patent family (Application No. 11/186,311, filed July 21, 2005), Applicants submitted a declaration under 37 C.F.R. § 1.132 by inventor Daniele Bonadeo. Ex. 1009.

28. The Bonadeo Declaration indicates that palonosetron concentration and pH were the first two parameters studied during formulation development for their effect on stability Ex. 1009, p. 2, ¶¶ 8 and 10.

29. The studies referred to in the Bonadeo Declaration showed that palonosetron was "extremely stable at a pH of 5.0" at low palonosetron concentrations. Ex. 1009, p. 3, ¶ 11.

30. The Bonadeo Declaration states that the inventors "settl[ed] on mannitol and citrate buffer for the formulation for practical reasons." Ex. 1009, p. 3, ¶ 13.

31. The Bonadeo Declaration states that the inventors studied stability of palonosetron formulations, at a pH of 5.0, as functions of palonosetron and EDTA concentrations. Ex. 1009, p. 3, ¶ 13.

32. The Bonadeo Declaration describes additional stability studies at a pH of 5.0. Ex. 1009, p. 8, ¶ 26.

33. Every stability study disclosed in the Bonadeo Declaration was performed at a pH of 5.0. Ex. 1009.

34. There is no suggestion in the Bonadeo Declaration that a formulation having a pH outside the range of about 4.0-6.0 could be, or would be, stable. Ex. 1009.

35. In Application No. 11/186,311 (the '311 application), Applicants filed an appeal on May 24, 2010, after receiving a final rejection. In part, the Appeal Brief stated:

> In this case, the Office has not cited any prior art to show that all of the features of the claimed formulation would have been combined as a matter of routine optimization. In contrast, Applicant has submitted substantial evidence which proves that the combination of features that defines the claimed formulation is anything but routine. This evidence shows that the claimed formulation was discovered after a sequence of experiments, each building on the prior experiment like a series of building blocks to arrive at the claimed invention. A different formulation could have been obtained at any step along the way if the experimental sequence had differed. For example, Applicant discovered that mannitol is the best tonicity agent for the formulation, but this discovery was only made after the inventors had settled on an aqueous formulation, using palonosetron HCl at a pH of 4-6. Bonadeo Dec. at par. 26. In like manner, Applicant discovered that

> EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl in an aqueous formulation of palonosetron HCl having a pH of 4-6. Bonadeo Dec. at par. 14.

Wherein the footnote reads:

> 1 These studies included: (1) a temperature stability study (Bonadeo Dec. par. 16); (2) a concentration stability study (Bonadeo Dec. par. 8); (3) a pH stability study (Bonadeo Dec. par. 10); (4) a tonicifying agent study (Bonadeo Dec. pars. 12 and 26), and (5) a multi-variate study in which concentrations of palonosetron HCl, buffer, and EDTA concentrations were varied and evaluated for six months (Bonadeo Dec. par. 14).

Ex. 1010, p. 9.

36. In the Appeal Brief referred to above, the applicants expressly stated that their development of the formulation was dependent on the order that they performed the various experiments:

> mannitol is the best tonicity agent for the formulation, but this discovery was made only after the inventors had settled upon an aqueous formulation, using palonosetron HCl at a pH of 4-6.

Ex. 1010, p. 9.

37. The Applicants argued that EDTA only stabilizes low concentrations of palonosetron HCl at a pH of 4-6:

> In like manner, Applicant discovered that EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl . . . having a pH of 4-6.

Ex. 1010, p. 9.

38. The prosecution histories of patent applications related to the '219 patent contain arguments about the importance of pH to the claimed subject matter. Ex. 1015, ¶¶ 51-76.

39. In Application No. 11/388,270 (the '270 application)(a continuation of the '311 application), in an Appeal Brief, the applicants made almost the identical remarks quoted above from the '311 application. Ex. 1011, pp. 10-11.

40. In a subsequent Supplemental Amendment in the '270 application (Ex. 1012), the applicants argued concerning the conditions under which EDTA was effective. In part, they wrote:

> [...] Importantly -- these results were obtained in a solution containing mannitol at a pH of 5 -- as recited in the claims. [...] The number of elements in this combination - and their inter-dependency - is also significant.1 The record demonstrates that each of the elements was selected from many possible options2, and that all of the elements must be carefully balanced to arrive at a stable formulation.3 Hindsight analysis would be needed to arrive at this unique combination.

Wherein footnotes 1 and 3 read:

> 1 The claims recite five variables: pH (4-6), tonicity agent (mannitol), salt (hydrochloride), concentration of palonosetron (0.03-0.2 mg/ml), and stabilizing agent (EDTA).
>
> 3 See Bonadeo Dec. at par. 26 (Exh. 5) (reporting that mannitol is the best tonicity agent for the formulation, but only for aqueous solutions of palonosetron HCl at a pH of 4-6); par 14. (reporting that EDTA stabilizes the formulation, but only at low concentrations of palonosetron HCl in aqueous solutions of palonosetron HCl at a pH of 4-6).

Ex. 1012, pp. 2-3.

41. In application 11/388,268 (the '268 application) (also a continuation of the '311 application), applicants argued:

> These principles are particularly appropriate in this case, where the elements of the formulation cooperate in an inter-dependent manner to produce a highly stable formulation. For example, Applicant has discovered that mannitol results in a more stable formulation, but this discovery was only made in the context of an aqueous formulation at a pH of 4-6 using palonosetron HCl. Bonadeo Dec. at par. 26. In like manner, Applicant has discovered that EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl in an aqueous formulation of palonosetron HC1 having a pH of 4-6. Bonadeo Dec. at par. 14. It is this combination and inter-cooperation of features that must be evaluated for purposes of patentability.

Ex. 1013, pp. 5-6.

42. Applicants effectively repeated the above argument on page 9 of the Amendment (Ex. 1013, p. 9).

43. The applicants argued in the Appeal Brief in the '268 application that the discovery of the stabilizing effect of EDTA was surprising, and only made in the context of formulations comprising mannitol at a pH of 4-6. Ex. 1014, p. 23.

44. Example 1 disclosed in the '219 patent is a study of the effect of pH on stability. (Ex. 1001), col. 7, lines 1-10.

45. The results of Example 1 are stated as follows:

> A study was conducted to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring the stability at 80° C. at pH 2.0, 5.0, 7.4, and 10.0. The results indicated that palonosetron hydrochloride is most stable at pH 5.0.

(Ex. 1001, col. 7, lines 6-10).

