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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

HERON THERAPEUTICS, INC.
Patent Owner.

PGR2025-00035
Patent 12,115,254

PETITION FOR POST GRANT REVIEW OF U.S. PATENT 12,115,254

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1014	Klang and Valenta, "Lecithin-based nanoemulsions," *J. Drug Del. Sci. Tech.*, 21 (1) 55-76 2011 ("Klang")
1015	Mahato and Narang, "Emulsions," in Pharmaceutical Dosage Forms and Drug Delivery, Second Ed. (Mahato and Narang, ed.) (2012) ("Mahato")
1016	Khan *et al.*, "Basics of pharmaceutical emulsions: A review," *African Journal of Pharmacy and Pharmacology*, Vol. 5(25) 2011, 2715-2725 ("Khan")
1017	Benita and Levy, "Submicron Emulsions as Colloidal Drug Carriers for Intravenous Administration: Comprehensive Physicochemical Characterization," *Journal of Pharmaceutical Sciences*, Vol. 82, No. 11, November 1993, 1069-1079 ("Benita")
1018	Hippalgaonkar *et al.*, "Injectable Lipid Emulsions—Advancements, Opportunities and Challenges," *AAPS PharmSciTech*, Vol. 11, No. 4, December 2010, 1526-1540 ("Hippalgaonkar")
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Azurity Pharmaceuticals, Inc., Azurity Pharma India LLP, and Slayback Pharma LLC ("Azurity" or "Petitioner") requests post-grant review ("PGR") of claims 1-30 ("Challenged Claims") of U.S. 12,115,254 ("the '254 patent") (Ex. 1001) purportedly owned by Heron Therapeutics, Inc. ("Heron").

I. INTRODUCTION

The '254 patent relates to emulsion formulations for intravenous or parenteral administration. Ex. 1001 at 1:22-24; Ex. 1002 ¶¶38-42. Independent claims 1, 22, and 27 require "about 0.7-0.8 wt % aprepitant" while broadly identifying common emulsion ingredients such as an "emulsifier," an "oil," a "co-surfactant," and "water." Ex. 1001 at 32:48-34:38. These claims also utilize a ratio of emulsifier to aprepitant of either "about 20:1 to 25:1" (claim 1), "about 23:1" (claim 22), or "about 24:1" (claim 27) to indirectly encompass emulsifier concentrations of anywhere between about 14% to 20% by weight. Such claims should never have been allowed.

Ground 1: Obviousness

The Challenged Claims would have been obvious over Zhou (Ex. 1003) in view of Washington (Ex. 1004), Bagwe (Ex. 1005), and Weng (Ex. 1006). Zhou is nearly anticipatory—disclosing a narrow range surrounding the claimed amount of aprepitant while identifying preferred excipients and concentrations that render obvious each of the broadly claimed, conventional emulsion components. Washington, Bagwe, and Weng, simply reflect common knowledge in the art

regarding emulsion components/amounts that shore up any shortcomings that Heron may allege regarding Zhou. Indeed, Zhou is a familiar reference to Heron as the claims of a related, but different patent directed to aprepitant emulsions that contained 14% by weight emulsifier barely survived an obviousness challenge over Zhou in District Court. Ex. 1007 at 57-58 ("The issue of obviousness in this case is a close one…. Clear and convincing evidence is a high standard, and even through Fresenius made a strong showing in various respects … in the end I concluded that Fresenius's showing was not clear and convincing….").

The crux of Heron's arguments in District Court related to the allegedly "unprecedented" and "critical" amount of emulsifier—14% by weight. Heron's argument hinged on differentiating between the content of emulsifier used in "microemulsions" and "emulsions." Such an argument loses force here in view of the specification's definition of "emulsion"—which encompasses both. It further loses force in view of the ranges for the amount of emulsifier disclosed in the prior art—which encompasses the broadly claimed ranges using either microemulsion or emulsion nomenclature. Thus, Azurity sets out a *prima facie* case of obviousness in this petition that cannot be rebutted by what is clearly non-commensurate allegations of criticality.

Grounds 2-3: Lack of Written Description and/or Enablement

Moreover, this petition intentionally places Heron in a patentability quandary. When Heron defended its prior claims to emulsions containing lesser amounts of emulsifier, Heron strenuously argued about the complexity of emulsions, the "unpredictable interactivity" of their components, and the "cascade of effects" that might result from changing the ingredients and amounts. According to Heron, the use of 14% (wt/wt) of emulsifier was "critical," "unprecedented," and afforded "unexpected," "surprising," and "unpredictable" results. In fact, Heron's position was that no POSA would ever increase the content of emulsifier because everyone knew that doing so could destabilize the emulsion. If true, and re-alleged before the PTAB, the Challenged Claims face a whole new host of patentability issues.

The Challenged Claims clearly exceed Heron's lesser, critical amount of emulsifier and encompass a landscape that Heron professed was uncertain. And they do so without a specification that demonstrated, explained, or conveyed to Heron's "skeptical" POSA that such emulsions could be obtained or how to do so. Accordingly, Heron should be hoisted with its own petard and have the Challenged Claims canceled for lack of written description and/or enablement for the reasons explained herein.

II. STATE OF THE ART

A. Aprepitant

Cancer treatment regimens often cause chemotherapy-induced nausea and vomiting ("CINV") in the patient. Ex. 1008 at 40; Ex. 1002 ¶43. In 2003, aprepitant received marketing approval for the control of CINV in cancer patients. Ex. 1008 at 41, 44; Ex. 1002 ¶44. It was also much more effective than alternative drugs. Ex. 1003 at [0002]-[0003]; Ex. 1002 ¶44. However, aprepitant was initially formulated as a capsule intended for oral administration. Ex. 1003 at [0006]; Ex. 1008 at 41, 44; Ex. 1002 ¶44. But if a patient is already experiencing nausea and vomiting, oral administration is not a particularly convenient or effective means to deliver this medication. Ex. 1003 at [0006]; Ex. 1002 ¶45. Thus, researchers had recognized that it would be advantageous to formulate aprepitant as a "soluble and stable form for parenteral administration" (i.e., a solution for injection). Ex. 1009 at [0009]; Ex. 1002 ¶¶45-47.

However, aprepitant exhibited formidable solubility properties that needed to be overcome to prepare an injectable formulation. Ex. 1008 at 44 ("The sparing water solubility of aprepitant precluded its formulation in a vehicle acceptable for intravenous administration in humans."); Ex. 1009 at [0054], [0005]-[0009]; Ex. 1002 ¶¶46-47. Aprepitant was "practically insoluble in water" and required "unacceptably high ethanol concentrations" to achieve pharmaceutically relevant

concentrations. Ex. 1009 at [0005]; Ex. 1002 ¶46. Moreover, it was also "substantially insoluble" in oil. Ex. 1009 at [0054]; Ex. 1002 ¶46. Thus, aprepitant is what is known in the art as a "Class III drug"—a substance that is "poorly soluble in both water and oil." Ex. 1004 at 139; Ex. 1002 ¶46. Such drugs are candidates for formulating as an "emulsion"—but only by adsorbing the drug at the interface between oil and water and creating "a large surface area" to accommodate their incorporation. Ex. 1004 at 139; Ex. 1002 ¶49.

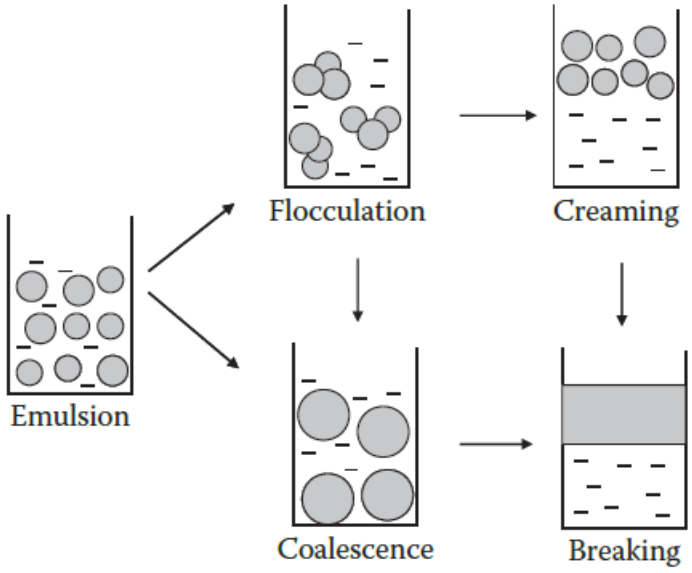
B. Emulsion Formulations

"Over the past several decades, emulsion formulations have been explored for resolving a variety of drug delivery challenges." Ex. 1011 at 196; Ex. 1012 at 89 ("promising carriers for drug delivery"); Ex. 1002 ¶¶48-49. Emulsion formulations were known to be useful for the intravenous administration of water-insoluble drugs as well as drugs that have poor solubility in both water and oil. Ex. 1004 at 138-139; Ex. 1011 at 196; Ex. 1002 ¶49. Emulsions also offered several advantages including reliable and reproducible delivery along with improved drug solubilization, chemical stability, and bioavailability. Ex. 1011 at 220; Ex. 1012 at 89; Ex. 1013 at [0029]; Ex. 1018 at 1527-1528; Ex. 1002 ¶49.

