

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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**AZURITY PHARMACEUTICALS, INC.**  
**AZURITY PHARMA INDIA LLP**  
**SLAYBACK PHARMA LLC**  
Petitioners,

v.

**HERON THERAPEUTICS, INC.**  
Patent Owner.

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Case No. Unassigned  
Patent 12,115,254

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**DECLARATION OF WILLIAM CHARMAN, Ph.D., IN SUPPORT OF  
PETITION FOR POST-GRANT REVIEW OF  
U.S. PATENT 12,115,254**

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**LIST OF DOCUMENTS CITED**

<b>Exhibit No.</b>	<b>Description</b>
1001	U.S. Patent 12,115,254 (“the ’254 patent”)
1003	Certified English Translation of CN102379845 (“Zhou”)
1004	Washington, “Stability of lipid emulsions for drug delivery,” <i>Advanced Drug Delivery Reviews</i> , 20, (1996), 131-145 (“Washington”)
1005	Bagwe <i>et al.</i> , “Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons,” <i>Critical Reviews<sup>TM</sup> in Therapeutic Drug Carrier Systems</i> , 18(1):77-140 (2001) (“Bagwe”)
1006	Weng <i>et al.</i> , “Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres,” <i>Eur. J. Lipid Sci. Technol.</i> 2012, 114, 1154-1164 (“Weng”)
1007	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), D.I. 193 (Findings of Fact and Conclusions of Law) (“Trial Opinion”)
1008	Hargreaves <i>et al.</i> , “Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting,” <i>Ann. N.Y. Acad. Sci.</i> 1222 (2011) 40-48 (“Hargreaves”)
1009	U.S. Application Publication No. 2013/0317016 (“Hingorani”)
1010	<i>Exhibit Number Not Used</i>
1011	Cannon <i>et al.</i> , “Emulsions, Microemulsions, and Lipid-Based Drug Delivery Systems for Drug Solubilization and Delivery—Part I: Parenteral Applications,” in <i>Water-Insoluble Drug Formulation</i> , Second Ed. (Rong Liu, ed.) (2008), 195-226 (“Cannon”)
1012	Rossi and Leroux, “Principles in the Development of Intravenous Lipid Emulsions,” in <i>Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery</i> , Basic Principles and Biological Examples, (Wasan, ed.) (2007), 88-123 (“Rossi”)

<b>Exhibit No.</b>	<b>Description</b>
1013	International Publication Number WO 2012/051116 (“Rajeshwar”)
1014	Klang and Valenta, “Lecithin-based nanoemulsions,” <i>J. Drug Del. Sci. Tech.</i> , 21 (1) 55-76 2011 (“Klang”)
1015	Mahato and Narang, “Emulsions,” in <i>Pharmaceutical Dosage Forms and Drug Delivery</i> , Second Ed. (Mahato and Narang, ed.) (2012) (“Mahato”)
1016	Khan <i>et al.</i> , “Basics of pharmaceutical emulsions: A review,” <i>African Journal of Pharmacy and Pharmacology</i> , Vol. 5(25) 2011, 2715-2725 (“Khan”)
1017	Benita and Levy, “Submicron Emulsions as Colloidal Drug Carriers for Intravenous Administration: Comprehensive Physicochemical Characterization,” <i>Journal of Pharmaceutical Sciences</i> , Vol. 82, No. 11, November 1993, 1069-1079 (“Benita”)
1018	Hippalgaonkar <i>et al.</i> , “Injectable Lipid Emulsions—Advancements, Opportunities and Challenges,” <i>AAPS PharmSciTech</i> , Vol. 11, No. 4, December 2010, 1526-1540 (“Hippalgaonkar”)
1019	Collins-Gold <i>et al.</i> , “Parenteral emulsions for drug delivery,” <i>Advanced Drug Delivery Reviews</i> , 5 (1990) 189-208 (“Collins-Gold”)
1020	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), D.I. 180 (“Heron’s Opening Post-Trial Brief”)
1021	<i>Exhibit Number Not Used</i>
1022	Prosecution History excerpt for U.S. Application Serial No. 18/408,486 which issued as the ’254 patent (“’254 Patent Prosecution History”)
1023	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), Trial Transcript (“Day 4 PM”)
1024	Rowe <i>et al.</i> , “Handbook of Pharmaceutical Excipients,” 6th Ed. (2009) (“Handbook”)
1025	U.S. Application Publication No. 2013/0236501 (“Booth”)

<b>Exhibit No.</b>	<b>Description</b>
1026	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), D.I. 175 (“Heron’s Opening Statement”)
1027	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), D.I. 185 (“Heron’s Responsive Post-Trial Brief”)
1028	Su <i>et al.</i> , “Drug solubility and solubilization,” in <i>Pharmaceutical Dosage Forms, Parenteral Medications Third Edition</i> (Nema and Ludwig, ed.) (2010) (“Su”)
1029	Baker and Naguib, “Propofol, The Challenges of Formulation,” <i>Anesthesiology</i> , V 103, No 4, Oct 2005, 860-876 (“Baker”)
1030	U.S. Patent 9,561,229 (“the ’229 patent”)
1031	U.S. Patent 9,974,794 (“the ’794 patent”)
1032	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), Trial Transcript (“Day 4 AM”)
1033	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), Trial Transcript (“Closing Arguments”)
1034	<i>Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.</i> (DDE-1-22-cv-00985), Trial Transcript (“Day 2 AM”)
1035	U.S. Patent 9,974,742 (“the ’742 patent”)
1036	U.S. Patent 10,624,850 (“the ’850 patent”)
1037	U.S. Patent 11,173,118 (“the ’118 patent”)
1038	U.S. Patent 11,878,074 (“the ’074 patent”)
1039	Prosecution History excerpt for U.S. Application Serial No. 15/012,532 which issued as the ’742 patent (“’742 Patent Prosecution History”)
1040	Declaration Under 37 C.F.R. §1.132 of Thomas Ottoboni submitted during prosecution of the ’229 patent (“Ottoboni Declaration”)

<b>Exhibit No.</b>	<b>Description</b>
1041	Prosecution History excerpt for U.S. Application Serial No. 15/965,630 which issued as the '850 patent (“’850 Patent Prosecution History”)
1042	Prosecution History excerpt for U.S. Application Serial No. 17/180,593 which issued as the '074 patent (“’074 Patent Prosecution History”)
1043	U.S. Patent 9,808,465 (“the '465 patent”)
1044	U.S. Patent 9,974,793 (“the '793 patent”)
1045	U.S. Patent 10,500,208 (“the '208 patent”)
1046	Prosecution History excerpt for U.S. Application Serial No. 15/083,071 which issued as the '229 patent (“’229 Patent Prosecution History”)
1047	Prosecution History excerpt for U.S. Application Serial No. 14/859,013 which issued as the '465 patent (“’465 Patent Prosecution History”)
1048	Prosecution History excerpt for U.S. Application Serial No. 15/705,201 which issued as the '793 patent (“’793 Patent Prosecution History”)
1049	Prosecution History excerpt for U.S. Application Serial No. 15/398,928 which issued as the '208 patent (“’208 Patent Prosecution History”)
1050	Vemuri, “Preformulation,” in Pharmaceutical Dosage Forms, Parenteral Medications Third Edition (Nema and Ludwig, ed.) (2010) (“Vemuri”)

1. I, William Charman, Ph.D., have been retained by Windels Marx Lane & Mittendorf, LLP, counsel for Azurity Pharmaceuticals, Inc., Azurity Pharma India LLP, and Slayback Pharma LLC (collectively “Azurity” or “Petitioners”). I understand from counsel that Azurity is petitioning for post-grant review (“PGR”) of U.S. Patent No. 12,115,254 (“the ’254 patent,” Ex. 1001) and requests that the United States Patent and Trademark Office (“PTO”) cancel claims 1-30 of the ’254 patent as unpatentable. The following discussion and analysis provide my opinions as to why claims 1-30 would have been obvious or fail to comply with the written description and enablement requirements.

## **I. BACKGROUND AND QUALIFICATIONS<sup>1</sup>**

2. I am an Emeritus Sir John Monash Distinguished Professor in the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University in Melbourne, Australia. I retired from Monash University in September 2024.

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<sup>1</sup> I have included section headings and sub-headings for the reader’s convenience. Often, information discussed in one section will be of interest to the reader in another section. I have attempted to include cross-citations in such instances to avoid being repetitive. Any omission of a cross-citation is inadvertent.

3. I have over 35 years of experience in the field of pharmaceutical sciences, pharmacology and drug delivery, and I have been recognized as an expert in these fields.

4. I was previously the Dean, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University from 2007 to 2019. While I was Dean, I was also the Founding Director of the Monash Institute of Pharmaceutical Sciences from 2007-2017. The Faculty and Institute are regularly ranked within the top three in the world in pharmacy and pharmacology.

5. In 2011, I was appointed as the seventh Sir John Monash Distinguished Professor, the University's most prestigious title conferred to Professors. Prior to serving as Dean, I held academic appointments at Monash University as Professor of Pharmaceutics from 1995 to 2006, and Associate Dean (Research) from 1999 to 2002.

6. I received my Bachelor of Pharmacy degree in 1981 from the Victorian College of Pharmacy (now the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University). In 1985, I completed my Ph.D. in Pharmaceutical Chemistry (awarded with honours) from the University of Kansas.

7. In 2021, I was appointed as an Officer of the Order of Australia, one of Australia's highest civilian honours, for my achievements and meritorious service to tertiary education, particularly the pharmaceutical sciences.

8. I also was the Chair of the International Pharmaceutical Federation ("FIP") Education Program, and a member of the FIP Board of Directors in The Hague, the Netherlands (2015 – 2020).

9. I am an author on over 380 publications and communications, including U.S. patents and patent applications. I have been recognised as a Highly Cited Researcher by Clarivate Analytics in the field of pharmacology and toxicology which recognises those in the top 1% of their field by impact-based citation analysis over the preceding 10 year period (2015, 2016, and 2018). I have given over 200 invited national and international presentations and lectures. Many of these publications and presentations relate to my research interests and expertise in pharmaceutical sciences, formulation sciences, drug delivery, and pharmacology.

10. I have been a member of the editorial advisory boards for five peer-reviewed research journals: the Journal of Pharmaceutical Sciences (2000 – 2011), the International Journal of Pharmaceutics (1999 – 2012), the Journal of Pharmacy and Pharmacology (2000 – 2012), Die Pharmazie (2001 – 2015), and Experimental Parasitology (2005 – 2010).

11. I have received numerous honours and awards in the pharmaceutical sciences such as the GlaxoWellcome International Achievement Award in Pharmaceutical Sciences awarded by the Pharmaceutical Society of Great Britain (1999), the Career Achievement Award in Oral Drug Delivery from the Controlled Release Society (2006), elected to Fellowship status of the American Association of Pharmaceutical Scientists (2003), an Honorary Fellowship of the Royal Pharmaceutical Society of Great Britain (2017), and I am a medallist of the Australasian Pharmaceutical Sciences Association (2005). I have been awarded both a Pharmaceutical Sciences World Congress Achievement Award (2007) and a Lifetime Achievement Award (2014) in Pharmaceutical Sciences from the International Pharmaceutical Federation. I have also received a Doctor of Science (honoris causa) degree from the University of London (2011).

12. I am or have been a member of various professional societies, including the American Association of Pharmaceutical Scientists, the International Pharmaceutical Federation, the Australian Pharmaceutical Sciences Association, and the Pharmaceutical Society of Australia.

13. Accordingly, I consider myself to be an expert in the pharmaceutical sciences, pharmacology, and drug delivery, and I believe I am qualified to provide opinions as to what the person of ordinary skill in the art (“POSA”) would have understood, known, or concluded regarding the subject matter of the ’254 patent.

14. I have served as an expert witness before. Specifically, in the last five years I have served as an expert for (i) Avadel CNS Pharmaceuticals LLC in C.A. No. 21-691-GBW, C.A. No. 21-1138-GBW and C.A. No. 21-1594-GBW in the United State District Court for the District of Delaware, (ii) Merck Sharp and Dohme B.V. and Merck Sharp and Dohme Corp in Civil Action No. 20-2576 (CCC) (LDW) (CONSOLIDATED) United States District Court, District of New Jersey, and (iii) I have provided Affidavits to the Federal Court of Australia as an independent expert witness, having been retained by the Solicitors acting for Biogen International GmbH.

15. A summary of my education, experience, publications, awards and honours, patents, publications, and presentations is provided in my CV, a copy of which is attached as Exhibit A to this Declaration.

16. I am being compensated for my time in connection with this PGR at my standard consulting rate, which is \$900 per hour. My compensation is not dependent in any way upon the outcome of this matter.

## **II. MATERIALS CONSIDERED**

17. At the front of this document is a list of materials that I considered and reviewed in connection with providing this declaration.

### **III. LEGAL STANDARDS**

18. I am not a patent attorney nor have I independently researched the law on patentability.

#### **A. Obviousness**

19. I understand from counsel that “prior art” includes patents and printed publications that existed before the earliest filing date (the “effective filing date”) of the claim in the patent. For the purposes of this declaration, I have been asked by counsel to utilize an effective filing date of Feb. 1, 2016.

20. I understand from counsel that 35 U.S.C. § 103 governs the determination of obviousness. I understand from counsel that 35 U.S.C. § 103 states:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

21. I further understand from counsel that the four factors to be considered in an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the

pertinent art; and (4) secondary considerations including long-felt need, commercial success, and unexpected results.

22. I further understand from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the anticipated success, it is likely the result is a product of ordinary skill and common sense, not innovation.

23. I also understand from counsel that when a patent's claims simply arrange old elements with each element performing the same function it had been known to perform and the combination yields no more than one would expect from such an arrangement, the claim to the combination of such elements is considered to be obvious.

**B. Written Description**

24. I understand from counsel that the written description requirement of 35 U.S.C. §112(a) requires that the patent application clearly allows a person of ordinary skill in the art to recognize that the inventor(s) invented what is claimed. I also understand from counsel that the key to meeting the written description requirement is an evaluation of the patent application itself.

25. I understand from counsel that the hallmark of written description is disclosure. Accordingly, a demonstration of possession as shown in the patent's disclosure is required. I understand that "possession" does not require actual reduction to practice. I understand from counsel that demonstration of invention of the claimed subject matter using evidence outside of the patent application is insufficient to fulfill the written description requirement. That is, I understand from counsel that the written description requirement is met only if the disclosure in the patent application itself reasonably conveys to a person of ordinary skill in the art that the inventors had invented the claimed subject matter as of the effective filing date. I further understand from counsel that this inquiry is carried out from the perspective of a skilled artisan at the time of the patent application's filing. Accordingly, I understand from counsel that the written description requirement requires an objective inquiry into the four corners of the patent application from the perspective of a person of ordinary skill in the art to determine whether the patent application demonstrates to a person of ordinary skill in the art that the inventor actually invented what is claimed.

26. I understand from counsel that factors relevant to the written description requirement include the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the

predictability of the aspect at issue. I also understand from counsel that written description must be conveyed for the entire scope of each and every claim.

**C. Enablement**

27. I understand from counsel that a patent must describe the invention and the manner and process of making and using it so as to enable a person of ordinary skill in the art to make and use the full scope of the claims without undue experimentation.

28. I understand from counsel that the enablement requirement of 35 U.S.C. §112(a) is satisfied when the patent specification enables those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. Accordingly, I understand that a reasonable amount of experimentation is allowed.

29. I understand from counsel that factors relevant to deciding whether experimentation is “undue” include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. I also understand from counsel that none of these factors alone is dispositive. Rather, determining whether the degree of experimentation required is undue requires weighing these factors in the context of the claimed invention and the state of the art as of the filing date.

30. I also understand from counsel that there is some overlap between the factors that are relevant to both enablement and the written description requirement.

#### **IV. THE PERSON OF ORDINARY SKILL IN THE ART**

31. I understand from counsel that legal standards of claim construction, obviousness, written description, and enablement are analyzed from the perspective of a hypothetical person of ordinary skill in the art.

32. I understand from counsel that Heron Therapeutics, Inc. (“Heron”) has previously proposed in a litigation over emulsion formulations that a person of ordinary skill in the art (“POSA”):

would have a bachelor’s degree in chemistry, pharmaceuticals, chemical engineering, or a related field, as well as three to five years of experience in formulating drug products, including parenteral drug products. This person could have an advanced degree in these fields and fewer years of experience. A POSA may also consult with individuals with experience in other disciplines. Such consultation would not alter the ‘ordinary’ skill of the POSA who is receiving and using the information.

Ex. 1020 (“Heron’s Opening Post-Trial Brief”) at 17. I have been asked to apply this definition. Accordingly, my opinions, as set forth herein, are from the perspective of a POSA, as set forth above.

33. Given my educational and professional background, I would have had more qualifications and experience than a POSA as of the effective filing date of the '254 patent. However, I am able to apply the understanding of a POSA as of the effective filing date and have done so with respect to the opinions provided herein.

## **V. CLAIM CONSTRUCTION**

34. I understand from counsel that “claim construction” is the interpretation of the meaning of patent claims. I also understand from counsel that, in a PGR, words of a claim are generally given their plain and ordinary meaning, which is the meaning the term or phrase would have to a POSA at the time of the invention.

35. I understand from counsel that both intrinsic and extrinsic evidence can be used to assist in understanding the meaning of a claim. Intrinsic evidence includes the claim language, language in other claims of the patent, the specification, and the prosecution history. I further understand from counsel that, unless required by the claim language or specification, claims should generally not be limited to embodiments in the specification, including preferred embodiments. I also understand from counsel that extrinsic evidence, which consists of all evidence external to the patent and prosecution history including expert and inventor testimony, dictionaries, and technical publications, including those known and authoritative in a particular technical field, may also be relevant to claim construction. I further understand from counsel that a patent applicant may act as

his or her own lexicographer and set forth a special definition of a claim term in the specification.

36. I understand from counsel that the '254 patent includes a definition for the term “emulsion” that appears in each of claims 1-30. Ex. 1001 ('254 patent) at column 9, lines 63-66 (“The term ‘emulsion’ or ‘emulsion formulation’ means a colloidal dispersion of two immiscible liquids in the form of droplets, whose diameter, in general, is between 10 nanometers and 100 microns.”). I have used the definition of “emulsion” from the specification in my analysis and applied it when considering claims 1-30.

37. Unless otherwise indicated, I have utilized the plain and ordinary meaning of all other claim terms in my analysis.

## **VI. INTRODUCTION TO THE '254 PATENT**

38. The '254 patent is entitled “Methods of Use of Emulsion Formulations of an NK-1 Receptor Antagonist.” Ex. 1001 ('254 patent) at (54).

39. In a section entitled “Technical Field,” the '254 patent states: “The disclosure relates generally to emulsion formulations and systems for the intravenous or parenteral administration of an NK-1 receptor antagonist for treatment of emesis.” Ex. 1001 ('254 patent) at col. 1, lines 22-24.

40. In a section entitled “Background,” the '254 patent identifies “emesis” as a problem resulting from anticancer cytotoxic therapy and notes that “[u]p to 80%

of patients will experience chemotherapy-induced nausea and vomiting (CINV) without prophylactic therapy.” Ex. 1001 at col. 1, lines 32-36 (internal citations omitted). The ’254 patent also identifies “aprepitant” as an NK-1 receptor antagonist this is currently approved and marketed in oral form. *Id.* at col. 1, lines 44-46. However, it is noted that an oral dosage form can be problematic for patients suffering from emesis and therefore “it is desirable to have injectable formulations to simplify treatment for these patients.” *Id.* at col. 1, lines 46-50. The ’254 patent then identifies an “emulsion” as a means for preparing an injectable formulation. *Id.* at col. 1, lines 60-63.

41. In the same “Background” section, the ’254 patent indicates that “[i]ntravenous emulsions should have a very small droplet size to circulate in the bloodstream without causing capillary blockage or embolization.” Ex. 1001 (’254 patent) at col. 1, lines 64-66. Such size limits had been defined for formulators to reference in the United States Pharmacopeia. *Id.* at col. 1, line 66 to col. 2, line 7. Additionally, the ’254 patent states:

Emulsion formulations must be physically stable. The droplet size limits defined in USP <729> apply throughout the assigned shelf life. All true emulsions are thermodynamically unstable and may over time undergo a range of processes which tend to increase the droplet size. These include direct droplet coalescence, when two droplets collide and form a single new droplet; and aggregation, in which droplets adhere

together to form larger masses. Aggregation may in some cases be a precursor of further coalescence into larger droplets. These processes may result in large aggregates rising to the surface of the container, a phenomenon known as ‘creaming’, and ultimately to free oil being visible on the emulsion surface, known as ‘cracking’.

Emulsion formulations must also be chemically stable. The drug substance may degrade; for example, lipophilic drugs will partition into the oil phase, which will confer some degree of protection, but hydrolytic degradation may still occur at the oil-water interface. Possible chemical degradation within parenteral fat emulsions includes oxidation of unsaturated fatty acid residues present in triglyceride and lecithin, and hydrolysis of phospholipids leading to the formation of free fatty acids (FFA) and lysophospholipids. Such degradants lower pH, which may then promote further degradation. Thus, pH should be controlled during manufacture and parenteral emulsion formulations may include a buffering agent to provide additional control. Any decrease in pH over the assigned shelf-life may be indicative of chemical degradation.

Ex. 1001 (’254 patent) at col. 2, lines 8-35.

42. There are 30 claims in the ’254 patent, and each relates to a “injectable pharmaceutical emulsion.” Ex. 1001 (’254 patent) at col. 32, line 48 to col. 34, line 38. I understand from counsel that the “Challenged Claims” with respect to

invalidity in this matter are claims 1-30. The following table contains a complete listing of the Challenged Claims:

<b>Claim 1</b>
1. An injectable pharmaceutical emulsion, comprising: about 0.7-0.8 wt % aprepitant; an emulsifier; an oil; a co-surfactant; and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %).
<b>Claim 2</b>
2. The emulsion of claim 1, wherein the emulsifier is a phospholipid.
<b>Claim 3</b>
3. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 16 wt/wt %.
<b>Claim 4</b>
4. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 17 wt/wt %.
<b>Claim 5</b>
5. The emulsion of claim 1, wherein the emulsifier is an egg lecithin.

**Claim 6**

6. The emulsion of claim **5**, wherein the egg lecithin is present in the emulsion at about 16 wt/wt %.

**Claim 7**

7. The emulsion of claim **5**, wherein the egg lecithin is present in the emulsion at about 17 wt/wt %.

**Claim 8**

8. The emulsion of claim **1**, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

**Claim 9**

9. The emulsion of claim **8**, wherein the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.

**Claim 10**

10. The emulsion of claim **1**, wherein the co-surfactant comprises an alcohol.

**Claim 11**

11. The emulsion of claim **10**, wherein the alcohol is present in the emulsion at less than 10 wt/wt %.

**Claim 12**

12. The emulsion of claim **10**, wherein the co-surfactant is ethanol.

**Claim 13**

13. The emulsion of claim <b>1</b> , further comprising an osmotic agent.
<b>Claim 14</b>
14. The emulsion of claim <b>13</b> , wherein the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol.
<b>Claim 15</b>
15. The emulsion of claim <b>14</b> , wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.
<b>Claim 16</b>
16. The emulsion of claim <b>1</b> , further comprising a pH modifier.
<b>Claim 17</b>
17. The emulsion of claim <b>16</b> , wherein the pH modifier is oleic acid or a salt thereof.
<b>Claim 18</b>
18. The emulsion of claim <b>1</b> , wherein the emulsifier is egg lecithin. <sup>2</sup>

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<sup>2</sup> I note that the only difference between claims 5 and 18 is the reference to “an egg lecithin” (claim 5) versus “egg lecithin” (claim 18). To the best of my knowledge, this grammatical difference has not affected any opinion in this declaration, and I reserve any right to further clarify the matter.

<b>Claim 19</b>
19. The emulsion of claim <b>1</b> , wherein the co-surfactant is ethanol.
<b>Claim 20</b>
20. The emulsion of claim <b>1</b> , further comprising sucrose.
<b>Claim 21</b>
21. The emulsion of claim <b>1</b> , further comprising sodium oleate.
<b>Claim 22</b>
22. An injectable pharmaceutical emulsion, comprising: about 0.7-0.8 wt % aprepitant; an emulsifier; an oil; a co-surfactant; and water, wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt %).
<b>Claim 23</b>
23. The emulsion of claim <b>22</b> , wherein the emulsifier is a phospholipid.
<b>Claim 24</b>
24. The emulsion of claim <b>23</b> , wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.
<b>Claim 25</b>

25. The emulsion of claim **22**, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

**Claim 26**

26. The emulsion of claim **22**, wherein the co-surfactant comprises an alcohol present in the emulsion at less than 10 wt/wt %.

**Claim 27**

27. An injectable pharmaceutical emulsion, comprising:  
about 0.7-0.8 wt % apreptant;  
an emulsifier;  
an oil;  
a co-surfactant; and  
water,  
wherein the ratio of the emulsifier to apreptant ranges about 24:1 (wt/wt %).

**Claim 28**

28. The emulsion of claim **27**, wherein the emulsifier is a phospholipid.

**Claim 29**

29. The emulsion of claim **27**, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

**Claim 30**

30. The emulsion of claim 27, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

## **VII. TECHNICAL BACKGROUND AND STATE OF THE ART**

### **A. Aprepitant**

43. Cancer treatment regimens often use cytotoxic chemotherapeutic agents which can produce “profound emesis and nausea” both on the day of treatment and for several days after. Ex. 1008 (Hargreaves) at 40. These side effects are well documented to result in delay and even withdrawal of patients from therapy prescribed to prolong or save their lives. *Id.* Thus, the control of chemotherapy-induced nausea and vomiting (“CINV”) is a “significant factor” in ensuring that oncology patients maintain quality of life and continue their chemotherapy treatments. *Id.*

44. Aprepitant is an antiemetic compound which belongs to a class of antagonists “that mediate their effect by blocking the neurokinin (NK1) receptor.” Ex. 1009 (Hingorani) at [0003]. In 2003, the U.S. Food & Drug Administration (“FDA”) approved Merck & Co., Inc.’s (“Merck”) New Drug Application to market oral capsules (EMEND®) containing aprepitant to prevent and control nausea and vomiting caused by chemotherapy treatment. Ex. 1008 (Hargreaves) at 41, 44.

Aprepitant was “the first and only” NK-1 receptor antagonist available for the prevention of CINV in cancer patients. Ex. 1008 (Hargreaves) at 46. Furthermore, aprepitant was more effective at controlling nausea than alternative drugs. Ex. 1003 (Zhou) at [0002]-[0003] (“[Aprepitant’s] complete antiemetic control rate is 14.98% higher than that of 5-hydroxytryptamine receptor antagonist drugs. Multiple clinical studies have proven that antiemetic regimens containing aprepitant are more effective in preventing acute and delayed CINV caused by drugs with high and medium emetogenic risks.”).

45. However, oral dosage forms can be problematic for patients suffering from emesis as patients may experience reduced drug absorption and ineffectiveness due to vomiting. Ex. 1003 (Zhou) at [0006] (“For patients with severe vomiting, oral administration brings great inconvenience to the patient, and the absorption and bioavailability of the drug are also greatly reduced.”). Thus, an alternative dosage form of aprepitant was desired. *Id.* (“The injection form of aprepitant is of great significance for clinical treatment.”); Ex. 1009 (Hingorani) at [0009] (“it would certainly be advantageous from a manufacturing, use, and cost standpoint to formulate aprepitant in a soluble and stable form for parenteral administration.”).

46. However, the formulation of alternative dosage forms was complicated by aprepitant’s poor solubility. Ex. 1008 (Hargreaves) at 44 (“The sparing water solubility of aprepitant precluded its formulation in a vehicle acceptable for

intravenous administration in humans.”). Aprepitant is “substantially insoluble in both oil and water” and is “sparingly soluble in ethanol and isopropyl acetate, and slightly soluble in acetonitrile.” Ex. 1009 (Hingorani) at [0054], [0005] (“pharmaceutically relevant concentrations [of aprepitant] are typically only achieved at unacceptably high ethanol concentrations.”). Thus, aprepitant can be classified as a “Class III” drug. Ex. 1004 (Washington) at 139 (“Class III drugs are poorly soluble in both water and oil.”).

47. In order to overcome aprepitant’s formidable solubility properties, Merck developed a water-soluble phosphorylated prodrug form of aprepitant, fosaprepitant dimeglumine, which is “rapidly converted to aprepitant after IV administration.” Ex. 1009 (Hingorani) at [0008]. In 2008, the FDA approved fosaprepitant dimeglumine (EMEND® for Injection) for intravenous administration. Ex. 1008 (Hargreaves) at 44. However, the synthesis of fosaprepitant added “significant complexity and cost to the drug” and the commercial formulation of fosaprepitant was reported to be stable for only 24 hours after reconstitution. Ex. 1009 (Hingorani) at [0008]. Thus, a stable liquid formulation of aprepitant for parenteral administration was still desired. Ex. 1009 (Hingorani) at [0009].

## **B. Emulsion Formulation**

48. Injectable lipid emulsions have been used clinically for decades as an intravenous source of calories and essential fatty acids through the administration of

total parenteral nutrition. Ex. 1019 (Collins-Gold) at 190; Ex. 1011 (Cannon) at 201; Ex. 1012 (Rossi) at 89. Beginning in the early 1970's, scientists began studying the use of lipid emulsions as drug delivery systems. Ex. 1019 (Collins-Gold) at 191; Ex. 1011 (Cannon) at 196 ("Over the past several decades, emulsion formulations have been explored for resolving a variety of drug delivery challenges."). As a result, "[a] number of drug-containing emulsions have been introduced in the market" while several others are "under development and in preclinical trials." Ex. 1018 (Hippalgaonkar) at 1527; Ex. 1012 (Rossi) at 89 ("As a result of the successful induction of lipid emulsions in parenteral nutrition, there has been increasing interest in developing emulsions as carriers for lipophilic drugs. Many intravenous lipid emulsion formulations are commercially available [] and a number of others are in clinical phase or in preclinical development []." ).

49. The use of emulsions as drug delivery vehicles was known to offer numerous advantages, such as improved solubility and stability, reduced toxicity, and even targeted drug delivery. Ex. 1018 (Hippalgaonkar) at 1527-1528; Ex. 1012 (Rossi) at 89 ("Lipid emulsions are promising carriers for drug delivery as a result of their biocompatibility, reasonable stability, ability to solubilize high quantities of hydrophobic compounds, and relative ease of manufacture on an industrial scale."). Furthermore, emulsion formulations were known to be useful for the solubilisation of water-insoluble drugs and drugs with limited solubilities in both water and oil.

For compounds with poor aqueous solubility, emulsions could offer improved solubility and stability in comparison to conventional aqueous solutions. Ex. 1013 (Rajeshwar) at [0029]; Ex. 1011 (Cannon) at 220 (disclosing that emulsions “offer an appealing alternative for the administration of water-insoluble compounds.”). For drugs with poor solubility in both water and oil, the drugs can be loaded into the emulsion by adsorbing to the droplet interface. Ex. 1004 (Washington) at 139; Ex. 1011 (Cannon) at 207 (describing if a “[d]rug is soluble in neither oil nor water” then the drug can be “retained at the interface of an emulsion.”).

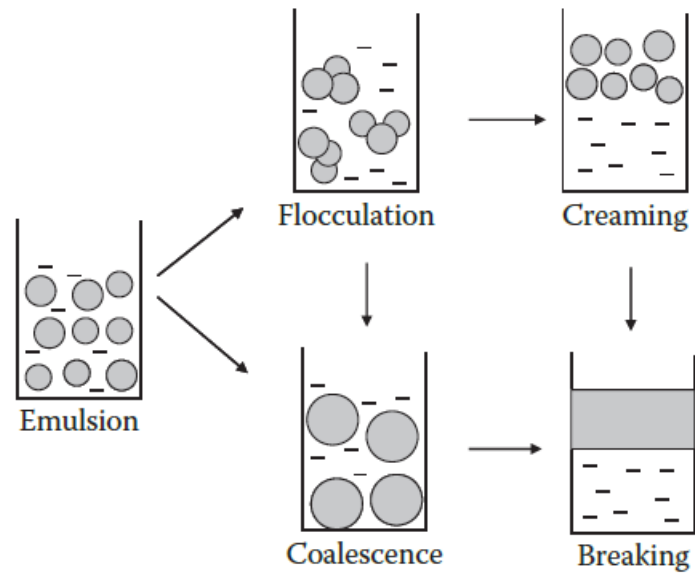
50. In its most basic form, an “emulsion” is a mixture of two immiscible phases (usually water and oil), wherein one of the phases (the dispersed phase) is uniformly dispersed as globules throughout the second phase (the continuous phase). Ex. 1011 (Cannon) at 196; Ex. 1012 (Rossi) at 88. An emulsion can be characterized by the identity of the dispersed and continuous phases, where an emulsion that consists of primarily water (i.e., water is the continuous phase) would be called an oil-in-water (o/w) emulsion. Ex. 1011 (Cannon) at 196.

51. As I explained in Paragraph 36, the ’254 patent defined “emulsion” as a “colloidal dispersion of two immiscible liquids in the form of droplets.” Ex. 1001 (’254 patent) at col. 9, lines 63-66. This definition is consistent with the basic understanding of a POSA as reflected in the formulation art. Ex. 1011 (Cannon) at 196; Ex. 1012 (Rossi) at 88. The ’254 patent’s definition of “emulsion” adds a

further specification as to the droplet size “whose diameter, in general, is between 10 nanometers and 100 microns.” Ex. 1001 (’254 patent) at col. 9, lines 63-66. As 10 nanometers to 100 microns is a very large range of droplet size, there is significant overlap in the droplet size range across various different sub-types of emulsions (often called macro-, micro-, and nanoemulsions) and the ’254 patent’s definition of emulsions. Despite this, differentiating types of “emulsions” by virtue of particle size is one common means of characterization. *See, e.g.*, Ex. 1015 (Mahato) at 255 (“The diameter of the dispersed phase globules is generally in the range of about 0.1-10  $\mu\text{m}$ , although it can be as small as 0.01 $\mu\text{m}$  or as large as 100  $\mu\text{m}$ .”); Ex. 1014 (Klang) at 57 (Table I) (disclosing nanoemulsions with a particle size of 150-300 nm and microemulsions with a particle size of 10-100 nm.); Ex. 1005 (Bagwe) at 82 (Table 2) (disclosing microemulsions having a droplet size range of under 0.1 microns and emulsions having a droplet size range of 0.5 to 5 microns.).