46. The Bonadeo Declaration shows that the results of the study to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring the stability at pH 2.0, 5.0, 7.4, and 10.0, showed that the stability of formulations at pH 2.0, 7.4, and 10.0 was less than one year. Ex. 1009, p. 2.

47. Example 1 of the '219 patent does not disclose the use of mannitol or EDTA. Ex. 1001, col. 7, lines 1-10.

48. Examples 2-5 and 8 of the ‘219 patent rely and build on the results of Example 1. Ex. 1015, ¶¶ 37-42.

49. Example 2 of the ‘219 patent was a study to determine concentration ranges of palonosetron with EDTA. Ex. 1001, col. 7, lines 11-27.

50. In Example 2 of the ‘219 patent, all of the formulations tested were at a pH of 5.0. Ex. 1001, col. 7, lines 21-24.

51. Example 2 of the ‘219 patent does not disclose the use of mannitol. Ex. 1001, col. 7, lines 21-24.

52. Example 3 of the ‘219 patent was a study to determine which tonicifying agent, sodium chloride or mannitol, led to better stability. Ex. 1001, col. 7, lines 30-38.

53. In Example 3 of the ‘219 patent, the pH of the tested formulations was also 5.0. Ex. 1001, col. 7, lines 1-38, Ex. 1015, ¶ 39.

54. Example 3 of the ‘219 patent does not disclose the use of EDTA. Ex. 1001, col. 7, lines 30-38.

55. Example 4 of the ‘219 patent discloses an intravenous formulation of palonosetron hydrochloride. Ex. 1001, col. 7, lines 40-59.

56. Example 4 of the ‘219 patent discloses an intravenous formulation having a pH of 5.0 ± 0.5. Ex. 1001, col. 7, line 56.

57. Example 5 of the ‘219 patent discloses an oral liquid formulation of palonosetron hydrochloride. Ex. 1001, col. 7, line 60 - col. 8 line 14.

58. Example 5 of the ‘219 patent discloses the use of 150 mg/ml of mannitol. Ex. 1001, col. 8, line 5.

59. Example 5 of the ‘219 patent discloses an oral liquid formulation having a pH of 5.0 ± 0.5. Ex. 1001, col. 8, line 9.

60. Example 6 of the ‘219 patent discloses formulations of palonosetron hydrochloride without dexamethasone. Ex. 1001, col. 8, lines 15-43.

61. The formulations of Example 6 of the ‘219 patent do not include mannitol or EDTA. Ex. 1001, col. 8, lines 15-43.

62. Example 7 of the ‘219 patent discloses formulation of palonosetron hydrochloride with dexamethasone. Ex. 1001, col. 8, lines 44 to col. 9, line 11.

63. The formulations of Example 7 of the ‘219 patent do not include mannitol or EDTA. Ex. 1001, col. 8, lines 44 to col. 9, line 11.

64. Example 8 of the ‘219 patent discloses an intravenous formulation of palonosetron hydrochloride. Ex. 1001, col. 9, lines 13-39.

65. Example 8 of the ‘219 patent does not disclose the use of mannitol. Ex. 1001, col. 9, lines 15-34.

66. Example 8 of the ‘219 patent discloses the use of EDTA. Ex. 1001, col. 9, lines 15-34.

67. Example 8 of the '219 patent discloses a pH of 4.8 ± 0.5. Ex. 1001, col. 9, line 29.

68. A POSA would understand from the Examples disclosed in the '219 patent that the disclosed formulations containing mannitol and EDTA require a pH of about 4.0-6.0 or narrower. Ex. 1015, ¶ 35.

69. A POSA would understand from the '219 patent disclosure that the inventors regarded as their alleged invention a stable formulation comprising specified amounts of palonosetron hydrochloride, mannitol and EDTA at a pH in the range of about 4.0-6.0. Ex. 1015, ¶¶ 34-50.

70. It would be apparent to a POSA that the alleged invention recited in claims 1-5 and 8 of the '219 patent require a pH in the range of about 4.0-6.0. Ex. 1015, ¶¶ 34-76.

VII. How the Challenged Claims Are To Be Construed Under 37 C.F.R. § 42.204(b)(3)

In a post grant review proceeding involving an unexpired patent, claims are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.200(b). As explained by the Federal Circuit:

> The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable

> construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.,* 367 F.3d 1359, 1364, [70 USPQ2d 1827, 1830] (Fed. Cir. 2004).

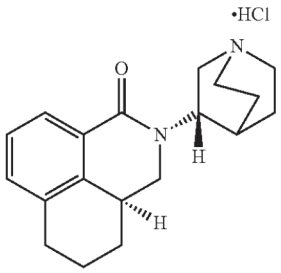
Phillips v. AWH Corp., 415 F.3d 1303, 1316 (Fed. Cir. 2005). The meaning and scope of a claim is what is reasonable from the perspective of one of ordinary skill in the art. *In re Suitco Surface, Inc.,* 603 F.3d 1255, 1260 (Fed. Cir. 2010).

The language of the claim defines the boundary of its scope and, as such, there is a "heavy presumption" in favor of the "ordinary meaning" of a claim[1]. *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed. Cir. 1999). With this standard in mind, for the purposes of this post grant review, Petitioner believes that each claim term, and the claims as a whole, should be given their broadest reasonable plain and ordinary meaning.

[1] It is Petitioner's position that the Patent Owner has disavowed claim scope such that the claims can only be construed to be valid if interpreted to include a pH of about 4.0-6.0. However, the claims as drafted fail to express a pH of about 4.0-6.0 and, as such, are unpatentable as extending beyond the scope of Patent Owner's invention and disclosure.

Petitioner submits that no term of any Challenged Claim is in means-plus-function or step-plus-function format. Petitioner offers the following definitions based on the plain and ordinary meanings:[2]

The term "**palonosetron hydrochloride,**" appearing in independent claims 1 and 8, means the drug having the structural formula:



(Ex. 1001, col. 3, lines 48-65) Repta Dec. (Ex. 1015) ¶ 30. Palonosetron hydrochloride can be used to treat nausea induced by chemotherapy agents (Ex. 1001, col. 1, lines 43-49).

The term "**EDTA,**" appearing in independent claims 1 and 8, is a chelating agent also known as ethylenediaminetetraacetic acid or edetic acid, and has chemical formula:

$$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$$

[2] Because the Board in a post grant review has different presumptions and standards of claim construction than an Article III court, the above definitions are for purposes of this post grant review only, and do not bind or commit Petitioners in any way in litigation.

Ex. 1001, col. 5, line 62; Ex. 1008, p. 3; Repta Dec. (Ex. 1015) ¶ 31.