In basic terms, an "emulsion" is a mixture of two immiscible phases (usually water and oil) in which one phase is finely and uniformly dispersed as "droplets" throughout the other phase (the continuous phase). Ex. 1011 at 196; Ex. 1012 at 88;

Ex. 1002 ¶50. Depending upon which phase is predominant—oil or water—the emulsion may be considered an "oil-in-water" or a "water-in-oil" emulsion. Ex. 1011 at 196; Ex. 1002 ¶50. The '254 patent's use of the term "emulsion" is consistent with this basic understanding, although it adds an additional restriction as to the droplet size "whose diameter, in general, is between 10 nanometers and 100 microns." Ex. 1001 at 9:63-66; Ex. 1012 at 88; Ex. 1002 ¶51.

Terminology in the field has not been consistent when referring to the type of "emulsion" that is being discussed. Ex. 1014 at 55-56; Ex. 1002 ¶¶51-53. In particular, one readily sees that there is substantial overlap in characteristics for certain types. Ex. 1005 at 82; Ex. 1014 at 57 (Table I); Ex. 1002 ¶¶51-53. However, a classical "emulsion" or "macroemulsion" is regarded as being thermodynamically unstable. Ex. 1015 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 at 82; Ex. 1002 ¶52. Such instability may manifest as any of four phenomena: flocculation, creaming, coalescence, and breaking. Ex. 1015 at 264-266; Ex. 1016 at 2718-19; Ex. 1002 ¶52. Each phenomenon involves the increase in droplet size or loss of "dispersion" in the aqueous phase for an oil-in-water emulsion, as represented in the following schematic:



Ex. 1015 at 265 (Figure 14.2); Ex. 1002 ¶52.

The "physical stability of an emulsion is perhaps one of the most important characteristics, which governs its commercial success." Ex. 1011 at 215; Ex. 1002 ¶¶52-53. Properties that are generally analyzed for stability include, *inter alia*, appearance, flocculation, creaming, coalescence, changes in droplet size, pH, and zeta ("ζ") potential. Ex. 1012 at 115; Ex. 1011 at 203; Ex. 1015 at 264; Ex. 1002 ¶¶52-53, 157.

C. Typical Emulsion Components

In general, an emulsion formulation contains emulsifiers and co-emulsifiers, oil, osmotic agents, pH modifiers, and water. Ex. 1012 at 108-113; Ex. 1011 at 197; Ex. 1017 at 1070; Ex. 1018 at 1529; Ex. 1050 at 71; Ex. 1002 ¶54. With the exception of water, each of these components is further discussed below.

1. Emulsifiers

Emulsions are stabilized by the addition of a substance referred to as an "emulsifier," "emulsifying agent," or "surfactant." Ex. 1011 at 196-197; Ex. 1006 at 1157; Ex. 1002 ¶55. The emulsifier works by forming a film at the oil/water interface and reducing the interfacial tension between the oil and water phases and increasing droplet-droplet repulsion. Ex. 1011 at 197; Ex. 1012 at 88, 110; Ex. 1015 at 262; Ex. 1018 at 1529; Ex. 1002 ¶55. Such a reduction in the interfacial tension delays the coalescence of the two phases. Ex. 1015 at 260; Ex. 1002 ¶55.

"The choice of emulsifier is driven by its toxicity profile." Ex. 1018 at 1529; Ex. 1011 at 197-198; Ex. 1002 ¶56. "Lecithin is perhaps the most widely used natural emulsifying agent" and has been used in the food industry for centuries while further enjoying use in pharmaceuticals. Ex. 1014 at 58; Ex. 1011 at 198; Ex. 1017 at 1070 ("The emulsifiers most frequently used in parenteral emulsion formulations are phospholipids (generally from egg yolk sources)…."); Ex. 1019 at 192 ("While a wide variety of surfactants are available … relatively few are approved for [intravenous] administration. Natural phosphatides, principally from egg yolk or soybean, are in most widespread use."); Ex. 1005 at 83; Ex. 1002 ¶56. Lecithin is a "phospholipid" obtained from either egg yolk or soybeans. Ex. 1011 at 199; Ex. 1012 at 110; Ex. 1002 ¶56. It "can be totally biodegraded and metabolized" while being recognized as "well-tolerated," "non-toxic," and "suitable for long-term use

and high-dose infusion." Ex. 1006 at 1157; Ex. 1002 ¶56. Accordingly, lecithin "should always be the first choice" of emulsifier. Ex. 1006 at 1157; Ex. 1002 ¶56. Indeed, for an aprepitant emulsion, "egg yolk phospholipids" had been identified as being "preferred." Ex. 1003 at [0010]; Ex. 1002 ¶75.

"The amount of emulsifying agent is one of the most important factors" affecting an emulsion's stability. Ex. 1016 at 2719; Ex. 1011 at 216; Ex. 1002 ¶¶57-58. Too little and the oil droplets will agglomerate while too much will allow for coalescence. Ex. 1014 at 64; Ex. 1011 at 218; Ex. 1016 at 2719; Ex. 1018 at 1532; Ex. 1019 at 194 (Table I); Ex. 1002 ¶¶58-60. Accordingly, in any emulsion there is an optimal concentration "window" for the emulsifier. Ex. 1002 ¶61. Depending upon the type of emulsion being prepared, the emulsifier concentration could be as little as 1% to as much as 20% by weight. Ex. 1005 at 82 (Table 2); Ex. 1002 ¶61.

2. Oil

For an oil-in-water emulsion, an "oil" is obviously one of the components. Ex. 1016 at 2715; Ex. 1002 ¶62. The oil phase is usually employed to assist dissolution of the drug; therefore, choice of the oil is often dictated by the solubility and stability of the drug molecule in the specific oil. Ex. 1018 at 1529; Ex. 1012 at 109; Ex. 1002 ¶62. Vegetable oils have been a popular choice because of their well-established biocompatibility. Ex. 1012 at 108-109; Ex. 1011 at 197; Ex. 1018 at 1527, 1529; Ex. 1002 ¶63. The oils most commonly used in parenteral emulsions

include, *inter alia*, long chain triglycerides such as soybean oil and safflower oil, medium chain triglycerides such as fractionated coconut oil, and fatty acids/derivatives such as oleic acid and ethyl oleate. Ex. 1011 at 197 and Table 10.1; Ex. 1017 at 1070 (referencing "soybean, safflower, and cottonseed oils"); Ex. 1002 ¶63. For an aprepitant emulsion, the choice of oil was noticeably similar, including triglycerides and ethyl oleate, with soybean oil being "preferred." Ex. 1003 at [0010]; Ex. 1002 ¶64.

3. Co-surfactants/Co-emulsifiers/Co-solvents

When drugs have little to no solubility in either water or oil, a common formulation strategy for preparing an emulsion is to incorporate a co-solvent in which the drug is soluble. Ex. 1011 at 201, 206-207; Ex. 1018 at 1530; Ex. 1002 ¶65. Such a component is also referred to as a "co-surfactant" or a "co-emulsifier." Ex. 1005 at 80, 82 (Table 2); Ex. 1003 at [0010]; Ex. 1002 ¶65. "Suitable pharmaceutically acceptable cosolvents include ethanol, propylene glycol, PEG300, dimethylacetamide, triacetin, and mixtures of these solvents." Ex. 1011 at 201; Ex. 1002 ¶66.

Despite its solubility issues, aprepitant was known to have some solubility in ethanol. Ex. 1009 at [0005], [0045]; Ex. 1002 ¶66. Accordingly, it was a "preferred" co-emulsifier/co-surfactant/co-solvent for the preparation of an aprepitant-containing emulsion formulation. Ex. 1003 at [0010]; Ex. 1002 ¶75.

4. pH modifier

For an emulsion formulation, there is a preference for a "slightly alkaline pH" because the pH of the formulation was known to decrease during sterilization and storage. Ex. 1018 at 1529; Ex. 1002 ¶¶67-68. Moreover, "[t]he pH of the emulsion is generally adjusted to 7-8 to allow physiological compatibility and maintain emulsion physical integrity…." Ex. 1017 at 1070; Ex. 1012 at 112; Ex. 1002 ¶68. A pH within this range also minimizes hydrolysis of the oil and phospholipids. Ex. 1012 at 112.

The addition of a pH modifier is a necessary component in some circumstances. Ex. 1011 at 217; Ex. 1006 at 1159; Ex. 1018 at 1532; Ex. 1002 ¶67. Sodium oleate was a known buffering agent that also functioned as a co-emulsifier and was a "well-known" stabilizer of emulsions. Ex. 1006 at 1159 (stating, *inter alia*, that "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 at 1070; Ex. 1002 ¶69.

5. Osmotic agents

The aqueous phase should also be modified with an osmotic agent to make the emulsion isotonic. Ex. 1011 at 203; Ex. 1006 at 1159-60; Ex. 1012 at 112; Ex. 1002 ¶70. Isotonicity is important to prevent the injected formulation from disturbing cells that come in contact with the emulsion. Ex. 1012 at 112; Ex. 1002

¶70. Accordingly, the tonicity or osmolarity of the emulsion is an important consideration during development. Ex. 1011 at 203; Ex. 1002 ¶71. The adjustment of tonicity/osmolarity is normally achieved using glycerin/glycerol, sorbitol, or xylitol. Ex. 1018 at 1529; Ex. 1017 at 1070 ("Glycerol is usually recommended as an isotonic agent and can be found in almost every parenteral emulsion."); Ex. 1011 at 203 ("[W]ater-soluble excipients such as glycerol are frequently added to adjust tonicity of emulsions intended for parenteral use."); Ex. 1002 ¶71. Sucrose was also a known tonicity adjuster in parenteral formulations. Ex. 1050 at 68.