52. Classical “emulsions” or “macroemulsions” are generally regarded as thermodynamically unstable. Ex. 1015 (Mahato) at 259 (“Emulsions are inherently *thermodynamically unstable* due to the differences in the molecular forces of interaction between the molecules of the two liquid phases.”); Ex. 1005 (Bagwe) at 82. Such instability in an emulsion may manifest as any of four phenomena: flocculation, creaming, coalescence, and breaking. Ex. 1015 (Mahato) at 264-266; Ex. 1016 (Khan) at 2718-2719. Flocculation, also referred to as aggregation, is the

association of small droplets to form large aggregates, but the droplets do not fuse, thus they can be re-dispersed upon shaking. Ex. 1016 (Khan) at 2718; Ex. 1015 (Mahato) at 265. Flocculation is often considered as a “precursor of coalescence.” Ex. 1016 (Khan) at 2718. Coalescence is the “process by which emulsified particles merge with each other to form large particles” and “is an irreversible process because the film that surrounds the individual globules is destroyed.” Ex. 1015 (Mahato) at 265. Creaming refers to the “upward movement of dispersed droplets relative to the continuous phase.” Ex. 1015 (Mahato) at 264. Similar to flocculation, in creaming the dispersed phase remains in globules, and therefore creaming can be reversible. However, creaming can increase the likelihood of coalescence due to the “closer proximity of the globules in the cream.” Ex. 1015 (Mahato) at 265. “Breaking of an emulsion refers to the complete separation of the two liquid phases.” Ex. 1015 (Mahato) at 265. Similar to coalescence, breaking is irreversible because “the film surrounding the particles has been destroyed and the oil tends to coalesce.” Ex. 1015 (Mahato) at 265. In sum, each of these phenomena involves an increase in droplet size or loss of “dispersion” in the aqueous phase, as represented in the following schematic:



Ex. 1015 (Mahato) at 265 (Figure 14.2).

53. In contrast, microemulsions are considered ‘physically’ or “thermodynamically stable for prolonged periods of time.” Ex. 1015 (Mahato) at 257. Thus, microemulsions typically do not exhibit phase separation which is an indicator of poor physical stability in conventional emulsions. Ex. 1011 (Cannon) at 206. One of the key factors that determines the physical stabilities of macro- and microemulsions is “believed to be the interfacial tension between the two phases, and lower interfacial tension (primarily governed by the surfactant) will increase the stability.” Ex. 1011 Cannon at 206 (internal citation omitted); *id.* (“Very low interfacial tension is thought to be the primary factor leading to the stability of microemulsions.”).

### **C. Typical Emulsion Components**

54. In addition to the “two immiscible liquids” (i.e., water and oil), emulsion formulations contain various other excipients. Emulsion formulations typically “consist of oils (long- and medium-chain triglycerides or high-quality food grade oils), emulsifiers (e.g., lecithins, poloxamers, Tweens, and Spans) and an aqueous phase containing appropriate additives to control pH, tonicity, etc.” Ex. 1050 (Vemuri) at 71; Ex. 1018 (Hippalgaonkar) at 1529 (describing components of injectable emulsions as lipids, emulsifiers, and an aqueous phase, which can contain additives such as tonicity modifiers, antioxidants, preservatives, and potentially pH adjustors and buffering agents); Ex. 1011 (Cannon) at 197, 196; Ex. 1012 (Rossi) at 108-113 (disclosing oils, emulsifiers, and an aqueous phase, wherein the aqueous phase can contain pH adjustors, osmotic agents, and antioxidants).

#### **1. Emulsifiers**

55. Emulsions are typically stabilized by the addition of an emulsifier such as a surfactant. Ex. 1011 (Cannon) at 196-197; Ex. 1006 (Weng) at 1157 (“Emulsifiers are another essential component of lipid emulsions. It is well known that the emulsification depends on the emulsifiers used.”). Emulsifiers form a film at the oil/water interface which “stabilize[s] the emulsion by reducing interfacial tension between the oil and the water phases.” Ex. 1011 (Cannon) at 197. Emulsifiers can also “provid[e] enough surface charge for droplet-droplet repulsion”

which helps prevent flocculation and coalescence. Ex. 1018 (Hippalgaonkar) at 1529; Ex. 1012 (Rossi) at 110 (“The purpose of surfactants is to emulsify the oil phase and provide physical stability against flocculation and coalescence during storage, which may be for extended periods of time. Surfactants provide physical stability by reducing the oil-water interfacial tension and promoting droplet-droplet repulsion.”)

56. “The choice of emulsifier is driven by its toxicity profile.” Ex. 1018 (Hippalgaonkar) at 1529. While multiple surfactants are available, “only a few are used in approved parenteral emulsion products.” Ex. 1011 (Cannon) at 197-198; Ex. 1019 (Collins-Gold) at 192 (“While a wide variety of surfactants are available for industrial manufacturing of foods, cosmetics, insecticides, paints, detergents and so forth, relatively few are approved for [intravenous] administration.”). Of the available emulsifiers, “[l]ecithin is perhaps the most widely used natural emulsifying agent.” Ex. 1014 (Klang) at 58; Ex. 1011 (Cannon) at 198 (“The most commonly used surfactant in parenteral products is lecithin [phosphatidylcholine (PC)], which is a natural emulsifying agent derived from egg yolk or soybean.”); Ex. 1018 (Hippalgaonkar) at 1529 (“Natural lecithin, obtained from egg yolk, has been used extensively to stabilize injectable emulsions.”); Ex. 1019 (Collins-Gold) at 192 (“Natural phosphatides, principally from egg yolk or soybean, are in most widespread use.”); Ex. 1005 (Bagwe) at 101 (“Phospholipids, particularly lecithin,

offer a possible nontoxic alternative emulsifier for parenteral use.”); Ex. 1006 (Weng) at 1157 (“lecithin should always be the first choice. The natural lecithins, including egg yolk lecithin and soybean lecithin, can be totally biodegraded and metabolized, so they are regarded as well-tolerated and non-toxic compounds with excellent biocompatibility, and suitable for long-term use and high-dose infusion.”); Ex. 1012 (Rossi) at 110 (“Injectable emulsions are frequently emulsified with natural lecithins obtained from either egg yolk or soybeans. These lipids are biocompatible and biodegradable, and have relatively good emulsifying properties.”); Ex. 1017 (Benita) at 1070 (“The emulsifiers most frequently used in parenteral emulsion formulations are phospholipids (generally from egg yolk sources).”).

57. As emulsifiers provide physical stability to an emulsion, the amount of emulsifier is a key variable that drives stability of an emulsion.

58. “The amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability. Emulsifier concentration has a great impact on emulsion stability. A concentration window existed, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence.” Ex. 1016 (Khan) at 2719.

59. Hippalgaonkar describes how a decrease in the emulsifier concentration would “lead to partial or minimal interfacial surface coverage by the emulsifier. This would lead to an increase in the surface tension and an increase in the droplet size. To stabilize this formulation with reduced droplet size, an excess amount of emulsifier would be needed.” Ex. 1018 (Hippalgaonkar) at 1532.

60. Similarly, Klang teaches that “an increase in [emulsifier] concentration leads to the production of smaller particles due to an increased surfactant to oil volume ratio which in turn leads to enhanced physical stability.” Ex. 1014 (Klang) at 64; Ex. 1011 (Cannon) at 218; Ex. 1019 (Collins-Gold) at 194. However, too much emulsifier can result in “emulsion instability [] because of rapid coalescence.” Ex. 1016 (Khan) at 2719.

61. Thus, emulsions have an optimal emulsifier concentration “window.” Depending on the type of emulsion the amount of surfactant could vary from as low as 1% to as high as 20% by weight. Ex. 1005 (Bagwe) at 82 (Table 2). Therefore, not only the type of surfactant (or emulsifier), but also the quantity of surfactant (or emulsifier) is an important parameter to manipulate in order to optimise the physical stability of an emulsion.

## 2. Lipids/Oils

62. Oils (sometimes referred to in the formulation art as “lipids”) are a ubiquitous component of an **oil**-in-water emulsion (or even a water-in-**oil** emulsion)

and constitute one of the phases of the emulsion. Ex. 1016 (Khan) at 2715. The oil phase typically assists in the solubilisation of poorly water-soluble drugs, thus “[t]he choice of oil usually depends on the solubility and stability of the drug.” Ex. 1012 (Rossi) at 109; Ex. 1018 (Hippalgaonkar) at 1529.

63. Oils/lipids that have been approved by regulatory agencies “are generally first-choice for developing drug emulsions.” Ex. 1018 (Hippalgaonkar) at 1529. Vegetable oils (triglycerides) have been a popular choice because of their long-established safety and biocompatibility profiles. Ex. 1012 (Rossi) at 109 (“LCTs [long-chain triglycerides] and MCTs [medium-chain triglycerides] should be considered in the initial stages of formulation because many of these oils are approved for injection and are found in a number of FDA [] approved products.”); Ex. 1018 (Hippalgaonkar) at 1527 (“Long-chain triglyceride (LCT) (*e.g.*, soybean oil and safflower oil) based emulsions have been widely used in the clinical setting for over 40 years now.”); Ex. 1011 (Cannon) at 197 (“Long- (LCT) and medium-chain triglycerides (MCT), either alone or in combination, are used in commercial parenteral emulsions owing to their long history of safety.”). Examples of LCTs include soybean oil, safflower oil, sesame oil, and cottonseed oil. Ex. 1018 (Hippalgaonkar) at 1529; Ex. 1011 (Cannon) at 197 and Table 10.1; Ex. 1012 (Rossi) at 109 (Table 4.4); Ex. 1017 (Benita) at 1070.

64. For an aprepitant-containing emulsion, many of the same choices of oil were known to be applicable and had been used. For example, soybean oil was preferred, while triglycerides and ethyl oleate (and various other oils) were also recognized as being useful. Ex. 1003 (Zhou) at [0010].

### **3. Co-Solvents**

65. Co-solvents can be included in emulsion formulations for a number of reasons. For example, the use of a co-solvent is a typical approach for solubilizing drugs that have minimal solubility in either water or oil. Ex. 1011 (Cannon) at 201, 206, and 207; Ex. 1018 (Hippalgaonkar) at 1530 (explaining that drugs which are only slightly soluble in oil can be incorporated into emulsions with the aid of cosolvents.). Sometimes, the formulation arts refer to the terms “co-solvent” and “co-surfactant” interchangeably. *See* Ex. 1014 (Klang) at 57 (Table 1) (referring to “Co-surfactant/co-solvent”), and 65 (“Another important point worth considering is the fact that lecithin is unable to form microemulsion structures in aqueous ternary systems unless a co-surfactant or co-solvent is added.”). Co-solvents can be used in combination with surfactants to enhance the solubility of the formulated drug in the final formulation. For example, the addition of a co-solvent was found to improve the solubilisation of aprepitant, where short-chain alcohols were found to work synergistically with the surfactant to “substantially improve[] solubility of aprepitant.” Ex. 1009 (Hingorani) at [0045].

66. Examples of “[s]uitable pharmaceutically acceptable cosolvents include ethanol, propylene glycol, PEG300, dimethylacetamide, triacetin, and mixtures of these solvents.” Ex. 1011 (Cannon) at 201. For solubilising aprepitant, ethanol was known to be a useful co-solvent. Ex. 1009 (Hingorani) at [0005], [0045]; Ex. 1003 (Zhou) at [0010].

#### **4. pH Modifiers**

67. pH modifiers, also known as pH adjusters, are a category of excipients that are typically added to an emulsion to modify and maintain a desired pH during the formulation and storage of an emulsion. Ex. 1011 (Cannon) at 217. It was described that “[t]he pH of these lipid emulsions decrease during sterilization and storage as a result of [an] increase in FFA [free fatty acid] content due to the hydrolysis of phosphatidylcholine (PC) and phosphatidylethanolamine (PE), the lysoderivatives of PC and PE, and the emulsified triglycerides.” Ex. 1018 (Hippalgaonkar) at 1532. Moreover, a change in pH of the emulsion system can affect the zeta potential of the emulsion droplets and ultimately lead to emulsion instability. Ex. 1018 (Hippalgaonkar) at 1532. Accordingly, a pH modifier is an important component of lipid emulsions.

68. The desired pH of an emulsion is usually between 7 and 8 “to maintain physiological compatibility and minimize hydrolysis of the oil and phospholipids.” Ex. 1012 (Rossi) at 112; Ex. 1017 (Benita) at 1070 (“The pH of the emulsion is

generally adjusted to 7-8 to allow physiological compatibility and maintain emulsion physical integrity by minimizing fatty acid ester hydrolysis of MCT-LCT and phospholipids.”); Ex. 1018 (Hippalgaonkar) at 1529 (“A slightly alkaline pH is preferred because the pH decreases during sterilization, and on storage, due to the production of free fatty acids (FFAs).”).

69. Sodium oleate has been used as a pH modifier/buffer in emulsion systems for intravenous injection and was a “well-known” stabilizer for emulsions. Ex. 1006 (Weng) at 1159 (“[Sodium oleate] had a certain buffering capacity to reduce the pH change to a minimum. ... it was obvious that the incorporation of [sodium oleate] made an important contribution to ... keep pH value nearly unchanged before and after autoclaving.”); Ex. 1017 (Benita) at 1070 (“A well-known stabilizer is oleic acid or its sodium salt.”).

## **5. Osmotic Agents**

70. Osmotic agents, also known as tonicity modifiers/agents, are a category of excipients that are included in injectable formulations to control the tonicity of the formulation “to avoid disturbing the state of cells in contact with the formulation.” Ex. 1012 (Rossi) at 112. As the “[o]smolarity of a conventional emulsion is largely determined by components of the continuous phase, and the disperse phase may contribute little to the osmolarity,” water-soluble osmotic agents are often added to the aqueous phase. Ex. 1011 (Cannon) at 203; Ex. 1006 (Weng)

at 1159-1160 (“The aqueous phase should be augmented by the incorporation of ionic or osmotic agents.”).

71. Ionic agents, such as sodium chloride, are widely used as osmotic agents in injectable compositions. However, ionic agents should be avoided in emulsion formulations because “the ions can destabilize emulsions.” Ex. 1012 (Rossi) at 112. Therefore, water-soluble excipients such as sugar alcohols (e.g., glycerol, sorbitol, xylitol) are typically used as osmotic agents. Ex. 1012 (Rossi) at 112; Ex. 1018 (Hippalgaonkar) at 1529; Ex. 1011 (Cannon) at 203 (“Thus, water-soluble excipients such as glycerol are frequently added to adjust tonicity of emulsions intended for parenteral use.”); Ex. 1006 (Weng) at 1160 (“Glycerol with the ability of tonicity was preferred by the manufacturers of commercial soybean oil emulsion.”). These are not, however, the exclusive agents in the field. For an aprepitant-containing emulsion, it was recommended that “one or more of glycerin, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids” be included. Ex. 1003 (Zhou) at [0010].

### **VIII. GROUND 1: OBVIOUSNESS**

72. In this section, I explain why it would have been obvious to a POSA as defined in Paragraph 32, above, to prepare an aprepitant emulsion containing the excipients in the proportions of the Challenged Claims in view of the disclosures of Zhou (Ex. 1003), Washington (Ex. 1004), Bagwe (Ex. 1005), and Weng (Ex. 1006).

**A. Introduction to Zhou**

73. Zhou is a Chinese patent application entitled “A type of aprepitant microemulsion for injection and its preparation method,” and was published in 2012. Ex. 1003 (Zhou) at (54) (“Invention Title”) and (43) (“Application publication date 2012.03.21”). Zhou teaches that “aprepitant is insoluble in water and insoluble in organic solvents.” *Id.* at Abstract. However, Zhou explains that emulsion formulations “can improve the solubility of poorly water-soluble drugs and fat-soluble drugs,” promote drug absorption, and improve bioavailability, therefore emulsions “are increasingly favored by medical workers as drug carriers, especially in injection drug delivery.” *Id.* at [0005]. Zhou teaches that “[t]he injection form of aprepitant is of great significance for clinical treatment,” and that “the purpose of the present invention is to provide an injectable aprepitant microemulsion to effectively solve the problems of inconvenient clinical application of oral aprepitant, poor absorption, and low bioavailability.” *Id.* at [0006]-[0007].

74. Zhou discloses an aprepitant emulsion for injection that is composed of the following mass percentage components:

***0.05% ~ 2% aprepitant, 5% ~ 30% injection oil, 0.5% ~ 10% emulsifier, 1 ~ 10% co-emulsifier, 5% ~ 20% protection agent;***

**60~80% water for injection**;<sup>3</sup> the oil for injection is one or more of **soybean oil** for injection, ethyl oleate, polyethylene glycol glyceryl oleate, triglycerides with medium fatty chain length, isopropyl myristate, peanut oil, corn oil, and olive oil; the emulsifier is one or more of **phospholipids**, poloxamer, polyoxyethylene castor oil and derivatives, polyethylene glycol-caprylic/capric glyceryl, and polysorbate 80; the co-emulsifier is one or more of **ethanol**, glycerol, 1,2-propanediol, and polyethylene glycol 400; the protective agent is one or more of glycerol, **sucrose**, trehalose, glucose, xylitol, mannitol, and amino acids.

*Id.* at claim 1, Abstract, [0008].

75. For the readers' convenience in paragraph 74, I have emphasized the components/amounts identified in Zhou's emulsions that are also present in the Challenged Claims. For example, Zhou identifies soybean oil as a preferred oil, egg yolk phospholipids as a preferred emulsifier, ethanol as a preferred co-emulsifier<sup>4</sup>,

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<sup>3</sup> Unless otherwise indicated, all bold emphases are added.

<sup>4</sup> I note that Zhou (Ex. 1003) refers to "ethanol" as a "co-emulsifier." However, the '254 patent (Ex. 1001) refers to "ethanol" as a "co-surfactant." *See, e.g.*, Ex. 1001 ('254 patent) at col. 3, line 20 ("In other embodiments, the co-surfactant is ethanol."). The different terminology between the references does not affect the substance of my opinions.

and glycerin as a preferred protective (osmotic) agent. *Id.* at [0010]. Zhou also provides and describes the composition of five example emulsions (out of a total of eight examples) using these specific excipients in combination (i.e., soybean oil, egg yolk phospholipid, ethanol, and glycerol). *Id.* at [0019]-[0020], [0027]-[0033]. Zhou also indicates that the particle sizes of the aprepitant-containing microemulsions are between 50 nm and 150 nm and the pH values of the microemulsions<sup>5</sup> is between 6.0 and 8.0. *Id.* at [0012] and [0011].

76. Zhou also teaches that the aprepitant emulsions offer “outstanding advantages” when compared with the existing oral dosage forms of aprepitant.

Compared with existing aprepitant oral dosage forms, the injectable aprepitant microemulsion of the present invention has outstanding advantages including: Since aprepitant is insoluble in water and insoluble in organic solvents, in order to achieve aprepitant injection, the present invention successfully prepares aprepitant microemulsion and aprepitant microemulsion freeze-dried powder, which can achieve

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<sup>5</sup> Heron’s expert (Dr. Little) has previously admitted that Zhou’s “microemulsions” are, in fact, “emulsions.” Ex. 1023 (Day 4 PM) at 1375:16-1376:7. For the reader’s clarity, I will refer to Zhou’s formulations as “emulsions” in accordance with this admission.

large-scale industrial production. Compared with fosaprepitant dimeglumine injection, the cost is greatly reduced, has good practicability, and can produce better economic and social benefits.

*Id.* at [0017] and Abstract.

77. There are numerous similarities between the '254 patent and Zhou -- Zhou discloses emulsions meeting nearly every limitation recited in the '254 patent: 0.05 to 2% (wt.) aprepitant, 5 to 30% (wt.) oil; 0.5 to 10% (wt.) emulsifier; 1 to 10% (wt.) co-emulsifier; 5 to 20% (wt.) protective (osmotic) agent; and 60 to 80% (wt.) water for injection. Ex. 1003 (Zhou) at Claim 1. Given the similarities between the teachings in Zhou and the claims of the '254 patent, it is unsurprising that Zhou was identified as the "closest prior art." Ex. 1022 ('254 patent notice of allowance) at 39.

**B. Introduction to Washington**

78. Washington is a journal article entitled "Stability of lipid emulsions for drug delivery," and was published in 1996. Washington discusses "factors influencing the stability of phospholipid-stabilized emulsions, and the effects of drug incorporation on the stability profile." Ex. 1004 (Washington) at Abstract. Washington teaches that "emulsion delivery systems have many advantages," such as easy preparation and administration. *Id.* at 131 ("[Emulsions] can be prepared easily in a single dispersion step; for correctly chosen drug candidates, entrapment

can be high, and they can be easily administered in liquid form.”). Washington explains that “[t]he stability of colloidal formulations is paramount in their use as drug delivery systems,” as emulsions can coalesce or aggregate during storage. *Id.* at 132 (“[Emulsions] must be sufficiently stable to be easily manufactured, sterilized (preferably by terminal autoclaving) and have a shelf life of at least a year, preferably more.”).

79. Washington teaches that “the effect of the drug [on emulsion stability] can often be predicted” based off the physicochemical properties of the drug, such as solubility characteristics and ionization properties. *Id.* at 138. Washington identifies three classes of drugs, “Class I drugs” which are largely water-soluble, “Class II drugs” which are predominately oil-soluble, and “Class III drugs” which are poorly soluble in both water and oil. *Id.* at 138-139. Washington explains that “Class I drugs” (i.e. water-soluble drugs) are not good candidates for emulsion formulations because “a significant fraction of the drug would be present in the aqueous phase.” *Id.* Whereas “Class II drugs” which are predominately oil-soluble “would be partitioned predominately into the oil phase” and therefore this class of drugs are “good candidates for emulsion delivery” and the emulsions can be “formulated by dissolving the drug in the oil prior to emulsification.” *Id.* at 139. In contrast to Class I and II drugs, Washington explains that Class III drugs pose a unique situation. Since these compounds lack sufficient solubility in both water and

oil, Class III drugs “can *only* be loaded into an emulsion by adsorbing to the *droplet interface*.” *Id.* Therefore “due to their unusual solubility characteristics” Class III drugs require emulsions with a “large surface area available for loading.” *Id.*

80. Aprepitant, which is known to be substantially insoluble in both oil and water would therefore be classified as a “Class III drug” according to Washington’s rubric. *See* Paragraph 46, above. As a “Class III drug,” aprepitant would be expected to adsorb to the droplet interface in an emulsion. Therefore, to ensure adequate solubilisation of aprepitant in the emulsion a large surface area of droplets would be useful in view of Washington.

**C. Introduction to Bagwe**

81. Bagwe is a journal article entitled “Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons,” and was published in 2001. Bagwe explains that various colloidal systems (e.g., micelles, microemulsions, emulsions, etc.) have different advantages and disadvantages that should be considered when designing a drug delivery system. Ex. 1005 (Bagwe) at 82. However, regardless of the type, “[i]deally, a colloidal delivery system should be designed to have low viscosity, small droplet size, simple preparation technique, long shelf life, low toxicity to the patient, high solubility of drug, controlled drug-release rate, slow degradation, and target specificity when administered.” *Id.*

82. Bagwe contains a table comparing various parameters for different colloidal systems:

	Micelles	Microemulsions	Emulsions	Liposomes
Spontaneously obtained	Yes	Yes	No	No
Thermodynamically stable	Yes	Yes	No	No
Turbidity	Transparent	Transparent	Turbid	Turbid
Size range	< 0.01 microns	< 0.1 microns	0.5–5 microns	0.025–25 microns
Cosurfactant used	No	Yes	No	No
Surfactant concentration	< 5%	> 10%	1–20%	0.5–20%
Dispersed phase concentration	< 1%	1–30%	1–30%	1–30 %

*Id.* (Table 2). Bagwe explains that microemulsions require a “relatively large amount of surfactant in order to stabilize the large interfacial area created by the nanodroplets.” *Id.* at 80. Accordingly, microemulsions require at least 10% emulsifier, while (macro)emulsions can require anywhere from 1 to 20% emulsifier. *Id.* at 82; *also id.* at 89 (disclosing that an “important condition[] for producing microemulsions” is a “sufficiently high concentration (10-40%) of surfactant to cover the newly created surface within the microemulsion.”). Bagwe also teaches that microemulsions “often require the addition of *cosurfactants* such as *alcohols*, amides, and sulphoxides to attain an appropriate fluidity or viscosity of the interface.” *Id.* at 80 (emphasis added).

83. Bagwe teaches that “[t]he surfactants used for pharmaceutical microemulsions should be nonirritating” and biocompatible. *Id.* at 101. Bagwe also

teaches that “[p]hospholipids, particularly lecithin, offer a possible nontoxic alternative emulsifier for parenteral use.” *Id.* Additionally, Bagwe teaches that “[t]he cosurfactant should be carefully chosen as well,” and of the short-chain alcohols commonly used as cosurfactants only ethanol is biocompatible. *Id.*

**D. Introduction to Weng**

84. Weng is a journal article entitled “Formulation, Preparation, And Stability of Intravenous Bufadienolides-Loaded Lipid Microspheres,” and was published in 2012. Weng explains that bufadienolides have “poor aqueous solubility” and therefore the development of an intravenous lipid emulsion was necessary “to overcome the problems associated with the poor solubility and the chemical instability of bufadienolides.” Ex. 1006 (Weng) at Abstract and 1163. Weng teaches that “lipid emulsions or microemulsions, have been considered promising parenteral drug delivery systems, attributable to the unique properties of low cost, low toxicity, good storage stability and easy large-scale production.” *Id.* at 1155.

85. Weng teaches that emulsifiers are an “essential component of lipid emulsions,” and that “[i]t is well known that the emulsification depends on the emulsifiers used” *Id.* at 1157. Weng explains that despite “various emulsifiers on the market ... lecithin should always be the first choice” because “[t]he natural lecithins, including egg yolk lecithin and soybean lecithin, can be totally

biodegraded and metabolized, so they are regarded as well-tolerated and non-toxic compounds with excellent biocompatibility, and suitable for long-term use and high-dose infusion.” *Id.* Weng also teaches that a single emulsifier can be “insufficient to maintain the stability of the emulsion,” and that “co-emulsifiers could help further emulsify the oil phase and form a tight complex interfacial film between the water phase and the oil phase to keep the emulsion stable.” *Id.* at 1158.

86. The lipid emulsion described in Weng contained sodium oleate as one of the excipients. *Id.* at 1155. Weng mentions that sodium oleate is a useful excipient that has multifaceted uses in an injectable emulsion. Weng explains that sodium oleate is “a water-soluble co-emulsifier” which helps to “stabilize the emulsion against coalescence” by adsorbing to the oil-water interfacial film and enhancing “the electrostatic repulsion between emulsion droplets.” *Id.* at 1159. Weng further explains that sodium oleate also has a “certain buffering capacity to reduce the pH change to a minimum,” and indicates that because of its versatile ability to impart stability sodium oleate is “often used in commercial parenteral emulsions ... to obtain stable formulations during the autoclaving process.” *Id.* (“[I]t was obvious that the incorporation of ... [sodium oleate] made an important contribution to ... keep [the] pH value nearly unchanged before and after autoclaving.”).

87. Weng also teaches the importance of incorporating osmotic agents into the aqueous phase to achieve an isotonic emulsion for injection. *Id.* Weng discloses that glycerol is an osmotic agent that is “preferred by the manufacturers of commercial soybean oil emulsion.” *Id.* at 1160.

1. **Claim 1 would have been obvious**

88. Claim 1 recites:

What is claimed is:

1. An injectable pharmaceutical emulsion, comprising:  
about 0.7-0.8 wt % aprepitant;  
an emulsifier;  
an oil;  
a co-surfactant; and  
water,  
wherein the ratio of the emulsifier to aprepitant ranges  
from about 20:1 to 25:1 (wt/wt %).

Ex. 1001 ('254 patent) at col. 32, lines 48-55.

89. Accordingly, claim 1 of the '254 patent identifies the following components: (a) “[a]n injectable pharmaceutical emulsion,” (b) “about 0.7-0.8 wt % aprepitant,” (c) “an emulsifier,” (d) “an oil,” (e) “a co-surfactant,” (f) “water” and has a value (g) in which “the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %).” I will address each of these components in turn.

a. **“An injectable pharmaceutical emulsion”**

90. Zhou discloses an “injectable pharmaceutical emulsion.” Ex. 1003 (Zhou) at (54) (“A type of aprepitant microemulsion for injection and its preparation

method”), Abstract (“The invention discloses an aprepitant microemulsion for injection”), claims 1-9 (all referring to an “aprepitant microemulsion for injection”), [0001] (“The invention belongs to the technical field of pharmaceutical preparations, and specifically relates to an injectable aprepitant microemulsion and a preparation method thereof.”), [0007] (“the purpose of the present invention is to provide an injectable aprepitant microemulsion to effectively solve the problems of inconvenient clinical application of oral aprepitant, poor absorption, and low bioavailability”), [0008] (“A type of aprepitant microemulsion for injection”), [0014] (“Aprepitant microemulsion for injection”), [0015] (“The dosage forms are small injections, infusions and freeze-dried powder injections suitable for clinical intravenous administration.”), [0017] (“the injectable aprepitant microemulsion of the present invention has outstanding advantages”).

91. Although Zhou refers to the formulations as “microemulsions,” Zhou indicates that “[t]he particle size of the aprepitant microemulsion for injection is 50nm~150nm.” *Id.* at [0012]. Accordingly, in view of Zhou’s description of the components of the “microemulsions” and the particle size that Zhou identifies, Zhou’s description of a “microemulsion” falls within the definition of an “emulsion” provided by the ’254 patent: “a colloidal dispersion of two immiscible liquids in the form of droplets, whose diameter, in general, is between 10 nanometers and 100 microns.” Ex. 1001 (’254 patent) at col. 9, lines 63-66. Furthermore, Zhou’s

description of preparing a “microemulsion” is very similar to the process provided in the ’254 patent. Compare, e.g., Ex. 1003 (Zhou) at [0020] with Ex. 1001 (’254 patent) at col. 7, lines 47-55. Such a similarity of processing further supports my opinion that Zhou’s microemulsions meet the definition of the term “emulsion” in the ’254 patent.

**b. “about 0.7-0.8 wt % aprepitant”**

92. Zhou is clearly directed to an emulsion that contains “aprepitant” as the active pharmaceutical ingredient. See, e.g., Ex. 1003 (Zhou) at (54) (“A type of *aprepitant* microemulsion for injection and its preparation method”), Abstract (“The invention discloses an *aprepitant* microemulsion for injection”), claims 1-10 (all referring to an “*aprepitant* microemulsion for injection”), [0001] (“The invention belongs to the technical field of pharmaceutical preparations, and specifically relates to an injectable *aprepitant* microemulsion and a preparation method thereof.”), [0002] (discussing aprepitant), [0007] (“the purpose of the present invention is to provide an injectable *aprepitant* microemulsion to effectively solve the problems of inconvenient clinical application of oral aprepitant, poor absorption, and low bioavailability”), [0008] (“A type of *aprepitant* microemulsion for injection”), [0009], [0011]-[0014], [0016]-[0017], [0019]-[0036] (describing “Aprepitant microemulsion[s]”).

93. Regarding the inclusion of “about 0.7-0.8 wt % aprepitant” in an emulsion, Zhou identifies a drug concentration range of 0.05-2% by weight for the aprepitant. Ex. 1003 (Zhou) at Abstract, claim 1 (“0.05% ~ 2% aprepitant”), [0008] (“0.05% ~ 2% aprepitant”). Thus, the concentration of aprepitant that Zhou discloses encompasses the range recited in claim 1 of the ’254 patent. It would have been a matter of routine optimisation for a POSA to arrive at a concentration of “about 0.7-0.8 wt % aprepitant” based upon the projected dose of aprepitant and the dose volume.

94. In addition to the range of 0.05-2% by weight of aprepitant, Zhou discloses a narrower window for a POSA’s consideration by virtue of Zhou’s “Embodiments.” Such examples utilised 0.5% and 1% aprepitant by weight. Ex. 1003 (Zhou) at [0019] (0.5 g aprepitant in a formulation whose components sum to 100 grams), [0025] (0.5 g aprepitant in a formulation whose components sum to 100 grams), [0029] (0.5 g aprepitant in a formulation whose components sum to 100 grams), [0035] (1.0 g aprepitant in a formulation whose components sum to 100 grams). In view of such exemplifications, it would be reasonable for a POSA to focus an optimisation of aprepitant concentration between these bounds, which are effectively the mid-region of the greater range of 0.05-2% that Zhou described. Indeed, the lower end of Zhou’s preferred range includes such values and would render “about 0.7-0.8 wt % aprepitant” from Claim 1 of the ’254 patent obvious due

to it either extending into Zhou's preferred range or abutting it. Ex. 1003 (Zhou) at [0009] ("1.0% ~ 1.5% aprepitant"); Ex. 1001 ('254 patent) at col. 9, lines 61-62 (defining the term "about").

95. Accordingly, a POSA would have likely chosen Zhou's range of aprepitant concentrations described in the Embodiments (i.e., 0.05 to 2.0%), which includes the claimed concentration of "about 0.7-0.8 wt % aprepitant." A POSA would have observed that there were more Embodiments in the middle of this range (e.g., Embodiments 1, 4, 6, and 8 including either 0.5% and 1% aprepitant) and thus, a POSA would have reasonably expected to prepare an emulsion (formulated using the other described components) in this concentration range in view of Zhou's exemplifications surrounding both endpoints.

**c. "an emulsifier"**

96. Zhou's aprepitant-containing emulsions include an "emulsifier." Ex. 1003 (Zhou) at Abstract ("The invention discloses an aprepitant microemulsion for injection, which is composed of the following mass percentage components: ... 0.5% ~ 10% emulsifier...."), claim 1 ("A type of aprepitant microemulsion for injection, characterized in that: Composed of the following mass percentage components: .... 0.5% ~ 10% emulsifier...."), claim 6 ("Aprepitant microemulsion for injection according to claim 1, characterized in that:[]The emulsifier is egg yolk phospholipid."), claim 9 ("Aprepitant microemulsion for injection according to

claim 1, characterized in that:[]Composed of the following mass percentage components: ... 8% ~ 10% emulsifier...”), claim 10 (referring to an “emulsifier”), [0008]-[0010] (referring to an “emulsifier”), [0016] (referring to an “emulsifier”).

97. Furthermore, Zhou characterizes “egg yolk phospholipids” as the “preferred” emulsifier in its emulsions. Ex. 1003 (Zhou) at [0010]. Zhou further provides “Embodiments” that exemplify the use of “egg yolk phospholipid” as an emulsifier in the emulsion. Ex. 1003 at [0019]-[0020] (Embodiment 1), [0025]-[0033] (Embodiments 4-7). An “egg yolk phospholipid” is, as the name indicates, a type of “egg phospholipid.” Such a material is synonymous with an “egg yolk lecithin.” Ex. 1004 (Washington) at 133-134 (discussing phospholipids from egg and “egg lecithin”); Ex. 1024 (Handbook) at 385-86 (discussing lecithin, its synonyms, and the manufacturing of egg lecithin from “the lecithin in egg yolks”). Accordingly, Zhou discloses a myriad of emulsions containing not just the broad category of “emulsifier” but also the inclusion of a “phospholipid” emulsifier, an “egg phospholipid” emulsifier, and an “egg lecithin” emulsifier.