The term "**mannitol,**" appearing in independent claims 1 and 8, is a sugar alcohol having empirical formula $C_6H_{14}O_6$. *See* Ex. 1008, pp. 7-8. Mannitol is used as a tonicifying agent in the disclosure. Ex. 1001, col. 6, line 16; col. 7, line 37; Repta Dec. (Ex. 1015) ¶ 32.

The term "**formulation,**" as recited in claims 1 and 8, refers to an acceptably stable pharmaceutical aqueous solution of palonosetron hydrochloride. Ex. 1001, col. 2, line 53 to col. 4, line 3; Repta Dec. (Ex. 1015) ¶ 33.

VIII. How The Construed Claims Are Unpatentable Under 37 C.F.R. § 42.204(b)(4)

A. Claims 1-5 And 8 Of The '219 Patent Are Unpatentable Under 35 U.S.C. §112(a) For Lack Of Written Description Of The Claimed Subject Matter Being Stable At 18 Or 24 Months When Stored At Room Temperature

Claims 1-5 and 8 of the '219 patent are unpatentable under 35 U.S.C. §112(a) because the specification fails to provide an adequate written description of the claimed subject matter being stable at 18 or 24 months when stored at room temperature.

Section 112(a) of Title 35 provides, in part, that the "specification shall contain a written description of the invention." 35 U.S.C. § 112(a).[3] "An applicant

[3] The quoted language from Section 112(a) is identical to the language recited in pre-AIA 35 U.S.C. §112, ¶1.

complies with the written description requirement 'by describing the invention, with all its claimed limitations.'" *Gentry Gallery, Inc. v. Berkline Corp.,* 134 F.3d 1473, 1479 (Fed. Cir. 1998) (*quoting Lockwood v. Am. Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997). To satisfy the written description requirement, the specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). The "level of detail required . . . varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* The Federal Circuit has held that the test for sufficiency "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

"[T]he hallmark of written description is disclosure." *Id.* Accordingly, the patent "must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." *Id.* "'The purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" *Atl. Research Mtg. Sys. v. Troy,* 659 F.3d 1345, 1354 (*quoting In re Katz Interactive Call Processing Patent Litig.,* 639 F.3d 1303, 1319 (Fed. Cir. 2011)).

Claiming more broadly than the specification describes renders the claims invalid, leading to the ironic situation of obtaining the requested broad claim scope at the expense of the patent's validity. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1380 (Fed. Cir. 2007)

In the present case, the specification, as well as the prosecution histories of the '219 patent and related patents, *i.e.,* Patent Nos. 7,947,724; 7,947,725; and 7,960,424; make clear that the specification does not provide a written description of the alleged invention, which shows that Applicants were not in possession of the claimed subject matter (Repta Dec. (Ex. 1015), ¶¶ 79, 88, 90). Additionally, the specification does not put the public in possession of what the applicant claims as the invention. *See Regents of the Univ. of Cal. v. Eli Lilly,* 119 F.3d 1559, 1566 (Fed. Cir. 1997), *cert.denied,* 523 U.S. 1089 (1998). The specification does not show that the inventors were in possession of at least one formulation that would achieve either the recited "stable at 24 months when stored at room temperature" (claim 1) or the recited "stable at 18 months when stored at room temperature" (claim 8) (Repta Dec. (Ex. 1015), ¶¶ 77-91). Further, the specification does not describe the recited pharmaceutical single-use, unit-dose formulations for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting that is stable at 18 or 24 months when stored a room temperature (Repta Dec. (Ex. 1015), ¶ 89).

The '219 patent discloses a multitude of formulations that have a goal of being shelf stable for periods greater than 24 months at room temperature. Ex. 1001, col. 2, lines 56-59.[4] However, the disclosure does not provide an indication of possession of an actual formulation that has the stated goal of 24 month stability (Repta Dec. (Ex. 1015), ¶¶ 77-91). The disclosure provides a shotgun description of a number of different embodiments by generally listing the ingredients of different formulations. Various forms of alternative language are used to provide a laundry list of possible ingredients used in the formulations. Moreover, the '219 patent merely contains general statements that it is "possible to increase stability of palonosetron formulations," but does not disclose any data showing a formulation that "is stable at 24 months when stored at room temperature" (claim 1) or a formulation that "is stable at 18 months when stored at room temperature" (claim 8). Repta Dec. (Ex. 1015), ¶¶ 80, 87.

For example, see Ex. 1001 at col. 5, lines 1-3, which states:

[4] In fact, this language was not present in the Provisional Application No. 60/444,352 (Ex. 1016) from which priority is claimed. Instead, the formulations were disclosed in the provisional application to be "shelf stable for periods greater than 18 months at room temperature." There is no disclosure in the '219 patent of any changes to the formulations in the provisional application that would increase the alleged 18 month stability to 24 month stability.

> The inventors have further discovered that by adjusting the formation's pH and/or expedient concentrations it is possible to increase the stability of palonosetron formulations.

Similarly, see Ex. 1001 at col. 5, lines 48-50, which states:

> The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations.

However, there is no disclosure of any formulation that is purported to be capable of obtaining the desired 18 or 24 month stability at room temperature (Repta Dec. (Ex. 1015), ¶¶ 80-82). An alleged general "increase" in stability of palonosetron formulations does not establish that the inventors actually invented any formulation that, in fact, has the recited stability of 18 or 24 months when stored at room temperature. Indeed, the exemplified embodiments in the Examples of the '219 patent, at most, show stability for 48 hours at 23° C, and up to 14 days (apparently in the dark) at 4° C (Ex. 1001, the '219 patent, Examples 6 and 7) (Repta Dec. (Ex. 1015), ¶¶ 85-87).

Examples 4 and 5 of the '219 patent are the only Examples containing mannitol and EDTA.[5] These Examples do not provide any indication as to storage

[5] However, the concentration of mannitol in Example 5 of 150 mg/ml is not in the range recited in the claims of the '219 patent. Repta Dec. (Ex. 1015), ¶ 41.

stability at room temperature of the disclosed Formulations I and II, let alone any disclosure of any length of storage stability at room temperature. These formulations appear to be merely prophetic examples illustrating possible representative pharmaceutical formulations that demonstrate a need for adjustment of the pH of the representative formulations to a pH of 5.0 ± 0.5 by addition of aqueous sodium hydroxide solution and/or hydrochloric acid solution to an aqueous solution containing citrate species as a buffer. Repta Dec. (Ex. 1015) ¶ 44.

As noted above, the specification merely discloses that,

> The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations.