For an aprepitant emulsion, it was recommended that "one or more of glycerin, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids" be included in the formulation. Ex. 1003 at [0010]; Ex. 1002 ¶71.

III. THE CHALLENGED CLAIMS ARE UNPATENTABLE

Azurity requests cancellation of claims 1-30.

A. Grounds of Challenges

PGR is requested for the following grounds:

Ground	Basis	Challenged Claims
1	Obviousness over Zhou (Ex. 1003) in view of Washington (Ex. 1004), Bagwe (Ex. 1005), and Weng (Ex. 1006)	1-30
2	Lack of Written Description	1-30
3	Lack of Enablement	1-30

B. The Prior Art

All asserted references are §102(a)(1)-(2) prior art in view of the earliest alleged effective filing date asserted by the '254 patent, February 1, 2016.

Reference	Publication	Exhibit No.
1. CN102379845 ("Zhou")	2012	Ex. 1003
2. Washington, "Stability of lipid emulsions for drug delivery," *Adv. Drug. Del. Rev.* 20 (1996), 131-145 ("Washington")	1996	Ex. 1004
3. Bagwe *et al.*, "Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons," *Critical Reviews™ in Therapeutic Drug Carrier Systems*, 18(1); 77-140 (2001) ("Bagwe")	2001	Ex. 1005
4. Weng *et al.*, "Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres," *Eur. J. Lipid Sci. Technol.* 2012, *114*, 1154-64 ("Weng")	2012	Ex. 1006

The accompanying declaration of Dr. William Charman (Ex. 1002) supports this Petition.

IV. LEVEL OF ORDINARY SKILL IN THE ART

Heron previously submitted during litigation concerning emulsion formulations that a person of ordinary skill ("POSA"):

> would have a bachelor's degree in chemistry, pharmaceutics, 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 at 17. This definition has been applied. Ex. 1002 ¶¶31-33.

V. CLAIM CONSTRUCTION

The Board need only construe claims to the extent necessary to resolve controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Claim language is given the meaning it would have to a POSA at the time the application was filed, in view of the patent specification. For the Board's clarity, Azurity sets forth the specification's express definition of "emulsion," which is recited in claims 1-30.

The term "emulsion" is expressly defined. Ex. 1001 at 9:63-66; Ex. 1002 ¶36. This definition encompasses any type of emulsion, including macro-, micro-, and nanoemulsions, so long as it is 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 at 9:63-66; Ex. 1002 ¶51 (discussing Ex. 1005 at 82, Ex. 1014 at 57, and Ex. 1015 at 255, all disclosing macro-, micro-, and nanoemulsions containing droplets within the size range of 10 nm - 100 μm). This definition has been applied in this petition.

Considering the closeness of the prior art and the specific arguments herein, Azurity does not believe that any other claim terms require construction.

VI. GROUND 1: OBVIOUSNESS OVER ZHOU IN VIEW OF WASHINGTON, BAGWE, AND WENG

Each limitation of the Challenged Claims was either expressly disclosed in the prior art or was manifestly obvious. Zhou (Ex. 1003) discloses emulsions meeting nearly every limitation: 0.05 to 2 % (wt.) aprepitant; 5 to 30 % (wt.) oil; 0.5 to 10 % (wt.) emulsifier; 1 to 10 % (wt.) co-surfactant (which is a co-emulsifier); 5 to 20 % (wt.) of protective agent (which is an osmotic agent); and 60 to 80 % (wt.) water for injection. Moreover, Zhou exemplified many of the same components that Heron now claims, such as soybean oil, egg yolk phospholipid as an emulsifier, ethanol as a co-emulsifier, and sucrose as the protective (i.e., osmotic) agent.

Anything not explicitly addressed by Zhou would have been obvious to a POSA in view of the knowledge in the art. For example, Bagwe (Ex. 1005) described various emulsion technologies and reported various components and their concentrations, including that for emulsifiers/surfactants. Weng (Ex. 1006) disclosed the use of sodium oleate as a pH adjusting agent for emulsions. Washington (Ex. 1004) explained that drugs with poor solubility in water and oil (such as aprepitant) can be loaded into an emulsion by adsorbing to the oil-water droplet interface. A POSA would have known that such loading would be facilitated by increasing the available interfacial area—which is readily achieved by increasing

emulsifier content to decrease droplet size. An optimally higher emulsifier concentration was also expected to provide superior long-term stability to the emulsion thereby avoiding any issue with incomplete dissolution or eventual precipitation of components from the emulsion.

A. Introduction to Zhou

Zhou is entitled "[a] type of aprepitant microemulsion for injection and its preparation method." Ex. 1003 at (54); Ex. 1002 ¶73. Zhou explains that emulsion preparations can, *inter alia*, "improve the solubility of poorly water-soluble drugs and fat-soluble drugs" and "are increasingly favored by medical workers as drug carriers, especially in injection drug delivery." Ex. 1003 at [0005]; Ex. 1002 ¶73. Zhou identifies the purpose of its disclosure as "provid[ing] an injectable aprepitant microemulsion to effectively solve the problems of inconvenient clinical application of oral aprepitant, poor absorption, and low bioavailability." Ex. 1003 at [0007]; Ex. 1002 ¶73.

For preparing an aprepitant emulsion, Zhou describes the use of the following components/amounts:

> ***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***;[1] the oil for injection is one or more of

[1] Unless otherwise indicated, all bold emphases are added.

> ***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.

Ex. 1003 at claim 1, Abstract, [0008]; Ex. 1002 ¶74. Zhou indicates that the particle size of the emulsions for injection is between 50-150 nm. Ex. 1003 at [0012]; Ex. 1002 ¶75. Zhou further identifies an optimal pH for injection in the range of 6.0 to 8.0. Ex. 1003 at [0011]; Ex. 1002 ¶75.

Zhou also identifies "[b]eneficial effects" for the described emulsions:

> 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 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.

Ex. 1003 at [0017]; Ex. 1002 ¶76. Unsurprisingly, Zhou was identified as the "closest prior art" to the '254 patent. Ex. 1022 at 39; Ex. 1002 ¶77.

B. Introduction to Washington

Washington is entitled "Stability of lipid emulsions for drug delivery." Washington describes "the factors influencing the stability of phospholipid-stabilized emulsions, and the effects of drug incorporation on the stability profile." Ex. 1004 at Abstract; Ex. 1002 ¶78. Washington explains that "[t]he stability of colloidal formulations [i.e., emulsions] is paramount in their use as drug delivery systems." Ex. 1004 at 132 (identifying, *inter alia*, "a shelf life of at least a year, preferably more"); Ex. 1002 ¶78.

Washington teaches that for a given emulsion, "the effect of the drug can often be predicted" from the physicochemical properties of the drug, such as solubility characteristics and ionization properties. Ex. 1004 at 138; Ex. 1002 ¶79. Washington teaches that "Class I drugs" are largely water soluble and hence a significant fraction of the drug would be present in the aqueous phase of the emulsion. Ex. 1004 at 138-39 (noting, inter alia, that such drugs are "not good candidates for emulsion formulations"); Ex. 1002 ¶79. Washington further explains that "Class II drugs" are predominantly oil-soluble and "are good candidates for emulsion delivery." Ex. 1004 at 139; Ex. 1002 ¶79. Lastly, Washington explains that "Class III drugs are poorly soluble in both water and oil, and can only be loaded

into an emulsion by absorbing to the droplet interface." Ex. 1004 at 139 (describing a need to "have a large surface area available for loading"); Ex. 1002 ¶¶79-80.

C. Introduction to Bagwe

Bagwe is entitled "Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons." Despite this title, Bagwe describes different types of colloidal drug delivery systems—including emulsions and microemulsions. Ex. 1005 at 78-79, 82-83; Ex. 1002 ¶¶81-82. For example, Bagwe contains a table listing various parameters for these 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 %

Ex. 1005 at 82 (Table 2); Ex. 1002 ¶82. In discussing the need for a biocompatible surfactant, Bagwe teaches that "[p]hospholipids, particularly lecithin, offer a possible nontoxic alternative emulsifier for parenteral use." Ex. 1005 at 101; Ex. 1002 ¶83.

D. Introduction to Weng

Weng is entitled "Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres." Weng explains 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." Ex. 1006 at 1155; Ex. 1002 ¶84.

Weng teaches that emulsifiers are an "essential component of lipid emulsions." Ex. 1006 at 1157; Ex. 1002 ¶85. Weng explains that "lecithin should always be the first choice" because egg yolk lecithin and soybean lecithin are "well-tolerated and non-toxic compounds with excellent biocompatibility." Ex. 1006 at 1157; Ex. 1002 ¶85. However, Weng explains that sometimes a co-emulsifier is needed to "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." Ex. 1006 at 1158; Ex. 1002 ¶85.