98. Accordingly, a POSA would have been motivated by Zhou and the knowledge in the art concerning the use and purpose of an “emulsifier” to prepare an “emulsion” and they would have reasonably expected to prepare an emulsion containing an “emulsifier” in view of such prior use.

d. “an oil”

99. Zhou’s aprepitant-containing emulsions include an “oil.” Ex. 1003 (Zhou) at Abstract (“The invention discloses an aprepitant microemulsion for injection, which is composed of the following mass percentage components: ... 5% ~ 30% injection oil....”), claim 1 (“A type of aprepitant microemulsion for injection, characterized in that: Composed of the following mass percentage components: ... 5% ~ 30% injection oil, ... the oil for injection is one or more of soybean oil for injection, ethyl oleate, polyethylene glycol glyceryl oleate, triglycerides with medium fatty chain length, isopropyl myristate, peanut oil, corn oil, and olive oil....”), claim 5 (“Aprepitant microemulsion for injection according to claim 1, characterized in that:[]The injection oil is soybean oil for injection.”), claim 9 (“Aprepitant microemulsion for injection according to claim 1, characterized in that:[]Composed of the following mass percentage components: ... 7% ~ 15% injection oil....”), claim 10 (preparing an “oil phase”), [0008] (“A type of aprepitant microemulsion for injection, characterized in that:[]Composed of the following mass percentage components: ... 5% ~ 30% injection oil ....”), [0009] (“The preferred mass percentage of each component is: ... 7% ~ 15% injection oil....”), [0016] (preparing an “oil phase”). Zhou explains that “[t]he *injection oil* used is one or more of soybean oil for injection, ethyl oleate, oleic acid polyethylene glycol glyceride, triglycerides of medium fatty chain length, isopropyl myristate, peanut

oil, corn oil, olive oil, *with soybean oil being preferred.*” Ex. 1003 (Zhou) at [0010] (emphasis added). Zhou further provides “Embodiments” that all include an “oil” in the resulting emulsion. Ex. 1003 (Zhou) at [0019]-[0036]. Moreover, Embodiments 1 and 4-7 of Zhou all utilise the preferred “oil”—soybean oil. *Id.*

100. Accordingly, a POSA would have been motivated to include an “oil” in view of Zhou’s consistent inclusion of such an excipient and the popularity of using vegetable oils, including soybean oil, for preparing emulsions. *See* Section VII.C.2, above. Moreover, a POSA would have known to include an “oil” in the preparation of an emulsion—particularly an *oil*-in-water emulsion as described in Zhou. A POSA would have likewise had a reasonable expectation that the inclusion of an “oil” would facilitate the preparation of an emulsion of aprepitant in view of Zhou.

e. **“a co-surfactant”**

101. Ethanol is an example of an alcohol and a co-surfactant according to the ’254 patent. Ex. 1001 (’254 patent) at col. 3, lines 19-20. Instead of the term “co-surfactant,” Zhou refers to this emulsion component using the term “co-emulsifier.” Ex. 1003 (Zhou) at claim 1 (“A type of aprepitant microemulsion for injection, characterized in that: Composed of the following mass percentage components: ... 1 ~ 10% co-emulsifier, ... the co-emulsifier is one or more of *ethanol*, glycerol, 1,2-propanediol, and polyethylene glycol 400....”) (emphasis

added), claim 9 (“Aprepitant microemulsion for injection according to claim 1, characterized in that:[]Composed of the following mass percentage components: ... 2 ~ 5% co-emulsifier....”), [0008] (“A type of aprepitant microemulsion for injection, characterized in that:[]Composed of the following mass percentage components: ... 1 ~ 10% co-emulsifier....”), [0009] (“The preferred mass percentage of each component is: ... 7 ~ 13% co-emulsifier....”). Zhou explains that “[t]he co-emulsifier used is one or more of *ethanol*, glycerin, 1,2-propanediol, and polyethylene glycol 400, *with ethanol being preferred.*” Ex. 1003 (Zhou) at [0010]. In fact, most of the “co-emulsifiers” Zhou identifies—“ethanol, glycerol, and 1,2-propanediol”—are readily understood to be “alcohols.” Ex. 1003 (Zhou) at claim 1, claim 7, claim 10, [0010], [0016]. Zhou further provides several “Embodiments” that include “alcohol” in the resulting emulsion. Ex. 1003 (Zhou) at [0019]-[0022], [0025]-[0036]. Moreover, Embodiments 1 and 4-7 of Zhou all utilise the preferred co-emulsifier—ethanol. *Id.*

102. Accordingly, a POSA would have been motivated to include an alcohol in view of Zhou’s consistent inclusion of such an excipient, and would have been further motivated to choose “ethanol” given Zhou’s explicit preference. *See* Sections VII.A. and VII.C.3, above. A POSA would have likewise had a reasonable expectation that the inclusion of an alcohol would facilitate the preparation of an emulsion of aprepitant in view of Zhou’s examples.

f. “water”

103. Zhou’s aprepitant-containing emulsions include “water.” Ex. 1003 (Zhou) at Abstract (“The invention discloses an aprepitant microemulsion for injection, which is composed of the following mass percentage components: ... 60~80% water for injection.”), claim 1 (“A type of aprepitant microemulsion for injection, characterized in that: Composed of the following mass percentage components: ... 60~80% water for injection...”), claim 9 (“Aprepitant microemulsion for injection according to claim 1, characterized in that:[]Composed of the following mass percentage components: ... water for injection 60~69%.”), claim 10 (referring to the preparation of a “water phase”), [0007] (“Another object of the present invention is to provide a method for preparing the above mentioned injectable aprepitant microemulsion small *water injection*, infusion solution and freeze-dried powder injection”), [0008] (“A type of aprepitant microemulsion for injection, characterized in that:[]Composed of the following mass percentage components: ... water for injection 60 ~ 80%.”), [0009] (“The preferred mass percentage of each component is: ... water for injection 60 ~ 69%.”), [0016] (referring to the preparation of a “water phase”). Zhou further provides “Embodiments” that all include “water” in the resulting emulsion. Ex. 1003 (Zhou) at [0019]-[0036].

104. Accordingly, a POSA would have been motivated to include water in the preparation of an emulsion—particularly an oil-in-*water* emulsion as described in Zhou—and would have reasonably expected to obtain an emulsion using water in view of Zhou and the prior use of water in the art to prepare oil-in-*water* emulsions.

g. **“the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %)”**

105. Claim 1 of the '254 patent does not explicitly state the weight percent of the emulsifier that is present. However, one can generally calculate the range of emulsifier concentration by using the recited emulsifier to aprepitant ratio of “about 20:1 to 25:1 (wt/wt %)” and the recited aprepitant concentration of “about 0.7-0.8 wt%” by multiplying the value of “20” with the value of “0.7” to establish an approximate value for the lower end of the claimed range of emulsifier and multiplying the value of “25” with the value of “0.8” to establish an approximate value for the upper end of the claimed range of emulsifier. Doing so, I am able to determine that the concentration of emulsifier permitted by claim 1 includes “about”<sup>6</sup>

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<sup>6</sup> The '254 patent defines the term “about” to mean “±5%, ±10%, or ±20% of the value being modified.” Ex. 1001 ('254 patent) at col. 9, lines 61-62. For purposes of my opinions herein, I need not determine the precise boundaries of the claimed

14% to 20% emulsifier by weight (I note that multiplying 0.7% with 20 affords a value of 14% and multiplying 0.8% with 25 affords a value of 20%). Based on Zhou's emulsions and known principles regarding colloids, emulsions, and their components, I will explain in this section why it would have been obvious to arrive at an emulsifier content in the range of 14-20% by weight. Moreover, because the range of 14-20% by weight emulsifier would have been obvious and the range of "about 0.7-0.8 wt%" aprepitant would have been obvious (*see* Section VIII.D.b, above), the resulting ratio of these two values—"about 20:1 to 25:1 (wt/wt %)"—would have been obvious.

**i. A stable aprepitant emulsion was clinically desired**

106. An emulsion's stability is an important property for the clinical usefulness of a formulation:

The stability of colloidal formulations is paramount in their use as drug delivery systems. They must be sufficiently stable to be easily manufactured, sterilized (preferably by terminal autoclaving) and have a shelf life of at least a year, preferably more. Shelf life considerations are particularly important for emulsion systems, since these are

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weight percentages. Instead, claim 1 clearly encompasses the range of 14-20% and my opinions rely on these numerical values.

generally stored as liquids, and coalescence or aggregation can occur during storage.

Ex. 1004 (Washington) at 132. This was widely recognised in the industry. Ex. 1012 (Rossi) at 115 (“The stability of an emulsion formulation is vital for its use in clinical applications. The formulation must display physical, chemical, and microbial stability *for at least 1 year, if not more* ... A long-term stability testing schedule should be performed on all promising formulation candidates, whereby each emulsion is stored at various temperatures ranging from 4 to 50°C.”) (emphasis added); *id.* (“[E]mulsions must be biocompatible, biodegradable, nontoxic, sterile, isotonic, physically and chemically stable, and nonimmunogenic.”); Ex. 1015 (Mahato) at 264 (“Emulsions must demonstrate physical, chemical, and microbial stability throughout their shelf life under recommended packaging and storage conditions.”); Ex. 1019 (Collins-Gold) at 205 (concluding that for emulsion-based drug delivery “[e]xtemporaneous systems are often associated with a third pitfall: failure to monitor stability of both the drug and the emulsion as a function of time and storage conditions.”).

107. In view of such teachings, a POSA would have evaluated the stability of any potential pharmaceutical emulsion, such as Zhou’s aprepitant-containing emulsion, and would have been motivated to improve upon any shortcomings that were observed. Indeed, a POSA would have known that instability of an emulsion,

such as incomplete incorporation or precipitation of drug, can lead to clinical concerns. Ex. 1011 (Cannon) at 213-214. I note that Heron has previously alleged that Zhou's emulsions did not exhibit acceptable stability. Ex. 1026 (Heron's Opening Statement) at 16, 17, 19-20; Ex. 1020 (Heron's Opening Post-Trial Brief) at 28 n.16. Accordingly, a POSA would have been motivated to investigate and improve the stability of Zhou's emulsions. If a POSA encountered such stability issues, the obvious first step would be to increase the amount of emulsifier in the formulation with the expectation that the stability of the emulsion could likely be improved for the following reasons.

ii. **Emulsifier content improves drug solubility and affects emulsion stability**

108. An emulsion is “a mixture of two immiscible phases (namely, water and oil).” Ex. 1011 (Cannon) at 196. An emulsifier, which is a type of surfactant, is included in an oil-in-water mixture to stabilise the oil droplets dispersed in the water and avoid separation of the phases. Ex. 1012 (Rossi) at 110 (“The purpose of surfactants is to emulsify the oil phase and provide physical stability against flocculation and coalescence during storage, which may be for extended periods of time”). Accordingly, they “provide physical stability against flocculation and coalescence during storage.” *Id.* In an oil-in-water emulsion, the emulsifier reduces the interfacial tension between the oil and water by surrounding the oil droplets. Ex.

1018 (Hippalgaonkar) at 1529 (“Emulsifiers stabilize emulsions by reducing the interfacial tension of the system and by providing enough surface charge for droplet–droplet repulsion.”), *id.* at 1533 (“Emulsifiers enhance emulsion stability not only by reducing the droplet size but also by forming an interfacial film at the [oil/water] interface.”).

109. Both the nature and the amount (or concentration) of the emulsifier will influence the stability of an emulsion because the emulsifier also influences a series of properties such as droplet size, zeta potential, and viscosity. Ex. 1018 (Hippalgaonkar) at 1530 (“Factors such as type and concentration of oil phase and surfactants ... can influence the mean droplet size”); *id.* (Hippalgaonkar) at 1531 (“Droplet size can have a direct impact on toxicity and stability of the emulsion system.”); *id.* (Hippalgaonkar) at 1532 (“pH, ionic strength, type and concentration of emulsifiers and presence of electrolytes can affect the zeta potential of the system”); Ex. 1011 (Cannon) at 215 (“Some of the factors that affect the physical stability of emulsions include the type and concentration of surfactant used to stabilize the emulsion, the phase volume ratio ... droplet size, compatibility of drug and excipients with the emulsion, and storage condition of the emulsion.”); Ex. 1019 (Collins-Gold) at 194 (Table I) (indicating that the “[e]xpected effect” of increasing “[s]urfactant concentration” is “smaller droplet size until optimum, then increased viscosity”).

110. Indeed, the effect of emulsifier concentration on an emulsion's stability was a well-understood principle:

The amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability. Emulsifier concentration has a great impact on emulsion stability. A concentration window existed, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence.

Ex. 1016 (Khan) at 2719 (internal citations omitted); Ex. 1011 (Cannon) at 216 (“Whereas an inadequate concentration of surfactant will do little to prevent coalescence, undue increase in its concentration often leads to problems like increased drug instability and difficulty in administration. Excess surfactant molecules will tend to self-associate, forming micellar or lamellar structures, which may compromise the effectiveness of the emulsion”).

111. Accordingly, a POSA would have been motivated to evaluate the effect of emulsifier content on stability by examining lower and higher concentrations of emulsifier to understand the stability “window” or formulation range for the emulsion as a function of the emulsifier content. It would have been a straightforward task for a POSA to conduct the necessary experimentation to increase the relative concentration of the emulsifier and determine the stability

“window.” Conducting such experimentation with Zhou’s aprepitant emulsion would have readily led a POSA to explore at least the claimed 14-20% emulsifier content as a simple matter of characterising the existence of a stability “window”.

112. A POSA would have also been motivated to increase the emulsifier content in Zhou’s aprepitant emulsions to understand the emulsifier’s contribution to drug solubilisation. Surfactant-based emulsifiers can aid the solubilization of poorly soluble drugs in an emulsion formulation. Ex. 1028 (Su) at 149 (“Surfactants in parenterals can increase drug solubility through micellization, improve drug wetting, prevent drug precipitation upon injection”); *id.* (Su) at 148 (“If a drug is not solubilized by aqueous pH-modification, cosolvents, complexation, or combinations of these, surfactants are often used”). These interactions often result in improved drug solubility.

113. Such improvement in solubility was known for aprepitant. Data from solubility experiments of aprepitant demonstrated an improvement in solubility with increasing emulsifier concentration. Ex. 1009 (Hingorani) at [0043]-[0047]. These experiments involved varying the nature of both emulsifier (Cremophor RH 40, Cremophor RH 60, Poloxamer 188, and Polysorbate 80) and solvents (water alone and ethanol-water mixtures (30:70 and 55:45 v/v %)). *Id.* Results indicated that irrespective of the nature of emulsifier or solvent employed, the solubility of

aprepitant increased with increasing amounts of the emulsifiers that were tested. *See e.g.*, Ex. 1009 (Hingorani) Table 2-5.

114. Accordingly, a POSA preparing an injectable emulsion of aprepitant with an objective of maintaining solubilisation of the drug would have been motivated to investigate the concentration range for emulsifier—as doing so would likely improve aprepitant’s solubility in the formulation and reduce concerns regarding either solubilisation or subsequent precipitation. *See e.g.*, Ex. 1011 (Cannon) at 213-214; Ex. 1028 (Su) at 149 (“Surfactants in parenterals can ... prevent drug precipitation upon injection, improve stability of a drug in solution...”). This is especially the case for low-solubility drugs because if the “drug concentration in the emulsion is close to the drug solubility, crystallization can sometimes occur.” Ex. 1015 (Mahato) at 258. At the same time, because crystal formation was reported to be “inhibited by the use of appropriate solubilizers and surfactants,” a POSA would have been motivated to increase the emulsifier content in Zhou’s aprepitant emulsions to decrease any drug precipitation occurring during storage. Ex. 1015 (Mahato) at 258.

115. Thus, a POSA would have been motivated to evaluate the effect of increasing emulsifier content on aprepitant solubility by examining higher concentrations of emulsifier with a view to improve solubility and reduce possible precipitation of the drug during storage. It would have been a straightforward task

for a POSA to conduct the necessary experimentation by increasing the relative content of the emulsifier in the formulation composition. Conducting such experimentation with Zhou's aprepitant emulsion would have led a POSA to explore at least the claimed 14-20% emulsifier content (as claimed in the '254 patent) as a matter of routine investigation to either address or limit issues of drug solubility or precipitation.

iii. **Increased emulsifier concentration produces smaller droplets, which were expected to improve stability and aprepitant loading**

116. Aprepitant has limited solubility in both water and oil. Ex. 1009 (Hingorani) at [0054]. For a drug with these characteristics, a POSA would reasonably expect it to adsorb at the oil-water interface of an emulsion. Ex. 1004 (Washington) at 139 (“[D]rugs [that] are poorly soluble in both water and oil ... can *only be loaded* into an emulsion by adsorbing to the *droplet interface*”); Ex. 1011 (Cannon) at 201 (“there are many drugs that have little or no solubility in either water or oil. In such a case, the *final locale* of drug would usually be the *interface of the emulsion droplet.*”) (emphasis added).

117. Based on the expected localisation of aprepitant at the droplet interface of an oil/water emulsion, a POSA would have understood that increasing the interfacial surface area of such an emulsion formulation would likely enhance the loading of aprepitant within the formulation. Such an increase in interfacial surface

area is readily achieved by reducing the droplet size of the dispersed phase (“oil”) of the emulsion. Ex. 1029 (Baker) at 862 (stating that a reduction in droplet size from 1.0  $\mu\text{m}$  in diameter to 0.1  $\mu\text{m}$  results in approximately a 42 time increase in the oil-water surface area); Ex. 1028 (Su) at 150 (indicating microemulsions have a very high surface area to volume ratio because of the numerous small droplets).

118. In addition to a smaller size of the dispersed phase providing an increased interfacial area, small oil droplets are also considered to be beneficial for emulsion stability and patient safety. Ex. 1019 (Collins-Gold) at 193 (“For parenteral use, a droplet mean diameter of less than 1  $\mu\text{m}$  is highly desirable”); Ex. 1015 (Mahato) at 260-261 (“physical stability of an emulsion can be enhanced by ... [d]ecreasing the globule size of the internal phase.”); Ex. 1018 (Hippalgaonkar) at 1531 (“Droplet size can have a direct impact on toxicity and stability of the emulsion system ... [t]herefore, droplet size and distribution are amongst the most important characteristics of an injectable emulsion.”). Accordingly, based on consideration of emulsion stability and safety benefits as well as the increase in interfacial surface area for drug loading into the emulsion, a POSA would have been motivated to decrease the droplet size in the emulsion.

119. Moreover, a POSA would have known that “[e]mulsifiers enhance emulsion stability ... by reducing the droplet size” and “by forming an interfacial film at the oil-water interface.” Ex. 1018 (Hippalgaonkar) at 1533; Ex. 1019

(Collins-Gold) at 194 (Table I) (increased “surfactant concentration” results in “smaller droplet size until optimum”); Ex. 1014 (Klang) at 64 (“an increase in lecithin concentration leads to the production of smaller particles due to an increased surfactant to oil volume ratio, which in turn leads to enhanced physical stability.”); Ex. 1028 (Su) at 150 (“Surfactants are added to emulsion systems to reduce interfacial tension, reduce initial droplet size and size distribution”).

120. Indeed, the prior art expressly warned that “[a]s the interfacial layer could only solubilize a certain amount of drug, exceeding the saturation concentration of the drug at the interfacial layer ... drug nanocrystals could form.” Ex. 1011 (Cannon) at 202. Therefore, a POSA with knowledge of the solubility profile of aprepitant and the potential issues with drug precipitation from an emulsion formulation would have been motivated to increase the amount of emulsifier with the expectation it would increase interfacial surface area, reduce the droplet size, and potentially improve loading of aprepitant in the emulsion.

iv. **Emulsifier concentrations greater than Zhou’s were known in the art**

121. A POSA would have known that higher emulsifier concentrations may be needed to prepare smaller droplets of the dispersed phase and afford sufficient interfacial surface coverage of the droplets. Ex. 1005 (Bagwe) at 80 (“a relatively large amount of surfactant” is needed “in order to stabilize the large interfacial area”

of the of the small droplets.); Ex. 1028 (Su) at 150 (explaining that the presence of “numerous small droplets” necessitate “high levels” of surfactants).

122. Emulsions were known to contain up to 20% emulsifier while microemulsions may contain “> 10%” or even as high as 40% (mentioning a “sufficiently high” concentration of “10-40%” emulsifier/surfactant might be required to sufficiently cover the droplet’s surface area). Ex. 1005 (Bagwe) at 82 (Table 2), 88-89; Ex. 1025 (Booth) at [0039]-[0041] (disclosing oil-in-water injectable emulsions containing emulsifiers such egg yolk lecithin at concentrations up to 15 wt.%).

123. Further, while the references discussing emulsifier content that I have cited pertain to both emulsions and microemulsions, both types of “emulsions” (i.e. emulsions and microemulsions, or a combination of each) are relevant here. First, according to the ’254 patent, the term “emulsion” refers to a “colloidal dispersion of two immiscible liquids in the form of droplets, whose diameter, in general, is between 10 nanometers and 100 microns.” Ex. 1001 (’254 patent) at col. 9, lines 63-66. This droplet size range overlaps with the usual range for “microemulsions.” Ex. 1005 (Bagwe) at 88 (disclosing that “microemulsions are in the range of 100-1000 Å [10-100 nm] in diameter”). Additionally, microemulsions are described as “excellent candidates as potential drug delivery systems because of their improved drug solubilization, long shelf life.” Ex. 1005 (Bagwe) at Abstract. For reasons that

I have explained, the greater amount of emulsifier in such emulsions (or indeed, microemulsions) leads to a reduction in droplet size and an increase in the interfacial surface area—both of which are favorable for improving emulsion stability and increasing loading of aprepitant within such a formulation.

124. Thus, even without the broad definition of “emulsion” provided by the ’254 patent (“colloidal dispersion of two immiscible liquids in the form of droplets, whose diameter, in general, is between 10 nanometers and 100 microns.”), a POSA would have gained insight from the teachings described above concerning “microemulsions” and would have been able to apply those teachings to improving the stability and aprepitant loading based on the emulsions/microemulsions described in Zhou (Ex. 1003). Indeed, for drugs possessing the solubility characteristics of aprepitant – i.e., limited solubility in both oil and water – microemulsion-based formulations have been used to solubilize them into pharmaceutical vehicles. Ex. 1005 (Bagwe) at 112 (“antifungal drugs with solubilities ranging from slightly soluble to practically insoluble in both water and oil can be successfully dissolved in a pharmaceutically acceptable ternary microemulsion system.”). Accordingly, a POSA would have recognized the relevance of microemulsion systems in developing an aprepitant emulsion.

125. Traditionally, toxicity concerns arising from some emulsifiers has limited their use in relatively higher concentrations. Ex. 1028 (Su) at 149 (“Quite

often the surfactant containing formulation is diluted prior to intravenous administration to reduce toxicity.”). Natural lecithins, such as egg lecithin, are considered to be biocompatible and well-tolerated when used in parenteral emulsions as they are metabolized in a manner similar to natural fats. Ex. 1018 (Hippalgaonkar) at 1529; Ex. 1006 (Weng) at 1157 (“The natural lecithins, including egg yolk lecithin and soybean lecithin, can be totally biodegraded and metabolized, so they are regarded as well-tolerated and non-toxic compounds with excellent biocompatibility, and suitable for long-term use and high-dose infusion.”). Accordingly, the broad safety profile of lecithins would have been assuring to a POSA looking to increase the concentration of lecithin as the emulsifier based on Zhou’s aprepitant emulsions.

126. In sum, based on the information regarding the solubility characteristics of aprepitant and potential precipitation, a POSA would have investigated the stability of compositions when prepared with higher emulsifier content. In this regard, the prior knowledge of the POSA that a higher emulsifier concentration typically leads to smaller droplet sizes and thus an increase in the interfacial area would provide a rational framework for such an approach. In essence, such studies would be routine formulation optimisations for a POSA to undertake – that is, to vary the quantity of one excipient and evaluate the resulting effect on stability. Further, because compositions with high emulsifier concentrations were known, and

a POSA had a reason to evaluate such higher concentrations as I have explained, a POSA would have performed such evaluations as a matter of routine experimentation and optimisation for an aprepitant-containing emulsion.

127. Thus, by increasing the emulsifier concentration for the reasons that I have described, such routine formulation optimisation would have led a POSA to determine the “window” or formulation range for emulsifier content. In doing so, a POSA would have at least conducted studies in the range of 14-20% emulsifier by weight along with the ratio of emulsifier to aprepitant of “about 20:1 to 25:1 (wt/wt%)” from such evaluations. Indeed, Zhou already disclosed emulsifier to aprepitant ratios ranging from 10:1 to as much as 120:1. Ex. 1003 (Zhou) at [0023], [0035]. Accordingly, the ’254 patent’s emulsifier to aprepitant ratio and emulsifier content as recited in claim 1, as well as the values in between, would have been obvious for the reasons provided.

**2. Claims 2-7 would have been obvious**

128. Claims 2-7 recite:

2. The emulsion of claim 1, wherein the emulsifier is a phospholipid.

3. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 16 wt/wt %.

4. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 17 wt/wt %.

5. The emulsion of claim 1, wherein the emulsifier is an egg lecithin.

6. The emulsion of claim 5, wherein the egg lecithin is present in the emulsion at about 16 wt/wt %.

7. The emulsion of claim 5, wherein the egg lecithin is present in the emulsion at about 17 wt/wt %.

Ex. 1001 ('254 patent) at col. 32, lines 56-67.

129. Accordingly, claims 2 and 5 refer back to claim 1 and identify the emulsifier as either a “phospholipid” (claim 2) or an “egg lecithin” (claim 5), claims 3 and 4 refer back to claim 2 and require a phospholipid concentration of either “about 16 wt/wt %” (claim 3) or “about 17 wt/wt %” (claim 4), and claims 6 and 7 refer back to claim 5 and require an egg lecithin concentration of either “about 16 wt/wt %” (claim 6) or “about 17 wt/wt %” (claim 7). I previously explained why claim 1 would have been obvious. *See* Section VIII.D.1, above. My prior analysis applies equally here.

130. Zhou identifies “phospholipids” as one of five emulsifiers for use in an aprepitant emulsion. Ex. 1003 (Zhou) at [0010]. Furthermore, Zhou indicates that “egg yolk phospholipids” are the “preferred” choice of emulsifier. *Id.* Zhou further includes claims and examples which all refer to the use of “phospholipids” or “egg yolk phospholipids” in the aprepitant emulsion. Ex. 1003 (Zhou) at claim 1 (“the

emulsifier is one or more of *phospholipids*, poloxamer, polyoxyethylene castor oil and derivatives, polyethylene glycol-caprylic/capric glyceryl, and polysorbate 80”), claim 6 (“The emulsifier is *egg yolk phospholipid*.”), paragraphs [0019]-[0020] (utilizing “egg yolk phospholipid”), and paragraphs [0025]-[0033] (all utilizing “egg yolk phospholipid”).

131. Moreover, as to the choice of an “egg yolk phospholipid” for use as an emulsifier, a POSA would have known that “phospholipids, or lecithins” are routinely used for preparing an injectable emulsion. Ex. 1004 (Washington) at 133. The most common source for such phospholipids is “egg or soya lecithin.” Ex. 1004 (Washington) at 133 (“The majority of phospholipids from egg or soya lecithin, the commonest sources, are unsaturated, and these materials are widely used as emulsifiers for intravenous use.”); Ex. 1019 (Collins-Gold) at 192 (“Natural phosphatides, principally from egg yolk or soybean, are in most widespread use.”). Additionally, “Lipoid® E80” was a commercially available, parenteral grade of lecithin that was recognized as providing “excellent emulsion stability.” Ex. 1004 (Washington) at 134 (“Because of the extensive interest in phospholipids as emulsifier, and for use as liposomes for drug delivery, a wide range of lecithins is commercially available. These are produced in a number of ways: crude egg or soy lecithin can be refined chromatographically, removing sterols, lysolipids and a range of other contaminants, to produce a parenteral grade of lecithin, such as Lipoid®

E80....”); *id.* (referring to “excellent emulsion stability” by Lipoid® E80). The ’254 patent identifies “LIPOID E 80” as an egg lecithin. Ex. 1001 (’254 patent) at col. 19, lines 41-43.

132. In view of the widespread use of phospholipids such as egg phospholipids and egg lecithin, and the commercial availability of such material in the form of Lipoid® E80, a POSA would have been motivated to use such materials by virtue of either Zhou’s preference of “egg yolk phospholipids” or Washington’s discussion of such materials. Moreover, a POSA would have had a reasonable expectation of successfully including a phospholipid in an aprepitant emulsion in view of Zhou’s teachings or the “excellent emulsion stability” indicated by Washington that was attributed to such materials.

133. With respect to the concentration of “phospholipid” or “egg lecithin” for use in an aprepitant emulsion, I previously explained when addressing claim 1 of the ’254 patent why it would have been a matter of routine optimisation to arrive at a concentration of emulsifier that was 14% or more by weight. For these same reasons utilising an emulsifier concentration of “about 16 wt/wt %” (claim 6) or “about 17 wt/wt %” (claim 7) would have been obvious.

### **3. Claims 8-9 would have been obvious**

134. Claims 8-9 recite:

8. The emulsion of claim 1, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

9. The emulsion of claim 8, wherein the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.

Ex. 1001 ('254 patent) at col. 33, lines 1-8.

135. Accordingly, claim 8 refers back to claim 1 and identifies the oil as one or more of a group that includes “olive oil,” “ethyl oleate,” “triglycerides,” and “soybean oil” while claim 9 refers back to claim 8 and requires “about 9 wt/wt % to 10 wt/wt %” of oil in the emulsion. I previously explained why claim 1 would have been obvious. *See* Section VIII.D.1, above. My prior analysis applies equally here.

136. For Zhou’s apreitant-containing emulsions, Zhou identifies “olive oil,” “ethyl oleate,” “triglycerides” as potential oils for use while further indicating that “soybean oil” is “preferred.” Ex. 1003 (Zhou) at [0010]. Zhou further includes claims and examples which all refer to the use of “olive oil,” “ethyl oleate,” “triglycerides,” or “soybean oil.” Ex. 1003 (Zhou) at claims 1 and 5, [0019]-[0020] (utilizing “soybean oil”), [0021]-[0022] (utilizing “ethyl oleate”), [0025]-[0026] (utilizing “soybean oil”), [0027]-[0028] (utilizing “soybean oil”), [0029]-[0030] (utilizing “soybean oil”), [0031]-[0033] (utilizing “soybean oil”), [0034]-[0036] (utilizing “olive oil”). Zhou’s preference for “soybean oil” was not surprising in view of its prior use to generally prepare emulsions. *See* Section VII.C.2, above.

Accordingly, a POSA would have been motivated to utilise any of “olive oil,” “ethyl oleate,” “triglycerides,” or “soybean oil” to prepare an aprepitant emulsion in view of Zhou’s identification of such oils for this particular use and would have had a reasonable expectation of successfully preparing an emulsion in view of Zhou and the art’s prior use of such oils, including soybean oil, for the same purpose.

137. With respect to the concentration of oil for use in an aprepitant emulsion, Zhou explains that the amount of oil may range from 5-30% by weight or, more preferably, from 7-15% by weight. Ex. 1003 (Zhou) at [0008] (“5% ~ 30% injection oil”), [0009] (“7% ~ 15% injection oil”). Such amounts encompass or overlap the amount of “about 9 wt/wt % to 10 wt/wt %” required by claim 9 of the ’254 patent. Arriving at “about 9 wt/wt % to 10 wt/wt %” from Zhou’s ranges would amount to no more than routine optimisation for the preparation of an emulsion.

138. Furthermore, Zhou provides additional guidance on specific concentrations of oil for use in the emulsion. Zhou’s “Embodiments” contain 9.5% soybean oil and 10% olive oil by weight, respectively. Ex. 1003 (Zhou) at [0031]-[0033], [0034]-[0036]. Such exemplified amounts fall within the range of “about 9 wt/wt % to 10 wt/wt %” in claim 9 of the ’254 patent.

139. With the knowledge that formulators routinely used oils such as “olive oil,” “ethyl oleate,” “triglycerides,” or “soybean oil” as well as Zhou’s preferred choice of “soybean oil” and the description of ranges with specific examples of

concentrations that meet the Challenged Claims' requirements, a POSA would have been motivated to continue such use and would have had a reasonable expectation of successfully including one of the claimed oils, e.g., soybean oil, within the claimed concentration range to prepare an aprepitant emulsion.

**4. Claims 10-12 would have been obvious**

140. Claims 10-12 recite:

10. The emulsion of claim 1, wherein the co-surfactant comprises an alcohol.

11. The emulsion of claim 10, wherein the alcohol is present in the emulsion at less than 10 wt/wt %.

12. The emulsion of claim 10, wherein the co-surfactant is ethanol.

Ex. 1001 ('254 patent) at col. 33, lines 9-14.

141. Accordingly, claim 10 refers back to claim 1 and identifies the co-surfactant as an "alcohol," claim 11 refers back to claim 10 and requires "less than 10 wt/wt %" of the alcohol in the emulsion, and claim 12 refers back to claim 10 and identifies the co-surfactant as "ethanol." I previously explained why claim 1 would have been obvious. *See* Section VIII.D.1, above. My prior analysis applies equally here.

142. For Zhou's aprepitant-containing emulsions, Zhou identifies "ethanol" as a "preferred" co-emulsifier for inclusion. Ex. 1003 (Zhou) at [0010]. Zhou further includes claims and examples which all refer to the inclusion of "ethanol."

Ex. 1003 (Zhou) at claims 1, 7, and 10 (all referencing “ethanol”), [0016], and [0019]-[0020], [0024]-[0033] (all utilizing “ethanol”). Zhou’s choice of ethanol was not surprising as the solubility of aprepitant in ethanol had been described. Ex. 1009 (Hingorani) at [0005].

143. Zhou further explains that the amount of “ethanol” (i.e., the “preferred” co-emulsifier) should be present in an amount ranging from 1-10% by weight, 7-13% by weight, or even 2-5% by weight. *See, e.g.*, Ex. 1003 (Zhou) at claim 1 (“1 ~ 10% co-emulsifier”), claim 9 (“2 ~ 5% co-emulsifier”), [0008] (“1 ~ 10% co-emulsifier”), [0009] (“7 ~ 13% co-emulsifier”). Each of these ranges substantially overlap with or, in the case of 2-5%, are encompassed by the range recited in claim 11 of the ’254 patent. Arriving at the “less than 10” percent by weight that is claimed would amount to no more than routine optimization driven by the desire to achieve an acceptable aprepitant emulsion.