(Ex. 1001, col. 3, lines 19-21 and col. 5, lines 48-50) However, there is no disclosure that this increase is for 18 or 24 months and/or any indication of how ingredients of the composition should be varied (Repta Dec. (Ex. 1015), ¶ 82). All that is disclosed is an invitation to try and achieve a product that is stable at 18 or 24 months when stored at room temperature. In fact, when describing formulations having the stated goals of achieving stability of the product for extended periods at room temperature (Ex. 1001, '219 patent, col. 6, lines 25-48), there is no recitation of mannitol in the formulations, let alone any combination of mannitol and EDTA, or any indication as to how to achieve "an increase" in

stability extending to 18 or 24 months at room temperature (Repta Dec. (Ex. 1015), ¶ 47).[6]

A POSA would understand Examples 4, 5, and 8 as teaching the need to adjust the pH to a range of 5.0±0.5 (or 4.8±0.5). A POSA would understand that if experiments, whether actual or prophetic, are disclosed to show a certain result, the certain result would be indicated in describing the experiment. In other words, the experiment would not be silent with respect to the results obtained or expected to be obtained. Examples 4, 5, and 8, are silent regarding achieving stability at 18 and 24 months when stored at room temperature. A POSA would understand that the formulations of Examples 4, 5, and 8, do not establish 18 or 24 months stability, when stored at room temperature, based on the disclosure of the patent. A POSA would be unable to conclude from this silence that 18 or 24 months

[6] The '219 patent issued from Application No. 13/901,437 ("the '437 application") which is a CIP of Application No. 13/087,012, which is a continuation of Application No. 11/186,311, which claims priority of 60/444,351. The application does not incorporate by reference any of the disclosures of the earlier applications and therefore to the extent that any disclosure may be relied upon in these applications. Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. §112 (CCPA 1973).

stability at room temperature was achieved and that the inventors were in possession of a palonosetron formulation comprising EDTA and mannitol which is stable at 18 or 24 months when stored at room temperature. Repta Dec. (Ex. 1015), ¶ 84.

Independent claim 1 recites 24-month stability, and dependent claims 2-5 include this limitation. Independent claim 8 recites 18-month stability. Accordingly, the Challenged Claims, claims 1-5 and 8, should be found unpatentable for lack of written description as required under §112(a). Repta Dec. (Ex. 1015), ¶¶ 77-91.

B. Claims 1-5 And 8 Of The '219 Patent Are Unpatentable Under 35 U.S.C. §112(a) Because The Specification Does Not Enable The Broadly Claimed Subject Matter Outside A pH Range Of About 4.0 To 6.0

Claims 1-5 and 8 of the '219 patent are unpatentable under 35 U.S.C. §112(a) because the specification does not enable, or show that the inventors were in possession of, the broadly claimed subject matter outside a pH range of about 4.0 to 6.0.

The full scope of the claimed invention must be enabled. *Automotive Technologies Int'l, Inc. v. BMW of North America, Inc.*, 501 F.3d at 1285. The rationale for this statutory requirement is straightforward. Enabling the full scope of each claim is "part of the *quid pro quo* of the patent bargain." *AK Steel Corp. v. Sollac,* 344 F.3d. 1234, 1244 (Fed. Cir. 2003). A patentee who chooses broad

claim language must make sure the broad claims are fully enabled. "'The scope of the claims must be less than or equal to the scope of the enablement' to 'ensure[] that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.'" *Sitrick v. Dreamworks, LLC,* 516 F.3d. 993, 999 (Fed. Cir. 2008)(*citing Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.,* 166 F.3d 1190, 1195-96 (Fed. Cir. 1999)).

A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record is not enabling. *See In re Mayhew,* 527 F.2d 1229 (CCPA 1976); *see also* MPEP § 2172.01.

The specification lacks direction or guidance for the claimed subject matter as to arrive at a formulation that is storage stable at room temperature at 18 or 24 months regardless of the pH of the formulation. As discussed in the previous section, the only Examples containing mannitol and EDTA are Examples 4 and 5 of the '219 patent (Repta Dec. (Ex. 1015), ¶ 40). Moreover, the only Example directed to an intravenous formulation containing mannitol and EDTA is Formulation I disclosed in Example 4 (Repta Dec. (Ex. 1015), ¶¶ 40, 41). Neither of these Examples provides any indication as to storage stability at room temperature let alone any disclosure of any length of storage stability at room temperature (Repta Dec. (Ex. 1015), ¶¶ 83, 84). These formulations appear to be prophetic examples illustrating possible representative pharmaceutical

formulations that demonstrate a need for adjustment of the pH to a pH of 5.0 ± 0.5 by addition of sodium hydroxide solution and/or hydrochloric acid solution. *E.g., see* Ex. 1001, col. 7, line 56. Repta Dec. (Ex. 1015), ¶¶ 43, 44.

To the extent that any formulation including mannitol and EDTA is disclosed in the '219 patent, these formulations would be understood by a POSA to have a pH of about 4.0 to 6.0 – which pH is repeatedly disclosed throughout the specification and exemplified in the Examples. Repta Dec. (Ex. 1015), ¶¶ 46, 48, and 50. At most, the specification provides in Example 4 a representative pharmaceutical formulation directed to a combination of mannitol, EDTA with a concentration of palonosetron hydrochloride that is useful for intravenous formulations. This formulation is disclosed as having a pH of 5.0 ± 0.5. Repta Dec. (Ex. 1015), ¶ 40.

Examples 1-5 show that a pH of about 5.0 is particularly important. Example 1 discloses "that palonosetron is most stable at pH 5.0" (7:8-10). Repta Dec. (Ex. 1015), ¶¶ 37, 45. Example 2 was also performed at pH 5.0. Repta Dec. (Ex. 1015), ¶¶ 38, 45. Example 3 does not disclose the pH, but a POSA would readily understand that the pH was about 5 because Example 3 uses a citrate buffer, Example 1 states that a pH of 5.0 is optimal, and Example 2 uses citrate buffer to maintain a pH of 5.0. Repta Dec. (Ex. 1015), ¶¶ 39, 45.