Weng explains that sodium oleate is a water-soluble emulsifier that, *inter alia*, stabilizes the emulsion against coalescence. Ex. 1006 at 1159; Ex. 1002 ¶86. Moreover, Weng teaches that "[sodium oleate] had a certain buffering capacity to reduce the pH change to a minimum.... Hence, a small amount of [sodium oleate] was often used in commercial parenteral emulsions … to obtain stable formulations during the autoclaving process." Ex. 1006 at 1159; Ex. 1002 ¶86.

E. Zhou in view of Washington, Bagwe, and Weng Renders the Challenged Claims Obvious

1. Claim 1

a. Preamble

Claim 1's preamble recites: "An injectable pharmaceutical emulsion…." Should the Board find that this preamble is limiting, Zhou discloses an "injectable pharmaceutical emulsion." Ex. 1003 at (54), Abstract, claims 1-9, [0001], [0007]-[0008], [0014]-[0015], [0017]; Ex. 1002 ¶90. Zhou's description of "microemulsions" falls squarely within the '254 patent's definition of "emulsion." *Compare, e.g.*, Ex. 1003 at [0012], [0020] *with* Ex. 1001 at 9:63-66, 19:41-54; Ex. 1002 ¶91. Indeed, Heron's trial expert previously admitted that Zhou disclosed "a conventional emulsion." Ex. 1023 at 1375:16-1376:7; Ex. 1007 at 36.

Thus, Zhou's disclosure meets the preamble of claim 1.

b. Aprepitant

Claim 1's emulsion requires "about 0.7-0.8 wt % aprepitant." Zhou is entitled "[a] type of ***aprepitant*** microemulsion for injection and its preparation method." Ex. 1003 at (54); Ex. 1002 ¶92. Zhou refers to aprepitant emulsions throughout its disclosure. Ex. 1003 at Abstract, claims 1-10, [0001]-[0002], [0007]-[0009], [0011]-[0014], [0016]-[0017], [0019]-[0036]; Ex. 1007 at 10 ("In 2012, a group of researchers in China succeeded in creating an injectable aprepitant formulation in

the form of a lipid emulsion."); Ex. 1002 ¶92. Thus, Zhou's emulsions include aprepitant.

With respect to the amount of "about 0.7-0.8 wt %," Zhou teaches that the aprepitant emulsions may include 0.05-2% by weight aprepitant. Ex. 1003 at Abstract, claim 1, [0008]; Ex. 1002 ¶93. Thus, Zhou discloses a range for aprepitant's concentration that fully encompasses the claimed range. Ex. 1002 ¶93; Ex. 1007 at 32-33 ("The recited features of the asserted claims are similar to those set forth in [Zhou] in several respects. The concentration of aprepitant in the asserted claims is 0.7 wt/wt%, which falls well within the range set forth in the [Zhou] specification (0.05% to 2%), and is close to the concentration set forth in several of the examples in [Zhou].") (internal citations and footnote omitted).

"[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *see also In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("[W]hen, as here, the claimed ranges are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap."). Decades of Federal Circuit precedent has recognized that "'where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'" *E.I. DuPont De Nemours & Co. v. Synvina C.V.*, 904 F.3d 996,

1006 (Fed. Cir. 2018) (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955). "'[I]t is to be expected that a change ... in concentration ... would be an unpatentable modification.'"); *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736-41 (Fed. Cir. 2013) (holding the prior art's disclosure of 0.01% to 1% of a component rendered obvious a claim directed to 0.3% of the component). As the active ingredient in Zhou's emulsions, a POSA would have expected the amount of aprepitant to affect the utility of the formulation and would have sought to optimize the amount of the drug. Ex. 1003 at [0002]-[0008]; Ex. 1002 ¶93. Thus, Zhou's disclosure of encompassing ranges renders obvious "about 0.7-0.8 wt % aprepitant."

Zhou further discloses the inclusion of more specific amounts of aprepitant—0.5% and 1% by weight. Ex. 1003 at [0019], [0025], [0029], [0035]; Ex. 1007 at 33 n.7; Ex. 1002 ¶94. These individual values collectively constitute a narrower range that fully encompasses the claimed range of "about 0.7-0.8 wt %." *Iron Grip*, 392 F.3d at 1322 ("The prior art disclosed weight plates with one, two and four elongated handles. Iron Grip is claiming a weight plate with three elongated handles, within the range of the prior art."). Accordingly, "about 0.7-0.8 wt % aprepitant" also falls within the narrower range of Zhou and is *prima facie* obvious. *Iron Grip*, 392 F.3d at 1321-23; *Galderma*, 737 F.3d at 736-41; *Peterson*, 315 F.3d at 1329; Ex. 1002 ¶95.

c. Emulsifier

Claim 1's emulsion requires an "emulsifier." Zhou describes the inclusion of an "emulsifier" in the aprepitant emulsion. Ex. 1003 at Abstract, claims 1, 6, and 9-10, [0008]-[0010], [0016]; Ex. 1007 at 11-12 ("As relevant to the patents in suit, the examples and claims of [Zhou] specifically call out the use of … egg yolk phospholipid as the emulsifier (examples 1, 4, 5, 6, and 7; claim 6)…."); Ex. 1002 ¶96. Moreover, Zhou identifies "egg yolk phospholipids" as the "preferred" emulsifier. Ex. 1003 at [0010]; Ex. 1002 ¶97. Zhou provides several working examples of emulsions that contain "egg yolk phospholipid" as the emulsifier. Ex. 1003 at [0019]-[0020], [0025]-[0033]; Ex. 1002 ¶97. A POSA would have understood that "egg yolk phospholipid" is a type of "egg phospholipid" that is synonymous with "egg yolk lecithin." Ex. 1002 ¶97; Ex. 1004 at 133-134; Ex. 1024 at 385-86; Ex. 1007 at 12 n.4 ("The parties and the witnesses refer variously to that emulsifier as "egg yolk phospholipid," "lecithin," and "egg yolk lecithin." For purposes of this case, the three terms refer to the same compound, which is a fatty substance that is both hydrophilic and lipophilic and is known to be suitable for use in emulsions.").

Thus, Zhou describes aprepitant emulsions that include an "emulsifier" such as a "phospholipid," an "egg phospholipid," and an "egg lecithin." Ex. 1002 ¶98.

d. Oil

Claim 1's emulsion requires an "oil." Zhou describes the inclusion of an "oil" in the aprepitant emulsion. Ex. 1003 at Abstract, claims 1, 5, and 9-10, [0008]-[0010], [0016]; Ex. 1007 at 11-12 ("As relevant to the patents in suit, the examples and claims of [Zhou] specifically call out the use of soybean oil as one of the components that can serve as the oil for injection (examples 1, 4, 5, 6, and 7; claim 1…."); Ex. 1002 ¶99. Moreover, Zhou identifies "soybean oil" as the "preferred" oil while, *inter alia*, identifying additional alternatives such as "olive oil," "ethyl oleate," and "triglycerides." Ex. 1003 at [0010]; Ex. 1002 ¶99. Each of Zhou's working examples contain an "oil" (Ex. 1003 at [0019]-[0036]) while embodiments 1 and 4-7 each utilize Zhou's preferred "soybean oil." Ex. 1002 ¶99.

Thus, Zhou describes aprepitant emulsions that include an "oil" such as a "soybean oil" while identifying alternatives such as "olive oil," "ethyl oleate," and "triglycerides." Ex. 1002 ¶100.

e. Co-surfactant

Claim 1's emulsion requires a "co-surfactant." The '254 patent describes "co-surfactants" as being an alcohol, such as ethanol. Ex. 1001 at 3:19-20, 14:5-8; Ex. 1002 ¶101. Instead of referring to a "co-surfactant," Zhou refers to the inclusion of the same excipient class when referencing the "co-emulsifier." Ex. 1003 at claims 1, 9, [0008]-[0010]; Ex. 1002 ¶101. Indeed, Zhou identifies "ethanol" as being

"preferred" for inclusion in the emulsion. Ex. 1003 at [0010]; *see also id*. at claim 1 (identifying four alcohols, including ethanol), 7 (ethanol), 10 (ethanol), [0016] (ethanol); Ex. 1007 at 11-12 ("As relevant to the patents in suit, the examples and claims of [Zhou] specifically call out the use of … ethanol as the co-emulsifier (examples 1, 4, 5, 6, and 7; claim 7)…."); Ex. 1002 ¶101. Each of Zhou's working examples contain an alcohol (Ex. 1003 at [0019]-[0036]) while embodiments 1 and 4-7 each utilize Zhou's preferred "ethanol." Ex. 1002 ¶101.

Thus, Zhou describes aprepitant emulsions that include a "co-surfactant" such as an "alcohol" or "ethanol." Ex. 1002 ¶102.

f. Water

Claim 1's emulsion requires "water." Zhou describes the inclusion of "water" in the aprepitant emulsion. Ex. 1003 at Abstract, claims 1, and 9-10, [0007]-[0009], [0016]; Ex. 1007 at 11-12 ("As relevant to the patents in suit, the examples and claims of [Zhou] specifically call out the use of … water for injection (all examples and claim 9); Ex. 1002 ¶103. Each of Zhou's working examples contain "water." Ex. 1003 at [0019]-[0036]; Ex. 1002 ¶103.