144. Furthermore, Zhou provides considerable guidance on specific concentrations of ethanol for use in the emulsion. Several of Zhou’s “Embodiments” include ethanol at a weight percentage of either 1.5%, 1%, 3%, 5.5%, or 10%. Ex. 1003 (Zhou) at [0019]-[0020], [0025]-[0026], [0027]-[0032]. Such exemplified amounts fall within the range of claim 12 of the ’254 patent.

145. With the knowledge that formulators had already studied aprepitant’s solubility in ethanol, as well as Zhou’s choice of ethanol and the described working

examples using ethanol, a POSA would have been motivated to continue such use and would have had a reasonable expectation of successfully including ethanol within the claimed concentration range to prepare an aprepitant emulsion.

**5. Claims 13-15 would have been obvious**

146. Claims 13-15 recite:

**13.** The emulsion of claim 1, further comprising an osmotic agent.

**14.** The emulsion of claim 13, wherein the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol.

**15.** The emulsion of claim 14, wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.

Ex. 1001 ('254 patent) at col. 33, lines 15-24.

147. Accordingly, claim 13 refers back to claim 1 and requires the inclusion of an “osmotic agent,” claim 14 refers back to claim 13 and identifies the “osmotic agent” as being one of “glycerol,” “mannitol,” “glucose,” or “sucrose,” and claim 15 refers back to claim 14 and requires “3 wt/wt % to 8 wt/wt %” osmotic agent. I previously explained why claim 1 would have been obvious. *See* Section VIII.D.1, above. My prior analysis applies equally here.

148. Zhou’s aprepitant emulsions may contain any of “glycerol,” “mannitol,” “glucose,” and “sucrose” as excipients. Ex. 1003 (Zhou) at claim 1 (“A

type of aprepitant microemulsion for injection, characterized in that: Composed of the following mass percentage components: . . . 5% ~ 20% protection agent . . . the protective agent is one or more of glycerol, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids.”), claim 8 (“Aprepitant microemulsion for injection according to claim 1, characterized in that:[]The protective agent used is glycerol”), [0010] (“The protective agent used is one or more of glycerin, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids, with glycerin being preferred.”).

149. Zhou refers to “glycerol,” “mannitol,” “glucose,” and “sucrose” as a “protective agent.” Although Zhou does not indicate what these agents are “protecting,” a POSA would have readily understood that these agents are examples of osmotic agents that modulate the tonicity/osmolarity so that the formulation does cause undue irritation upon injection to the patient. *See* Section VII.C.5, above. Such excipients are frequently added to emulsions for this purpose. *Id.*

150. Any of “glycerol,” “mannitol,” “glucose,” or “sucrose” would have been an obvious choice for including in the aprepitant emulsion in view of Zhou’s use of such excipients. *See, e.g.,* Ex. 1003 (Zhou) at [0019]-[0033]. However, “glycerol” is specifically identified in Zhou’s claim 8 while “glycerin” is singled out as being “preferred.” Ex. 1003 (Zhou) at claim 8, [0010]. Despite the difference in name, these excipients are synonymous. Ex. 1024 (Handbook) at 283.

151. Accordingly, a POSA would have been motivated to include any of “glycerol,” “mannitol,” “glucose,” or “sucrose” in an aprepitant emulsion and would have had a reasonable expectation of success in view of Zhou’s interchangeable exemplifications of these choices in the Embodiments. Ex. 1003 (Zhou) at [0019]-[0020] (glycerin), [0021]-[0022] (sucrose), [0023]-[0024] (glucose), [0025]-[0026] (glycerin), [0027]-[0028] (glycerin), [0029]-[0030] (glycerol), [0031]-[0033] (glycerin). Indeed, glycerol was a known osmotic agent “preferred by the manufacturers of commercial soybean oil emulsion” that would “reduce the globule size and improve the creaming stability of [oil-in-water] emulsions.” Ex. 1006 (Weng) at 1160. Accordingly, a POSA would have been motivated to include an osmotic agent, such as glycerol, in an aprepitant emulsion to capitalize on these additional advantages afforded by its inclusion and would have had a reasonable expectation of successfully including an osmotic agent in view of such additional advantages.

152. With respect to including “about 3 wt/wt % to 8 wt/wt %” osmotic agent in an aprepitant emulsion, Zhou teaches the inclusion of any of “glycerol,” “mannitol,” “glucose,” or “sucrose” in an amount of 5-20% by weight as well as 8-13% by weight. Ex. 1003 (Zhou) at claim 1, [0009]. Such amounts overlap and/or abut the claimed range of “about 3 wt/wt % to 8 wt/wt %.” Arriving at such concentrations would amount to no more than routine optimisation driven by the

desire to achieve an acceptable tonicity for injecting the emulsion into a subject. Additionally, certain Embodiments of aprepitant emulsions in Zhou contain 5% or 8% by weight glycerol/glycerin and 5.95% by weight glucose. Ex. 1003 (Zhou) at [0019]-[0020], [0023]-[0030]. Such exemplified amounts fall within the range of claim 15.

153. Accordingly, in view of Zhou, a POSA would have selected one of “glycerol,” “mannitol,” “glucose,” or “sucrose” to adjust tonicity of the aprepitant emulsion. Additionally, given the overlapping nature of the concentrations of these agents described in the examples of Zhou (5% or 5.95% or 8% by weight) with the range recited by claim 15 (3-8 wt/wt %), a POSA would have had a reasonable expectation of successfully including one of these agents within the claimed concentration range to prepare an aprepitant emulsion.

**6. Claims 16-17 would have been obvious**

154. Claims 16-17 recite:

**16.** The emulsion of claim 1, further comprising a pH modifier.

**17.** The emulsion of claim 16, wherein the pH modifier is oleic acid or a salt thereof.

Ex. 1001 ('254 patent) at col. 33, lines 25-28.

155. Accordingly, claims 16 refers back to claim 1 and requires the inclusion of a “pH modifier” while claim 17 refers back to claim 16 and identifies the pH

modifier as “oleic acid or a salt thereof.” I previously explained why claim 1 would have been obvious. *See* Section VIII.D.1, above. My prior analysis applies equally here.

156. With respect to the inclusion of a “pH modifier,” Zhou explicitly describes “adjusting the pH to 6.0-8.0.” Ex. 1003 (Zhou) at [0016]; *see also id.* at [0011]. Similarly, several of Zhou’s examples indicate pH adjustment to a specific value. *See e.g.*, Ex. 1003 (Zhou) at [0020] (“add an appropriate amount of water for injection to adjust the pH to 7.2 to obtain initial solution”), [0022] (“add an appropriate amount of water for injection at the same time to adjust the pH to 6.8 to obtain initial solution”), and [0028] (“add an appropriate amount of water for injection at the same time to adjust the pH to 6.8 to obtain the initial solution”). Accordingly, a POSA would have been motivated to monitor the pH and make any necessary adjustment to the pH of the emulsion to bring the pH value within the range identified in Zhou.

157. Including a pH modifier to adjust the pH of an emulsion was routine and useful for enhancing stability. Lipid emulsions were known to undergo hydrolysis during storage or autoclaving thereby liberating fatty acids. Ex. 1018 (Hippalgaonkar) at 1529 (“A slightly alkaline pH is preferred because the pH decreases during sterilization, and on storage, due to the production of free fatty acids (FFAs).”); Ex. 1011 (Cannon) at 202 (“autoclaving has been found to cause

some hydrolysis of lipids and lecithins resulting in liberation of free fatty acids, which lowers the pH of the emulsions. To counter the pH dropping during autoclave, it is suggested to adjust the pH of the emulsion to slightly alkaline pH (8.0) before autoclaving.”); Ex. 1012 (Rossi) at 112 (“The pH of the final emulsion may need to be adjusted and this can be done by adding small amounts of HCl or NaOH. The desired pH is usually between 7 and 8 to maintain physiological compatibility and minimize hydrolysis of the oil and phospholipids.”). Moreover, a variation in pH was reported to affect the zeta potential of the emulsion and ultimately its stability, and therefore adjusting the pH of an emulsion was a common practice while developing such compositions. Ex. 1018 (Hippalgaonkar) at 1532 (“Zeta potential ... is a useful parameter for stability assessment. A number of factors such as pH ... can affect the zeta potential of the system.”).

158. Additionally, sodium oleate was a commonly used excipient in lipid emulsions and the ability of the compound to have an effect on the pH of a solution was also known. *See e.g.*, Ex. 1018 (Hippalgaonkar) at 1528 and 1535 (disclosing several commercial emulsions that contain oleic acid or sodium oleate). Sodium oleate was known to be associated with a number of beneficial effects for use in a lipid emulsion. For example, sodium oleate is water soluble agent that can function as a “co-emulsifier” and thus “stabilize the emulsion against coalescence [and] also decrease the granularity of emulsion particles.” Ex. 1006 (Weng) at 1159. Sodium

oleate also possesses “a certain buffering capacity to reduce the pH change to a minimum” and thus can even “keep pH value nearly unchanged before and after autoclaving.” Ex. 1006 (Weng) at 1159. Indeed, these advantageous effects prompted frequent inclusion of a small amount of sodium oleate in commercial injectable lipid-based emulsions. Ex. 1006 (Weng) at 1159 (“Hence, a small amount of [sodium oleate] was often used in commercial parenteral emulsions (Lipofundin<sup>®</sup> MCT, Abbolipid<sup>®</sup>, Schiwalipid<sup>®</sup> and others) to obtain stable formulations during the autoclaving process.”) (internal citation omitted).

159. The combination of the useful properties of sodium oleate and the need to adjust pH to offset changes during processing that I discussed above would have further motivated a POSA to include a pH modifier, and particularly choose sodium oleate, for inclusion in an aprepitant emulsion. A POSA would have had a reasonable expectation of successfully including a pH modifier, including sodium oleate, in an aprepitant emulsion in view of these advantageous properties along with its use in other emulsions.

7. **Claims 18-21 would have been obvious**

160. Claims 18-21 recite:

18. The emulsion of claim 1, wherein the emulsifier is egg lecithin.

19. The emulsion of claim 1, wherein the co-surfactant is ethanol.

20. The emulsion of claim 1, further comprising sucrose.

21. The emulsion of claim 1, further comprising sodium oleate.

Ex. 1001 ('254 patent) at col. 33, lines 29-35.

161. Accordingly, claims 18-21 each refer back to claim 1 and identify the emulsifier as “egg lecithin” (claim 18), identify the co-surfactant as “ethanol” (claim 19), require the inclusion of “sucrose” (claim 20), or require the inclusion of “sodium oleate” (claim 21). I previously explained why claim 1 would have been obvious. *See* Section VIII.D.1, above. Moreover, I have previously explained why each of the components recited in claims 18-21 would have been obvious choices for including in an aprepitant emulsion. *See* Section VIII.D.2, above (discussing “egg lecithin”); Section VIII.D.4, above (discussing ethanol); Section VIII.D.5, above (discussing sucrose); Section VIII.D.6, above (discussing sodium oleate). My prior analyses apply equally here.

**8. Claim 22 would have been obvious**

162. Claim 22 recites:

22. An injectable pharmaceutical emulsion, comprising:  
about 0.7-0.8 wt % aprepitant;  
an emulsifier;  
an oil;

a co-surfactant; and  
water,  
wherein the ratio of the emulsifier to aprepitant ranges  
about 23:1 (wt/wt %).

Ex. 1001 ('254 patent) at col. 33, line 36 to col. 34, line 4.

163. Accordingly, other than the phrase “wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt %),” claim 22 recites the same components in the same concentrations as claim 1. I previously explained why claim 1 would have been obvious and my analysis for the common components/concentrations applies equally here. *See* Section VIII.D.1, above.

164. Moreover, using the range of “about 0.7-0.8 wt % aprepitant” and the “ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt %),” I am able to determine that the concentration of emulsifier permitted by claim 22 includes 17% emulsifier by weight (I note that multiplying 0.7% with 23 affords a value of 16.1% and multiplying 0.8% with 23 affords a value of 18.4%). As I discussed above in Section VIII.D.1.g, a value of 17% was encompassed by the ranges of emulsifier content described in the art and would have been arrived at by virtue of routine optimization. Moreover, in Section VIII.D.2, above, I also explained why the value of 17% would have been obvious when addressing claims 4 and 7. My analysis from claims 1, 4 and 7 applies equally here with respect to claim 22.

**9. Claims 23-26 would have been obvious**

165. Claims 23-26 recite:

**23.** The emulsion of claim **22**, wherein the emulsifier is a phospholipid.

**24.** The emulsion of claim **23**, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

**25.** The emulsion of claim **22**, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

**26.** The emulsion of claim **22**, wherein the co-surfactant comprises an alcohol present in the emulsion at less than 10 wt/wt %.

Ex. 1001 ('254 patent) at col. 34, lines 5-18.

166. Accordingly, claims 23-26 each refer back to either claim 22 or claim 23 and identify the emulsifier as a “phospholipid” (claim 23), “egg phospholipids” or “soy phospholipids” (claim 24), indicate that the “oil” is one or more of, *inter alia*, “olive oil,” “ethyl oleate,” “triglycerides,” and “soybean oil.” (claim 25), or indicate that the “co-surfactant” is an “alcohol” at a concentration of “less than 10 wt/wt %” (claim 26). I previously explained why claim 22 would have been obvious. *See* Section VIII.D.8, above. Moreover, I have previously explained why each of the components recited in claims 23-26 would have been obvious choices for including in an aprepitant emulsion. *See* Section VIII.D.2, above (discussing

“phospholipid”); Section VIII.D.2, above (discussing egg phospholipids); Section VIII.D.3, above (discussing oils); Section VIII.D.4, above (discussing the inclusion of an alcohol in a concentration of less than 10% by weight). My prior analyses apply equally here.

167. Additionally, I note that my prior discussion of these components was in reference to independent claim 1 and an apreitant to emulsifier ratio of “about 20:1 to 25:1 (wt/wt %). Ex. 1001 (’254 patent) at col. 32, lines 48-55 (claim 1). The apreitant to emulsifier ratio of “about 23:1 (wt/wt %)” required by claim 22 does not affect my obviousness opinions here.

**10. Claim 27 would have been obvious**

168. Claim 27 recites:

**27. An injectable pharmaceutical emulsion, comprising:**  
about 0.7-0.8 wt % apreitant;  
an emulsifier;  
an oil;  
a co-surfactant; and  
water,  
wherein the ratio of the emulsifier to apreitant ranges  
about 24:1 (wt/wt %).

Ex. 1001 (’254 patent) at col. 34, lines 20-27.

169. Accordingly, other than the phrase “wherein the ratio of the emulsifier to apreitant ranges about 24:1 (wt/wt %),” claim 27 recites the same components in the same concentrations as claim 1. I previously explained why claim 1 would

have been obvious and my analysis for the common components/concentrations applies equally here. *See* Section VIII.D.1, above.

170. Moreover, using the range of “about 0.7-0.8 wt % aprepitant” and the “ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt %),” I am able to determine that the concentration of emulsifier permitted by claim 27 includes 17% emulsifier by weight (I note that multiplying 0.7% with 24 affords a value of 16.8% and multiplying 0.8% with 24 affords a value of 19.2%). As I discussed above in Section VIII.D.1.g, a value of 17% was encompassed by the ranges of emulsifier content described in the art and would have been arrived at by virtue of routine optimization. Moreover, in Section VIII.D.2, above, I also explained why the value of 17% would have been obvious when addressing claims 4 and 7. My analysis from claims 1, 4, and 7 applies equally here with respect to claim 27.

**11. Claims 28-30 would have been obvious**

171. Claims 28-30 recite:

**28.** The emulsion of claim **27**, wherein the emulsifier is a phospholipid.

**29.** The emulsion of claim **27**, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

**30.** The emulsion of claim **27**, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

Ex. 1001 ('254 patent) at col. 34, lines 28-38.

172. Accordingly, claims 28-30 each depend directly from claim 27 and identify the emulsifier as a “phospholipid” (claim 28), “egg phospholipids” or “soy phospholipids” (claim 29)<sup>7</sup>, or indicate that the “oil” is one or more of, *inter alia*, “olive oil,” “ethyl oleate,” “triglycerides,” and “soybean oil.” (claim 30). I previously explained why claim 27 would have been obvious. See Section VIII.D.10, above. Moreover, I have previously explained why each of the

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<sup>7</sup> If it is of interest to the reader, I note that claim 27 does not use the term “phospholipid.” Accordingly, it is not clear what the phrase “the phospholipid” is referring to in claim 29. Despite this possible drafting error, I analyzed claim 29 as requiring “a phospholipid” rather than an indeterminate reference to “the phospholipid.”

components recited in claims 28-30 would have been obvious choices for including in an aprepitant emulsion. *See* Section VIII.D.2, above (discussing “phospholipid”); Section VIII.D.2, above (discussing egg phospholipids); Section VIII.D.3, above (discussing oils). My prior analyses apply equally here.

173. Additionally, I note that my prior discussion of these components was in reference to independent claim 1 and an aprepitant to emulsifier ratio of “about 20:1 to 25:1 (wt/wt %). Ex. 1001 (’254 patent) at col. 32, lines 48-55 (claim 1). The aprepitant to emulsifier ratio of “about 24:1 (wt/wt %)” required by claim 27 does not affect my obviousness opinions here.

**E. Motivation to Combine Principles from Zhou, Washington, Bagwe, and Weng**

174. A POSA would have been motivated to combine the teachings in Zhou with the teachings in Washington, Bagwe, and Weng to arrive at the Challenged Claims. As I have discussed previously (*see*, Paragraphs 46 and 73), Zhou teaches that aprepitant is “insoluble in water and insoluble in organic solvents.” Ex. 1003 (Zhou) at Abstract. Due to aprepitant’s poor solubility, Zhou teaches that “in order to achieve [an] aprepitant injection” aprepitant must be formulated as a microemulsion. *Id.* Zhou teaches the formulation of said aprepitant emulsions using components such as emulsifiers, co-emulsifiers, oils, etc. and identifies egg yolk

phospholipid (lecithins) as a preferred emulsifier. *Id.* at claims 1 and 6, [0010], [0019]-[0020], [0027]-[0033].

175. Washington teaches “factors influencing the stability of phospholipid-stabilized emulsions.” Ex. 1004 (Washington) at Abstract. Thus, Washington is focused on emulsion preparation using the preferred emulsifier in Zhou. Washington also teaches that “Class III drugs are poorly soluble in both water and oil, and can only be loaded into an emulsion by adsorbing to the droplet interface.” *Id.* at 139. Based off the teachings in Zhou and the known properties of aprepitant, a POSA would recognize that aprepitant is a “Class III” drug and thus the methods for formulating “Class III” drugs described in Washington would be relevant and applicable to the aprepitant emulsions in Zhou.

176. Bagwe identifies several properties of emulsions that overlap with Zhou’s emulsions, such as droplet size, use of a co-surfactant/co-emulsifier, surfactant concentrations, and the benefits of using phospholipids as an emulsifier. *See*, Ex. 1005 (Bagwe) at 82 (Table 2) disclosing a droplet size of less than 0.1 microns to 5 microns *vs.* Ex. 1003 (Zhou) at [0012] disclosing particle sizes of 50 – 100 nm (0.05-0.15 microns); *see*, Ex. 1005 (Bagwe) at 82 (Table 2) disclosing that microemulsions use cosurfactants *vs.* Ex. 1003 (Zhou) at claims 1 and 9, [0008]-[0010], disclosing the use of a co-emulsifier; *see*, Ex. 1005 (Bagwe) at 82 (Table 2), 88, disclosing the use of greater than 10% (and up to 40%) surfactant for

microemulsions and the use 1-20% surfactant for emulsions *vs.* Ex. 1003 (Zhou) at Abstract, claims 1 and 9, [0008]-[0009], disclosing the use of up to 10% surfactant; *see*, Ex. 1005 (Bagwe) at 101 disclosing the use of phospholipids as an emulsifier for parenteral use *vs.* Ex. 1003 (Zhou) at claims 1 and 6, [0010], [0019]-[0020], [0027]-[0033] disclosing egg yolk phospholipid as the preferred emulsifier for aprepitant emulsions and examples of aprepitant emulsions containing egg yolk phospholipid. Due to the similarities between the emulsions described in Bagwe and Zhou, a POSA would recognise that the teachings in Bagwe are relevant to the aprepitant emulsions in Zhou.

177. Lastly, similarly to Zhou, Weng describes formulating a poorly water-soluble drug as an emulsion using as an emulsifier such as egg yolk lecithin, in addition to other components such as oils, co-emulsifiers, etc. Ex. 1006 (Weng) at 1157-1159. Weng teaches the use of a co-emulsifier and pH modifier such as sodium oleate. *Id.* at 1158-1159. Because of the significant overlap between the emulsions in Zhou and Weng, a POSA would be motivated to combine the teachings of Weng with the teachings in Zhou when formulating an aprepitant emulsion.

178. Accordingly, due to the similarities between the teachings in Zhou and the teachings in the prior art, a POSA would be motivated to apply the features taught in Washington, Bagwe, and Weng to improve upon the aprepitant emulsions taught in Zhou and arrive at the Challenged Claims.

**F. No Secondary Considerations**

179. I understand that Heron previously alleged that claims 9-11 of the '229 patent and claims 9-10 of the '794 patent were non-obvious due to long-felt but-unmet need, unexpected results, industry skepticism regarding the invention and praise from the industry, and commercial success. Ex. 1007 (Trial Opinion) at 43-44. However, I note that the District Court concluded the following regarding these secondary considerations:

In sum, I find that the long-felt, unmet need evidence weighs moderately in Heron's favor; the commercial success factor weighs slightly in Heron's favor; and the failure of others and unexpected results evidence weighs moderately in Heron's favor. The remaining categories of secondary evidence have no significant bearing on the issue of obviousness in this case. Taken all together, the evidence of objective considerations provides some support for Heron's argument that the two asserted patents would not have been obvious, but the objective considerations are not powerful factors bearing on the issue of obviousness here.

Ex. 1007 (Trial Opinion) at 52.

180. Each of claims 9-11 of the '229 patent and claims 9-10 of the '794 patent require "14 wt/wt % egg yolk lecithin." See Ex. 1030 ('229 patent) at claims 9-11 (all referring back to claim 8, which recites "14 wt/wt % egg yolk lecithin"); Ex. 1031 ('794 patent) at claims 9-10 (both referring back to claim 8, which recites

“14 wt/wt % egg yolk lecithin”). Each of the Challenged Claims, however, allow for an emulsifier concentration of greater than 14% (and as much as up to 20%) by weight. Thus, the scope of claims 9-11 of the '229 patent and claims 9-10 of the '794 patent with respect to the emulsifier content is clearly not the same as the scope of the Challenged Claims.

181. I understand from counsel that evidence of secondary considerations of non-obviousness must be commensurate in scope with the claims. Accordingly, any evidence of secondary considerations for emulsions containing “14 wt/wt % egg yolk lecithin” would not be not commensurate with the scope of the Challenged Claims. Therefore, it is my opinion that any evidence of secondary considerations for emulsions containing lesser amounts of emulsifying agent than described in the Challenged Claims would not be probative of non-obviousness for the Challenged Claims, which describe greater amounts of emulsifying agent.

182. I also understand from counsel that the law recognises that a claim that is clearly obvious is not saved by secondary considerations, particularly weak ones. As I explained in Section VIII, the Challenged Claims are clearly obvious. Accordingly, I am not aware of any secondary considerations of non-obviousness that affect my opinions disclosed herein. Should Heron provide any in response, I reserve my right to address them.

## **IX. GROUND 2: LACK OF WRITTEN DESCRIPTION**

183. In this section, I explain why the '254 patent does not provide written description support for each of claims 1-30. In order to comply with the written description requirement, the '254 patent must convey to a POSA that the inventors possessed aprepitant emulsions having an emulsifier concentration of greater than 14% (and as much as 20%) by weight and also convey possession of such emulsions having a ratio of emulsifier to aprepitant that is greater than 20:1 (and as much as 25:1) as required by the particular claims. *See* Paragraphs 24-26 (discussing the standards for written description). In my opinion, claims 1-30 are either obvious or lack written description.

184. I have assumed, for purposes of analyzing written description of the Challenged Claims, that the statements I discuss in this Section that are by or on behalf of Heron are correct, and I adopt those statements solely for purposes of my written description analysis. It is reasonable to apply Heron's statements concerning claims 9, 10, and 21 of the '229 patent (Ex. 1030) and claims 9-10 of the '794 patent (Ex. 1031) to the Challenged Claims of the '254 patent (Ex. 1001) in the manner that I have in view of the similarity and overlap in subject matter. For the reader's convenience, I have reproduced claims 9, 10, and 21 of the '229 patent and claims 9-10 of the '794 patent below (as well as including the claims that they reference):

<b>'229 patent (Ex. 1030)</b>	<b>'794 patent (Ex. 1031)</b>
<p>8. An injectable pharmaceutical emulsion comprising:  0.7 wt/wt % aprepitant;  14 wt/wt % egg lecithin;  9 wt/wt % to 10 wt/wt % soybean oil;  and  a pH modifier, wherein the pH modifier is sodium oleate; wherein the pH of the emulsion ranges from 7.5 to 9.0.</p>	<p>8. A physically stable pharmaceutical composition suitable for intravenous administration comprising:  0.7 wt/wt % aprepitant;  14 wt/wt % egg yolk lecithin;  9 wt/wt % to 10 wt/wt % soybean oil;  and  a pH modifier, wherein the pH modifier is sodium oleate; wherein the pH of the composition ranges from 7.5 to 9.0.</p>
<p>9. The emulsion according to claim 8, wherein the emulsion further comprises 5 wt/wt % sucrose.</p>	<p>9. The composition according to claim 8, wherein the composition further comprises 5 wt/wt % sucrose.</p>
<p>10. The emulsion according to claim 8, wherein the emulsion further comprises 2 wt/wt % to 6 wt/wt % ethanol.</p>	<p>10. The composition according to claim 8, wherein the composition further comprises 2 wt/wt % to 6 wt/wt % ethanol.</p>
<p>17. A method for treating nausea and vomiting in a subject in need thereof comprising administering to the subject the pharmaceutical emulsion according to claim 8.</p>	

21. The method according to claim 17, wherein the administering is intravenous.	
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**A. Heron’s prior statements regarding emulsion formulations**

185. I have reviewed several documents that set forth statements by Heron, one of the inventors of the ’254 patent, or an expert on behalf of Heron regarding aprepitant, emulsion formulations, and excipient content (including emulsifiers). *See, e.g.*, Ex. 1023 (Day 4 PM); Ex. 1026 (Heron’s Opening Statement); Ex. 1027 (Heron’s Responsive Post-Trial Brief); Ex. 1032 (Day 4 AM); Ex. 1033 (Closing Arguments); Ex. 1034 (Day 2 AM). Numerous statements by or on behalf of Heron describe how and why a POSA would have a very doubtful outlook concerning the preparation of an aprepitant emulsion:

- “[A]prepitant was widely understood to be very difficult to formulate for intravenous use, and an emulsion was ‘one of the more complex formulation strategies,’ so the POSA would be ‘adding complexity’, further detracting from any reasonable expectation of success. After over 20 years of industry failure, a POSA would have been skeptical of an aprepitant emulsion being stable and safe for intravenous use.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 44 (internal citations omitted).

- “Aprepitant has characteristics of ‘cement dust’ with high crystallinity and low solubility, and because of aprepitant’s poor physical characteristics, an intravenous formulation of aprepitant was considered impossible.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 53.
- “As of September 2014, any attempt to develop an intravenous aprepitant product was considered a failure.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 54.
- “A POSA would have had no expectation that a physically stable intravenous aprepitant formulation could be made and used safely. Intravenous emulsion formulations were reported in the prior art to be difficult to develop, and the prior art attempts at developing an intravenous aprepitant emulsion were not successful.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 54-55.
- “[A]ll available data shows that the prior art formulations were not physically stable, and could not be injected into the arm of a human for treating CINV.” Ex. 1026 (Heron’s Opening Statement) at 16.
- “Q. How would a POSA have viewed the properties of aprepitant from a formulation point of view in 2014? A. Yeah, I mean, we would have viewed it as a tough compound. You know, it's insoluble in water. It has very limited solubility in oil. It’s referred to as a brickdust compound....I mean, this case

at least dissolves in ethanol, but this is one of those tough compounds.” Ex. 1032 (Day 4 AM) at 1270:7-23 (Heron’s expert testifying).

186. Thus, when the state of the art and the known significant challenges are being viewed by a POSA from such a “skeptical” vantage point as Heron has described, a POSA would expect a patent’s description to provide a commensurate and robust disclosure demonstrating the preparation of emulsions, the components that can be successfully utilized, and the amount of these components that lead to the preparation of an emulsion in order to convey that the inventors actually possessed the full scope of what they have claimed. Proof over the full scope of the invention would be a prerequisite for Heron’s “skeptical” POSA to understand that the inventors truly possessed what has been claimed.

187. Heron also made numerous statements that were specifically related to the emulsifier content in an aprepitant emulsion and these statements would necessitate a commensurate and robust disclosure for a POSA to understand that the inventors actually possessed the full scope of the claimed range of emulsifier:

- “A POSA Would Not Simply Increase Emulsifier Because That Can Destabilize an Emulsion” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 36 (Heading).

- “Additionally, the prior art undisputedly showed that increasing an emulsifier could cause stability issues....” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 44.
- “Fresenius is wrong that a POSA would have expected that increasing egg lecithin content beyond the 10% upper limit of CN ’845 to 14% (*i.e.*, 40% more) would yield a physically stable aseptant emulsion. CN ’845 provides no stability data whatsoever for any of its emulsions, let alone those with the full amount of 10% egg lecithin.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 45.
- “[T]he emulsifier concentration window is tight. And afterwards you quickly – emulsion stability quickly declines. And at high emulsifier concentrations, emulsion instability occurs because of rapid coalescence.” Ex. 1033 (Closing Arguments) at 77:2-8 (Heron’s Counsel).
- “The point being is that increasing emulsifier is not just simply, oh, I go as high as I – just keep going higher and higher until I achieve stability. No, what it’s saying is that increasing emulsifier can lead to instability and that be very careful going higher.” Ex. 1033 (Closing Arguments) at 77:16-24 (Heron’s Counsel).

- “Khan also recognized that ‘[a]t high emulsifier concentration emulsion instability occurs because of rapid coalescence,’ citing a study showing that even 0.5% emulsifier can destabilize some emulsions.” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 12.
- “If anything, a POSA would have thought that using dramatically more than the industry-standard ~1% emulsifier of the only FDA-approved emulsions would not have resulted in a stability formulation, particularly in view of, e.g., Khan, which warns *against* using too much emulsifier.” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 19 (emphasis in original).
- “Further, a POSA would not have expected that adding *five times* the level of emulsifier used in the optimized Zhou formulation would result in a stable commercial product.” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 23 (emphasis in original).
- “Moreover, Dr. Little will explain how the literature that Dr. Rabinow cited cautioned against higher amounts of emulsifier in emulsions because the excess emulsifier can trigger destabilization, including through flocculation (clumping of oil droplets).” Ex. 1026 (Heron’s Opening Statement) at 13-14.
- “Well, so we’ve been talking about this, and I think the Court even recognized that if you’re going to change things in a formulation, if you change it such

that the emulsifier concentration goes up, there's going to be at one point in time an issue with that, too." Ex. 1032 (Day 4 AM) at 1281:16-21.

- "But if you are working with an emulsifier, you don't just go up, okay, because you could have a stability problem if you go up, as well. And there's lots of scientific reasons as to why that would be the case. And certainly if you're going up beyond the stability – or beyond the concentrations of emulsifier that you see in the art – I mean, the standard amounts in the art are like 1.2 percent. So then going up to 14 percent is not what a person of ordinary skill in the art would even be thinking about doing." Ex. 1032 (Day 4 AM) at 1282:8-19.
- "That you would go up like that is not something somebody would be thinking of in terms of routine optimization. It's anything but routine, in my opinion." Ex. 1032 (Day 4 AM) at 1283:13-16.

188. The above statements by Heron, or on its behalf, indicate that the "skeptical" POSA would have been concerned that increasing the concentration of emulsifier may result in destabilisation of the emulsion. Thus, for purposes of satisfying the written description requirement, Heron's "skeptical" POSA would expect the patent to present evidence of successful emulsion preparation over the full scope of emulsifier content that is claimed.

189. Such disclosure would be of the utmost importance for the higher concentrations of emulsifier beyond 14% by weight that is claimed in view of Heron's earlier statements about this lesser amount:

- “[T]he inventors developed a novel emulsion containing specific ingredients at specific concentrations—including an unusually high amount of egg yolk lecithin as an emulsifier—to achieve a stable IV formulation that permits injection into humans.” Ex. 1026 (Heron's Opening Statement) at 6 (footnote omitted).
- “In contrast, Heron succeeded in developing a stable intravenous aprepitant emulsion by using an unprecedented amount (14%) of the emulsifier egg lecithin in combination with other specific ingredients at specific concentrations and conditions.” Ex. 1020 (Heron Opening Post-Trial Brief) at 1.
- “[N]o prior art emulsion ever had the claimed combination of ingredients, or anything close to the high amount of emulsifier of 14% lecithin.” Ex. 1020 (Heron Opening Post-Trial Brief) at 4.
- “In a departure from all prior conventions, Heron's intravenous NK-1 receptor antagonist program experimented with an amount of emulsifier that went far beyond anything in the prior art. Many experiments resulted in crystals and/or

phase separations (creaming, flocculation), among other failures. And, the inventors explained that numerous experiments were necessary to obtain a stable product.” Ex. 1020 (Heron Opening Post-Trial Brief) at 7 (internal citations omitted).

- “The amount of lecithin, in combination with other ingredients, was ultimately critical for the developing [sic] a stable product.” Ex. 1020 (Heron Opening Post-Trial Brief) at 7 n.1.

190. Thus, assuming Heron’s above statements are correct, one can reasonably characterise written description considerations such as the existing knowledge in the field of emulsions or even aprotic emulsions, the extent and content of the prior art, and the maturity of emulsion science/technology as being limited. Assuming this is true as I have done for purposes of analyzing compliance with the written description requirement (*see* Paragraphs 183-184), this further supports my opinion that Heron’s “skeptical” POSA would expect evidence of successful emulsion preparation over the full scope of emulsifier content that is claimed in order to understand whether the inventors actually possessed such emulsions.