In fact, the importance of having a pH of about 4.0 to 6.0 is confirmed by the arguments and evidence presented by applicants during prosecution of the parent applications. Repta Dec. (Ex. 1015) ¶¶ 74, 75. For the sake of brevity, reference is made to VIII.C.2, *infra*, wherein statements set forth in the Bonadeo Declaration and the corresponding attorney arguments from the related applications are discussed. Applicants' own arguments during prosecution support the understanding that a POSA would obtain from reading the specification and Examples of the '219 application. For example, Applicants argued that (a) mannitol was identified for the formulations, but only ***after*** the pH range of 4-6 was determined to be necessary; and (b) EDTA was identified for the formulations, but again only ***after*** the pH range of 4-6 was determined to be necessary. Repta Dec. (Ex. 1015), ¶ 62. Applicants argued that palonosetron formulations comprising mannitol require a pH of 4-6. Repta Dec. (Ex. 1015), ¶ 60. The Applicants also argued that palonosetron formulations comprising EDTA require a pH of 4-6. Repta Dec. (Ex. 1015), ¶ 61.

Still further, paragraph 10 of the Bonadeo Declaration (Ex. 1009) confirms the understanding of a POSA as to importance of a pH of 5.0 following Examples 1-4 of the '219 patent. Table 2 in paragraph 10 of the Bonadeo Declaration is directed to a pH-stability study of solutions of palosetron hydrochloride conducted at 80° C. This appears to be the study that is referenced in Example 1. Repta Dec.

(Ex. 1015), ¶ 54. In contrast to the general statement in Example 1 of "most stable at pH 5.0," the Bonadeo Declaration appears to provide the actual results of the study in Table 2. A review of Table 2 shows that none of the solutions was tested for stability for more than 270 days. Repta Dec. (Ex. 1015), ¶ 54. However, solutions at pH values of 2.0, 7.4 and 10 only had a maximum T_{90} of 270 days; whereas, the pH 5.0 solution has an indication of 99.2% palonosetron remaining at 252 days. Repta Dec. (Ex. 1015), ¶ 54.

Thus, the specification lacks sufficient guidance to direct a POSA to the recited formulations having a pH other than about 4.0 to 6.0 when employing a combination of mannitol and EDTA. Repta Dec. (Ex. 1015), ¶ 72. A POSA who reads and follows the teachings of the '219 patent would limit development activities within the pH range of about 4.0-6.0 for an aqueous palonosetron formulation comprising EDTA and mannitol. Repta Dec. (Ex. 1015), ¶ 46. A POSA following the disclosure of the '219 patent would not attempt to develop a formulation comprising EDTA and mannitol with a pH outside the range of 4-6. Repta Dec. (Ex. 1015), ¶ 50. Moreover, Applicants' arguments of record render it clear a pH of about 4.0 to 6.0 is essential to the recited formulations so that the Challenged Claims, which omit a pH of about 4.0 to about 6.0, omit essential matter, and are therefore not enabled. Ex. 1015, ¶ 73

Independent claims 1 and 8 do not recite a pH limitation, and dependent claims 2-5 also do not recite a pH limitation. Accordingly, the Challenged Claims, claims 1-5 and 8, should be found unpatentable under §112(a) because the specification does not enable the broadly claimed subject matter outside a pH range of about 4.0 to 6.0. Repta Dec. (Ex. 1015), ¶¶ 34-76.

C. Claims 1-5 And 8 Of The '219 Patent Are Unpatentable Under 35 U.S.C. §112(b) Because The Claims Do Not Particularly Point Out And Distinctly Claim The Subject Matter Which The Inventors Regard As The Invention.

1. A Claim Is Unpatentable Where It Would Be Apparent To One Of Skill In The Art That The Claimed Invention Is Not What The Patentee Regarded As The Invention

By statute, the specification of every patent must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention." 35 U.S.C. §112(b). The language in Section 112(b) is substantially identical, in all material respects, to the language recited in pre-AIA 35 U.S.C. §112, ¶2.

The Federal Circuit has recognized that the "regards as invention" requirement is distinct from the requirement that the claim be sufficiently clear to be definite. *Lochner Technologies, LLC v. Vizio, Inc.,* 2014 US App. LEXIS 12103, *24 (Fed. Cir. 2014) (*citing Allen Eng'g Corp. v. Bartell Indus., Inc.,* 299 F.3d 1336, 1348 (Fed.Cir. 2002)). "Where it would be apparent to one of skill in the art, based on the specification, that the invention set forth in a claim is not what

the patentee regarded as his invention, we must hold that claim invalid under § 112, paragraph 2." *Id.*

It is well settled that there is no legally recognizable or protected "essential" element, gist or "heart" of the invention in a combination patent. *Aro Mfg. Co. v. Convertible Top Replacement Co.,* 365 U.S. 336, 345 (1961). Rather, the invention is defined by the claims. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1565 (Fed. Cir. 1991). Nevertheless, a patent claim must set forth what the applicant regards as the invention, and it must do so with sufficient particularity and distinctness. *Solomon v. Kimberly-Clark Corp.,* 216 F.3d 1372, 1377 (Fed. Cir. 2000).

The evidence that may be considered when determining whether an issued claim complies with the "regards the invention" requirement of 35 U.S.C. §112(b) [previously §112 ¶2], typically involves "the way one of skill in the art would interpret the claims in view of the written description portion of the specification." *Solomon v. Kimberly-Clark Corp.*, 216 F.3d at 1378. However, the Federal Circuit acknowledges that, "despite this general rule, in some circumstances evidence beyond the claims and written description may be reviewed." *Solomon v. Kimberly-Clark Corp.*, 216 F.3d at 1378, n. 4.

For example, the Federal Circuit has relied upon the prosecution history of the patent-in-suit and also on the prosecution history of a related, parent patent of

the patent-in-suit to assist in determining whether a claim complies with the requirements of §112, ¶2. *See Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1217-19, (Fed. Cir. 1991) (considering the prosecution history of patent-in-suit to determine scope of claims); *Texas Instruments Inc. v. ITC,* 871 F.2d 1054, 1063 (Fed. Cir. 1989) (relying upon the prosecution history of the parent patent to the patent-in-suit to determine scope of the claims). Similarly, the Supreme Court recently indicated that the prosecution history should be consulted in addition to the specification when deciding whether a claim meets the definiteness requirement of 35 U.S.C. §112, ¶2, stating:

> Cognizant of the competing concerns, we read *§112*, ¶2 to require that a patent's claims, ***viewed in light of the specification and prosecution history***, inform those skilled in the art about the scope of the invention with reasonable certainty.

Nautilus, Inv. v. BioSig Instruments, Inc., 572 U.S. __, 134 S. Ct. 2120, 2129 (2014)(emphasis added).