Thus, Zhou describes aprepitant emulsions that include "water." Ex. 1002 ¶104.

g. An emulsifier to aprepitant ratio that ranged from "about 20:1 to 25:1 (wt/wt %)" would have been obvious

Claim 1's emulsion also requires that "the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %)." Claim 1 further recites "about 0.7-0.8 wt % aprepitant." Thus, using basic arithmetic, a POSA would understand that the amount of emulsifier falling within the ratio of claim 1 would be "about"[2] 14-20% by weight. Ex. 1002 ¶105 (calculating that 20 times 0.7% equals 14 and 25 times 0.8% equals 20). Including such an amount of emulsifier, and thereby arriving at the claimed ratio, would have been obvious. Ex. 1002 ¶¶105-127.

As an initial matter, a POSA would have been motivated to develop a stable aprepitant emulsion. Ex. 1002 ¶¶106-107. For example, Washington explained:

> 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

[2] The '254 patent states: "[a]s used herein, the term 'about' means ±5%, ±10%, or ±20% of the value being modified." Ex. 1001 at 9:61-62. For purposes of this petition, the additional breadth surrounding the claimed weight percentages that is afforded by the term "about" does not render the claims any less obvious.

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

Ex. 1004 at 132; Ex. 1012 at 108 ("[E]mulsions must be biocompatible, biodegradable, nontoxic, sterile, isotonic, physically and chemically stable, and nonimmunogenic."); Ex. 1025 at [0005]; Ex. 1012 at 115 ("The stability of an emulsion formulation is vital for its use in clinical applications….A long-term stability testing schedule should be performed on all promising formulation candidates."); Ex. 1011 at 213-214 (identifying a clinical concern "perhaps due to incomplete incorporation of the drug into the emulsion droplets and precipitation of drug"), 215 ("physical stability of an emulsion is perhaps one of the most important characteristics, which governs its commercial success."); Ex. 1002 ¶106.

Accordingly, a POSA would have evaluated the stability of any aprepitant emulsion being prepared, including Zhou's emulsions, and would have monitored known parameters for any precipitation in view of aprepitant's poor solubility profile. *See* Section II.A, *supra*; Ex. 1002 ¶107. Indeed, Heron has repeatedly argued that Zhou's emulsions were not suitably stable. Ex. 1026 at 16, 17, 19-20; Ex. 1020 at 28 n.16, 38; Ex. 1027 at 18. Thus, a POSA having encountered any such stability concerns from Zhou's emulsions would have been motivated to improve upon their stability and would have reasonably expected that increasing the

emulsifier content would facilitate dissolution of aprepitant and stabilize the emulsion. Ex. 1002 ¶107.

i. Emulsifiers were known to influence emulsion stability and improve drug solubility

An emulsifier is a type of surfactant. Ex. 1012 at 110-112 (discussing surfactants under the heading "Emulsifiers"); Ex. 1002 ¶108. Their purpose in the formulation "is to emulsify the oil phase and provide physical stability against flocculation and coalescence during storage." Ex. 1012 at 110; Ex. 1002 ¶108. They accomplish this "by reducing the oil-water interfacial tension and promoting droplet-droplet repulsion." Ex. 1012 at 110; *id*. at 90; Ex. 1018 at 1529, 1533 ("Emulsifiers enhance emulsion stability not only by reducing the droplet size but also by forming an interfacial film at the [oil/water] interface."); Ex. 1002 ¶108.

A POSA would have also been aware of the effect of emulsifier concentration on stability:

> 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 at 2719 (internal citations omitted); Ex. 1011 at 215-216; Ex. 1019 at 194 (Table I); Ex. 1002 ¶¶109-110. Thus, a POSA would have been motivated to evaluate both low and high concentrations of emulsifier to determine the "window" in which emulsion stability was afforded. Ex. 1002 ¶111. A POSA would have also had a reasonable expectation of determining this "window" to arrive at the claimed emulsion simply by designing experiments to increase the relative concentration of the emulsifier. Ex. 1002 ¶111.

Moreover, a POSA would have known that a surfactant/emulsifier is "often used" to improve drug solubility. Ex. 1028 at 148-149 ("Surfactants in parenterals can … prevent drug precipitation upon injection…."); Ex. 1002 ¶112. Indeed, aprepitant's solubility was known to be improved by a concentration dependent increase in surfactant. Ex. 1009 at [0043]-[0047]; Ex. 1002 ¶113. Accordingly, a POSA would have been further motivated to evaluate a range of emulsifier concentrations to improve aprepitant's solubility in the formulation and reduce the likelihood of precipitation—which was a clinical concern encountered when administering emulsions of poorly soluble drugs. Ex. 1011 at 213-214; Ex. 1015 at 258; Ex. 1028 at 149; Ex. 1002 ¶¶111-115. Thus, a POSA would have had a reasonable expectation of arriving at claim 1 by increasing the relative concentration of the emulsifier to improve solubility and avoid precipitation. Ex. 1002 ¶¶111-115.

ii. Smaller emulsion droplets were preferred for stability and aprepitant dissolution

Droplet size was known to have a direct impact on emulsion stability and was recognized as being "amongst the most importance characteristics of an injectable emulsion." Ex. 1018 at 1531; Ex. 1019 at 193 ("[A] droplet mean diameter of less than 1 μm is highly desirable."); Ex. 1002 ¶118. Moreover, for a drug like aprepitant, which is poorly soluble in both water and oil, a POSA would have known to load it into an emulsion by adsorbing it to the droplet interface. Ex. 1004 at 139; Ex. 1011 at 201 ("[T]here 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."), 207; Ex. 1002 ¶116. However, since "the interfacial layer could only solubilize a certain amount of drug" a POSA would have known that sufficient interface area would be needed for complete loading of the drug otherwise "drug nanocrystals could form." Ex. 1011 at 202. Smaller droplets were known to have an advantageous effect for this purpose by providing increased interfacial surface area to an emulsion. Ex. 1029 at 862; Ex. 1028 at 150; Ex. 1002 ¶¶116-117. Accordingly, a POSA would have been motivated to decrease the droplet size in the emulsion to increase the available interfacial surface area to facilitate the loading of aprepitant and improve stability. Ex. 1002 ¶¶118-120.

iii. Increasing emulsifier concentration was known to produce smaller droplets

An increase in emulsifier concentration was expected to afford smaller droplet size. Ex. 1018 at 1533; Ex. 1019 at 194 (Table I); Ex. 1028 at 150 ("Surfactants are added to emulsion systems to … reduce initial droplet size…."); Ex. 1002 ¶119. Accordingly, a POSA would have been motivated to evaluate increasingly higher concentrations of emulsifier to optimize droplet size for stability and aprepitant loading. Ex. 1002 ¶¶119-120.

Indeed, it was well-understood that for certain types of emulsions, relatively large amounts of emulsifier were required "in order to stabilize the large interfacial area created by" the small droplets that were present. Ex. 1005 at 80; Ex. 1028 at 150 (discussing the need for high levels of surfactants in emulsions having "numerous small droplets."); Ex. 1002 ¶121. Moreover, Bagwe explains that emulsions may contain from "1-20%" emulsifier/surfactant while microemulsions may contain "> 10%" emulsifier/surfactant. Ex. 1005 at 82, 88-89 (identifying "10-40%" surfactant for microemulsions); Ex. 1002 ¶122. Such emulsifier concentrations were not outliers. Ex. 1025 at [0039]-[0041] (discussing emulsifiers, including egg yolk lecithin phospholipids and concentrations of "about 0.001 wt% to about 15 wt %"); Ex. 1002 ¶¶122-124. Accordingly, it would have been *prima facie* obvious to evaluate greater concentrations of emulsifier than reported in Zhou to identify the optimal window of stability. *See* Section VI.E.1.b, *supra* (collecting

cases). A POSA would have further understood that increasing the emulsifier concentration would be needed to decrease droplet size and increase the interfacial surface area to facilitate aprepitant loading. Ex. 1002 ¶¶123-124. Thus, a POSA would have had a reasonable expectation of arriving at claim 1 by increasing the emulsifier content to decrease droplet size and facilitate aprepitant loading and emulsion stability. Ex. 1002 ¶¶125-127.

Heron has previously defended against obviousness by alleging that microemulsions are of little relevance. Ex. 1007 at 35-36. The district court did not fully agree. *Id*. However, any attempt to distinguish the claimed "emulsions" from microemulsions or even Bagwe's teachings is meritless. The '254 patent's definition of "emulsion" encompasses any type of emulsion so long as the droplets are "between 10 nanometers and 100 microns." Ex. 1001 at 9:63-66. By its terms, this definition encompasses "microemulsions" as described in Bagwe. Ex. 1005 at 88; Ex. 1002 ¶124. Additionally, Bagwe contains teachings for both emulsions and microemulsions—either of which encompass the presently claimed emulsifier concentrations. Ex. 1005 at 82 (Table 2); Ex. 1002 ¶123. Lastly, Bagwe's teachings are particularly relevant here because a POSA would have recognized that Bagwe describes using large amounts of emulsifier/surfactant as a method for stabilizing an emulsion with a reduced droplet size and increased interfacial area as Petitioner has described for facilitating aprepitant loading. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S.