191. With respect to the predictability of emulsion preparation, many of the statements by Heron that I have identified above indicate that this technology was very unpredictable. Moreover, Heron has made many other statements to this effect:

- “As Dr. Han explained, ‘[t]he emulsion is very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion.’ Ex. 1020 (Heron’s Opening Post-Trial Brief) at 7.
- “Additionally, the prior art undisputedly showed that increasing an emulsifier could cause stability issues, that adding sodium oleate to emulsions could cause hemolysis, and that emulsions are complex systems in which changing ingredients and their amounts could have a cascade of effects.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 44-45 (internal citations omitted).
- “Fresenius also failed to show that its proposed ‘optimization’ would have been routine (or had a reasonable expectation of success) in the face of the unpredictable interactivity of the components of aprepitant emulsions and the lack of success in the art.” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 7.
- “[E]vidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious,’ and the evidence in this case shows that aprepitant emulsion are just such a system....” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 8 (internal citations omitted).
- “Fresenius fails to consider the most salient facts about the prior art that would inform whether a POSA would have reasonably expected success for the

claimed formulation as a whole, including: that aprepitant was known to be very difficult for formulate for intravenous use; that over 20 years of efforts to do so had failed; the hemolytic risk of sodium oleate; and that emulsions, in particular, were one of the more complex formulation strategies in which changing ingredients and amounts could have a cascade of effects.” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 20.

- “The emulsion in very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion. And Tom and I – Tom and I came up with this together through a lot of trial-and-error experiments.” Ex. 1034 (Day 2 AM) at 508:6-11 (inventor testifying).

192. In view of such professed unpredictability, Heron’s “skeptical” POSA would naturally expect evidence of successful emulsion preparation over the full scope of the Challenged Claims in order to understand whether the inventors actually possessed such claimed emulsions.

193. Such evidence would be of considerable importance for the claimed concentration range of emulsifier in view of Heron’s prior statements that were specifically directed to this issue:

- “The amount of lecithin, in combination with other ingredients, was ultimately critical for the developing [sic] a stable product.” Ex. 1020 (Heron Opening Post-Trial Brief) at 7 n.1.
- “The examiner also stated that Heron ‘demonstrated criticality of the range in regard to the wt. / wt. % egg yolk lecithin and the ratio of egg yolk lecithin to aprepitant’ and that this could be viewed as either a demonstration of criticality or unexpected results.” Ex. 1020 (Heron Opening Post-Trial Brief) at 12.
- “Q. And in terms of the egg yolk lecithin itself, let’s go back to Claim 8 [referring to U.S. Patent Nos. 9,561,229 and 9,974,794] and talk about the egg yolk lecithin. The only test that you’re identifying to show some kind of a special result is the 14 weight-weight percent egg yolk lecithin, as used in Examples 1, 2, 3, and 6? A. The way I describe this is differently. I think that the overall formulation, based on what I’ve seen, including the 14 weight-per-weight percent egg yolk lecithin, had those unexpected properties.” Ex. 1023 (Day 4 PM) at 1408:21-1409:7.
- “They have to prove that there was a motivation to combine and a reasonable expectation of success. That’s not Heron’s burden. But, regardless, we did prove criticality. Criticality is shown through the Examples 4 and 5 of the

patent-in-suit, which are the prior art for CN '845 and Zhou.” Ex. 1033 (Closing Arguments) at 53:6-12.

194. Given such professed unpredictability concerning the preparation of aprepitant emulsions, Heron’s “skeptical” POSA would expect evidence of successful emulsion preparation over the full scope of the emulsifier content recited in the Challenged Claims in order to understand whether the inventors actually possessed such emulsions. Indeed, Heron has previously emphasised the need for such evidence:

- “Given the physical attributes of aprepitant, the difficulty of working with intravenous emulsions that was reported in the art, the number of significant modifications that Fresenius asserts over CN '845 (and even Zhou), and *the paucity of available experimental results*, Fresenius failed to prove that a POSA would have had a reasonable expectation of success.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 45.
- “Q. And the CN '845 reference showed in a published document how to make an emulsion with aprepitant, in particular, in 2012; correct? A. I thought you asked me this question already before. I mean, *they did disclose various formulations where they were at least attempting to make emulsions. It’s just you don’t have any information about whether they worked or not or the stability or anything like that.*” Ex. 1023 (Day 4 PM) at 1439:17-25.

- “So what does all this suggest, Your Honor, that a POSA would not have expected that CN '845 was stable. *It had no stability data*. And if a POSA would have made and tested it, they would have seen it's not stable.” Ex. 1033 (Closing Argument) at 66:5-9.

195. Accordingly, if Heron is correct in its assertion that a POSA would expect information showing that a particular combination of excipients in the prior art will afford an acceptable emulsion, then the same POSA would likewise similarly expect such information relevant to the '254 patent. In such instances, this would require the '254 patent's disclosure to demonstrate the preparation of acceptable emulsions over the full range of components and concentrations that are claimed. However, the '254 patent does not do so.

**B. The Challenged Claims allow for a much broader emulsifier content than what Heron previously deemed “critical” during prosecution**

196. I note that the Challenged Claims (which allow for an emulsifier content of greater than 14% by weight) represent a departure from other claims that Heron has obtained in patents such as the '742 patent (Ex. 1035), the '850 patent (Ex. 1036), the '118 patent (Ex. 1037), and the '074 patent (Ex. 1038). Such other

claims were focused on emulsifiers in an amount of no more than 15% (wt/wt)<sup>8</sup> or having an emulsifier to aprepitant ratio centered on 20:1. *See* Ex. 1035 ('742 patent) at claim 1 (“11 wt/wt % to 15 wt/wt % of an emulsifier” and a ratio of emulsifier to NK-1 receptor antagonist of “about 18:1 to 22:1 (wt/wt %)”); Ex. 1036 ('850 patent) at claim 1 (“11 wt/wt % to 15 wt/wt % of an emulsifier” and a ratio of emulsifier to NK-1 receptor antagonist of “about 18:1 to 22:1 (wt/wt %)”); Ex. 1037 ('118 patent) at claim 1 (ratio of emulsifier to NK-1 receptor antagonist of “about 18:1 to 22:1 (wt/wt %)”); Ex. 1038 ('074 patent) at claim 1 (ratio of emulsifier to NK-1 receptor antagonist of “about 18:1 to 22:1 (wt/wt %)”) and claim 4 (“about 11 wt/wt % to 15 wt/wt% of an emulsifier”).

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<sup>8</sup> Although these other patents are not presently before the Board in this dispute, there would be a natural concern regarding their compliance with the written description and enablement requirements in view of those patents' disclosures. I note, for example, that the highest concentration of emulsifier exemplified for an aprepitant emulsion in the '742 patent is 14.3% by weight (*see* Example 2). Accordingly, much of my discussion in this declaration would apply to these other patent claims. I reserve my right to further address any of these patents/claims at the appropriate time and in the appropriate forum.

197. I also note that Heron informed the Examiner that was reviewing these claims that within the range of 11-15% by weight emulsifier, the art was unpredictable:

Assuming that one of ordinary skill in the art would be motivated to modify the amount of the emulsifier to be within the range as recited in claim 1 [i.e., 11%-15% wt/wt], ***the results are unpredictable with respect to, for example, stability.*** As discussed above, the stability of an emulsion comprising an emulsifier in the the [sic] amount in accordance with the current claims is much improved compared to prior art emulsions comprising the emulsifier in an amount outside the scope of the current claims. ***The improved stability cannot be predicted.*** See the Ottoboni Declaration, ¶9.

Ex. 1039 ('742 Patent Prosecution History) at 45 (emphasis added); *id.* ('742 Patent Prosecution History) at 44 n.1 (“The evidence provided hereafter indeed shows that ***the amount of the emulsifier in the claimed range*** [i.e., 11%-15% wt/wt] ***increase the stability of an emulsion, which is unexpected.***”) (emphasis added).

198. Furthermore, I note that Heron relied upon a declaration by an inventor, Thomas Ottoboni, to assert that aprepitant emulsions exhibited unpredictable results. Ex. 1040 (Ottoboni Declaration) ¶9 (“[T]he instant claims were not obvious over Zhou for at least the reason that ***the claimed pharmaceutical emulsion possessed unexpected and unpredictable properties*** relative to Zhou.”); ¶10 (“[T]he claimed

range of 13 to 15 wt% egg yolk lecithin results in an unpredictable increase in stability of the claimed pharmaceutical aprepitant emulsion in view of Zhou.”).

199. Heron presented these arguments and the Examiner(s) charged with reviewing those particular Heron patent applications were ultimately convinced of the “surprising and unexpected” results for aprepitant emulsions containing a lower amount of emulsifier than what is now claimed. For example:

- “Further, as discussed in the Declaration submitted by Thomas Ottoboni (heretofore the ‘Ottoboni Declaration’) in US application serial No. 15/083,071 (now US patent 9,561,229) cited by Applicant in the Remarks filed 2/26/2018, the claimed injectable emulsion formulations exhibit surprising and unexpected properties compared to the emulsions of Zhou (Example 4, disclosed in the instant specification)...By comparison, Examples 1, 2, 3, and 6 (Table 7, pages 31-32 of the present specification) which contain between 11.7 and 14.3 wt/wt% of the emulsifier (within the range recited in instant Claim 1) were stable....As such, the claimed emulsion formulations exhibit stability that is surprising and unexpected compared to the closest prior art.” Ex. 1039 (’742 Patent Prosecution History) at 70-71 (Examiner’s Reasons for Allowance).
- “Further, as discussed in the Declaration submitted by Thomas Ottoboni (heretofore the ‘Ottoboni Declaration’) in US application serial No.

15/083,071 (now US patent 9,561,229) cited by Applicant in the Remarks filed 9/6/2017 of said US application, the claimed injectable emulsion formulations exhibit surprising and unexpected properties compared to the emulsions of Zhou (Example 4, disclosed in the instant specification)...By comparison, Examples 1, 2, 3, and 6 (Table 7, pages 31-32 of the present specification) which contain between 11.7 and 14.3 wt/wt% of the emulsifier (within the range recited in instant Claim 1) were stable...As such, the claimed emulsion formulations exhibit stability that is surprising and unexpected compared to the closest prior art.” Ex. 1041 (’850 Patent Prosecution History) at 44-45 (Examiner’s Reasons for Allowance).

- “However, Zhou’s ratio of emulsifier to aprepitant (the NK-1 antagonist) is below the ratio required by the claimed invention. It appears that the amount of emulsifier is critical to the claimed emulsion...” Ex. 1042 (’074 Patent Prosecution History) at 37 (Examiner’s Reasons for Allowance).
- “Applicant’s arguments and evidence appear to show criticality of the claimed range for the emulsifier and criticality of the ratio of aprepitant to emulsifier.” Ex. 1046 (’229 Patent Prosecution History) at 23.
- “An emulsifier present in a range of 13-15 wt/wt% unpredictably and unexpectedly results in a pharmaceutical emulsion which is more stable (e.g., lack of crystal formation) than an aprepitant emulsion with 0.5-10 or 8-10

wt/wt% emulsifier as taught by Zhou.” Ex. 1046 (’229 Patent Prosecution History) at 25.

- “Applicants assert that stability (e.g., the lack of crystal formation)<sup>9</sup> of aprepitant emulsions resulting from a formulation comprising *inter alia* 0.4 to 1.0 wt/wt% aprepitant and 13 to 15 wt/wt% egg yolk lecithin demonstrates an unexpected and unpredictable advantage of the claimed pharmaceutical emulsions over the aprepitant formulations of Zhou.” Ex. 1046 (’229 Patent Prosecution History) at 36.
- “The following is an examiner’s statement of reasons for allowance: No reference anticipates the instantly claimed composition and Applicant has demonstrated criticality of the range in regard to the wt. / wt.% of egg yolk lecithin and the ratio of egg yolk lecithin to aprepitant....” Ex. 1046 (’229 Patent Prosecution History) at 61.
- “Importantly, the stability (e.g., the lack of crystal formation) of aprepitant emulsions resulting from a formation comprising 11 to 15 wt/wt% egg yolk lecithin (Lipoid E 80) and an emulsifier:aprepitant ratio ranging from 18:1 to

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<sup>9</sup> I note that the ’254 patent also mentions other forms of stability. *See, e.g.*, Ex. 1001 (’254 patent) at col. 10, lines 5-30.

22:1 demonstrates an unexpected and unpredictable advantage of the aprepitant emulsions....” Ex. 1047 (’465 Patent Prosecution History) at 49.

- “The following is an examiner’s statement of reasons for allowance: Per the Examiner’s discussion with Primary Examiner Ernst Arnold, and the Interview summary, Applicant has demonstrated unexpected results in regard to physical stability of the instantly claimed composition.” Ex. 1047 (’465 Patent Prosecution History) at 88-89.
- “The following is an examiner’s statement of reasons for allowance: As indicated in the Allowability Notice for parent application 14/859,013, Examiner Levin and Primary Examiner Ernst Arnold acknowledge that Applicant demonstrated unexpected results in regard to the physical stability of the instantly claimed composition....” Ex. 1048 (’793 Patent Prosecution History) at 37-38.
- “Importantly, the stability (e.g., the lack of crystal formation) of aprepitant emulsions resulting from a formulation comprising 11 to 15 wt/wt% egg yolk lecithin (Lipoid E 80) demonstrates an unexpected and unpredictable advantage of the aprepitant emulsions....” Ex. 1049 (’208 Patent Prosecution History) at 44.

- “However, as argued by Applicant, the instantly claimed composition exhibits unexpected results in terms of physical stability, i.e. lack of crystal formation. (Remarks, pp. 5 – 6) Examples 1 – 3 and 6 of the instant specification have emulsifier weight percentages falling within the range of 11 – 15 wt. %, i.e. 11.7 – 14.3 wt % and lacked crystal formation when the emulsions were stored at room temperature for at least 2 months....As argued by Applicant, one of skill in the art would not have expected the difference between 9.95 wt. % egg yolk lecithin (Ex. 4) and 11.7 wt. % egg yolk lecithin (Ex. 3) to produce such a difference in physical stability....” Ex. 1049 (’208 Patent Prosecution History) at 56.

200. Each of the statements that I have identified above further emphasise the lack of predictability in preparing an aprepitant emulsion as argued by Heron and adopted by the Examiner(s). Indeed, Heron argued that “one of skill in the art would not have expected the difference between 9.95 wt. % egg yolk lecithin (Ex. 4) and 11.7 wt. % egg yolk lecithin (Ex. 3) to produce such a difference in physical stability.” Ex. 1049 (’208 Patent Prosecution History) at 56. Such a statement is particularly appropriate to consider in the context of the Challenged Claims. According to Heron, increasing the content of emulsifier by less than 2% wt/wt (i.e., 11.7% minus 9.95%) afforded an unexpected difference in stability. Yet, as I further explain below, the Challenged Claims encompass a content of emulsifier that is

greater than the highest concentration exemplified in the '254 patent for an emulsion of aprepitant. *See* '254 patent at Table 2 (identifying 14.3% by weight Lipoid E 80).

201. In sum, given all that Heron has said regarding predicting the stability and ability to formulate aprepitant emulsions, the effect of changing amounts/concentrations of components, and particularly the expectations in the art regarding increasing emulsifier concentration, the “skeptical” POSA would expect that the '254 patent would describe the successful preparation of emulsions over the full scope of the claimed ranges (and particularly for higher contents of emulsifier) in order to demonstrate that the inventors actually possessed such emulsions. The '254 patent does not do so.

**C. The Challenged Claims allow for a much broader emulsifier content than what Heron exemplified**

202. The Challenged Claims encompass substantially greater amounts of emulsifier than the range of 11%-15% that Heron previously ascribed as being “critical” and affording “unexpected” attributes that I have described above. *See* Paragraphs 193 and 197-199, above. For example, by utilising the amount of aprepitant in claim 1 of the '254 patent (“about 0.7-0.8 wt %”) and the emulsifier to aprepitant ratio of “about 20:1 to 25:1 (wt/wt %),” simple mathematics indicates that the amount of emulsifier allowed by claim 1 is on the order of about 14% to 20% by weight (obtained by multiplying 0.7 by 20 and 0.8 by 25, respectively). Similarly,

math can be applied to the ratio of “about 23:1” in claim 22 and the ratio of “about 24:1” in claim 27 to derive amounts of emulsifier on the order of about 17 or 18 weight percent. Moreover, claims 3 and 6 explicitly recite “about 16 wt/wt %” while claims 4 and 7 explicitly recite “about 17 wt/wt %” for the emulsifier content. Importantly, each of these ranges/amounts of emulsifier exceed values beyond 15% by weight.

203. Despite the broader claimed content of emulsifier in the '254 patent, the Examiner charged with reviewing such claims provided the same rationale (reproduced below) when allowing the Challenged Claims as when allowing the '074 patent and its lesser-claimed amounts of emulsifier:

However, Zhou's ratio of emulsifier to aprepitant (the NK-1 antagonist) is below the ratio required by the claimed invention. It appears that the amount of emulsifier is critical in the claimed emulsion because, according to the instant specification, the aprepitant emulsion possess favorable stability properties when the amount of emulsifier in the oil phase is greater than the amount of oil, wherein the amount of emulsifier have been found to impart greater stability on a final emulsion compared to a similar aprepitant emulsion with the oil phase comprises emulsifier less than the claimed amount. [Instant specification, pg. 16, 0099]. For example, the instant specification provides preparation of an alternate aprepitant emulsion, wherein the ratio of aprepitant: emulsion is 1: 14.8, wherein with 4 days post preparation, crystals were observed which indicates less stable emulsion. [Instant Specification, Example 4, pg. 28].

In order to arrive at the claimed composition, one of ordinary skill in the art would have to modify

Zhou's aprepitant emulsion to increase the ratio of the emulsifier to the NK-1 receptor antagonist to about 18:1 to 22:1 (wt/wt%). However, neither Zhou's disclosure, nor this disclosure provides sufficient guidance and motivation to one of ordinary skill in the art to perform the modification to arrive at instantly claimed emulsion.

Ex. 1022 ('254 Patent Prosecution History) at 39-40.

However, Zhou's ratio of emulsifier to aprepitant (the NK-1 antagonist) is below the ratio required by the claimed invention. It appears that the amount of emulsifier is critical in the claimed emulsion because, according to the instant specification, the aprepitant emulsion possess favorable stability properties when the amount of emulsifier in the oil phase is greater than the amount of oil, wherein the amount of emulsifier have been found to impart greater stability on a final emulsion compared to a similar aprepitant emulsion with the oil phase comprises emulsifier less than the claimed amount. [Instant specification, pg. 16, 0099]. For example, the instant specification provides preparation of an alternate aprepitant emulsion, wherein the ratio of aprepitant: emulsion is 1: 14.8, wherein with 4 days post preparation, crystals were observed which indicates less stable emulsion. [Instant Specification, Example 4, pg. 28].

In order to arrive at the claimed composition, one of ordinary skill in the art would have to modify Zhou's aprepitant emulsion to increase the ratio of the emulsifier to the NK-1 receptor antagonist to about 18:1 to 22:1 (wt/wt%). However, neither Zhou's disclosure, nor this disclosure provides sufficient guidance and motivation to one of ordinary skill in the art to perform the modification to arrive at instantly claimed emulsion.

Ex. 1042 ('074 Patent Prosecution History) at 37.

204. For the sake of clarity, I want to specifically note the first aspect of the Examiner's rationale: "However, Zhou's ratio of emulsifier to aprepitant (the NK-1 antagonist) is below the ratio required by the claimed invention. It appears that the amount of emulsifier is critical to the claimed emulsion...." *Compare, e.g.,* Ex. 1022 ('254 Patent Prosecution History) at 39 *with* Ex. 1042 ('074 Patent Prosecution History) at 37 (Examiner's Reasons for Allowance).

205. Moreover, the Examiner stated: "In order to arrive at the claimed composition, one of ordinary skill in the art would have to modify Zhou's aprepitant emulsion to increase the ratio of the emulsifier to the NK-1 receptor antagonist to about 18:1 to 22:1 (wt/wt%). However, neither Zhou's disclosure, nor this disclosure provides sufficient guidance and motivation to one of ordinary skill in the art to perform the modification to arrive at instantly claimed emulsion." Ex. 1022 ('254 Patent Prosecution History) at 39-40. It bears mentioning that the claims of the '254 patent that the Examiner allowed recited different *and higher* ratios (i.e., 20:1 to 25:1) of emulsifier to aprepitant. Moreover, if the Examiner was correct in stating that "neither Zhou's disclosure, nor this disclosure provides sufficient guidance and motivation to one of ordinary skill in the art to perform the modification to arrive at instantly claimed emulsion" then it is difficult to imagine how the Challenged Claims comply with the written description or even the

enablement requirement when different ranges of emulsifier content are being claimed in each patent.

206. Despite this, the Examiner's "Freudian slip"<sup>10</sup> of acknowledging that the '254 patent's disclosure did not "provide[] sufficient guidance and motivation" for a POSA "to perform the modification to arrive at the instantly claimed emulsion" is the correct conclusion in view of the statements of Heron that I have described. The '254 patent simply contains no description that would have informed the "skeptical" POSA that the inventors possessed emulsions utilizing an amount of emulsifier that was greater than 15% or ratios of emulsifier to aprepitant that were more than 20:1.

207. As Heron placed such an emphasis on examples and results in its prior statements in support of patentability that I identified above (*see* Paragraph 194), I will begin my analysis of the '254 patent's disclosure with the aprepitant emulsions that Heron actually prepared. *See* Ex. 1001 ('254 patent) at Section IV (Examples), col. 19, line 35 to col. 32, line 45. The inventors describe the preparation of six aprepitant emulsions, providing a table of the constituents for each that I have reproduced below:

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<sup>10</sup> *See* Paragraph 203, above, for the Examiner's complete statement.

TABLE 1

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.750	0.679	1
Lipoid E 80	15.0	13.6	20
Soybean Oil	10.0	9.05	13.3
Ethanol <sup>1</sup>	8.59	7.78	11.5
Sucrose	5.60	5.07	7.5
Sodium Oleate	0.500	0.453	0.667
Water for Injection	70.0	63.4	93.3
Total	110	100	—

<sup>1</sup>Final amount after taking into account the ethanol that was evaporated during processing.

Ex. 1001 ('254 patent) at col. 20, lines 5-19.

TABLE 2

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.450	0.714	1
Lipoid E 80	9.00	14.3	20
Soybean Oil	6.00	9.52	13.3
Ethanol <sup>1</sup>	1.89	3.00	4.20
Sucrose	3.36	5.33	7.47
Sodium Oleate	0.300	0.476	0.667
Water for Injection	42.0	66.7	93.3
Total	63.0	100	—

<sup>1</sup>Final amount after taking into account the ethanol that was evaporated during processing.

Ex. 1001 ('254 patent) at col. 20, lines 53-66.

TABLE 3

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.450	0.587	1
Lipoid E 80	9.00	11.7	20
Soybean Oil	6.00	7.83	13.3
Ethanol <sup>1</sup>	3.27	4.26	7.26
Sucrose	15.6	20.4	34.7
Sodium Oleate	0.300	0.391	0.667
Water for Injection	42.0	54.8	93.3
Total	76.6	100	—

<sup>1</sup>Final amount after taking into account the ethanol that was evaporated during processing.

Ex. 1001 ('254 patent) at col. 21, lines 33-48.

TABLE 4

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.450	0.672	1
Lipoid E 80	6.67	9.95	14.8
Soybean Oil	6.00	8.96	13.3
Sucrose	3.36	5.02	7.47
Water for Injection	50.5	75.4	112
Total	67.0	100	—

Ex. 1001 ('254 patent) at col. 22, lines 11-22.

TABLE 5

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.250	0.250	1
Lipoid E 80	2.50	2.50	10
Soybean Oil	15.0	15.0	60
Oleic Acid	0.125	0.125	0.5
Water for Injection	82.1	82.1	328
Total	100	100	—

Ex. 1001 ('254 patent) at col. 22, lines 47-59.

TABLE 6

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.773	0.688	1
Dexamethasone	0.0935	0.0832	0.121
Sodium Phosphate			
Lipoid E 80	15.5	13.8	20
Soybean Oil	10.3	9.17	13.3
Ethanol <sup>1</sup>	7.31	6.51	9.47
Sucrose	5.77	5.14	7.47
Sodium Oleate	0.515	0.459	0.667
Water for Injection	72.1	64.2	93.3
Total	112	100	—

<sup>1</sup>Final amount after taking into account the ethanol that was evaporated during processing.

Ex. 1001 ('254 patent) at col. 23, lines 45-60.

208. As Tables 1-6 indicate, only one type of emulsifier was utilised in all 6 Examples of the formulated emulsions—"Lipoid E 80." The '254 patent identifies "Lipoid E 80" as an "egg lecithin." Ex. 1001 ('254 patent) at col. 19, lines 41-43. Accordingly, only a single emulsifier is exemplified in the '254 patent despite the greater scope of the Challenged Claims—which never limit the emulsifier to the single example or the particular embodiment that the inventors utilized. Given Heron's prior statements that I described in Section IX.A, above, and in particular Heron's argument that "changing the ingredients and amounts could have a cascade of effects" and the "unpredictable interactivity of the components of aprepitant emulsions" (*see* Paragraphs 191 and 193) nothing about the '254 patent's examples would indicate that the inventors possessed emulsions that utilised an emulsifier other than Lipoid E 80. There is no explanation in the '254 patent that would guide

the selection of any one emulsifier over other members in the class—despite the Handbook of Pharmaceutical Excipients identifying approximately 70 different types of emulsifying agents and emulsion stabilisers. Ex. 1024 (Handbook) at 866. These many different types of emulsifying agents and emulsion stabilisers comprise different classes of such agents whereby the mechanism of stabilisation of such agents differs depending on the class of the emulsifier.

209. Depending on the class of emulsifier, there are often sub-classifications within each class of emulsifier (with the origin of such emulsifiers being natural or synthetic). For example, where surfactants are considered as one of a general class of emulsifiers, surfactants are typically further categorised as being neutral, anionic, or cationic in nature. Thus, considering Heron’s statements regarding the “unpredictable interactivity of [] components” and how “changing the ingredients ... could have a cascade of effects” a POSA would be skeptical that the inventors of the ’254 patent possessed emulsions utilising an emulsifier other than Lipoid E 80.

210. Additionally, as Tables 1-6 above indicate, the concentration of the Lipoid E 80 emulsifier was 13.6%, 14.3%, 11.7%, 9.95%, 2.5%, and 13.8% by weight, respectively for each of Examples 1-6. However, the concentration of 9.95% and 2.5% Lipoid E 80 (in Examples 4 and 5, respectively) did not afford a stable emulsion in the particular formulations. Ex. 1001 (’254 patent) at col. 22, lines 7-9 (“Within 4 days post preparation at room temperature, crystals were observed in the

product by microscopy.”); *id.* at col. 22, lines 44-46 (same). Additionally, the inventors reported that Examples 1, 2, 3, and 6 failed to exhibit stability for more than either 2 or 3 months when stored at room temperature. Ex. 1001 (’254 patent) at col. 24, lines 4-14. Thus, none of the 6 formulation examples in the ’254 patent fully achieved the criteria for physical stability described in the patent. *See* Ex. 1001 (’254 patent) at col. 10, lines 16-21 (“An emulsion is physically stable if it meets the criteria under USP <729> and NK-1 receptor antagonist crystals are not visible upon storage at 5° C. or room temperature for a time period equal to or at least 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 6 months, 1 year or 2 years.”).

211. More importantly for my analysis, however, the ’254 patent’s Examples 1-3 and 6 only had a difference of 2.6% (w/w %) in the actual emulsifier (Lipoid E 80) -- from the lowest emulsifier concentration being 11.7% w/w % (Ex. 3) to the highest being 14.3% w/w % (Ex 2). Accordingly, each of these Examples are in the range that Heron previously argued was “critical.” *See* Paragraphs 193 and 197-199, above. However, the Challenged Claims encompass more emulsifier—amounts being 16%, 17% and even 20% by weight. The claimed values correspond to about 12%, 19%, and 40% more emulsifier than the single, highest emulsifier concentration exemplified (Example 2). Laying aside all the concerns that Heron argued a POSA would have regarding increasing the content of emulsifier and its potentially detrimental effect on stability, *see* Section IX.A, above, Heron

specifically argued that a POSA would not have expected that including “40% more” egg lecithin “would yield a physically stable aprepitant emulsion.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 45. Yet, for the Challenged Claims to satisfy written description requirements, Heron would now have to argue the opposite—that a POSA would understand that the amount of egg lecithin can be increased by “40% more” than what was explicitly demonstrated in the ’254 patent. The exemplified amounts of emulsifier provided in the ’254 patent simply do not rise to the necessary level of description that was dictated by Heron’s prior statements.

212. Lastly, the highest ratio of Lipoid E 80 emulsifier to aprepitant in each of Tables 1-6 was precisely 20:1. However, each of the Challenged Claims explicitly allow for even higher ratios. *See* Ex. 1001 (’254 patent) at claim 1 (“wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %)”), claim 22 (“wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt %)”), claim 27 (“wherein the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt %)”). There is no evidence in the ’254 patent from which a POSA would understand that such higher claimed ratios would actually afford an emulsion. Indeed, such an understanding is belied by what one of the named inventors stated: “As Dr. Han explained, “[t]he emulsion is very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 7. If “everything

is important”—including the ratio of lecithin to aprepitant—a disclosure indicating that higher ratios than those exemplified would still afford an aprepitant emulsion would be needed for a POSA to understand that the inventors actually possessed the compositions described within the Challenged Claims.

213. At best, the examples suggest a specificity or criticality of the composition of the formulations in view of the stability data reported in Table 7. They certainly do not suggest that aprepitant emulsions are robust across a broader range of different concentrations and components. When considering the Examples, only a single example of each functional formulation component is exemplified. And of the single example of each formulation component that is exemplified, even then, the ratio of the emulsifier (Lipoid E, a phospholipid), oil phase (soybean oil), aqueous phase (water), and pH modifier (sodium oleate) to aprepitant are identical, with the only differences in the other formulation components being in the ratio of tonicity agent (sucrose) and co-surfactant (ethanol) to aprepitant. This is evidenced by the following compilation which describes the ratio of the listed Formulation Component relative to the amount of aprepitant in each formulation:

<b>Functional Component</b>	<b>Exemplified Excipient</b>	<b>Table 1 (Ex. 1)</b>	<b>Table 2 (Ex. 2)</b>	<b>Table 3 (Ex. 3)</b>	<b>Table 6 (Ex. 6)</b>
Active	Aprepitant	1	1	1	1
Emulsifier	Lipoid E 80	20	20	20	20
Oil	Soybean Oil	13.3	13.3	13.3	13.3
Co-surfactant	Ethanol	11.5	4.2	7.26	9.47

Tonicity Agent	Sucrose	7.5	7.47	34.7	7.47
pH Modifier	Sodium Oleate	0.667	0.667	0.667	0.667
Aqueous Phase	Water	93.3	93.3	93.3	93.3

214. Accordingly, as there is (i) only a single exemplar excipient from each broad Functional Component category, and (ii) the ratios of 4 of the 6 exemplar excipients to aprepitant are fixed, these examples fail to convey any guidance to a POSA as to what may happen if the identity or ratios of components was altered. Given Heron's statements as to the expectations of a "skeptical" POSA, the '254 patent's examples cannot possibly convey possession of the full breadth of the Challenged Claims.

215. I have also considered remaining aspects of the '254 patent's disclosure to discern whether there is any description that would convey to a POSA that the inventors possessed the full breadth of the Challenged Claims. For example, I note that the '254 patent contains an explicit statement concerning the amount of emulsifier:

In some embodiments, the composition comprises about 10 wt/wt% to 20 wt/wt %, 12 wt/wt % to 17 wt/wt %, 13 wt/wt % to 16 wt/wt %, 13 wt/wt % to 15 wt/wt %, 14 wt/wt % to 15 wt/wt %, or 13 wt/wt % to 14 wt/wt % emulsifier. In other embodiments, the composition

comprises about 13 wt/wt %, 13.5 wt/wt %, 14 wt/wt %, 14.5 wt/wt %, 15 wt/wt %, 16 wt/wt %, 17 wt/wt %, 18 wt/wt %, 19 wt/wt % or 20 wt/wt % emulsifier.

Ex. 1001 ('254 patent) at col. 3, lines 49-56.

The amount of phospholipids, by weight, in the emulsions of the present disclosure may be within a range of about 10 wt/wt % to about 20 wt/wt %, 11 wt/wt % to 19 wt/wt %, 11 wt/wt % to 15 wt/wt %, 12 wt/wt % to 13 wt/wt %, 13 wt/wt % to 14 wt/wt %, 13 wt/wt % to 20 wt/wt %, or 12 wt/wt % to 18 wt/wt %. In certain embodiments, the phospholipids in the emulsions are at a concentration, by weight, about 11 wt/wt %, 12 wt/wt %, 12.5 wt/wt %, 13 wt/wt %, 13.5 wt/wt %, 14 wt/wt %, 14.5 wt/wt %, or 15 wt/wt %.

Ex. 1001 ('254 patent) at col. 11, lines 51-60.

216. However, “listing” something in a patent’s description and actually “conveying” something to Heron’s “skeptical” POSA through a patent’s description are two different concepts. They are also distinctly different concepts in view of the state of the art and the vantage of the POSA that Heron has described. Short of evidence of actual success across the identified ranges of weight percentages for emulsifier that are recited here, a POSA could not understand that the inventors possessed emulsions of such a ranging scope.

217. Instead, a POSA would more likely view these weight percentages from the standpoint of what was actually exemplified. Each of these ranges successively narrow until they focus on lesser values of emulsifier (e.g., 11-15% by weight). When read in context with the patent's examples, these values focus a POSA to the 11.7%, 13.6%, 13.8%, and 14.3% values the inventors exemplified. *See* Paragraph 207. Thus, rather than convey possession of apreitant emulsions having the amount of emulsifier recited in the Challenged Claims, these weight percentage ranges (when placed in perspective by the remainder of the description) would have suggested the opposite to a POSA—that it was the lesser values of emulsifier concentration that were possessed.

218. With respect to the Challenged Claims' recited ratios of emulsifier to apreitant, I note that the '254 patent contains the following statements:

In some embodiments, the ratio of emulsifier to NK-1 receptor antagonist (wt %:wt %) in the composition ranges from about 10:1 to 30:1, 10:1 to 20:1, 15:1 to 30:1, 20:1 to 25:1, 18:1 to 22:1, 19:1 to 20:1, or 10:1 to 30:1. In other embodiments, the ratio of emulsifier:NK-1 receptor antagonist (wt %:wt %) in the composition is about 10:1, 11:1, 13:1, 14:1, 15:1, 18:1, 19:1, 20:1, 21:1, 22:1 23:1, 24:1, 25:1, or 30:1.