While these cases involved determining whether the claims met the "definite" requirement of §112 ¶2, the Federal Circuit has made clear that the same standard applies to the "regards the invention" requirement. *Solomon v. Kimberly-Clark Corp.*, 216 F.3d at 1378-79 ("Although we have not specifically addressed the types of evidence that may be considered in analyzing whether a claim complies with the 'which the applicant regards as his invention' portion of that

statute, we see no reason for a different standard to apply, as the rationale for reviewing a limited range of evidence under either portion of the statute is the same.") It is, moreover, particularly important to consult the prosecution history of the patent family where, for example, the inventor has made express arguments and statements that disavow the scope of what the inventors regard as their invention. As the Federal Circuit has stated in the context of determining whether a claim is invalid under §112, ¶2: "The public is entitled to know the scope of the claims but must look to both the patent specification and the prosecution history, especially where there is doubt concerning the scope of the claims." *Texas Instruments Inc. v. ITC,* 871 F.2d at 1063.

As will be shown below, the Patent Owner has clearly articulated, in the prosecution histories of family member applications, as well as the specification of the patent-at-issue, that it regards its invention as requiring a pH in the range of 4-6. Moreover, a POSA reading the '219 patent would understand the recited formulations as requiring a pH in the range of 4-6. The failure of the claims to include an appropriate pH limitation renders the Challenged Claims unpatentable under 35 U.S.C. §112(b).

2. The Prosecution History Demonstrates That The pH Of The Formulation Must Be Limited To 4-6

U.S. Patent No. 7,947,725, currently the subject of a broadening reissue application (Application No. 14/184,305 (the '305 reissue application)), is a family

member of the '219 patent. During prosecution of the '305 reissue application, the reissue Applicants have made arguments that the specification indicates that pH is merely one optional way in which to stabilize palonosetron solutions. Ex. 1017, p. 30; Ex. 1018, pp. 8-11; Ex. 1019, p. 3. However, this is contradicted by Applicants' own arguments made during prosecution of family members in the patent family.

During prosecution of the first-filed non-provisional application in this patent family (Application No. 11/186,311, filed July 21, 2005), Applicants submitted a Declaration under 37 C.F.R. § 1.132 by inventor Daniele Bonadeo. Ex. 1009. Repta Dec. (Ex. 1015) ¶ 52.

In particular, the Bonadeo Declaration (Ex. 1009) indicates that palonosetron concentration and pH were the first two parameters studied for their effect on stability (Ex. 1009, p. 2, ¶¶ 8 and 10; Repta Dec. (Ex. 1015) ¶ 53). These studies showed that palonosetron was "extremely stable at a pH of 5.0" at low palonosetron concentrations. Ex. 1009, p. 3, ¶ 11; Repta Dec. (Ex. 1015) ¶ 53.

The inventors then "settl[ed] on mannitol and citrate buffer for the formulation for practical reasons," and studied stability of palonosetron formulations, at a pH of 5.0, as functions of palonosetron and EDTA concentrations. Ex. 1009, p. 3, ¶13. The Bonadeo Declaration describes additional

stability studies, again at a pH of 5.0. Ex. 1009, p. 8, ¶ 26. Repta Dec. (Ex. 1015) ¶ 55.

As can be seen in the Bonadeo Declaration, the pH value and palonosetron concentration were the first two stability parameters optimized by the inventors. Once these optimizations were done, *every* stability study disclosed was performed at a pH of 5.0. There is no hint or suggestion in the Bonadeo Declaration that a formulation having a pH outside the range of about 4.0 to 6.0 could be, or would be, suitably stable at room temperature for 18 or 24 months (*i.e.,* 540 or 720 days). Repta Dec. (Ex. 1015) ¶ 56.

This is corroborated by the Applicants in arguments they submitted to the US PTO in one or more patent applications in the same patent family. Repta Dec. (Ex. 1015) ¶ 65.

For example, in Application No. 11/186,311, Applicants filed an appeal on May 24, 2010, after receiving a final rejection. In relevant portion, the Appeal Brief stated:

> In this case, the Office has not cited any prior art to show that all of the features of the claimed formulation would have been combined as a matter of routine optimization. In contrast, Applicant has submitted substantial evidence which proves that the combination of features that defines the claimed formulation is anything but routine. This evidence shows that the claimed formulation was discovered after a sequence of experiments, each building on the prior

> experiment like a series of building blocks to arrive at the claimed invention.[1] A different formulation could have been obtained at any step along the way if the experimental sequence had differed. For example, Applicant discovered that mannitol is the best tonicity agent for the formulation, but this discovery was only made after the inventors had settled on an aqueous formulation, using palonosetron HCl at a pH of 4-6. Bonadeo Dec. at par. 26. In like manner, Applicant discovered that EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl in an aqueous formulation of palonosetron HCl having a pH of 4-6. Bonadeo Dec. at par. 14.

(emphases added) wherein the footnote reads:

> [1] These studies included: (1) a temperature stability study (Bonadeo Dec. par. 16); (2) a concentration stability study (Bonadeo Dec. par. 8); (3) a pH stability study (Bonadeo Dec. par. 10); (4) a tonicifying agent study (Bonadeo Dec. pars. 12 and 26), and (5) a multi-variate study in which concentrations of palonosetron HCl, buffer, and EDTA concentrations were varied and evaluated for six months (Bonadeo Dec. par. 14).

Ex. 1010, p. 9. Here, the Applicants (now patent owners) expressly state the interdependency of various aspects of their alleged invention. Repta Dec. (Ex. 1015) ¶¶ 58, 59, 63.

The Applicants expressly state that their development of the formulation was dependent on the order that they performed the various experiments:

> mannitol is the best tonicity agent for the formulation, but this discovery was made only after the inventors had settled upon an aqueous formulation, using palonosetron HCl at a pH of 4-6.

Ex. 1010, p. 9. Nevertheless, even though the Challenged Claims require mannitol, they do not recite the pH of 4-6 that the Applicants argued is a condition precedent to the use of mannitol. Repta Dec. (Ex. 1015), ¶¶ 60, 63, 71.

Further, the Applicants argued that EDTA only stabilizes the formulation at a pH of 4-6:

> In like manner, Applicant discovered that EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl . . . having a pH of 4-6.

Ex. 1010, p. 9. Yet the Challenged Claims recite EDTA, but do not recite the condition precedent of a pH of 4-6. Repta Dec. (Ex. 1015), ¶¶ 61, 71.