398, 419–20, (2007) ("One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims."); *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). Indeed, Bagwe's additional teachings regarding microemulsions have been utilized to formulate drugs having solubility limitations like aprepitant and a POSA would have recognized such relevance to an aprepitant emulsion. Ex. 1002 ¶124.

iv. The ratio of "about 20:1 to 25:1 (wt/wt %)" was a matter of routine experimentation

Based on the combined teaching of Zhou, Washington, and the knowledge in the art regarding emulsifiers, a POSA would have understood that increasing the emulsifier was reasonably expected to decrease the droplet size, increase the interfacial surface area, and afford better loading of aprepitant while increasing the emulsion's stability. The only parameter to be determined was the appropriate "window" for emulsifier concentration—a matter of routine experimentation when considering the justifications to do so that the prior art afforded. *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 730 (Fed. Cir. 2017) (holding that experimental details that a POSA "would have utilized via routine experimentation, armed with the principles disclosed in the prior art" were obvious); Ex. 1002 ¶127.

It is of no moment that Zhou did not itself include an additional disclosure of a range of emulsifier content that overlapped/encompassed the claimed amount.

Obviousness does not demand such a disclosure. As Petitioner has explained, the "general conditions" regarding emulsifier concentration were known, including overlapping and encompassing concentrations. Moreover, Petitioner identified particular motivations for increasing the emulsifier concentration of Zhou—particularly in view of Heron's allegations that Zhou's emulsions were not suitably stable. Accordingly, "it is not inventive to discover the optimum or workable ranges by routine experimentation" for the emulsifier concentration now claimed. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *Aller*, 220 F.2d at 456). Moreover, the Federal Circuit recently clarified that there is no "brightline rule" that would restrict the application of "routine experimentation" here even in the absence of overlapping/encompassing emulsifier concentrations in view of the motivations for increasing such amounts that Petitioner has identified. *Purdue Pharma L.P. v. Accord Healthcare, Inc.*, No. 2023-1953, 2024 WL 5244764, at *12 (Fed. Cir. Dec. 30, 2024). Thus, even the absence of a prior art aprepitant emulsion that overlapped/encompassed the emulsifier concentrations now claimed does not negate a finding of obviousness.

Because it would have been obvious to increase the emulsifier concentrations in Zhou (and arrive at the claimed concentration of "about 0.7-0.8 wt % aprepitant," *see* Section VI.E.1.b, *supra*), a POSA would have arrived at the ratio of emulsifier to aprepitant of "about 20:1 to 25:1 (wt/wt %)" as a matter of course during the

routine experimentation. Ex. 1002 ¶127. Indeed, holding the amount of aprepitant constant while increasing the emulsifier content will cause the ratio to rise. Moreover, a POSA would have known from Zhou that ratios of emulsifier to aprepitant ranging from 10:1 to as much as 120:1 were already being considered. Ex. 1003 at [0035], [0023]; Ex. 1002 ¶127. Thus, through routine experimentation, a POSA would have arrived at "about 0.7-0.8 wt % aprepitant" and an emulsifier to aprepitant ratio of "about 20:1 to 25:1 (wt/wt %)" simply by increasing the emulsifier content to anywhere in the range of about 14-20% by weight. Ex. 1002 ¶127.

***

Accordingly, a POSA would have had ample motivation and expectation of success to have combined the teachings of Zhou and make the slightest of modifications to emulsifier content to arrive at the features of claim 1. As such, claim 1 would have been obvious.

2. Claims 2-7 recite obvious emulsifiers and amounts

Claims 2 and 5 depend from claim 1 and require that the emulsifier is either a "phospholipid" (claim 2) or "egg lecithin" (claim 5). Ex. 1001 at claims 2, 5; Ex. 1002 ¶¶128-129. Such an emulsifier would have been obvious.

Zhou explains that "phospholipids" are to be included in the aprepitant emulsion as the emulsifier, and further identified "egg yolk phospholipid" as the

preferred emulsifier. Ex. 1003 at [0010]; *see also id*. at claims 1, 6, [0019]-[0020] (utilizing "egg yolk phospholipid"), [0025]-[0033] (same); Ex. 1002 ¶130. Washington further teaches that "phospholipids, or lecithins," are "used in the preparation of most parenteral emulsions." Ex. 1004 at 133; Ex. 1002 ¶131. Washington further teaches that phospholipids from "egg or soya lecithin" are the most common sources that "are widely used as emulsifiers for intravenous use." Ex. 1004 at 133; Ex. 1019 at 192; Ex. 1002 ¶131. Washington specifically identifies "Lipoid® E80" as a commercially available, parenteral grade of lecithin (a phospholipid emulsifier) produced from crude egg lecithin that was known to provide "excellent emulsion stability." Ex. 1004 at 134; Ex. 1002 ¶131. Repeating the choice of such emulsifiers is the epitome of obviousness. *See* Section VI.E.1.c, *supra*.

A POSA would have been motivated to utilize a "phospholipid" emulsifier, including an "egg phospholipid" or "egg lecithin" such as Lipoid E80 in view of Zhou and/or Washington. Ex. 1002 ¶132. Such materials were identified as "widely used," "commercially available," and "common sources," that were known to provide "excellent emulsion stability," thereby reinforcing their selection and reasonable expectation of affording an emulsion. Ex. 1002 ¶¶131-132. Because a POSA "has good reasons to pursue the known options within his or her technical grasp," claims 2 and 5 would have been obvious. *KSR*, 550 U.S. at 417, 421.

In addition, claims 3, 4, 6, and 7 each recite that the "phospholipid" or "egg lecithin" is present in the emulsion in an amount of "about 16 wt/wt %" or "about 17 wt/wt %." Ex. 1001 at claims 3-4, 6-7; Ex. 1002 ¶133. For the reasons discussed above with respect to claim 1, such concentrations would have been obvious. *See* Section VI.E.1, *supra*.

3. Claims 8-9 recite obvious oils and amounts

Claim 8 depends from claim 1 and requires that the "oil" is selected from a series of choices that includes, *inter alia*, "olive oil," "ethyl oleate," "triglycerides," and "soybean oil." Ex. 1001 at claim 8; Ex. 1002 ¶¶134-135. Claim 9 depends from claim 8 and requires that "the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %." Ex. 1001 at claim 9; Ex. 1002 ¶¶134-135. Such oils and concentrations would have been obvious.

Zhou identifies "olive oil," "ethyl oleate," "triglycerides," and a preference for "soybean oil" to include in the aprepitant emulsion. Ex. 1003 at claims 1 and 5, [0010], [0027]-[0036] (embodiments 5-8); Ex. 1002 ¶136. Zhou further indicates that the amount of oil may be between 7-15% by weight. Ex. 1003 at claim 9, [0009]; Ex. 1002 ¶137. Thus, Zhou discloses a range of oil that fully encompasses the claimed range of 9-10% by weight. Ex. 1002 ¶137. Accordingly, the claimed concentration of oil is presumptively obvious. *DuPont*, 904 F.3d at 1006 ("[I]t is to be expected that a change ... in concentration ... would be an unpatentable

modification.") (internal quotations marks omitted); *Galderma*, 737 F.3d at 736-41; *Iron Grip*, 392 F.3d at 1322; *Peterson*, 315 F.3d at 1329, 1330. Moreover, Zhou provides working examples of emulsions containing 9.5% soybean oil and 10% olive oil by weight, respectively. Ex. 1003 at [0031]-[0033], [0034]-[0036]; Ex. 1002 ¶138. Repeating the choice of such oils and values is the epitome of obviousness.

A POSA would have been motivated by Zhou's express disclosure to utilize the "preferred" soybean oil in an aprepitant emulsion and would have had a reasonable expectation of successfully using such an oil in an amount of 9-10% by weight in view of Zhou's working examples using concentrations of the claimed oils in the claimed amounts. Ex. 1002 ¶139. Accordingly, for these reasons, and those discussed above with respect to claim 1, a POSA would have found claims 8-9 obvious.

4. Claims 10-12 recite obvious co-surfactants and amounts

Claim 10 depends from claim 1 and requires the "co-surfactant" to include an "alcohol." Ex. 1001 at claim 10; Ex. 1002 ¶¶140-141. Claim 11 depends from claim 10 and requires an alcohol concentration of "less than 10 wt/wt %." Ex. 1001 at claim 11; Ex. 1002 ¶¶140-141. Claim 12 also depends from claim 10 and requires that the co-surfactant be "ethanol." Ex. 1001 at claim 12; Ex. 1002 ¶140-141. The use of ethanol in a concentration of less than 10% by weight would have been obvious.

Zhou identifies ethanol as a "preferred" co-emulsifier for an aprepitant emulsion. Ex. 1003 at [0010]; *see also id*. at claims 1 (reciting, *inter alia*, ethanol) 7, and 10, [0016], [0019]-[0020], [0024]-[0033] (utilizing ethanol); Ex. 1002 ¶¶142. Zhou further identifies the amount of co-emulsifier as either 1-10% or 2-5% by weight. Ex. 1003 at claim 1 and 9, [0008]; Ex. 1002 ¶143. Accordingly, such a claimed amount would have been *prima facie* obvious. *See* Section VI.E.1.b, *supra* (collecting cases). Moreover, Zhou provides working examples that utilize ethanol at a concentration of either 1.5%, 1%, 3%, 5.5%, or 10% by weight. Ex. 1003 at [0019]-[0020], [0025]-[0026], [0027]-[0032]; Ex. 1002 ¶144. Repeating the choice of such co-emulsifiers and values is the epitome of obviousness.