Ex. 1001 ('254 patent) at col. 4, lines 63 to col. 5, line 3.

The ratio of emulsifier to NK-1 receptor antagonist in the final emulsion can be about 20:1 but may also vary. For example, the ratio of emulsifier:NK-1 receptor antagonist (wt %:wt%) within the oil portion ranges from about 15:1 to 30:1, 20:1 to 25:1, 18:1 to 22:1, 19:1 to 20:1, or 10:1 to 30:1. In one embodiment, the emulsifier:NK-1 receptor antagonist (wt %:wt %) is about 15:1, 18:1, 19:1, 20:1, 21:1, 22:1 or 23:1.

Ex. 1001 ('254 patent) at col. 17, lines 38-45.

219. For reasons similar to what I indicated above with respect to the listing of various weight percentages for the emulsifier, the listing of ratios as in the '254 patent does not convey possession of the ratios of emulsifier to aprepitant that are now recited in the Challenged Claims. When read in context with the patent's examples, these ratios directly focus a POSA to the 20:1 ratio. That was the only exemplified ratio and it is precisely what Heron previously identified as being "critical."

220. Moreover, there is nothing in the '254 patent that would guide a POSA to any understanding that the now claimed greater amounts of emulsifier or higher ratios of emulsifier to aprepitant were "critical" or even important for obtaining an aprepitant emulsion. However, the '254 patent is not similarly silent concerning other ratios of formulation components:

For example, in formulating an oil phase comprising aprepitant, use of an oil:aprepitant ratio of about 13:1 was surprisingly found to produce, when mixed with the water phase, an emulsion which is more stable as compared to an emulsion in which the oil phase contains an oil:aprepitant ratio of less than about 12:1 or 11:1, and/or greater than about 15:1, 20:1, or 30:1.

Ex. 1001 ('254 patent) at col. 12, lines 43-49.

Moreover, the present compositions also possess favorable stability properties when the amount of emulsifier in the oil phase is greater than the amount of oil. For example, the oil phase contains an emulsifier:oil ratio of about 5:1 to 1:1, 3:1 to 1:1 or a ratio of about 1.5:1. Such ratios of emulsifier:oil have surprisingly been found to impart greater stability on a final emulsion which is suitable for injection into a patient. For example, an aprepitant emulsion having a phospholipid:oil ratio within the oil phase of about 1.5:1 was found to have greater stability than a similar aprepitant emulsion, wherein the oil phase comprises a phospholipid:oil ratio of about 0.01:1, 0.1:1, 0.5:1 or 0.9:1.

Ex. 1001 ('254 patent) at col. 12, lines 56-67.

221. Accordingly, the inventors clearly understood how to convey the importance or criticality of these described variables yet failed to do so with respect

to the amount of emulsifier or the ratio of emulsifier to aprepitant. Thus, for all the reasons that I have explained in this declaration, the inventors did not convey possession of the full scope of the Challenged Claims to a POSA. The Challenged Claims therefore fail to satisfy the written description requirement.

### **X. GROUND 3: LACK OF ENABLEMENT**

222. In this section, I explain why claims 1-30 of the '254 patent are not enabled across their full scope. In order to enable the full scope of claims 1-30, the specification must teach a POSA how to prepare aprepitant emulsions having an emulsifier concentration of greater than 14% (and as much as 20%) by weight as well as teach how to prepare such emulsions utilising a ratio of emulsifier to aprepitant that is greater than 20:1 (and as much as 25:1). *See* Paragraphs 27-30 (discussing the standards for enablement). In my opinion, claims 1-30 are either obvious or not enabled by the '254 patent.

223. Many of the statements by Heron, or on its behalf, that I identified in Section IX.A, above, also speak directly to the factors that are considered when determining if a patent enables the full scope of its claims. Although I do not want to be repetitive, I have grouped some of the more salient statements under the corresponding factor for enablement below.

A. **The quantity of experimentation necessary to practice the full scope of the Challenged Claims**

224. To obtain an aprepitant emulsion, Heron argued that doing so would require numerous “trial-and-error” experiments:

- “Many experiments resulted in crystals and/or phase separations (creaming, flocculation), among other failures. And the inventors explained that numerous experiments were necessary to obtain a stable product.” Ex. 1020 (Heron Opening Post-Trial Brief) at 7 (internal citations omitted).
- “The emulsion is very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion. And Tom and I – Tom and I came up with this together through a lot of trial-and-error experiments.” Ex. 1034 (Day 2 AM) at 508:6-11 (inventor testifying).
- “That you would go up like that is not something somebody would be thinking of in terms of routine optimization. It’s anything but routine, in my opinion.” Ex. 1032 (Day 4 AM) at 1283:13-16.

225. In sum, many variables such as the specific components and specific ratios must be manipulated in a trial-and-error fashion in order to determine if an emulsion could be prepared. According to one of the inventors, “everything is important.” Moreover, “numerous experiments were necessary.” And with respect

to the particular amount of emulsifier or the ratio of emulsifier to aprepitant in the Challenged Claims, Heron's prior expert alleged that increasing the amount of emulsifier (and, in effect, the ratio of emulsifier to aprepitant) was not "routine optimization." Ex. 1032 (Day 4 AM) at 1283:13-16. Such optimization is no less routine to advance beyond the exemplified amounts in Heron's own patents than it is to advance from the amounts exemplified in the prior art (e.g., Zhou (Ex. 1003)) in view of the teachings I discussed regarding obviousness in Section VIII, above.

226. Thus, and particularly in view of Heron's prior arguments, the quantity of experimentation necessary to practice the full scope of the Challenged Claims does not weigh in favor of enablement if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Accordingly, if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then my opinion concerning the quantity of experimentation needed to practice the full scope of the claims would reflect Heron's arguments and reinforce a finding of lack of enablement.

**B. The amount of direction or guidance presented for practicing the full scope of the Challenged Claims**

227. In Section IX.C, above, I discussed the limited amount of direction and guidance presented in the '254 patent as it pertained to both the emulsifier content as well as the ratio of emulsifier to aprepitant. This analysis applies equally here.

As a summary, it was my opinion that the statements regarding the amount of emulsifier and the ratio of emulsifier to aprepitant described within the specification of the '254 patent would not have guided a POSA to the higher amounts and ratios that are encompassed by the Challenged Claims. Moreover, I noted that the absence of guidance with respect to the emulsifier and ratio of emulsifier to aprepitant was at odds with guidance provided for the ratios of oil to aprepitant and emulsifier to oil. *See* Paragraphs 220-221, above (discussing the disparate treatment of component ratios).

228. In view of Heron's prior arguments regarding the difficulties in formulating aprepitant and the complexity of emulsion formulations, this factor weighs against a finding of enablement if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Furthermore, the absence of guidance in the '254 patent concerning the higher amounts of emulsifier and the greater ratios of emulsifier to aprepitant that are now claimed also weighs against a finding of enablement if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Accordingly, if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then my opinions would reflect Heron's assertions and reinforce a finding of lack of enablement.

**C. The presence or absence of working examples**

229. In Section IX.C, above, I discussed the lack of guidance provided by the exemplified aprepitant emulsions as they pertained to the amounts of emulsifier and ratios of emulsifier to aprepitant encompassed by the Challenged Claims. This analysis applies equally here. As a summary, it was my opinion that the examples, which at most utilised 14.3% by weight of a single emulsifier (see Example 2) — Lipoid E 80—and at most utilised a 20:1 ratio of Lipoid E 80 to aprepitant (see Examples 1-3 and 6) failed to provide any guidance to a POSA regarding the potential preparation of aprepitant emulsions containing the un-exemplified amounts and ratios that are encompassed by the Challenged Claims.

230. Given Heron's assertions about the difficulties in formulating aprepitant and the complexity of emulsion formulations, the absence of examples over the full scope of the Challenged Claims weighs against a finding of enablement if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Accordingly, if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then my opinion concerning the absence of examples over the full scope of the claims would reflect Heron's assertions and reinforce a finding of lack of enablement.

**D. The nature of the Challenged Claims**

231. Each of claims 1-30 relate to an injectable pharmaceutical emulsion containing aprepitant. Heron has made numerous allegations that cast considerable doubt upon the ability of the '254 patent to enable the full scope of the claimed emulsifier and ratios of emulsifier to aprepitant:

- “[A]prepitant was widely understood to be very difficult to formulate for intravenous use, and an emulsion was ‘one of the more complex formulation strategies,’ so the POSA would be ‘adding complexity’, further detracting from any reasonable expectation of success.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 44 (internal citations omitted).
- “A POSA would have had no expectation that a physically stable intravenous aprepitant emulsion formulation could be made and used safely. Intravenous emulsion formulations were reported in the prior art to be difficult to develop, and the prior art attempts at developing an intravenous aprepitant emulsion were not successful.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 54-55.
- “[T]he inventors developed a novel emulsion containing *specific ingredients at specific concentrations—including an unusually high amount of egg yolk lecithin as an emulsifier*—to achieve a stable IV formulations that

permits injection into humans.” Ex. 1026 (Heron’s Opening Statement) at 6 (footnote omitted).

- “In contrast, Heron succeeded in developing a stable intravenous aprepitant emulsion by using *an unprecedented amount (14%) of the emulsifier egg lecithin in combination with other specific ingredients at specific concentrations and conditions.*” Ex. 1020 (Heron Opening Post-Trial Brief) at 1.
- “The amount of lecithin, in combination with other ingredients, was ultimately critical for the developing [sic] a stable product.” Ex. 1020 (Heron Opening Post-Trial Brief) at 7 n.1.

232. The Challenged Claims encompass a drug Heron considered “to be very difficult to formulate for intravenous use” and recite a “complex” formulation that extends in scope well-beyond the “specific ingredients” and “specific concentrations and conditions” that resulted in a stable intravenous aprepitant emulsion. Given Heron’s assertions about the difficulties in formulating aprepitant and the complexity of emulsion formulations, the nature of the claimed emulsions weight against a finding of enablement if the claims of the ’254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Accordingly, if the claims of the ’254 patent are deemed non-obvious, in contradiction to my opinions in

Section VIII, then my opinion of the nature of the claimed emulsions would reflect Heron's assertions and reinforce a finding of lack of enablement.

**E. The state of the prior art**

233. Heron has previously made numerous allegations that cast considerable doubt upon the ability of the '254 patent to enable the full scope of the claimed emulsifier and ratios of emulsifier to aprepitant in view of the state of the art:

- After over 20 years of industry failure, a POSA would have been skeptical of an aprepitant emulsion being stable and safe for intravenous use.” Ex. 1020 (Heron's Opening Post-Trial Brief) at 44.
- “Aprepitant has characteristics of ‘cement dust’ with high crystallinity and low solubility, and because of aprepitant's poor physical characteristics, an intravenous formulation of aprepitant was considered impossible.” Ex. 1020 (Heron's Opening Post-Trial Brief) at 53.
- “As of September 2014, any attempt to develop an intravenous aprepitant product was considered a failure.” Ex. 1020 (Heron's Opening Post-Trial Brief) at 54.
- “A POSA would have had no expectation that a physically stable intravenous aprepitant formulation could be made and used safely. Intravenous emulsion formulations were reported in the prior art to be difficult to develop, and *the*

*prior art attempts at developing an intravenous aprepitant emulsion were not successful.*” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 54-55.

- “[N]o prior art emulsion ever had the claimed combination of ingredients, or anything close to the high amount of emulsifier of 14% lecithin.” Ex. 1020 (Heron Opening Post-Trial Brief) at 4.
- “In a departure from all prior conventions, Heron’s intravenous NK-1 receptor antagonist program experimented with an amount of emulsifier that went far beyond anything in the prior art.” Ex. 1020 (Heron Opening Post-Trial Brief) at 7 (internal citations omitted).
- “Additionally, the prior art undisputedly showed that increasing an emulsifier could cause stability issues, that adding sodium oleate to emulsions could cause hemolysis, and that emulsions are complex systems in which changing ingredients and their amounts could have a cascade of effects.” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 44-45 (internal citations omitted).

234. Given Heron’s assertions about the difficulties in formulating aprepitant and the complexity of emulsion formulations, Heron’s own view of the state of the art weighs against a finding of enablement if the claims of the ’254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Accordingly, if the claims of the ’254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then I would assume that Heron’s

assertions are correct and this would reinforce my opinion that the full scope of the claims is not enabled.

**F. The relative skill of those in the art**

235. In paragraph 32, above, I provided Heron's definition of a POSA. This level of "ordinary skill" is broadly consistent with the formulation development activities in an industrial setting. Heron's definition of a POSA allows a person to only have the educational level of a bachelor's degree and three years of formulation experience that is not necessarily related to emulsion formulations or even parenteral formulations. Such an individual would require substantial guidance and direction.

236. Given Heron's assertions about the difficulties in formulating aprepitant and the complexity of emulsion formulations, the level of skill as described for a POSA weighs against a finding of enablement if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Accordingly, if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then my opinions would reflect Heron's assertions and, in conjunction with the level of skill in the art and the amount of guidance and direction such an individual would require, would reinforce a finding of lack of enablement.

**G. The unpredictability of preparing aprepitant emulsions**

237. Heron has made numerous arguments concerning the unpredictability of preparing an aprepitant emulsion and the unexpected nature of formulations containing less than the full scope of emulsifier or ratio of emulsifier to aprepitant that is now claimed. See Section IX.A, above. In order to avoid being overly repetitive, I have identified some of the more salient statements below:

- “[T]he emulsifier concentration window is tight. And afterwards you quickly – emulsion stability quickly declines. And at high emulsifier concentrations, emulsion instability occurs because of rapid coalescence.” Ex. 1033 (Closing Arguments) at 77:2-8 (Heron’s Counsel).
- “As Dr. Han explained, ‘[t]he emulsion is very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion.’” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 7.
- “Additionally, the prior art undisputedly showed that increasing an emulsifier could cause stability issues, that adding sodium oleate to emulsions could cause hemolysis, and that *emulsions are complex systems in which changing ingredients and their amounts could have a cascade of effects.*” Ex. 1020 (Heron’s Opening Post-Trial Brief) at 44-45 (internal citations omitted).
- “[E]vidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious,’ and the evidence in this case

shows that aprepitant emulsion are just such a system....” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 8 (internal citations omitted).

- “[E]mulsions, in particular, were one of the more complex formulation strategies in which changing ingredients and amounts could have a cascade of effects.” Ex. 1027 (Heron’s Responsive Post-Trial Brief) at 20.
- “Assuming that one of ordinary skill in the art would be motivated to modify the amount of the emulsifier to be within the range as recited in claims 1 [i.e., 11%-15% wt/wt], ***the results are unpredictable with respect to, for example, stability.... The improved stability cannot be predicted.*** See the Ottoboni Declaration, ¶9.” Ex. 1039 (’742 Patent Prosecution History) at 45.

238. Given Heron’s assertions about the difficulties in formulating aprepitant, the complexity of emulsion formulations, and the unpredictable changes that result from altering the identity of one component or even the amount of one component, the Challenged Claims’ encompassing even higher emulsifier content and ratios of emulsifier to aprepitant than the previously identified “critical” and “unexpected” level weighs against a finding of enablement if the claims of the ’254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Moreover, if the claims of the ’254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then my opinion on the unpredictability of preparing

aprepitant emulsions would reflect Heron's assertions and reinforce a finding of lack of enablement.

#### **H. The breadth of the Challenged Claims**

239. Section IX.B, above, explained why the Challenged Claims encompass much greater amounts of emulsifier than the range of 11%-15% that Heron previously ascribed as being "critical" and affording "unexpected" attributes during the prosecution of the patent application that led to the '742 patent. Such additional breadth of emulsifier content in the '254 patent's claims is particularly problematic for enablement in view of Heron's statements concerning the destabilisation of emulsions that was allegedly expected to occur upon increasing emulsifier content. I have identified those statements in Paragraphs 187 and 189, above.

240. Given Heron's assertions about the difficulties in formulating aprepitant and the complexity of emulsion formulations, the Challenged Claims' encompassing of even higher emulsifier content and ratios of emulsifier to aprepitant than the previously identified "critical" and "unexpected" level weighs against a finding of enablement if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII. Moreover, if the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then my opinion concerning the breadth of the Challenged Claims would reflect Heron's assertions and reinforce a finding of lack of enablement.

## **I. Summary of the enablement factors**

241. Given Heron's statements regarding the inter-relatedness of the components and amounts in an emulsion formulation, a POSA would need to engage in trial-and-error experimentation to evaluate the preparation of aprepitant emulsions over the full scope of the Challenged Claims with little guidance or direction being provided from the specification or any of the Examples for reasons I have identified. If the claims of the '254 patent are deemed non-obvious, in contradiction to my opinions in Section VIII, then such experimentation would be "undue."

242. To illustrate such experimentation, a factorial design is a commonly practiced strategy by a formulations scientist might evaluate multiple independent variables. When each component itself may have various concentration values, the number of experiments to evaluate all conditions is equal to the number of values of each component times the number of components.

243. In the Challenged Claims, at least five components are identified—(1) aprepitant, (2) emulsifier, (3) oil, (4) co-surfactant, and (5) water.<sup>11</sup> If one was to

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<sup>11</sup> Certain claims further identify an "osmotic agent" (e.g., claims 13-15) and a "pH modifier" (e.g., claims 16-17) as formulation components. Such components were also included in the Examples. *See* Paragraphs 207 and 213. Such components, if

only analyse each of the 5 components described in weight percentages measured to one decimal place, then the number of values for aprepitant would be 2 (i.e. 0.7% and 0.8%). If one did the same for the emulsifier and only considered the range of 14%-20% by weight, there would be 60 values multiplied by every type of emulsifier to consider (i.e. 14.0%, 14.1%, 14.2%, etc.). The components and values continue to multiply for each type and quantity of oil and co-surfactant or quantity of water that is evaluated. Conservatively speaking, I would estimate that it would require a prohibitively large number of experiments to explore the full scope of emulsifier content encompassed by the Challenged Claims, even if only a fraction of components (e.g., emulsifiers, oils, co-surfactants) and values (e.g., to one decimal place by weight percent) are evaluated. The '254 patent, in contrast, reports 6 individual experiments (using emulsifier concentrations lower than presently claimed). Moreover, none of these experiments exhibited stability over the full range of conditions contemplated by the '254 patent. Accordingly, these experiments are not representative of the full scope of the Challenged Claims—let alone the full scope of the emulsifier content that is claimed.

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present in the formulation, would receive considerations similar to what I am discussing in this paragraph.

244. I estimate that to conduct the necessary experiments across the full scope of the Challenged Claims it would require many months to evaluate, especially if considering aspects of stability. In my opinion, such experimentation would be undue. That is particularly so when, as I indicate in Paragraphs 224-240, above, none of the factors that I have considered weigh in favor of finding that the full scope of the Challenged Claims is enabled by the '254 patent.

### **XI. CONCLUSION**

245. For the reasons described above, a POSA would have found claims 1-30 of the '254 patent obvious over Zhou in view of Washington, Bagwe, and Weng. Moreover, a POSA would have also found claims 1-30 of the '254 patent invalid for failing to satisfy the written description and enablement standards.

246. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 26 Feb 2025

By: William Charman

William Charman, Ph.D.

# Exhibit A

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**Curriculum Vitae: William N. Charman AO, BPharm, PhD, FAAPS, DSc (Hon), FRPharmS (Hon), FFIP**

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Bill Charman was appointed an Emeritus Sir John Monash Distinguished Professor at Monash University in Melbourne, Australia upon his retirement in 2024. He was previously the Dean, Faculty of Pharmacy and Pharmaceutical Sciences at Monash University (1/2007-5/2019); the Founding Director of the Monash Institute of Pharmaceutical Sciences (1/2007-4/2017); Chair of the International Pharmaceutical Federation (FIP) Education Program (FIPeD) and a member of the FIP Board of Directors in The Hague, The Netherlands (8/2015-4/2020).

He was appointed an Officer of the Order of Australia (AO), one of Australia's highest civilian honours, by the Governor-General in the 2021 Australia Day Honours List (26 January, 2021). Instituted in 1975 by Queen Elizabeth II, the award is "an Australian society honour for according recognition to Australian citizens and other persons for achievement or meritorious service."

He received his B Pharm from the Victorian College of Pharmacy (now Monash University) in 1981, his PhD in pharmaceutical chemistry (with honours) from the University of Kansas in 1985, and a DSc (*honoris causa*) from the University of London in 2011. He was appointed as the seventh Sir John Monash Distinguished Professor in 2011 (the University's most prestigious title conferred to Professors of exceptional distinction who have made high-level and sustained contributions to their discipline, the University and the community).

During his term as Dean, Bill led the strategic redevelopment of the Faculty's education, staffing, research profile and campus infrastructure. Major initiatives include new curricula supported by Faculty-designed education innovations and establishment of the Monash Institute of Pharmaceutical Sciences (MIPS). He led the formation of the "PharmAlliance" partnership to undertake major education, research and professional engagement projects with the Schools of Pharmacy at the University of North Carolina at Chapel Hill and University College London.

As Dean, he was responsible for approximately 100 academic and professional staff and 260 full time research-only staff; 2,000 students in pharmacy and pharmaceutical sciences undergraduate course programs and 240 students in the PhD program.

The average annual QS World University Subject Rankings during 2015 to 2020 (in the pharmacy and pharmacology discipline) ranked Monash University as the number one program in Australia, the number one program in the AsiaPacific, and top three worldwide. During this period, Monash was the number one ranked University pharmacy program in the world.

As Chair of FIPeD, he positioned education as one of the three defining pillars of FIP (through changes to the FIP Statutes) and a driver of change of the international pharmaceutical workforce. Under his leadership, the First Global Conference on Pharmacy and Pharmaceutical Sciences Education held in Nanjing in November 2016 (sponsored by FIP in conjunction with the Chinese Pharmaceutical Association) charted an ambitious pathway of education reform in the context of contemporary workforce development goals to support a needs-based approach to health workforce development.

His research has been characterised by a multidisciplinary and collaborative approach to address major issues in drug discovery (especially for neglected diseases such as malaria), drug delivery and the pharmaceutical sciences. His research has helped develop new areas of discovery and inquiry, new areas of inter-disciplinary collaboration for the pharmaceutical sciences, and he has pioneered major advances in discovery science and drug delivery technologies. He has published more than 370 scientific papers and communications (h-index = 77; >24,000 citations) and given over 200 invited

national and international presentations. Highlights include leading the establishment of the Centre for Drug Candidate Optimisation; founding the Monash Institute of Pharmaceutical Sciences; co-founding Acrux Limited that commercialised Evamist® and Axiron®; collaborative design of one approved anti-malarial medicine (OZ277, Synriam® which is approved for treatment in India and 7 African countries) and three anti-malarial drug candidates including OZ439 (artefenomel) in Phase 2b clinical trials as a single oral dose cure<sup>1</sup>; and establishing numerous basic and translational research programs in drug delivery with international pharmaceutical companies.

He received the GlaxoWellcome International Achievement Award from the Pharmaceutical Society of Great Britain in 1999; Drug Discovery Project of the Year awards from the Medicines for Malaria Venture (Geneva, Switzerland) in 2001, 2006, 2007 and 2010; Australasian Pharmaceutical Sciences Association Medal in 2005; Controlled Release Society International Career Achievement in Oral Drug Delivery Award in 2006; the International Pharmaceutical Federation Pharmaceutical Sciences World Congress Research Achievement Award in 2007. He was elected a Fellow of the American Association of Pharmaceutical Scientists in 2002. In 2013, he received the Australian Business Higher Education Round Table (B-HERT) awards for Best Research and Development Collaboration, and Outstanding Excellence in Collaboration. In 2014, he received the International Pharmaceutical Federation Lifetime Achievement Award in Pharmaceutical Sciences, and in 2015 the Asian Federation of Pharmaceutical Sciences Nagai Distinguished Scientist Award. In 2015/2016/2018, he was recognised by Thomson Reuters/Clarivate Analytics as a HiCi researcher in Pharmacology and Toxicology which recognises those in the top 1% of their field by impact-based citation analysis over the preceding 10 year periods. He was awarded an Honorary Fellowship by the Royal Pharmaceutical Society (FRPharmS (Hon)) in 2017; and a Fellowship by the International Pharmaceutical Federation (FFIP) in 2020. He led the team that received a 2020 Grand Gold Award from the Council for Advancement and Support of Education (CASE, Washington, DC) for the Faculty's World War One "Five Soldiers" Remembrance Project and Posthumous Award Ceremony. In 2020, he was the first recipient of the Kamal K. Midha award for Exceptional Leadership awarded by the International Pharmaceutical Federation. In 2022, he received the Takeru and Aya Higuchi Memorial Award and an International Fellowship from The Academy of Pharmaceutical Sciences and Technology, Japan.

Previously, he was Chairman (2006-2010) of the Wellcome Trust Seeding Drug Discovery Funding Committee (a £210M early stage drug discovery initiative over 10 years); a member (2005-2011) of the Expert Scientific Advisory Committee of the Medicines for Malaria Venture ([www.mmv.org](http://www.mmv.org)); an advisor to the World Health Organisation; and a Chair/member of Scientific Advisory Boards and two Corporate Boards.

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<sup>1</sup> In his 2008 speech to the United Nations on the Millennium Development Goals, Bill Gates highlighted this pioneering medical advance stating "In early animal studies, a single dose of this drug cured malaria – something we've never seen before."

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<b>Full Name</b>	William Neil Charman
<b>E-mail</b>	bill.charman@monash.edu
<b>Birthplace</b>	Melbourne, Australia

### Academic Qualifications

1978-1980	Victorian College of Pharmacy, Melbourne, Australia. B Pharm degree awarded May, 1981
1981-1982	Victorian College of Pharmacy. Completion of the Australian requirement of the Takeru Higuchi Intersearch Ph.D program. <sup>2</sup> Advisors: Prof. Barry L. Reed and Dr. Barrie C. Finnin
1983-1985	Dept of Pharmaceutical Chemistry, The University of Kansas, USA. Completion of the USA requirement of the Takeru Higuchi Intersearch Ph.D. program. <sup>1</sup> Advisor: Prof. Valentino J. Stella. Ph.D degree awarded (with honours) by The University of Kansas, May, 1986  Graduate coursework completed (GPA 4.0/4.0): Chemical dynamics, Spectroscopy and structure identification, Principals of organic chemical reactions, Stereochemistry and conformation, Advanced chemical thermodynamics, Physical organic chemistry, Pharmaceutical analysis, Mechanisms of drug deterioration and stabilisation, Pharmaceutical equilibria and diffusion, Advanced topics in biopharmaceutics and pharmacokinetics
2011	Doctor of Science degree ( <i>honoris causa</i> ), The University of London.

### Professional Appointments

1983 -1985	Graduate Research Assistant, University of Kansas, Lawrence, KS, USA
1986 -1987	Senior Research Scientist, Dept of Pharmaceutical Sciences, Sterling-Winthrop Research Institute, Division of Sterling Drug Inc., Rensselaer, NY, USA
1988	Group Leader, Dept of Pharmaceutical Sciences, Sterling-Winthrop Research Institute, Division of Sterling Drug Inc., Rensselaer, NY, USA
1989 - 1995	Senior Lecturer in Pharmaceutics, Department of Pharmaceutics, Victorian College of Pharmacy, Monash University, Melbourne, Australia
6/95 - 12/06	Personal Chair as Professor of Pharmaceutics, Victorian College of Pharmacy, Monash University, Melbourne, Australia
11/97 - 12/05	Member, Board of Directors; Member, Audit Committee, Sigma Company Limited
4/99 - 4/03	Co-Founder and Member, Board of Directors, Acrux Limited, Melbourne, Australia
3/99 - 3/02	Associate Dean (Research), Victorian College of Pharmacy, Monash University
3/99 - 11/02	Member of Steering Committee, Drug Discovery Research Program, UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR), World Health Organisation, Geneva, Switzerland
4/00 - 4/04	Member, Scientific Advisory Board, Lipocine Inc, USA
10/02 - 12/06	Director, Centre for Drug Candidate Optimisation, Victorian College of Pharmacy, Monash University, Australia

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<sup>2</sup> The Takeru Higuchi Intersearch Ph.D. program is a Doctor of Philosophy degree conducted jointly by the Victorian College of Pharmacy (Australia) and The University of Kansas (USA)

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- 3/03 - 9/05 Member of Chemotherapy Portfolio Review Committee, UNDP/World Bank/ WHO Special Program for Research and Training in Tropical Diseases (TDR), World Health Organisation, Geneva, Switzerland
- 7/03 - 12/08 Associate Editor, *Journal of Pharmaceutical Sciences*
- 8/03 - 5/06 Member, Scientific Advisory Board, Acrux Limited
- 11/05 - 7/11 Member, Expert Scientific Advisory Committee, Medicines for Malaria Venture, Geneva
- 4/06 - 12/10 Chair, Seeding Drug Discovery Funding Committee, Wellcome Trust, London
- 6/06 - 6/11 Board Member of LTS Academy, LTS Lohmann Therapie-Systeme, Germany
- 1/07 - 7/19 Dean, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University
- 1/07 - 4/17 Director, Monash Institute of Pharmaceutical Sciences, Monash University
- 6/08 - 6/14 Board Member of Scientific Committee, Fondation Gattefosse, Lyon, France
- 12/10 - 10/12 Member, Pharmaceutical Sciences Scientific Advisory Panel, Pfizer Inc, New York, USA
- 1/11 - 9/24 Appointed the seventh Sir John Monash Distinguished Professor at Monash University
- 11/12 - 3/18 Chair, Pharmaceutical Sciences Scientific Advisory Panel, Pfizer Inc, New York, USA
- 4/18 - 4/20 Member, Pharmaceutical Sciences Scientific Advisory Panel, Pfizer Inc, New York, USA
- 1/15 - 5/18 Member, Premier's Award for Health and Medical Research Selection Panel, Victorian Government
- 3/15 - 4/17 Member, Steering Committee of \$80M venture catalyst between Monash University and The University of Melbourne to support drug discovery/biomedical translation
- 8/15 - 8/17 Chair, FIP Education Executive Committee (umbrella directorate of the International Pharmaceutical Federation's (FIP) Education Initiatives, including projects and partnerships with the WHO and UNESCO, working to stimulate transformational change in pharmaceutical education and pharmaceutical workforce development) by appointment of the FIP Bureau
- 3/17 - 9/18 Visiting Professor, School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore
- 6/17 - 6/19 Member, Project Mercury Implementation and Relationship Group (to provide high level guidance regarding major collaborative research opportunities between Monash University and The University of Melbourne)
- 8/17 - 12/18 Member, Scientific Advisory Board, Glyph Biosciences (subsidiary of PureTech Health)
- 9/17 - 4/20 Chair, International Pharmaceutical Federation (FIP) Education Executive Committee; Member of FIP Executive Committee and Member of FIP Bureau (Board of Directors) for the term 2017-2021 ratified by the FIP Council meeting in Seoul, Korea
- 1/18 - 4/20 Director, World War One Remembrance Project, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University
- 3/18 - 4/20 Member, Steering Board, Eshelman Institute for Innovation, University of North Carolina at Chapel Hill, North Carolina, USA
- 8/18 - 10/21 Adjunct Professor, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, USA
- 7/19 - 7/23 Member, Scientific Advisory Board, ARC Industrial Transformation Training Center for Fragment-based Drug Design
- 8/19 - 8/23 Board Member, Monash Research Management Shenzhen Company Limited
- 3/20 - 3/23 Board Member, Med Aditus International Inc
- 7/20 - 5/21 Senior Advisor, Senior Vice Provost (Research), Monash University
- 9/20 - 8/22 Chair, Collaboration Council, Australian National Fabrication Facility Victorian Node (ANFF-VIC), the Melbourne Centre for Nanofabrication (nanomelbourne.org)
- 6/21 - 4/24 Senior Advisor, Deputy Vice Chancellor (Research), Monash University
- 6/21 - 2/24 Member, Scientific Advisory Group, mRNA Victoria

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### Professional Affiliations and Service

- American Association of Pharmaceutical Scientists (charter member)
- Australian Pharmaceutical Sciences Association (member)
- Pharmaceutical Society of Australia (member)
- North Eastern USA Regional Pharmaceutics Association Executive Committee (1985-1989)
- Reviewer for various scientific journals
- Examiner of post-graduate MSc and PhD theses
- External PhD viva examiner in the UK and The Netherlands
- Member of Scientific Committee CRS/APSA Conference entitled Advances in Delivery of Therapeutic and Diagnostic Agents, Sydney, December, 1992
- Co-Editor, Physicochemical Data Section, Australian Pharmaceutical Formulary, 1994
- Chair of Scientific and Program Committees, Member of Organising Committee - APSA 1996, Stability Testing and Prediction, Melbourne, December, 1996
- Member, Program Committee, Drug Information Association, Australia (1998-1999)
- Program Chair, 1999 Annual Gattefosse Symposium, St Remy, France, June, 1999
- Member, Editorial Advisory Board, *International Journal of Pharmaceutics* (1999 - 2012)
- Member, Editorial Advisory Board, *Journal of Pharmaceutical Sciences* (2000 - 2011)
- Member, Editorial Advisory Board, *Journal of Pharmacy and Pharmacology* (2000 - 2012)
- Member, Editorial Advisory Board, *Die Pharmazie* (2001- 2015)
- Member, Editorial Advisory Board, *Experimental Parasitology* (2005 -2010)
- Program Chair, Dissolution 99: Practical Applications and Regulatory Considerations, RACI Pharmaceutical Sciences Symposium, Melbourne, July, 1999
- Member, Scientific and Planning Committee, World Conference on Drug Absorption and Drug Delivery, EUFEPS, Copenhagen, June, 2001
- Chair, Scientific and Program Committees, APSA 2001, Drug Development - Making the most of your molecule, Melbourne, December, 2001
- Award selection panel for the 2008 Maurice-Marie Janot Award, APGI/APV International Conference of Pharmaceutical Technology, Barcelona, Spain
- Co-Chair, Strengthening the Academy Taskforce, Monash University, 2010
- Chair, 2010 Accreditation Review, Faculty of Pharmacy, University of Sydney
- Member, Expenditure Review Committee, Monash University, 2010-2012
- Chair, 2011 Uppsala University (Sweden) Research Quality Review (Faculty of Pharmacy)
- Chair, Program Committee, 2014 FIP Pharmaceutical Sciences World Congress, Melbourne
- Chair, Pharmacy and Pharmacology Review Panel, The University of Sydney 2016
- Chair, 50<sup>th</sup> Anniversary of the Jourenees Galeniques of St Remy de Provence, Gattefosse Corporation, France, June 2016
- Overseas Expert of the Accreditation Panel cum Visiting Team, Pharmacy and Poison Board Hong Kong, for the Chinese University of Hong Kong and The University of Hong Kong Bachelor of Pharmacy programs (2016 – 2022)