These arguments in the Appeal Brief are not merely in relation to the claims then pending. Rather, these arguments clarify just how the named inventors developed their formulation, and therefore are highly enlightening as to the scope of what the named inventors regarded as the scope of their invention. Repta Dec. (Ex. 1015) ¶¶ 52, 57. Specifically, per the Applicants' own arguments, mannitol was identified for the formulations, but only ***after*** the pH range of 4-6 was determined to be necessary. EDTA was identified for the formulations, but again only ***after*** the pH range of 4-6 was determined to be necessary. The Applicants

themselves freely admitted that had the experiments been done in a different order, a ***different*** formulation than the one they allegedly invented could have been obtained. Repta Dec. (Ex. 1015) ¶ 64. The guidance provided in the '219 patent as well as in the prosecution histories would lead a POSA to experiment at a pH of about 5.0, and would have certainly prompted a POSA to avoid a pH outside of the range of about 4.0 to 6.0 when performing experiments to maximize stability for a solution containing palonosetron, mannitol and EDTA. Repta Dec. (Ex. 1015) ¶ 64.

The Applicants argued that palonosetron formulations comprising mannitol require a pH of 4-6. The Applicants also argued that palonosetron formulations comprising EDTA require a pH of 4-6. Therefore, any palonosetron formulation comprising mannitol and EDTA also requires a pH of 4-6 if the formulation is to come within the scope of what the inventors regarded as their invention.

However, although the Challenged Claims of the '219 patent recite mannitol and EDTA, the Challenged Claims omit the limitation that the pH must be in the range of 4-6. The Challenged Claims do not recite pH, even though they recite other limitations (*e.g.,* mannitol and EDTA) which Applicants have admitted and argued ***require*** a pH of 4-6.

It must also be emphasized that the original '311 application is not the only family member application, in which the Applicants made these arguments

regarding pH. Rather, the prosecution histories of related patent applications are replete with arguments emphasizing the centrality of pH to the alleged invention.

For example, in Application No. 11/388,270 (a continuation of the '311 application), in an Appeal Brief, the Applicants made almost the identical remarks quoted above from the '311 application. Ex. 1011, pp. 10-11. Repta Dec. (Ex. 1015) ¶ 66.

Yet further, in a subsequent Supplemental Amendment in the '270 application (Ex. 1012), the Applicants argued concerning the conditions under which EDTA was effective. In relevant part, they wrote:

> [. . .] Importantly -- these results were obtained in a solution containing mannitol at a pH of 5 -- as recited in the claims. [. . .]
>
> The number of elements in this combination — and their inter-dependency — is also significant.[1] The record demonstrates that each of the elements was selected from many possible options[2], and that all of the elements must be carefully balanced to arrive at a stable formulation.[3] Hindsight analysis would be needed to arrive at this unique combination.

wherein footnotes 1 and 3 read:

> [1] The claims recite five variables: pH (4-6), tonicity agent (mannitol), salt (hydrochloride), concentration of palonosetron (0.03-0.2 mg/ml), and stabilizing agent (EDTA).

> [3] See Bonadeo Dec. at par. 26 (Exh. 5) (reporting that mannitol is the best tonicity agent for the formulation, ***but only*** for aqueous solutions of palonosetron HCl at a pH of 4-6); par 14. (reporting that EDTA stabilizes the formulation, ***but only*** at low concentrations of palonosetron HCl in aqueous solutions of palonosetron HCl at a pH of 4-6).

Ex. 1012, pp. 2-3 (emphases in footnote 3 added). Repta Dec. (Ex. 1015) ¶ 67. Thus, the Applicants emphasized again that the five listed variables were significant and interdependent, and that all of these parameters had to be ***balanced*** with respect to each other. More importantly, the Applicants also again stressed the dominance of pH on the formulation, arguing that each of mannitol and EDTA are ***only*** effective in a pH range of 4-6. Repta Dec. (Ex. 1015) ¶ 63.

In Application No. 11/388,268 (also a continuation of the '311 application), the Applicants attempted to overcome an obviousness rejection by arguing that the rejection merely patched together disparate teachings from the prior art, and that the proper question is whether the invention as a whole is obvious. When discussing the '268 application itself, Applicants argued:

> These principles are particularly appropriate in this case, where the elements of the formulation cooperate in an inter-dependent manner to produce a highly stable formulation. For example, Applicant has discovered that mannitol results in a more stable formulation, but this discovery was only made in the context of an aqueous formulation at a pH of 4-6 using palonosetron HCl. Bonadeo

> Dec. at par. 26. In like manner, Applicant has discovered that EDTA stabilizes the formulation, but it only does so at low concentrations of palonosetron HCl in an aqueous formulation of palonosetron HC1 having a pH of 4-6. Bonadeo Dec. at par. 14. It is this combination and inter-cooperation of features that must be evaluated for purposes of patentability.

Ex. 1013, pp. 5-6. The Applicants effectively repeat and re-emphasize this argument on page 9 of the Amendment (Ex. 1013, p. 9). The Applicants argued in the '268 application that ***the various elements are interdependent***, and backed up that assertion by arguing that ***mannitol requires a pH of 4-6***, and that ***EDTA requires a pH of 4-6***. Repta Dec. (Ex. 1015), ¶¶ 68-70; Repta Dec. (Ex. 1015), ¶ 70.

This was re-phrased and re-stated in an Appeal Brief in the '268 application, in which Applicants again argued that the discovery of the stabilizing effect of EDTA was surprising, and only made in the context of formulations comprising mannitol at a pH of 4-6. Ex. 1014, p. 23.

The Challenged Claims of the '219 patent all recite mannitol, but do not recite the pH of 4-6 that mannitol requires. The challenged claims of the '219 patent all additionally recite EDTA, but do not recite the pH of 4-6 that EDTA requires.

The Board in a post grant review must give claims their broadest reasonable meanings.[7] In this case, the Challenged Claims do not recite pH, and so read on compositions having a pH below 4 and/or above 6. This is despite the Applicants' own arguments and admissions that the mannitol and EDTA recited in the claims each require a pH in the range of 4-6. Repta Dec. (Ex. 1015), ¶¶ 51-76. And this is despite the teaching in the '219 patent that links instability of a prior art formulation to its pH of 3.7. Ex. 1001, col. 1 lines 65-67; Repta Dec. (Ex. 1015), ¶ 46.

In view of the Applicants' repeated arguments and admissions that the mannitol and EDTA recited in the claims each requires a pH in the range of 4-6, it would be apparent to a POSA that the invention set forth in the Challenged Claims

[7] In the associated litigation—where there is a presumption of validity and courts generally construe claims (if possible) to preserve validity—Petitioners also intend to argue in the alternative that the term "formulation" must be interpreted to include a pH of about 4.0-6.0 if the claim recites a chelating agent (e.g., EDTA) and/or a tonicifying agent (e.g., mannitol). Because this is not an invalidity argument, Petitioners do not request this interpretation in the present Request for Post Grant Review. However, Petitioners would not object if the Board were to construe the term "formulation" recited in claims 1-5 and 8 as requiring a pH of about 4.0-6.0.

are not what the patentee regarded as the invention. Independent claims 1 and 8 do not recite a pH limitation, and dependent claims 2-5 also do not recite a pH limitation. Accordingly, the Challenged Claims, claims 1-5 and 8, should be found unpatentable under 35 U.S.C. § 112(b).