A POSA would have been motivated by Zhou's express disclosure to utilize ethanol as the "preferred" co-emulsifier in an aprepitant emulsion and would have had a reasonable expectation of successfully using ethanol in an amount of "less than 10 wt/wt %" in view of Zhou's working examples using precisely such concentrations. Ex. 1002 ¶145. Accordingly, for these reasons, and those discussed above with respect to claim 1, a POSA would have found claims 10-12 obvious.

5. Claims 13-15 recite obvious osmotic agents and amounts

Claim 13 depends from claim 1 and requires the emulsion contain an "osmotic agent." Ex. 1001 at claim 13; Ex. 1002 ¶¶146-147. Claim 14 depends from claim 13 and limits the "osmotic agent" to a Markush group that includes, *inter alia*,

"glycerol," "mannitol," "glucose," or "sucrose." Ex. 1001 at claim 14; Ex. 1002 ¶¶146-147. Claim 15 depends from claim 14 and requires that "the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %." Ex. 1001 at claim 15; Ex. 1002 ¶¶146-147. Such claims would have been obvious.

Zhou identifies each of "glycerol," "mannitol," "glucose," and "sucrose" as excipients to include in an aprepitant emulsion. Ex. 1003 at claim 1 ("[T]he protective agent is one or more of glycerin, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids.") and 8, [0010]; Ex. 1002 ¶148. Glycerin, which is synonymous with glycerol, is identified as being "preferred." Ex. 1003 at [0010]; Ex. 1024 at 283; Ex. 1002 ¶¶149-151. Zhou further describes the inclusion of such excipients in the amount of 8-13% by weight. Ex. 1003 at [0009]; Ex. 1002 ¶152. Accordingly, such a claimed amount would have been *prima facie* obvious. *See* Section VI.E.1.b, *supra* (collecting cases). Moreover, Zhou provides working examples of aprepitant emulsions that contain 5% or 8% by weight glycerol/glycerin and 5.95% by weight glucose. Ex. 1003 at [0019]-[0020], [0023]-[0030]; Ex. 1002 ¶152.

A POSA would have been motivated by Zhou's express disclosure to include any of "glycerol," "mannitol," "glucose," and "sucrose" in the emulsion. Ex. 1002 ¶153. Moreover, a POSA would have had a reasonable expectation of successfully preparing an emulsion containing "about 3 wt/wt % to 8 wt/wt %" of such an

excipient in view of Zhou's working examples (which used a concentration falling within the claimed range). Ex. 1002 ¶153. Indeed, Zhou provided several working examples that included the claimed "osmotic agent," lending further credence to the interchangeability of excipients like "glycerol," "mannitol," "glucose," and "sucrose" in the emulsion. Ex. 1003 at [0019]-[0020] (glycerin), [0021]-[0022] (sucrose), [0023]-[0024] (glucose), [0025]-[0026] (glycerin), [0027]-[0028] (glycerin), [0029]-[0030] (glycerol), [0031]-[0032] (glycerin). Ex. 1002 ¶151. Repeating the choice of such excipients and/or concentrations is the epitome of obviousness.

Indeed, a POSA would have known that "glycerol" was an osmotic agent that should be used to augment the aqueous phase of an emulsion as is needed. Ex. 1006 at 1159-60; Ex. 1002 ¶149. Glycerol was "preferred by the manufacturers of commercial soybean oil emulsion" and was known to "reduce the globule size and improve the creaming stability of [oil-in-water] emulsions." Ex. 1006 at 1160; Ex. 1002 ¶151. Thus, a POSA would have had further reasons to include glycerol in the claimed aprepitant emulsion to capitalize on tonicity and stability improvements and would have had a reasonable expectation of preparing such an emulsion in view of Zhou's working examples and prior usage in the art for the same purpose now claimed. Ex. 1002 ¶¶151-153.

Accordingly, for these reasons, and those discussed above with respect to claim 1, a POSA would have found claims 13-15 obvious.

6. Claims 16-17 recite the obvious use of a pH modifier

Claim 16 depends from claim 1 and further requires the inclusion of "a pH modifier." Ex. 1001 at claim 16; Ex. 1002 ¶¶154-155. Claim 17 depends from claim 16 and requires the pH modifier to be "oleic acid or a salt thereof." Ex. 1001 at claim 17; Ex. 1002 ¶¶154-155. Such claims would have been obvious.

Zhou teaches that the pH range of the aprepitant emulsion should be 6-8. Ex. 1003 at [0011], [0016]; Ex. 1002 ¶156. Accordingly, it would have been obvious to a POSA to include a pH modifier to bring the pH of an aprepitant emulsion within this range. Ex. 1002 ¶¶156-157; Ex. 1011 at 202; Ex. 1012 at 112; Ex. 1018 at 1529, 1532. Sodium oleate was known to afford several benefits when included in an emulsion, including stabilization against coalescence, decreasing the granularity of particles, and providing "a certain buffering capacity to reduce the pH change to a minimum." Ex. 1006 at 1159; Ex. 1002 ¶158. Thus, "a small amount of [sodium oleate] was often used in commercial parenteral emulsions…to obtain stable formulations during the autoclaving process." Ex. 1006 at 1159; Ex. 1018 at 1528, 1535; Ex. 1002 ¶158. Indeed, Weng remarked about its formulations: "it was obvious that the incorporation of 0.05% [sodium oleate] made an important contribution to increase the absolute value of the [zeta]-potential and keep pH value

nearly unchanged before and after autoclaving." Ex. 1006 at 1159; Ex. 1002 ¶158. Once again, and as the district court previously found, repeating such a choice is obvious. Ex. 1007 at 42-43 ("[T]he choice of sodium oleate would have been obvious.").

A POSA would have been motivated to include sodium oleate in Zhou's aprepitant emulsions as a pH modifier for the beneficial effects noted by Weng. Ex. 1002 ¶159; Ex. 1007 at 43 ("I find that the sodium oleate limitation would have been obvious based on the disclosures in the common specification of the asserted patents, and the knowledge of a POSA regarding pH modifiers."). Moreover, several commercial emulsions included sodium oleate. Ex. 1018 at 1528 (Table I); Ex. 1002 ¶158. Indeed, including a pH modifier in an emulsion was common knowledge because pH was known to "decrease during sterilization and storage as a result of increase in [free fatty acid] content due to the hydrolysis of" the oil or emulsifier. Ex. 1018 at 1532; Ex. 1002 ¶157. Such acidification was also known to cause instability. Ex. 1018 at 1532; Ex. 1002 ¶157. Thus, a POSA would have been motivated to include sodium oleate in an aprepitant emulsion to further improve its stability and would have had a reasonable expectation of successfully preparing such an emulsion in view of the favorable teachings and use of this excipient in prior art emulsions. Ex. 1002 ¶159.

Accordingly, for these reasons, and those discussed above with respect to claim 1, a POSA would have found claims 16-17 obvious.

7. Claims 18-21 would have been obvious

Claims 18-21 each depend from claim 1 and recite that "the emulsifier is egg lecithin" (claim 18), "the co-surfactant is ethanol" (claim 19), the inclusion of "sucrose" (claim 20), or the inclusion of "sodium oleate" (claim 21). Ex. 1001 at claims 18-21; Ex. 1002 ¶¶160-161. Each of these claims would have been obvious for reasons previously discussed. *See* Section VI.E.2, *supra* (discussing "egg lecithin"); Section VI.E.4, *supra* (discussing ethanol); Section VI.E.5, *supra* (discussing sucrose); Section VI.E.6, *supra* (discussing sodium oleate).

8. Claim 22

Claim 22 recites the same limitations as claim 1 with the exception that "the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt %)." Ex. 1001 at claim 22; Ex. 1002 ¶¶162-163. For the reasons discussed above with respect to claim 1, it would have been obvious for the emulsion to contain the recited ingredients. *See* Sections VI.E.1, *supra*.

The emulsifier to aprepitant ratio of "about 23:1 (wt/wt %)" recited in claim 22 is also encompassed by the corresponding ratio for these ingredients specified by claim 1 and discussed above. Accordingly, this ratio would have been *prima facie* obvious. *See* Section VI.E.1.b (collecting cases). Moreover, "about 0.7-0.8 wt %

aprepitant" and a ratio of "about 23:1 (wt/wt %)" emulsifier to aprepitant encompasses an emulsion containing 17% emulsifier. Ex. 1002 ¶164. Thus, for the reasons discussed above with respect to claim 4 (*see* Section VI.E.2, *supra*), claim 22 would have been obvious.

9. Claims 23-26 would have been obvious

Claims 23-26 each depend directly or indirectly from claim 22 and recite that "the emulsifier is a phospholipid" (claim 23), the phospholipid is "egg phospholipids" or "soy phospholipids" (claim 24), the "oil" is a series of oils that include "olive oil," "ethyl oleate," "triglycerides," and "soybean oil." (claim 25), or the "co-surfactant" is an alcohol present in a concentration of "less than 10 wt/wt %" (claim 26). Ex. 1001 at claims 23-26; Ex. 1002 ¶¶165-166. Each of these limitations were previously addressed as being obvious to include in an aprepitant emulsion. *See* Section VI.E.2, *supra* (discussing "phospholipid"); Section VI.E.2, *supra* (discussing egg phospholipids); Section VI.E.3, *supra* (discussing oils); Section VI.E.4, *supra* (discussing the inclusion of an alcohol in a concentration of less than 10% by weight). The emulsifier to aprepitant ratio of "about 23:1 (wt/wt %)" does not affect the obviousness analysis for reasons discussed above with respect to claim 22. Ex. 1002 ¶167.