### Honours and Awards

- 1981 Pharmaceutical Society of Australia Research Scholarship
- 1982 Recipient of a Harry Braithwaite Memorial Scholarship
- 1985 M.Sc degree (non-thesis) awarded with honours (University of Kansas)
- 1986 Ph.D degree awarded with honours (University of Kansas)
- 1995 First appointee under Monash University's accelerated promotion to a personal chair
- 1999 Recipient of The GlaxoWellcome International Achievement Award in Pharmaceutical Sciences awarded by the Pharmaceutical Society of Great Britain

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- 2001 Medicines for Malaria Venture (Geneva, Switzerland) Drug Discovery Project of the Year for 2001 for a collaborative drug discovery project between Monash University, The University of Nebraska, Swiss Tropical Institute and F. Hoffman–La Roche (Basle)
- 2003 Co-author of paper awarded the 2003 Post-doctoral award (Dr. A-M. Kaukonen) from the Controlled Release Society and Pfizer/Capsugel
- 2003 Elected to Fellowship status of the American Association of Pharmaceutical Scientists
- 2004 Research paper published in *Nature* which was described by *Nature* as an “Object lesson in drug development” and listed by Chemical and Engineering News (USA) as one the “Chemistry Highlights of 2004”
- 2005 Australasian Pharmaceutical Sciences Association Medallist
- 2006 Career Achievement Award in Oral Drug Delivery, Controlled Release Society, USA
- 2006 Medicines for Malaria Venture (Geneva, Switzerland) Drug Discovery Project of the Year for 2006 for a collaborative drug discovery project between Monash University, The University of Nebraska, Swiss Tropical Institute and F. Hoffman–La Roche (Basle)
- 2007 International Pharmaceutical Federation (FIP) Pharmaceutical Sciences World Congress Research Achievement Award
- 2007 Medicines for Malaria Venture (Geneva, Switzerland) Drug Discovery Project of the Year for 2006 for a collaborative drug discovery project between Griffith University, Queensland Institute of Medical Research and Monash University
- 2010 Medicines for Malaria Venture (Geneva, Switzerland) Drug Discovery Project of the Year for 2006 for a collaborative drug discovery project between Southwestern Medical Centre (Dallas, TX), University of Washington (Seattle, WA) and Monash University
- 2011 Doctor of Science (*honoris causa*), School of Pharmacy, University of London, UK
- 2011 Appointed as Monash University’s eighth Sir John Monash Distinguished Professor
- 2013 Australian Business Higher Education Round Table (B-HERT) award for Best Research and Development Collaboration (MIPS and GSK Centre for Pharmaceutical Innovation)
- 2013 Australian Business Higher Education Round Table (B-HERT) award for Outstanding Excellence in Collaboration (MIPS and GSK Centre for Pharmaceutical Innovation)
- 2014 International Pharmaceutical Federation (FIP) Lifetime Achievement Award in Pharmaceutical Sciences
- 2015 Asian Federation of Pharmaceutical Sciences Nagai Distinguished Scientist Award
- 2015 Thomson Reuters HiCi (highly cited) researcher in the field of Pharmacology and Toxicology (determined from citation analysis for the period 2004-2013, for papers that rank within the top 1% of the most cited papers in the subject field and year of publication)
- 2016 Clarivate Analytics HiCi (highly cited) researcher in the field of Pharmacology and Toxicology (determined from citation analysis for the period 2005-2014, for papers that rank within the top 1% of the most cited papers in the subject field and year of publication)
- 2017 Honorary Fellowship of the Royal Pharmaceutical Society (FRPharmS (Hon)), United Kingdom
- 2018 Graduation commencement speaker, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill
- 2018 Clarivate Analytics HiCi (highly cited) researcher in the field of Pharmacology and Toxicology (determined from citation analysis for the period 2007-2016, for papers that rank within the top 1% of the most cited papers in the subject field and year of publication)
- 2019 Varro E. Tyler Distinguished Lectureship, College of Pharmacy, Purdue University, West Lafayette, Indiana, USA
- 2019 Barry L. Reed Distinguished Lectureship, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia
- 2020 Grand Gold Award, CASE (Council for Advancement and Support of Education, Washington, DC, USA) Circle of Excellence Award (Special Events | Single-Day Events) for World War One “Five Soldiers” Remembrance Project and Posthumous Award Ceremony

- 2020 Inaugural recipient of the Kamal K. Midha award for Exceptional Leadership, International Pharmaceutical Federation, The Hague, The Netherlands
- 2020 Fellowship, International Pharmaceutical Federation (FFIP), The Hague, The Netherlands
- 2021 Appointed an Officer of the Order of Australia (AO), General Division, by the Governor-General in the 2021 Australia Day Honours List for “Distinguished service to tertiary education, particularly to the pharmaceutical sciences, and to professional organisations”
- 2022 Takeru and Aya Higuchi Memorial Lectureship Award, Academy of Pharmaceutical Sciences and Technology, Japan
- 2022 International Fellow, Academy of Pharmaceutical Sciences and Technology, Japan

### Research Interests

- Lead optimisation and early-ADME studies for new drug candidates. These programs involve extensive collaborations with drug discovery medicinal chemistry and biological scientists.
- Drug discovery and hit-to-lead candidate progression of drug discovery projects in the field of malaria and G Protein-Coupled Receptors. Studies involve lead optimisation and compound design using a variety of structural biology, in vitro activity and in vivo animal models, pharmacokinetic and metabolic studies and exploratory toxicology studies.
- Lymphatic drug transport and the major factors that can be manipulated, or exploited, to increase intestinal drug transport. This work also includes assessment of the effects of post-prandial plasma lipoproteins on drug metabolism and drug clearance.
- Integration of interfacial and colloidal chemistry for the optimal design and evaluation of multiphase pharmaceutical formulations which include microemulsions, self-emulsifying lipid emulsions, interactive solids and a variety of colloidal-based formulations.
- Formulation design and assessment of oral modified and controlled release formulations, and other novel drug delivery systems and technologies.

### Post-Graduate Students

#### *Honours Degree Students (coursework and research components)*

Michelle Moore (joint supervision with C.J.H. Porter)	1995	Grade H1
Sarah Urquhart	1995	Grade H1
Kylie Banks (joint supervision with S.A. Charman)	1995	Grade H1
Nicolleta Muner (joint supervision with S.A. Charman)	1996	Grade H1
Yee Ming Lee (joint supervision with C.J.H. Porter)	1997	Grade H1
Brendon Johnson (joint supervision with C.J.H. Porter)	1998	Grade H1
Aaron Bawden (joint supervision with S.A. Charman)	1998	Grade H1
Greg Kossena (joint supervision with C.J.H. Porter)	2000	Grade H1

#### *Graduated Masters and PhD Degree Students*

Christine S. Lai (M Pharm) Thesis title: Preformulation studies of nicotinamide. Awarded 1991. Deceased.

Nancy L. Pochopin (PhD) Thesis title: Amino acid amides as water-soluble prodrugs of primary aromatic amines. Awarded 1992. Now Vice President, Bristol-Myers Squibb, New Brunswick, NJ, USA.

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Kaye L. Mason (M Pharm) Thesis title: Effects of selected pharmaceutical excipients on the physical and conformation stability of porcine growth hormone. Awarded 1992. Now at Progen Limited, Brisbane.

David C. Bibby (M Pharm) Thesis title: Synthesis and evaluation of 5' alkyl ester prodrugs of AZT (Zidovudine) for directed lymphatic delivery. Awarded 1994. Now at Bionomics, South Australia.

Louise E. McCrossin (PhD) Thesis title: Effect of conformation on the stability of recombinant porcine growth hormone at alkaline pH. Awarded 1995. Now at CSL Limited, Melbourne.

Margaret M. Doherty (PhD) Thesis title: Pharmacokinetic and pharmacodynamic evaluation of hyaluronate-based local anesthetic formulations for prolongation of epidural analgesia. Awarded 1996. Now a consultant to the pharmaceutical industry.

Lori D. Simon (PhD) Thesis title: The design, application and evaluation of hyaluronate esters for protein drug delivery. Awarded 1996. Now at Bristol Myers Squibb, Princeton, NJ, USA.

Louise E. Bennett (PhD) Thesis title: An investigation of the thermal stability of bovine colostrum anti-retroviral immunoglobulin G. Awarded 1997. Now at CSIRO, Melbourne.

Andrew J. Humberstone (Ph.D) Thesis title: Physicochemical and biological factors which impact on the bioavailability and pharmacokinetics of Halofantrine. Awarded 1997. Now at MMV, Switzerland.

Jeffrey P. Krise (PhD) Thesis title: N-phosphonoxyethyl prodrugs of poorly water soluble amine. Awarded 1998. Now at School of Pharmacy, University of Kansas, USA.

Nicoletta Muner (M Pharm Sci) Thesis title: Stability assessment of investigational neuroprotective agents. Awarded 2000. Now at Pfizer/Hospira, Melbourne.

Michelle P. McIntosh (Ph.D) Thesis title: An investigation into the association of halofantrine with plasma lipoproteins. Awarded 2000. Now at Faculty of Pharmacy and Pharmaceutical Sciences, Monash University.

Suzanne Caliph (M Pharm Sci) Thesis title: An investigation of the impact of lipidic formulations on the lymphatic transport and oral bioavailability of halofantrine. Awarded 2001. Now at Faculty of Pharmacy and Pharmaceutical Sciences, Monash University.

Yee-Ming Lee (M Pharm Sci) Thesis title: The role of the acidic microclimate in the absorption of lipidic drugs from intestinal mixed micelles. Awarded 2001. Now at Aptuit Inc, Singapore.

Shui-Mei Khoo (PhD) Thesis title: An investigation of the factors which impact on the absorption and metabolism of halofantrine. Awarded 2002. Now at Pfizer/Hospira, Melbourne. Mei's PhD thesis and research was recognized by Monash University as an outstanding achievement and she was awarded the Mollie Holman medal in 2002.

Kylie A. McIntosh (PhD) Thesis title: Intestinal absorption of human growth hormone in the presence of a novel carrier compound. Awarded 2002. Now at GlaxoSmithKline, Melbourne.

Leab Sek (PhD) Thesis title: An in vitro method of lipid digestion for assessing the oral bioavailability enhancement potential of lipidic formulations. Awarded 2003. Now at Quay Pharmaceuticals, UK.

Brendan M. Johnson (PhD) Thesis title: Intestinal efflux and metabolism processes as biochemical barriers to drug absorption. Awarded 2003. Now at GlaxoSmithKline Pharmaceuticals, North Carolina, USA. Brendan's PhD thesis was the outstanding thesis within the faculty in 2003 for which he awarded the Mollie Holman medal by Monash University.

Greg Kossena (PhD) Thesis title: Assessing phase behaviour, solubilisation and bioavailability enhancement provided by digestion products of formulation lipids. Awarded 2005.

Natalie Trevaskis (PhD) Thesis title: An examination of biological factors which influence intestinal lymphatic drug transport in the rat. Awarded 2006. Now at the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University. Natalie's PhD thesis was the outstanding thesis within the faculty in 2006 for which she awarded the Mollie Holman medal by Monash University.

Christine Perry (PhD) Thesis title: Chemical stability and pharmacokinetic studies of a new class of synthetic ozonide antimalarials. Awarded 2006. Now at GlaxoSmithKline Pharmaceuticals, Australia.

Jean Cuine (PhD) Thesis title: In vitro – in vivo evaluation of self-emulsifying lipid-based formulations for the oral administration of poorly water soluble drugs. Awarded 2007. Now at NextPharma, UK.

Darren Creek (PhD) Thesis title: Iron-mediated reactivity of peroxide antimalarials. Awarded 2008. Now at the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University.

Ravi Bhamidipati (PhD) Thesis title: Basis for the dose-dependent systemic clearance of a novel 1,2,4-trioxolane antimalarial, OZ277, in rats. Awarded 2009. Now at the Centre for Drug Candidate Optimisation, Monash University.

Lukas Stingelin (PhD). Thesis title: Structural dependency of iron- and blood-mediated degradation and heme alkylation for a series of novel ozonides. Awarded 2013.

Yan Yean Yap (PhD) Thesis title: Supersaturation as a driving force for drug absorption from colloidal lipid species in the intestine. Awarded 2013. Now at the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University.

### Research Funding

1989/92	\$ 30,000	Physicochemical characterization of Leukemia Inhibitory Factor. AMRAD Corporation, Melbourne (co-PI).
1989/90	\$ 4,900	Local anaesthetic formulation design. Pharmasearch Ltd (PI).
1989/90	\$ 10,000	Pharmaceutics research, Sigma Pharmaceuticals, Melbourne.
1990/91	\$ 5,900	Effect of divalent cations on protein stability. Pharmasearch Inc.
1990/92	\$ 24,000	Pharmacokinetic studies of medroxyprogesterone acetate in humans. Farmatalia Carlo Erba, Melbourne (co-PI).
1991/93	\$151,000	Design and evaluation of novel long acting analgesic formulations. Sigma Pharmaceuticals, Melbourne (PI).
1991/93	\$ 50,000	National Teaching Company Scheme Award, Department of Industry, Trade and Commerce, Canberra (PI).
1992/94	\$213,000	Formulation design research. Sigma Pharmaceuticals (PI).
1992/94	\$ 82,281	Aspects of the chemical and physical stability of bovine IgG antibodies. ARC APRA-Industry grant.
1992/93	\$ 20,000	Pharmaceutical chemistry research studies. SmithKline Beecham Pharmaceuticals, King of Prussia, PA (PI).

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1993/94	\$145,177	Physical and chemical stability assessment of a recombinant protein drug. CSL Limited, Melbourne (PI).
1993	\$ 6,958	Identification of formulation-related factors which limit intestinal lymphatic drug transport. Australian Research Council (PI).
1993/94	\$127,645	Design and in vivo evaluation of novel oral and parenteral lipid formulations. SmithKline Beecham Pharmaceuticals, UK (PI).
1993/94	\$ 41,897	Assessment of oral self-emulsifying glass formulations. Tegra Pharmaceuticals Inc., RCT Corp., AZ, USA (PI).
1994/96	\$135,800	The effects of pharmaceutical excipients on the physical and conformational stability of model proteins. Australian Research Council Large Grant (co-PI).
1994	\$ 60,000	Circular dichroism as a probe of structure and conformation of protein folding intermediates. Monash University Research Fund contribution towards purchase of CD spectropolarimeter (co-PI).
1994/95	\$192,979	Design and in vivo evaluation of novel oral and parenteral lipid formulations. SmithKline Beecham Pharmaceuticals, UK (PI).
1995/96	\$145,024	Biopharmaceutical evaluation and preformulation studies of novel antiviral compounds. AMRAD Corporation (co-PI).
1995/96	\$ 41,825	Formulation and in vivo assessment of reconstituted intravenous emulsion formulations. RCT Corporation, AZ, USA (PI).
1995/96	\$ 25,650	Studies on the conformational stability of a protein-based drug. Emisphere Technologies Inc., NY, USA.
1995/96	\$132,177	Design and in vivo evaluation of novel oral and parenteral lipid formulations. SmithKline Beecham Pharmaceuticals, UK (PI).
1996	\$ 35,000	Development of stability indicating assays for liquid yeast sucrase enzyme. Orphan Medical Inc, MN, USA (PI).
1996	\$302,033	Prefomulation and analytical characterization of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
1996	\$ 18,000	Assessment of intestinal lymphatic transport of a novel anti-viral candidate. Ciba Geigy Pharmaceuticals, Basle, Switzerland (PI).
1996	\$ 72,000	Equipment donation. SmithKline Beecham Pharmaceuticals, UK.
1997	\$149,707	Design and in vivo evaluation of novel oral and parenteral lipid formulations. SmithKline Beecham Pharmaceuticals, UK (PI).
1997	\$265,367	Prefomulation and analytical characterisation of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
1997/98	\$157,863	Biopharmaceutical evaluation and preformulation studies of novel compounds. AMRAD Corporation, Melbourne (co-inv).
1998	\$115,327	Biopharmaceutical evaluation of novel compounds in pre-clinical development. Peptech Inc, Sydney (co-PI).
1998	\$ 60,000	Research donation. SmithKline Beecham Pharmaceuticals, UK.
1998	\$ 20,000	The role of lipid transport systems in the absorption and metabolism of lipophilic drugs. Monash Research Fund (co-PI).
1998/99	\$170,708	Biopharmaceutical evaluation and preformulation studies of novel compounds. AMRAD Corporation, Melbourne (co-PI).
1998	\$205,995	Prefomulation assessment and analytical characterisation of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
1998/99	\$169,300	Formulation development and biopharmaceutic assessment for a lipophilic drug candidate. ATTORI Ltd, Lismore, NSW (co-PI).
1998/99	\$120,000	Research donation. SmithKline Beecham Pharmaceuticals, UK
1998/99	\$135,000	Transdermal formulation research studies. Acrux Ltd, Melbourne.

1999	\$218,071	Prefomulation assessment and characterisation of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
1999/2000	\$262,679	Lipids and lipidic excipients to enhance the oral bioavailability of poorly water soluble drugs. GlaxoWellcome, UK (PI).
1999/2001	\$ 68,654	Salary support for Dr Ann-Marie Kaukonen. The Finnish Academy and The Finnish Cultural Foundation.
1999/2000	\$253,856	Biopharmaceutical evaluation and preformulation studies of novel compounds. AMRAD Corporation, Melbourne (co-PI).
1999/2001	\$340,000	Funding of an LC-MS and establishment of a Drug Absorption Facility. Strategic Monash University Research Fund (co-PI).
1999/2000	\$401,440	Transdermal formulation research studies. Acrux Ltd, Melbourne.
2000	\$175,659	Prefomulation assessment and analytical characterisation of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
2000/01	\$550,000	Transdermal formulation research studies. Acrux Ltd, Melbourne (co-PI).
2000/03	USD 3,600,000	Identification of a potent orally active antimalarial trioxolane. Medicines for Malaria Venture, Geneva, Switzerland. J. Vennestrom (University of Nebraska) and W.N. Charman (co-PI).
2000/03	\$3,850,000	START grant to Acrux Limited for the development and commercialisation of a new transdermal drug delivery product for female hormone replacement therapy (co-PI).
2001	\$204,163	Prefomulation assessment and analytical characterisation of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
2001/02	\$184,313	Lipids and lipidic excipients to enhance the oral bioavailability of poorly water soluble drugs. GlaxoWellcome, UK (PI).
2001	\$137,061	Lymphatic transport studies. GlaxoWellcome, UK (PI).
2001	\$120,000	Studies of testosterone undecanoate formulations. Organon NV, The Netherlands (PI).
2001/02	\$290,000	Exploratory drug metabolism facility to support lead optimisation programs. Strategic Monash University Research Fund (co-PI).
2001/02	\$740,000	Transdermal formulation research studies. Acrux Ltd, Melbourne (co-PI).
2002/04	\$736,488	Prefomulation assessment and analytical characterisation of new drug candidates. SmithKline Beecham Pharmaceuticals, UK (PI).
2002	\$144,973	ADME studies for new drug candidates. Cytopia Pty Ltd (co-PI).
2002/05	\$4,000,000	Establishment of a Centre for Drug Candidate Optimisation, Victorian State Government, Science, Technology and Innovation Initiative, Round 2. (PI).
2003/04	\$273,059	Evaluation of polyaphrons as drug delivery systems. Disperse Limited, Guilford, UK (co-PI).
2002/03	\$598,764	Collaborative lead optimisation studies, with various commercial partners, conducted through the Centre for Drug Candidate Optimisation (role as either PI or co-PI).
2003/04	\$1,701,905	Collaborative lead optimisation studies with various commercial partners, conducted through the Centre for Drug Candidate Optimisation (role as either PI or co-PI).
2003/04	\$87,070	Identification of lipid or other materials that will slow gastro-intestinal transit and therefore enhance absorption of some compounds. GlaxoSmithKline Pharmaceuticals, UK (co-PI). Part of an overall USD \$1,500,000 clinical study program.

2004/05	USD 1,040,000	Identification of a potent orally active antimalarial trioxolane. Medicines for Malaria Venture, Geneva, Switzerland. J. Vennestrom (University of Nebraska) and W.N. Charman (co-PI).
2004/05	\$936,122	Identification of new candidate drug classes for tropical diseases. World Health Organisation/TDR. I. Street (Walter and Eliza Hall Institute of Medical Research) and W.N. Charman (co-PI).
2004/05	USD 936,000	New inhibitors of Plasmodium dihydrofolate reductase. Medicines for Malaria Venture, Geneva, Switzerland. Y. Yuthavong (BIOTEC, Thailand) and W.N. Charman (co-PI).
2004/06	\$193,906	DsbA: A target for the design of drug candidates as selective inhibitors of oxidative protein folding in Gram negative bacteria. ARC Linkage Grant in partnership with GBS Ventures. M.J. Scanlon and W.N. Charman.
2004/05	\$151,768	Evaluation of polyaphrons as drug delivery systems. Disperse Limited, Guilford, UK (co-PI).
2004/05	\$2,270,000	Collaborative lead optimisation studies with various commercial partners, conducted through the Centre for Drug Candidate Optimisation (role as either PI or co-PI).
2005/06	\$3,100,000	Collaborative lead optimisation studies with various commercial partners, conducted through the Centre for Drug Candidate Optimisation (role as either PI or co-PI).
2006/07	\$3,200,000	Collaborative lead optimisation studies with various commercial partners, conducted through the Centre for Drug Candidate Optimisation (role as co-PI).
2007/09	\$540,000	DsbA inhibitors as potential antimicrobials. NHMRC Project Grant. J. Martin, M.J. Scanlon, W.N. Charman, B. Heras and R. Reid.
2007/12	USD 5,796,633	Optimising novel dihydroorotate dehydrogenase inhibitors for treating malaria. National Institutes of Health NIH U010AI075594. M.A. Phillips, P. Rathrod and W.N. Charman.
2008/10	\$377,125	Recognition of macromolecular complexes by cell surface receptors: A novel mechanism of lipid and drug absorption. NHMRC Project Grant 491181. C.J.H. Porter, W.N. Charman and P. Tso.
2007/08	\$1,500,000	Collaborative lead optimisation studies conducted through the Centre for Drug Candidate Optimisation (role as co-PI).
2008/09	\$1,400,000	Collaborative lead optimisation studies conducted through the Centre for Drug Candidate Optimisation (role as co-PI).
2009/12	\$780,000	Targeting virulence of <i>Pseudomonas Aeruginosa</i> by inhibiting oxidative protein folding. ARC Linkage Grant in partnership with Biota Holdings. M.J. Scanlon, J.L. Martin, W.N. Charman, J.S. Simpson, R.L. Nation and C.J. Morton.
2010/11	USD 784,000	Kinase drug discovery for malaria. Medicines for Malaria Venture (Geneva, Switzerland). A.F. Wilks and W.N. Charman.
2010/12	\$3,300,000	Australian Centre for Pharmaceutical Innovation. Funding from GSK Australia and Victoria Science Agenda Innovation Scheme. W.N. Charman.
2010/12	\$6,500,000	Pharmaceutical and preclinical development elements of the Translating Health Discovery EIF project. Department of Innovation, Industry, Science and Research, Commonwealth Government of Australia. W.N. Charman.

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2010/12	\$1,500,000	Contribution towards establishment of a translational medicinal chemistry facility. Funding from Victoria Science Agenda Innovation Scheme. W.N. Charman.
2011/13	\$533,390	Drug treatment of immune disease: integrating drug delivery into drug design to transform therapeutic utility. NHMRC project Grant 606433. C.J.H. Porter, W.N. Charman, F. Alderuccio and N.L. Trevaskis.
2011	\$249,622	Los-cost, needle-free and non-refrigerated treatment for post-partum haemorrhage. US Agency for International Development (USAID). M.P. McIntosh, R.J. Pranker, D. Morton, W.N. Charman, R. Bischof, E. Meesun and H. Parkinton.
2011/13	\$471,000	Lymphotropic prodrugs: A novel mechanism for targeted drug delivery. ARC Discovery Project. C.J.H. Porter, W.N. Charman and V.J. Stella.
2012/14	\$553,900	Integrating drug delivery principles into drug design to transform the treatment of immune disease. NHMRC Project Grant. C.J.H. Porter, W.N. Charman, F. Alderuccio and N. Trevaskis.
2012/14	\$505,470	Structure-based design of inhibitors of oxidative protein folding in <i>Enterobacteriaceae</i> . NHMRC Project Grant. M.J. Scanlon, W.N. Charman, J. Simpson and B. Heras.
2013	\$288,619	Audit of the National Return and Disposal of Unwanted Medicines (NATRUM) project. P. Bergen, D. Kong, S. Hussainy, J. George, C. Kirkpatrick and W.N. Charman.
2014	\$755,000	High throughput cell genomics centre. ARC infrastructure grant. P. Hertzog, J. Whisstock, F. Mackay-Fisson, W.N. Charman, J. Polo, E. Hartland, M. Pera and P. Hansbro.
2012/19	\$23,500,000	GPCR Drug Discovery. Servier Research, Paris, France. A. Christopoulos, W.N. Charman, P. Sexton and R.J. Summers.
2017/28	\$10,000,000	Department of Economic Development, Jobs, Transport and Resources, State Government of Victoria. R. Coppel and W.N. Charman.
2017/28	\$50,000,000	Monash University and The University of Melbourne to support the formation and operation of BioCurate P/L.
2020/22	\$4,900,000	GPCR Drug Discovery. Servier Laboratories (Australia). A. Christopoulos, W.N. Charman, P. Sexton and R.J. Summers.

**Publications (research papers, book chapters, patents and review articles)**

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2. Lymphatic appearance of DDT in thoracic and mesenteric lymph duct cannulated rats. T. Noguchi, W.N. Charman and V.J. Stella. *Int. J. Pharmaceut.*, 24, 185-192, 1985.
3. Prodrugs: Do they have advantages in clinical practice? V.J. Stella, W.N. Charman and V.H Naringrekar. *Drugs*, 29, 445-473, 1985.
4. Effect of drug lipophilicity and lipid vehicles on the lymphatic absorption of various testosterone esters. T. Noguchi, W.N. Charman and V.J. Stella. *Int. J. Pharmaceut.*, 24, 173-184, 1985.
5. Pralidoxime: A stability monograph. In *Chemical Stability of Pharmaceuticals. A Handbook for Pharmacists*, Eds. K.A. Connors, G.L. Amidon, and V.J. Stella, 2nd Edition, J. Wiley and Sons, New York, NY. pp. 685-692, 1986.
6. An experimental system designed to study the in situ intestinal lymphatic transport of drugs in anesthetized rats. W.N. Charman, T. Noguchi and V.J. Stella. *Int. J. Pharmaceut.*, 33, 155-164, 1986.
7. Effect of lipid class and lipid vehicle volume on the intestinal lymphatic transport of DDT. W.N. Charman and V.J. Stella. *Int. J. Pharmaceut.*, 33, 165-172, 1986.
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9. Estimating the maximal potential for intestinal lymphatic transport of lipophilic drug molecules. W.N. Charman and V.J. Stella. *Int. J. Pharmaceut.*, 34, 175-178, 1986.
10. Characterization of biopolymers by the technique of pyrolysis gas chromatography and multi-dimensional pattern recognition: Application to synthetic melanins. W.N. Charman, C.J. Farquhar, B.C. Finnin and B.L. Reed. *J. Chromatogr.*, 388, 389-396, 1987.
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13. Provisional Australian Patent Application #PK28940/90, entitled pharmaceutical composition, filed on October 16, 1990. Application refiled on March 18, 1992 (# PL 1409/92). P.J. Hughes and W.N. Charman.
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16. Transport of lipophilic molecules by the intestinal lymphatic system. W.N. Charman and V.J. Stella. *Adv. Drug Deliv. Rev.*, 7, 1-14, 1991.
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**Published Scientific Abstracts and Communications**

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134. Development of a high throughput screening assay for potential hERG K channel blockers. M.A. Polidano, M.G. Waldhuber, C.W. Pouton, W.N. Charman and S.A. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, A-112, Melbourne, December, 2004.
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136. Biliquid foams for the oral delivery of poorly water soluble, lipophilic drugs: A case study with halofantrine. D.F. Steele, D.A. Wheeler, G.A. Edwards, C.W. Pouton, W.N. Charman and C.J.H. Porter. Proceedings of the Australasian Pharmaceutical Sciences Association, A-124, Melbourne, December, 2004.
137. Measurement and in silico prediction of distribution coefficients during lead optimisation. M. Campbell, N. Pham, S.A. Charman and W.N. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, A-127, Melbourne, December, 2004.
138. Aqueous degradation pathways of novel, synthetic ozonide antimalarial drug candidates. C.S. Perry, R.J. Prankerd, J.L. Vennerstrom, F.C.K. Chiu, S.A. Charman and W.N. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, A-137, Melbourne, December, 2004.
139. The effect of different reaction conditions on the iron-mediated degradation of artemisinin. D.J. Creek, F.C.K. Chiu, R.J. Prankerd, W.N. Charman and S.A. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, A-138, Melbourne, December, 2004.

140. LC-MS analytical throughput enhancement with staggered chromatography. F.C.K. Chiu, J. Morrizzi, J.M. O'Connor and W.N. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, A-138, Melbourne, December, 2004.
141. The role of lipids in the absorption of lipophilic drugs. W.N. Charman. Proceedings of the EUFEPS 3<sup>rd</sup> World Conference on Drug Absorption, Transport and Delivery, P-60. Barcelona, Spain, April, 2005.
142. Public private partnerships in drug discovery and development – Case Study: Antimalarials. *Journées Galéniques De Saint-Remy De Provence*, 39, S-25, 2005. Gattefosse Symposium, Provence, France, June, 2005.
143. The design of a new, synthetic, peroxide-based anti-malarial drug candidate. ARC/NHMRC Research Network for Parasitology. S-55, 2005. WEHI, Melbourne, July, 2005.
144. In vitro methodologies to optimize lipid-based formulations for the oral administration of lipophilic drugs. J.F. Cuiné, W.N. Charman, C.W. Pouton and C.J.H. Porter. Proceedings of the 32nd CRS Annual Meeting and Exposition, Abstract 754, Miami, FL, June 2005.
145. Fluoroartemisins as new orally active antimalarials: hydrolytically stable analogs of anhydrodihydroartemisinin, artemether and artesunate. D. Bonnet-Delpon, J.P. Bégué, P. Grellier, G. Magueur, F. Grellepois, F. Chorki, C. Chollet, B. Crousse, S. Charneau, K.A. McIntosh and W.N. Charman, B. Pradines. *Parassitologia* 47 (Suppl 1), 47, 2005.
146. How critical is the inclusion of simple glyceride lipids to the in vivo performance of self-emulsifying drug delivery systems? J.F. Cuine, W.N. Charman, C.J.H. Porter and C.W. Pouton. 2005 Annual Meeting of the American Association of Pharmaceutical Scientists, Abstract M1145, Nashville, TN, November, 2005.
147. The susceptibility of non-ionic surfactants to lipase-mediated digestion may dictate their utility as components of lipid-based formulations. J.F. Cuine W.N. Charman, H. Benameur, C.J.H. Porter and C.W. Pouton. 2005 Annual Meeting of the American Association of Pharmaceutical Scientists, Abstract M1156, Nashville, TN, November, 2005.
148. The impact of formulation surfactants on the in vitro dispersion, digestion and bioavailability of a lipid-based formulation containing atovaquone. B.J. Boyd, W.N. Charman, C.J.H. Porter and L. Sek. 2005 Annual Meeting of the American Association of Pharmaceutical Scientists, Abstract M1138, Nashville, TN, November, 2005.
149. Systemic exposure of a model lipophilic drug is changed when drug enters the circulation in association with lymph as opposed to plasma. S.M. Caliph, W.N. Charman and C.J.H. Porter. 2005 Annual Meeting of the American Association of Pharmaceutical Scientists, Abstract M1141, Nashville, TN, November, 2005.
150. Reactivity of novel ozonide antimalarials with ferrous iron. D.J. Creek, F.C.K. Chiu, R.J. Pranker, J.L. Vennerstrom, S.A. Charman and W.N. Charman. Proceedings of the ASCEPT and APSA Joint Meeting, Poster 2-79, Melbourne, December 2005.
151. How critical is the inclusion of long chain lipids in the in vivo performance of self-emulsifying drug delivery systems? J.F. Cuine, W.N. Charman, C.W. Pouton and C.J.H. Porter. Proceedings of the ASCEPT and APSA Joint Meeting, Oral 16, Melbourne, December 2005.
152. The mouse brain uptake assay: A rapid and validated approach for assessing blood-brain barrier permeability. J.A. Nicolazzo, S.A. Charman and W.N. Charman. Proceedings of the ASCEPT and APSA Joint Meeting, Oral 07, Melbourne, December 2005.
153. APSA Medal Lecture: Public private partnerships in anti-malarial drug discovery and development. W.N. Charman. Proceedings of the ASCEPT and APSA Joint Meeting, Oral 166, Melbourne, December 2005.
154. Lipids and the absorption of lipophilic drugs. W.N. Charman. Proceedings of the EUFEPS Conference: When poor solubility becomes an issue: From early stage to proof of principles. P-38. Verona, Italy, April 2006.