3. The Specification Demonstrates That The pH Of The Formulation Must Be In The Range Of 4.0-6.0

Example 1 of the '219 patent is a study of the effect of pH on stability. The results of Example 1 are set forth quite clearly:

> A study was conducted to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring the stability at 80° C. at pH 2.0, 5.0, 7.4, and 10.0. The results indicated that palonosetron hydrochloride is most stable at pH 5.0.

(Ex. 1001, col. 7, lines 6-10, emphasis added). The remaining Examples containing EDTA and/or mannitol rely and build on the results of Example 1. Repta Dec. (Ex. 1015), ¶ 37.

Example 2 is a study to determine concentration ranges for palonosetron. All of the formulations tested had the "optimal" pH of 5.0. Ex. 1001, col. 7, lines 21-24. Repta Dec. (Ex. 1015), ¶ 38.

Example 3 is a study to determine which tonicifying agent, sodium chloride or mannitol, led to better stability. Example 3 does not disclose the pH, but a POSA would readily understand that the pH was about 5 because Example 3 uses a

citrate buffer, Example 1 states that a pH of 5.0 is optimal, and Example 2 uses citrate buffer to maintain a pH of 5.0. Repta Dec. (Ex. 1015), ¶¶ 39, 45.

The only formulation that the Challenged Claims could arguably read on is Example 4[8], since only that one formulation meets the structural limitations recited in the claims (*e.g.,* concentrations of palonosetron, EDTA, and mannitol).[9] Repta Dec. (Ex. 1015), ¶ 40. Example 4 is prepared to have "pH 5.0 ± 0.5." Ex. 1001, col. 7, line 56 *and* col. 8, line 9. Repta Dec. (Ex. 1015), ¶ 40.

While Example 8 does not comprise mannitol, it does comprise EDTA, and has a pH of 4.8 ± 0.5. Ex. 1001, col. 7, lines 20-30. Repta Dec. (Ex. 1015), ¶ 42.

A POSA would understand from the '219 disclosure that stability of a palonosetron formulation containing EDTA, or mannitol and EDTA, requires a pH of 4-6 or narrower. Repta Dec. (Ex. 1015), ¶¶ 35, 46. This is perfectly consistent with the Bonadeo Declaration discussed above, and with Applicants' arguments in

[8] The specification gives no indication whether these formulations meet the claimed limitation that the formulation be stable at 24 (or 18) months when stored at room temperature. Indeed, there is no indication in the '219 patent of any formulation that meets this recitation.

[9] Examples 6 and 7 do not comprise EDTA or mannitol as required by the claims, such that Examples 6 and 7 are irrelevant to the claims regardless what their (undisclosed) pH might have been. Repta Dec. (Ex. 1015) ¶ 49.

prosecution of family member applications, by which ***EDTA is effective but only at a pH of 4-6***, and ***mannitol is effective but only at a pH of 4-6***. Repta Dec. (Ex. 1015) ¶ 63.

Accordingly, in view of the specification and the file history, it would be apparent to a POSA that the alleged invention recited in the Challenged Claims requires mannitol, EDTA **and** a pH in the range of about 4.0-6.0. However, independent claims 1 and 8 require mannitol and EDTA, but do not recite a pH limitation, and dependent claims 2-5 also do not recite a pH limitation. Since the Challenged Claims do not recite what the patentee regarded as the invention, the Challenged Claims, claims 1-5 and 8, should be found unpatentable under § 112(b).

D. Claims 1-5 And 8 Of The '219 Patent Are Unpatentable Under 35 U.S.C. §112(a) For Lack Of Written Description Of The Claimed Subject Matter Which Omits A pH Range Of About 4.0 To 6.0

As noted earlier, a patent must describe an invention so that it is understandable to a skilled artisan. A patent must also show that the inventor actually invented the invention claimed and the purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification. Claiming more broadly than the specification describes renders the claims invalid.

In *Gentry Gallery, Inc. v. Berkline Corp.,* 134 F.3d 1473 (Fed. Cir. 1998), the Federal Circuit held that a claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement. *Id.* at 1480 (claims to a sectional sofa comprising, *inter alia,* a console and a control means were held invalid for failing to satisfy the written description requirement where the claims were broadened by removing the location of the control means).

While the Federal Circuit has held that the *Gentry Gallery* case "did not announce a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements," the Federal Circuit has likewise made clear that it "applied and merely expounded upon the unremarkable proposition that a broad claim is invalid when the entirety of the specification clearly indicates that the invention is of a much narrower scope." *Cooper Cameron Corp. v. Kvaerner Oilfield Prods.,* 291 F.3d 1317, 1323 (Fed. Cir. 2002) (*citing Gentry*, 134 F.3d at 1479-80). *See also Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1127 (Fed. Cir. 2008).

As explained in detail in Section VIII.C, the specification and prosecution history of the '219 patent, and the prosecution histories of the related patents, establish that the formulations recited in the Challenged Claims, which recite both

EDTA and mannitol, must have a pH in the range of 4.0-6.0. Thus, a pH value in the range of 4.0-6.0 is an essential or critical feature of the alleged invention.

Independent claims 1 and 8 require mannitol and EDTA, but do not recite a pH limitation, and dependent claims 2-5 also do not recite a pH limitation. The failure to recite a pH within the range of 4.0–6.0 in the Challenged Claims, claims 1-5 and 8, renders them unpatentable as unsupported by the written description. Repta Dec. (Ex. 1015), ¶ 76. Accordingly, the Challenged Claims should be found unpatentable under § 112(a).

IX. CONCLUSION

For the reasons described above, it is more likely than not that claims 1-5 and 8 of the '219 patent are unpatentable, and more likely than not that at least one of claims challenged in this Petition is unpatentable. Accordingly, post grant review of claims 1-5 and 8 of the '219 is respectfully requested.

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CERTIFICATE OF SERVICE

I hereby certify that the attached Petition For Post Grant Review Of U.S. Patent No. 8,598,219 Under 35 U.S.C. §§ 320-329 And 37 C.F.R. § 42.200 et seq. and supporting materials were served as of the below date by Federal Express on the Patent Owner at the correspondence address indicated for U.S. Patent No. 8,598,219:

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