155. Lipids, lipophilic drugs and oral drug delivery. CRS career achievement award lecture in oral drug delivery. W.N. Charman. 33<sup>rd</sup> Annual Meeting of the Controlled Release Society, Vienna, Austria, July, 2006.
156. Relationship between iron-mediated reactivity and biological activity of peroxide antimalarials. D.J. Creek, F.C.K. Chiu, R.J. Pranker, J.L. Vennerstrom, W.N. Charman and S.A. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, Podium 2-4 Adelaide, December, 2006.
157. Metabolism of a novel antimalarial trioxolane in the isolated perfused rat liver model. R.K. Bhamidipati, D.M. Shackelford, F.C.K. Chiu, W.N. Charman and S.A. Charman. Proceedings of the Australasian Pharmaceutical Sciences Association, Poster 2-4, Adelaide, December, 2006.
158. A novel and highly potent class of compounds for the treatment of trypanosomiasis. T. Armstrong, W.M. Best, W.N. Charman, C. Laverty, G. Luna, C.G. Simms and R.C. A. Thompson. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, January 2007.
159. High throughput screening-based drug discovery: The search for new and effective treatments for tropical diseases. I. Street, J. Baell, R. Brun, W.N. Charman, A. Fairlamb, G. Holloway, J. Hyde, W. Kasekarn, E. Kostewicz, P. Novello, E. Oldfield, J. Parisot, J. Richardson, W. Sirawaraporn and K. Watson. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, January, 2007.
160. Drug discovery for neglected diseases: Examples of successful partnerships in malaria. S1-05. World congress of pharmacy and pharmaceutical sciences. 68<sup>th</sup> International Congress of FIP, Basle, Switzerland, September, 2008.
161. Public private partnerships and drug discovery for malaria. 10<sup>th</sup> Annual Scientific Meeting of Australian Society for Antimicrobials. Melbourne, February, 2009.
162. Basis for the dose-dependent systemic clearance of OZ277 in rats. R.K. Bhamidipati, A. Mannila, D.M. Shackelford, F.C.K. Chui, W.N. Charman and S.A. Charman. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009. P-109.
163. Reactivity of peroxide antimalarials with biologically relevant iron sources. D.J. Creek, F.C.K. Chui, R.J. Pranker, J.L. Vennerstrom, W.N. Charman and S.A. Charman. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009. P-116.
164. A metabolically stable, triazolopyrimidine-based dihydroorotate dehydrogenase inhibitor with activity in a mouse model for malaria. R. Gullar, A. Marwaha, F. El Mazouni, J. White, K.L. White, S. Creason, D.M. Shackelford, J. Baldwin, W.N. Charman, F.S. Buckner, S.A. Charman, M.A. Phillips and P. Rathod. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009. P-129.
165. Isosteric transformations and permutations on triazolopyrimidine-based Plasmodium DHODH inhibitors. A. Marwhala, R. Gullar, J. White, F. El Mazouni, W.N. Charman, F.S. Buckner, S.A. Charman, M.A. Phillips and P. Rathod. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009. P-202.
166. OZ277 and dihydroartemisinin do not accumulate in parasite infected red blood cells. L. Stingelin, F.C.K. Chui, W.N. Charman and S.A. Charman. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009. P-230.
167. Drug discovery for protozoan parasites – The essential P's. W.N. Charman. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009. K-001.

168. Intestinal lymphatic drug transport in mice, rats and dogs is dictated by inter-species differences in lipid absorption. N. Trevaskis, W.N. Charman and C.J.H. Porter. 24th Annual Meeting of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November, 2009. M-1036
169. The pathway of endogenous lipid entry into enterocytes determines the potential for support of intestinal lymphatic drug transport. N. Trevaskis, W.N. Charman and C.J.H. Porter. 24th Annual Meeting of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November, 2009. M-1037.

**Note: From 2010 onwards, a record of published abstracts has no longer been kept**

**Invited Presentations and Lectures**

1. Aspects of melanin. Dermatological Research Group, St. Vincents Hospital, Melbourne, Australia, September, 1981.
2. The development of an EC-HPLC assay for 5-S-Cysteinyl-dopa. Nicholas Research Laboratories, Melbourne, Australia, December, 1981.
3. Bioavailability of topical depigmenting agents: 5-S-Cysteinyl-dopa as an index of pigment cell activity. Annual Meeting of the Australian Pharmaceutical Association, Sydney, Australia, May, 1982.
4. Approaches to the characterization of melanin. The Royal Australian Chemical Institute, Pharmaceutical Sciences Group, Melbourne, Australia, June, 1982.
5. Monitoring the activity of pigment cells. Annual Meeting of the Society of Hospital Pharmacists, Melbourne, Australia, August, 1982.
6. Pyrolysis of melanin and aspects of 5-S-Cysteinyl-dopa. Nicholas Research Laboratories, Melbourne, Australia, December, 1982.
7. Approaches to measuring the cutaneous bioavailability of topically applied depigmenting agents. The University of Kansas, March, 1983.
8. Biopolymer characterization using pyrolysis capillary gas chromatography and multi-dimensional pattern recognition techniques - Application to synthetic melanins. 37th National Meeting of the Academy of Pharmaceutical Sciences, Philadelphia, PA, October, 1984.
9. Lymphatic absorption of drugs III: An experimental system applied to biopharmaceutical studies in anesthetized rats. 37th National Meeting of the Academy of Pharmaceutical Sciences, Philadelphia, PA, October, 1984.
10. Part I: Skin pigment characterization, Part II: Aspects of the intestinal lymphatic transport of lipophilic drugs. The University of Michigan, Ann Arbor, MI, March, 1985.
11. The potential of the intestinal lymphatic route for drug absorption. Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA, March, 1985.
12. Methodological approaches for estimating the intestinal lymphatic transport of drug molecules. Victorian College of Pharmacy, Australia, April, 1985.
13. Drug delivery systems. Technical Research and Development, F.H. Faulding and Co., Adelaide, Australia, April, 1985.
14. The mechanism of intestinal lymphatic transport of hydrophobic drugs. Department of Pharmaceutical Chemistry, University of Kansas, April, 1985.
15. Part I: Skin pigment characterization; Part II: Aspects of the intestinal lymphatic transport of drugs. Nutrition Chemicals Division, Monsanto Company, St. Louis, MO, April, 1985.
16. The mechanism of intestinal lymphatic transport of drugs. Pharmaceutical Research, Bristol-Myers Company, Syracuse, NY, April, 1985.
17. Part 1: Skin pigment characterization; Part II: Aspects of the intestinal lymphatic transport of drugs. Sterling-Winthrop Research Institute, Rensselaer, NY, May, 1985.
18. Part 1: Skin pigment characterization, Part II: Aspects of the intestinal lymphatic transport of drugs. Pharmaceutical Research and Development, Pfizer Central Research, Groton, CT, May, 1985.
19. The mechanism of intestinal lymphatic drug transport and potential dosage form strategies. Department of Biopharmaceutics, Sandoz AG, Basle, Switzerland, June, 1985.
20. Intestinal lymphatic drug transport. Pharmaceutical Research, G.D. Searle and Co., Chicago, IL, October, 1985.
21. Lymphatic absorption of drugs IV: Chylomicron flow is an important factor controlling the intestinal lymphatic transport of hydrophobic drugs. 39th National Meeting of the Academy of Pharmaceutical Sciences, Minneapolis, MN, October, 1985.

22. Lymphatic absorption of drugs V: Estimating the potential for intestinal lymphatic transport of lipophilic drugs. 1st Annual Meeting of the American Association of Pharmaceutical Scientists, Washington, D.C., November, 1986.
23. Drug absorption studies as an aid to dosage form design. Robert S. First, Inc., Latest Advances in Drug Delivery Symposium, Philadelphia, PA, June, 1988.
24. Controlled release formulation design: Physical and biological aspects. College of Pharmacy, University of Texas at Austin, September, 1988.
25. Development strategies for dose forms of generic drugs. Sigma Pharmaceuticals, Melbourne, Australia, October, 1990.
26. Lymphatic transport of drugs. Plenary Lecture at the Biannual Meeting of the Australian Pharmaceutical Sciences Association, Adelaide, July, 1991.
27. Lymphatic transport of drugs. Albany College of Pharmacy, Albany, NY, November, 1991.
28. Lipids, lymph and bioavailability. Faulding Research, Adelaide, May, 1993.
29. Food, lipids and bioavailability. Glaxo Research, Melbourne, August, 1993.
30. Physical pharmacy and formulation development: Selected chemical and clinical examples. Center for Cardiovascular Science, Department of Medicine and Experimental Therapeutics, University College Dublin, Ireland, November, 1993.
31. Low-dose aspirin and cardiovascular disease: Formulation and bioequivalence issues. 1993 Aspirin Forschungspreis Symposium, Bayer AG, Cologne, Germany, December, 1993.
32. Pharmaceuticals and contemporary product formulation strategies. CSL Limited, Melbourne, Australia, February, 1995.
33. Opportunities for the transdermal delivery of specific inhibitors of platelet function. Cygnus Therapeutic Systems, CA, USA, March, 1995.
34. Recent biopharmaceutical and oral formulation studies conducted with halofantrine. SmithKline Beecham Pharmaceuticals, Great Burgh, Surrey, UK, June, 1995.
35. Pre-clinical developmental studies with an emphasis on optimal compound selection. Biomolecular Research Institute, CSIRO, Division of Chemicals and Polymers, Clayton, October, 1995.
36. Lipids, lymph and lipidic systems. 31st Journées Galéniques De Saint-Remy De Provence, Gattefosse s.a., St Remy, France, June, 1997.
37. Lipids, lymph and lipidic systems. Department of Pharmaceutical Technologies, SmithKline Beecham Pharmaceuticals, Harlow, UK, June, 1997.
38. Lipids, lymph and lipidic systems. Royal Australian Chemical Institute, Pharmaceutical Sciences seminar, Melbourne, July, 1997.
39. Drug delivery technologies and future opportunities. Sigma Business Conference, Rio de Janeiro, Brazil, August, 1997.
40. The gastrointestinal processing of lipids: Pharmaceutical implications. Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, MA, November, 1997.
41. The gastrointestinal processing of lipids: Pharmaceutical implications. Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, November, 1997.
42. Physicochemical characteristics - A key determinate of the developability of a drug candidate. Annual meeting of the Australian Pharmaceutical Sciences Association, Sydney, November, 1997.
43. Occasional Address at the Opening Ceremony of the Academic Year, Victorian College of Pharmacy, Monash University, March, 1998.
44. Lipids and oral bioavailability: Are there yet-to-be realised opportunities? 32nd Journées Galéniques De Saint-Remy De Provence, Gattefosse s.a., St Remy, France, June, 1998.
45. The key aspects of oral bioavailability. Tropical Disease Research Meeting, World Health Organisation, Geneva, Switzerland, June, 1998.
46. Lipids and oral bioavailability: Are there yet-to-be realised opportunities? GlaxoWellcome Research and Development, Ware, UK, June, 1998.

47. Lipids and oral bioavailability: Are there yet-to-be realised opportunities? Alphapharm lecture, Department of Pharmacy, The University of Queensland, Brisbane, Australia, August, 1998.
48. Pharmacy: What an exciting future in research, drug delivery and community healthcare. Alphapharm lecture, Department of Pharmacy, The University of Queensland, Brisbane, Australia, August, 1998.
49. Pharmaceutical R and D: The exciting road ahead. Sigma Business Conference, Sanctuary Cove, Queensland, September, 1998.
50. The process of compound selection: A developmental perspective. Tropical Disease Research Meeting, World Health Organisation, Geneva, Switzerland, October, 1998.
51. Lipids: Unique excipients for orally administered dose forms. GlaxoWellcome Research and Development, Ware, UK, October, 1998.
52. The process of compound selection: A developmental perspective. Drug Information Association Conference: Taking a Drug Discovery Into Pre-clinical Development, Melbourne, October, 1998.
53. Design, evaluation and manufacture of lipid-based dose forms. Chairman, Capsugel Round Table Meeting on semi-solids in Hard Gelatin Capsules, 13th Annual Meeting of the American Association of Pharmaceutical Scientists, San Francisco, CA, November, 1998.
54. Lipids: Unique excipients for orally administered dose forms. Abbott Laboratories, North Chicago, IL, November, 1998.
55. Lipidic formulations: Are they part of your formulation strategy? 33rd Journées Galéniques De Saint-Remy De Provence, Gattefosse s.a., St Remy, France, June, 1999.
56. Transdermal drug development strategies. European Commission Workshop on Topical Treatment of Cutaneous Leishmaniasis, London School of Hygiene and Tropical Medicine, University of London, June, 1999.
57. Lipids and oral drug delivery. 26th International Symposium on Controlled Release of Bioactive Materials Conference, Society, Boston, MA, June, 1999.
58. Lipids, lipophilic drugs and oral drug delivery. Pharmaceutical Research and Development, Pharmacia and Upjohn Inc, Kalamazoo, Michigan, September, 1999.
59. Lipids, lipophilic drugs and oral drug delivery. Department of Pharmaceutical Technology, Warner Lambert Inc, New Jersey, September, 1999.
60. Lipids, lipophilic drugs and oral drug delivery. Parke-Davis Pharmaceutical Research Institute, Ann Arbor, Michigan, September, 1999.
61. Lipids, lipophilic drugs and oral drug delivery. 136th British Pharmaceutical Conference, GlaxoWellcome International Achievement Award Lecture, Cardiff, Wales, September, 1999.
62. The process of compound selection: A developmental perspective. Biota Holdings Limited, Melbourne, October, 1999.
63. Lipid-based formulation project: A progress report. GlaxoWellcome Research and Development, Ware, UK, March, 2000.
64. Some recent advances in transdermal drug delivery. SmithKline Beecham Consumer Health, Brentford, UK, March, 2000.
65. Drug delivery and formulation support for the new anti-malarial drug series. Swiss Tropical Institute, Basle, Switzerland, June, 2000.
66. Halofantrine: Biopharmaceutics, lymphatic transport and formulation opportunities. SmithKline Beecham Research and Development, Harlow, UK, June, 2000.
67. Developability – A fundamental consideration in lead candidate optimisation. Invited lecture, Australian Biotechnology Association Annual Meeting, Brisbane, July, 2000.
68. Developability – A fundamental consideration in lead candidate optimisation. Drug Discovery Research, World Health Organisation, Geneva, Switzerland, September, 2000.
69. Classifying the Oral Biopharmaceutics of Drugs. 137th British Pharmaceutical Conference, Birmingham, England, September, 2000.
70. Intestinal lymphatic drug transport. SmithKline Beecham Research and Development, Harlow, UK, September, 2000.

71. Lipid-based formulation project: A progress report. GlaxoWellcome Research and Development, Ware, UK, September, 2000.
72. Physiological considerations in the application of oral lipid-based drug delivery systems W.N. Charman. 15th Annual Meeting of the American Association of Pharmaceutical Scientists, Indianapolis, IN, November, 2000.
73. Lipid-based formulations – Why the increasing interest? Annual meeting of the Australian Pharmaceutical Sciences Association, Newcastle, December, 2000.
74. Oral biopharmaceutics and intestinal lymphatic transport of halofantrine – A highly lipophilic drug. NV Organon, AkzoNobel, Oss, The Netherlands, January, 2001.
75. Pharmacokinetics, physicochemical and metabolism support for the OZ series. Swiss Tropical Institute, Basel, Switzerland, January, 2001.
76. Lipid-based Formulation Design Studies I. GlaxoSmithKline, Pharmaceutical Sciences R and D, Ware, UK, January, 2001.
77. Lipid-based Formulation Design Studies II. GlaxoSmithKline, Pharmaceutical Sciences R and D, Ware, UK, January, 2001.
78. Developability – A fundamental consideration in lead candidate optimisation. Chiron Mimotopes, Melbourne, February, 2001.
79. Pharmaceutics research at the Victorian College of Pharmacy. Department of Pharmaceutics, University of Helsinki, Finland, June, 2001.
80. Preclinical screening of oral drug absorption – Formulation and physiological factors. W.N. Charman. XVI Helsinki University Congress of Drug Research, Helsinki, Finland, June, 2001.
81. Pharmacokinetics, physicochemical and metabolism support for the OZ series. Swiss Tropical Institute, Basel, Switzerland, June, 2001.
82. Intestinal lymphatic transport of lipophilic drugs. EUFEPS World Conference on Drug Absorption and Drug Delivery, Copenhagen, June, 2001.
83. Biopharmaceutical and formulation issues associated with lipid-based dose forms for poorly water soluble drugs. GlaxoSmithKline Pharmaceuticals, Collegeville, PA, August, 2001.
84. Biopharmaceutical and formulation issues associated with lipid-based dose forms for poorly water soluble drugs. Boehringer-Ingelheim Pharmaceuticals Inc, Ridgefield, CT, August, 2001.
85. Lead optimization – the difference between a ligand and a drug. School of Biomedical Sciences, Monash University, October, 2001.
86. Solubility-limited oral drug absorption: New approaches to an old problem. Annual meeting of the Australian Pharmaceutical Sciences Association, Melbourne, December, 2001.
87. Synthetic peroxide anti-malarial development project – open presentation. Expert Scientific and Advisory Committee, Medicines for Malaria Venture, Geneva, Switzerland, January, 2002.
88. Synthetic peroxide anti-malarial development project – progress report and data review. Expert Scientific and Advisory Committee, Medicines for Malaria Venture, Geneva, Switzerland, January, 2002.
89. Lipid formulation strategies and assessment of lymphatic transport. TransForm Pharmaceuticals Inc, Waltham, MA, April, 2002.
90. Lipid formulation strategies and assessment of lymphatic transport. Drug Delivery and Pharmaceutics Conference, American Association of Pharmaceutical Scientists, Washington DC, April, 2002.
91. Synthetic peroxide anti-malarial drug discovery. Annual Board and Stakeholders Meeting, Medicines for Malaria Venture, Montreux, Switzerland, May, 2002.
92. The delivery and assessment of BCS Class II drugs. Workshop co-sponsored by the American Association of Pharmaceutical Scientists and the FDA, Washington DC, September, 2002.
93. The design and evaluation of lipid-based formulations. Boehringer-Ingelheim Pharmaceuticals Inc, Ridgefield, CT, September, 2002.
94. Synthetic peroxide anti-malarial development project – progress report and data review. Medicines for Malaria Venture, Basle, Switzerland, October, 2002.

95. Lipid formulations strategies and assessment of lymphatic transport. F. Hoffman-La Roche, Basle, Switzerland, October, 2002.
96. Lipid formulations strategies and assessment of lymphatic transport. Gilead Sciences Inc., San Francisco, CA, October, 2002.
97. Physiological and biopharmaceutical considerations in the design and assessment of lipid formulations. 17th Annual Meeting of the American Association of Pharmaceutical Scientists – Short course entitled “Lipid formulations for the oral administration of drugs, emulsions, microemulsions and self-emulsifying microemulsions. Toronto, Canada, November, 2002.
98. Lipid formulations strategies and assessment of lymphatic transport. Allergan Inc, Irvine, CA, November, 2002.
99. Lead optimisation: Enhancing the value and developability of drug candidates. Australian Health and Medical Research Congress, Melbourne, November, 2002.
100. Lead optimisation: Enhancing the value and developability of drug candidates. Alchemia Limited, Brisbane, January, 2003.
101. Clinical candidate selection of a new synthetic anti-malarial peroxide. Expert Scientific and Advisory Committee, Medicines for Malaria Venture, Frankfurt, Germany, March, 2003.
102. Lead optimization: Enhancing the value and developability of drug candidates. Biopharmaceuticals: Concept to clinic. A Satellite Meeting of the XIX International Congress of Genetics, Melbourne, July, 2003.
103. Lipid-based approaches to addressing oral delivery issues. Annual Meeting of the Controlled Release Society, Glasgow, Scotland, July, 2003.
104. Drug Delivery: Where have we come from? Where are we going? World Congress of Pharmacy and Pharmaceutical Sciences, 63<sup>rd</sup> International Congress of FIP, Sydney, Australia, September, 2003.
105. Drug candidate optimisation. Biomedical Research Cluster Linkage Seminar Series. School of Biomedical Sciences, Monash University, September, 2003.
106. The design of lipid-based formulations for oral administration – a 5 lecture short course. Allergan Inc, Irvine, CA, October 2003.
107. Lead optimisation: Enhancing the value and developability of drug candidates. Allergan Inc, Irvine, CA, October 2003.
108. Lipid-based formulation: Design considerations. Merck and Co, Philadelphia, PA, October 2003.
109. Lipid-based formulation: In vitro assessment and an update on lymphatic transport. Merck and Co, Philadelphia, October 2003.
110. Lipid-based formulations for oral administration: What to consider and why? TransForm Pharmaceuticals Inc, Waltham, MA, October, 2003.
111. The intestinal lymphatics: An often ignored absorption pathway. Pfizer Inc, Groton, CT, October, 2003.
112. Lipid-based formulations for oral administration: What to consider, and why? 18th Annual Meeting of the American Association of Pharmaceutical Scientists, Salt Lake City, UT, October, 2003.
113. The mechanism of testosterone undecanoate absorption after oral administration. An Organon Satellite Symposium, The 4<sup>th</sup> World Congress on the Aging Male, Prague, Czech Republic, February, 2004.
114. Lymphatic drug transport and some aspects of lipid-based formulation design. Schering AG, Berlin, Germany, April, 2004.
115. Lymphatic drug transport and some aspects of lipid-based formulation design. National Centre for Natural Product Research and Pharmacognosy, School of Pharmacy, The University of Mississippi, May 2004.
116. The design of lipid-based formulations for oral administration – a 6 lecture short course. NV Organon, Oss, The Netherlands, September, 2004.

117. Lipid-based system to enhance exposure of otherwise difficult compounds. Optimization of drug-like properties during lead optimization. Workshop co-sponsored by the American Association of Pharmaceutical Scientists and the FDA, Parsippany, NJ, September, 2004.
118. Identification of an antimalarial synthetic trioxolane drug development candidate. Malaria in Melbourne 2004 Symposium, La Trobe University, October, 2004.
119. Synthetic peroxide anti-malarial development project – progress report and data review. Medicines for Malaria Venture and Ranbaxy, New Delhi, India, December, 2004.
120. Lead optimisation: Enhancing the value and developability of drug candidates. Progen Industries, Brisbane, February, 2004.
121. Dihydrofolate reductase drug discovery project. Presentation to the Expert Scientific and Advisory Committee, Medicines for Malaria Venture, Geneva, Switzerland, January, 2005.
122. Design and development of a new, synthetic, antimalarial peroxide. CSIRO, Division of Human Sciences and Nutrition, CSIRO, March 2005.
123. The role of lipids in the absorption of lipophilic drugs. 3<sup>rd</sup> World Conference on Drug Absorption, Transport and Delivery, Barcelona, April, 2005.
124. Public private partnerships in drug discovery and development – Case Study: Antimalarials. Gattefosse Symposium, Provence, France, June, 2005.
125. The design of a new, synthetic, peroxide-based anti-malarial drug candidate. ARC/NHMRC Research Network for Parasitology, Melbourne, July, 2005.
126. Design of an ozonide antimalarial drug candidate. Natural Product Discovery Centre, Griffith University, Brisbane, August, 2005.
127. Dihydrofolate reductase drug discovery project. Presentation to the Expert Scientific and Advisory Committee, Medicines for Malaria Venture, Geneva, Switzerland, November, 2005.
128. Second generation synthetic peroxide drug discovery project. Presentation to the Expert Scientific and Advisory Committee, Medicines for Malaria Venture, Geneva, Switzerland, November, 2005.
129. 2005 APSA Medal Lecture: Public private partnerships and anti-malarial drug discovery. ASCEPT and APSA Joint Meeting, Melbourne, December, 2005.
130. Selection of a synthetic anti-malarial trioxolane candidate for development. 54<sup>th</sup> Annual meeting of The American Society of Tropical Medicine and Hygiene, Washington DC, December, 2005.
131. Lipids and the absorption of lipophilic drugs. EUEPS Conference: When poor solubility becomes an issue: From early stage to proof of principles. Verona, Italy, April 2006.
132. Lead optimisation: A key driver of value for drug candidates. Wellcome Trust Drug Discovery Frontiers Meeting, Wellcome Trust Genome Research Centre, Cambridge, UK, May, 2006.
133. Achieving change in an academic environment. AVCC leadership program for middle managers. Deakin Management Centre, May, 2006.
134. The design on a new, synthetic peroxide antimalarial drug. The biology of host-parasite interactions, Gordon Research Conference, Newport, Rhode Island, USA, June, 2006.
135. CRS career achievement award lecture in oral drug delivery: Lipids, lipophilic drugs and oral drug delivery. 33<sup>rd</sup> Annual Meeting of the Controlled Release Society, Vienna, Austria, July, 2006.
136. Drug delivery for lipophilic drugs – the present and the future. LTS Academy, Frankfurt, Germany, October, 2006.
137. Public private partnerships: A new model for drug discovery in malaria and other neglected diseases. Victorian College of Pharmacy Public Lecture, October, 2006.
138. Public private partnerships: A new model for drug discovery in malaria and other neglected diseases. Invited keynote speaker at the AAPS Post-Graduate Student Symposium. University of Kentucky, USA, April, 2007.
139. Public private partnerships: A new model for drug discovery in malaria and other neglected diseases. Nottingham University, UK, May, 2007.
140. New drugs – what are around the corner? Pharmaceutical Society of Australia, Melbourne, August, 2007.

141. Discovery treatments for neglected diseases. Science Week Presentation, Melbourne, August, 2007.
142. The new pharmacist: Changes in pharmacy education and training. Pharmacy Australia Congress, Melbourne, August, 2007.
143. Better Medicines by Design. Public Lecture in Monash Research Matters Month. Melbourne, August, 2007.
144. Public private partnerships: A new model for drug discovery in malaria and other neglected diseases. Sansom Institute, University of South Australia, August, 2007.
145. Oral drug delivery for lipophilic drugs. LTS Academy, Petersberg, Bonn, Germany, October, 2007.
146. Public private partnerships: A new model for drug discovery in malaria and other neglected diseases. Centenary Lecture, Bath University, UK, October, 2007.
147. Malaria, Bill Gates and Global Warming. The Pacific Institute, Melbourne Club, November, 2007.
148. Lipids, lymph and the oral delivery of poorly water soluble drugs. Plenary lecture at the European Drug Absorption Network, Leuven, Belgium, March, 2008.
149. Public private partnerships: A new model for drug discovery in malaria and other neglected diseases. European Drug Absorption Network, Leuven, Belgium, March, 2008.
150. Malaria drug discovery and public private partnerships. Academia and Drug Discovery Symposium. Institute of Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, April, 2008.
151. Three P's: Program, Process and People. Liver stage malaria drug discovery and development tools strategy meeting. Bill and Melinda Gates Foundation, Seattle, WA, April, 2008.
152. Malaria drug discovery and public private partnerships. School of Pharmacy, University of London, June, 2008.
153. Lipids, lymph and the oral delivery of poorly water soluble drugs. GSK Verona, Italy, June, 2008.
154. Malaria drug discovery and public private partnerships. AAPS invited lecture, Department of Pharmaceutical Chemistry, University of Kansas, July, 2008.
155. Lipids, lymph and the oral delivery of poorly water soluble drugs. AAPS invited lecture, Department of Pharmaceutical Chemistry, University of Kansas, July, 2008.
156. Keynote Address. Drug discovery for neglected diseases: Examples of successful partnerships in malaria. World congress of pharmacy and pharmaceutical sciences. 68<sup>th</sup> International Congress of FIP, Basle, Switzerland, September, 2008.
157. Public private partnerships and drug discovery for malaria. 10<sup>th</sup> Annual Scientific Meeting of Australian Society for Antimicrobials. Melbourne, February, 2009.
158. Keynote Address. Drug discovery for protozoan parasites – The essential P's. Keystone Symposia on Molecular and Cellular Biology (Drug Discovery for Protozoan Parasites). Breckenridge, Colorado, USA, March, 2009.
159. Working with drug discovery and medicinal chemistry programs. 5<sup>th</sup> Symposium of the LTS Academy (Chairs: P. Artusson and W.N. Charman). Petersberg, Bonn, Germany, October, 2009.
160. Creating and sustaining high performance organisations. CEO Forum Series Network, BioMelbourne Network, Melbourne, October 2009.
161. Drug discovery in academia. Seeding Drug Discovery Initiative Frontiers Meeting. Wellcome Trust, London, November, 2009.
162. Plenary lecture. Drug discovery and development for neglected diseases: the time is now. 24<sup>th</sup> Annual Meeting of the American Association of Pharmaceutical Scientists, Los Angeles, CA, November, 2009.
163. Malaria drug discovery and public private partnerships. Baker IDI Institute, Melbourne, August, 2010.
164. Multi-disciplinary collaboration and high-impact, translational biomedical research. Australialive Biomedical Forum, Australia House, London, September, 2010.
165. Drug discovery for malaria: The essential P's. Department of Pharmaceutical Chemistry, University of Kansas, October, 2010.

166. A significant life experience: Being a graduate student at the University of Kansas. Dedication ceremony of new pharmacy building and 125th anniversary celebration of the School of Pharmacy. University of Kansas, October, 2010.
167. Drug discovery for neglected diseases – The essential P's. GPEN 2010, University of North Carolina, Chapel Hill, NC, November, 2010.
168. Drug discovery for neglected diseases – The essential P's. PSWC 2010 Congress for Students and Postdoctoral Fellows. New Orleans, LA, November, 2010.
169. Private Partnerships and Drug Discovery for Neglected Diseases: MMV and Malaria. Invited keynote lecture in symposium entitled "Pharmaceuticals without Borders". PSWC 2010 and 25th Annual Meeting of the American Association of Pharmaceutical Scientists, New Orleans, LA, November, 2010.
170. Drug discovery for neglected diseases – The essential P's. Plenary lecture. Academy of Pharmaceutical Sciences of Great Britain, East Midlands Conference Centre, UK, August, 2011.
171. Drug discovery for neglected diseases – The essential P's. Honorary DSc degree lecture, The School of Pharmacy, University of London, London, November 2011.
172. Pharmaceutical Sciences 2020: An Australian and Pan-Asian Perspective. Invited plenary lecture. 5<sup>th</sup> FIP Pharmaceutical Sciences World Congress, Melbourne, Australia, April 2014.
173. Monash Institute of Pharmaceutical Sciences: Integrating discovery, delivery and development. Invited lecture in a Symposium entitled "Can academic drug discovery deliver?" 17<sup>th</sup> World Congress of Basic and Clinical Pharmacology, Cape Town, July 2014.
174. Pharmaceutical Sciences: Relevance | Innovation | Education. Invited plenary lecture at 30<sup>th</sup> Annual Congress of the Academy of Pharmaceutical Sciences and Technology Japan, Nagasaki, Japan, May 2015.
175. Pharmacy and Pharmaceutical Sciences: Monash | Innovation | Education. Invited Keio University International Exchange Seminar and Academy of Pharmaceutical Sciences and Technology Japan Nagai Distinguished Lectureship, Tokyo, Japan, May, 2015.
176. Decision-making in Practice: The integration of Science – the Dean's role. Invited lecture. 75<sup>th</sup> Annual Congress of the International Pharmaceutical Federation, Dusseldorf, Germany, September, 2015.
177. Drug discovery and translation at MIPS: Experiences and lessons learnt. Melbourne Brain Symposium 2015, The Florey Institute of Neurosciences and Mental Health and the Melbourne Neurosciences Institute, University of Melbourne, October 2015.
178. Teaching and learning methodologies to advance pharmacy education. Plenary lecture. 7<sup>th</sup> Asian Association of Schools of Pharmacy Annual Conference, Taipei, Taiwan, October, 2015.
179. Pharmaceutical sciences: Relevance and Impact. Plenary lecture. 7<sup>th</sup> Asian Association of Schools of Pharmacy Annual Conference, Taipei, Taiwan, October, 2015.
180. Relevance Innovation | Education. Keynote and award lecture, Asian Federation of Pharmaceutical Sciences Nagai Distinguished Scientist Award, Bangkok, Thailand, November, 2015.
181. Entrepreneurship as an essential 21<sup>st</sup> century skill for pharmacists. Keynote lecture. The Art and Science of Integrated Pharmacy Practice, Hong Kong Pharmacy Conference, Hong Kong, February, 2016.
182. Scientific and practical considerations of modified release formulations. Invited lecture. The Art and Science of Integrated Pharmacy Practice, Hong Kong Pharmacy Conference, Hong Kong, February, 2016.
183. Collaborations and partnerships: Perspectives from MIPS. Opening event, MedTech and Pharma Growth Centre, Commonwealth Government Industry Growth Centre, July, 2016.
184. BioCurate: A new venture catalyst. AusBiotech Annual National Conference, Melbourne, October, 2016.
185. Defining objectives to meet future needs: The FIP pharmaceutical workforce development goals. First Global Conference on Pharmacy and Pharmaceutical Sciences Education, Nanjing, China, November, 2016.

186. Pharmacy education at Monash University. Chinese Symposium on Higher Education in Pharmacy. First Global Conference on Pharmacy and Pharmaceutical Sciences Education, Nanjing, China, November, 2016.
187. Pharmaceutical education and workforce development. FIP Forum 2017: International education trends for pharmaceutical researchers in the next generation. At the 137<sup>th</sup> Annual Meeting of the Pharmaceutical Society of Japan, Sendai, Japan, March, 2017.
188. Entrepreneurship: An essential 21<sup>st</sup> century skill for pharmacists. Invited Distinguished Lecture, School of Pharmacy, The Chinese University of Hong Kong, Hong Kong, April, 2017.
189. E-learning and contemporary education. Invited Distinguished Lecture, School of Pharmacy, The Chinese University of Hong Kong, Hong Kong, April, 2017.
190. Academic Industry Partnerships: Learnings | Models | The Future. Invited Distinguished Lecture, School of Pharmacy, The Chinese University of Hong Kong, Hong Kong, April, 2017.
191. Education and training in the Pharmaceutical Sciences. W.N. Charman and G. Pauletti. 6<sup>th</sup> FIP Pharmaceutical Sciences World Congress. Invited plenary lecture. Stockholm, Sweden, May, 2017.
192. Education and Workforce Development. Invited lecture. 8<sup>th</sup> AIM Global Dean's forum at the 77th Annual Congress of the International Pharmaceutical Federation, Seoul, Korea, September, 2017.
193. Education – The enabler of Change. Plenary Lecture in session entitled "What is the Soul of Pharmacy". 77th Annual Congress of the International Pharmaceutical Federation, Seoul, Korea, September, 2017.
194. Pharmaceutical education and research: A Monash perspective. China Pharmaceutical University, Nanjing, China, September, 2017.
195. Transformation within the Monash Institute of Pharmaceutical Sciences, Monash Sustainable Development Institute Strategy Retreat, May, 2018.
196. Graduation commencement keynote speaker, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, May, 2018.
197. Monash Institute of Pharmaceutical Sciences. Cipla R&D Centre, Mumbai, India, November, 2018.
198. Pharmaceutical education and workforce development. 1<sup>st</sup> International symposium on the development of pharmacy schools. China Pharmaceutical University, Nanjing, China, November, 2018.
199. Pharmacy Education: Today and into the Future. Mini symposium entitled "Celebrating 10 years of Excellence in Pharmacy Education in Malaysia", Monash University Malaysia, May 2019.
200. Graduation Keynote Speaker, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, May, 2019.
201. Varro E. Tyler Distinguished Lectureship, College of Pharmacy, Purdue University, West Lafayette, Indiana, USA, September, 2019.
202. Knowledge shared is knowledge squared. Medicines for Malaria Venture 20<sup>th</sup> Anniversary symposium, Geneva, Switzerland, November, 2019.
203. Making Tomorrow Better. Barry L. Reed Distinguished Lectureship, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, November, 2019.
204. Making Tomorrow Better. Takeru and Aya Higuchi Memorial Lecture, Academy of Pharmaceutical Sciences and Technology of Japan, May, 2022.