10.Claim 27

Claim 27 recites the same limitations as claim 1 with the exception that "the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt %)." Ex. 1001 at claim 27; Ex. 1002 ¶¶168-169. For the reasons discussed above with respect to claim 1, it would have been obvious for the emulsion to contain the recited ingredients. *See* Sections VI.E.1, *supra*.

The emulsifier to aprepitant ratio of "about 24:1 (wt/wt %)" recited in claim 27 is also encompassed by the corresponding ratio for these ingredients specified by claim 1 and discussed above. Accordingly, this ratio would have been *prima facie* obvious. *See* Section VI.E.1.b (collecting cases). Moreover, "about 0.7-0.8 wt % aprepitant" and a ratio of "about 24:1 (wt/wt %)" emulsifier to aprepitant encompasses an emulsion containing 17% emulsifier. Ex. 1002 ¶170. Thus, for the reasons discussed above with respect to claim 4 (*see* Section VI.E.2, *supra*), claim 27 would have been obvious.

11.Claims 28-30 would have been obvious

Claims 28-30 each depend directly from claim 27 and recite that "the emulsifier is a phospholipid" (claim 28), the phospholipid is "egg phospholipids" or

"soy phospholipids" (claim 29)[3], or the "oil" is a series of oils that include "olive oil," "ethyl oleate," "triglycerides," and "soybean oil." (claim 30). Ex. 1001 at claims 28-30; Ex. 1002 ¶¶171-172. Each of these limitations were previously addressed as being obvious to include in an aprepitant emulsion. *See* Section VI.E.2, *supra* (discussing "phospholipid"); Section VI.E.2, *supra* (discussing egg phospholipids); Section VI.E.3, *supra* (discussing oils). The emulsifier to aprepitant ratio of "about 24:1 (wt/wt %)" does not affect the obviousness analysis for reasons discussed above with respect to claim 27. Ex. 1002 ¶173.

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

A POSA would have been motivated to combine the disclosures of Zhou with each of Washington, Bagwe, and Weng, to arrive at the Challenged Claims. Ex. 1002 ¶174. As discussed in Section VI.A, *supra*, Zhou disclosed an advancement in emulsion formulations of aprepitant using, *inter alia*, egg yolk phospholipids as emulsifiers. Zhou also teaches that aprepitant has poor solubility in water and in common organic solvents that limits the absorption and bioavailability of the drug.

[3] Petitioner notes that "the phospholipid" term recited in claim 29 has no antecedent basis in claim 27. Thus, claim 29 is either indefinite or does not comply with 35 U.S.C. §112(d). This error, however, does not affect Petitioner's obviousness argument.

Ex. 1003 at Abstract, [0007]. Washington disclosed "factors influencing the stability of phospholipid-stabilized emulsions" and provides guidance relevant to formulating Class III drugs such as aprepitant (*i.e.*, the ones with low solubility in water and oil) in an emulsion. Ex. 1004 at Abstract, 139. Washington explains that because of the lack of solubility of these drugs in both the primary phases (water and oil) of an emulsion, they primarily accumulate only at the oil-water interface and hence require adequate interface area for effective dissolution. *Id.*; Ex. 1002 ¶175. Similarly, Bagwe provided an overview of various types of emulsions—including macroemulsions and microemulsions. Ex. 1005 at 82 (Table 2); Ex. 1002 ¶176. Bagwe's descriptions of macroemulsions and microemulsions identified several relevant properties that overlapped with Zhou's emulsions such as droplet size, use of a cosurfactant, surfactant concentrations, and the benefits of using a phospholipid as the emulsifier/surfactant. Ex. 1005 at 82 (Table 2), 101; Ex. 1002 ¶176. Lastly, Weng described the use of egg yolk phospholipids such as "egg yolk lecithin" in the preparation of emulsions and the benefits of using a co-emulsifier and pH modulator such as sodium oleate—all of which were present or relevant to Zhou's aprepitant emulsions. Ex. 1006 at 1157-1159; Ex. 1002 ¶177. Additionally, lack of an explicit reference to aprepitant in some of these references is inconsequential since the references collectively outline an approach for developing an emulsion for drugs having the solubility profile of aprepitant. Ex. 1002 ¶¶174-178. Accordingly, and

as previously explained, each of these references have relevant discussions for the technology within one another as well as for the broadly defined "emulsions" of the Challenged Claims. Ex. 1002 ¶178.

Thus, the inclusion of features from each of these references to arrive at the claimed emulsions "does not require a leap of inventiveness." *Boston Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009). It is the natural result of applying the prior art's teachings concerning emulsion components to Zhou.

G. No Secondary Considerations

Heron previously argued that long-felt but-unmet need, unexpected results, industry skepticism regarding the invention and praise from the industry, and commercial success were secondary considerations of nonobviousness with respect to patents claiming a lesser amount of emulsifier. Ex. 1007 at 44-52. The district court rejected Heron's "industry skepticism" and praise arguments while concluding that the remaining allegations only slightly or moderately weighed in Heron's favor. *Id*.

However, "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (quoting *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983)). The claims asserted in the district court case recited "0.7 wt/wt % aprepitant" and "14 wt/wt % egg yolk lecithin." The Challenged

Claims recite a broader range of emulsifier and, importantly, encompass greater amounts of emulsifier than described or enabled. *See* Sections VII and VIII, *infra*. Decades of precedent conclude that Heron's alleged considerations are now insufficient to rebut Petitioner's obviousness argument. *Vanda Pharms. Inc. v. Teva Pharms. USA, Inc.*, No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023); *Peterson*, 315 F.3d at 1331 (affirming obviousness where the applicant claimed an alloy with 1–3% rhenium, yet presented unexpected results only for 2% rhenium, and evidence suggested that 3% rhenium possessed inferior properties); *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (concluding that unexpected results "limited to sodium only" were not commensurate in scope with claims to a catalyst having "an alkali metal"); *In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) (affirming the obviousness of a genus containing "several hundred compounds," where unexpected results were proved for "only one" such compound). This is particularly so when considering Heron's admissions regarding emulsion formulations, which are discussed in detail in Sections VII and VIII, *infra*.

Accordingly, Petitioner is not presently aware of any allegations that would support a conclusion of nonobviousness. *See Leapfrog v. Fisher-Price*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (holding that "substantial evidence of commercial success, praise, and long-felt need" was inadequate "given the strength of the prima facie obviousness showing"); Ex. 1002 ¶¶179-182.

VII. GROUND 2: LACK OF WRITTEN DESCRIPTION

Patent claims may simultaneously fail the written description requirement and still be obvious. That is the case here. The Challenged Claims are unpatentable for failing to comply with the written description requirement. "[T]he purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (en banc) (quoting *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1346 (Fed. Cir. 2000)). The test for sufficiency under the written description requirement "is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad*, 598 F.3d at 1351. Relevant factors may 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." *Id*. (quoting *Capon v. Esher*, 418 F.3d 1349, 1359 (Fed. Cir. 2008)).

Importantly, here, possession demands "meaningful guidance" that must be conveyed for "the entire scope of the claimed invention." *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1160-65 (Fed. Cir. 2019); *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1337 (Fed. Cir. 2021). Accordingly, "***a***

specification must describe the claimed invention in such a way that a person of skill in the art would understand that the genus that is being claimed has been invented...." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008). "[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute...." *Ariad*, 598 F.3d at 1350. Likewise, "[A] description which renders obvious a claimed invention is not sufficient." *Ariad*, 598 F.3d at 1356 (quoting *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1567 (Fed. Cir. 1997)).

Here, the Challenged Claims require "about 0.7-0.8 wt % aprepitant" while reciting an emulsifier in varying degrees of breadth (i.e., a phospholipid, an egg phospholipid, or egg lecithin) in a ratio of emulsifier to aprepitant of "about 20:1 to 25:1 (wt/wt %)" (claim 1), "about 23:1 (wt/wt %)" (claim 22), or "about 24:1 (wt/wt %)" (claim 27). Ex. 1001 at claims 1-30; Ex. 1002 ¶183. Accordingly, the Challenged Claims recite a range of emulsifier weight percentages that greatly exceed 14% (wt/wt) and emulsifier to aprepitant ratios that are often greater than 20:1. Ex. 1002 ¶183. In view of Heron's numerous post-issuance admissions regarding the "critical," "unprecedented," "unexpected," "surprising," and "unpredictable" emulsions that represent a much different slice of the emulsifier content that is now claimed, the '254 patent fails to satisfy the written description requirement for the Challenged Claims.

A. Heron's Broadly Claimed Emulsifier Content Makes Compliance with the Written Description Requirement Impossible

The Challenged Claims all allow for emulsifier weight percentages in excess of 14% (wt/wt). Ex. 1002 ¶183. Accordingly, the '254 patent's written description must convey possession of emulsions having emulsifier contents as broadly claimed. Heron's prior admissions for claimed emulsions requiring less than the now claimed amount—only 14% (wt/wt)—render this impossible.

Heron previously asserted claims 9-10 and 21 from U.S. 9,561,229 (Ex. 1030) and claims 9-10 from U.S. 9,974,794 (Ex. 1031) in a litigation with Fresenius. Ex. 1007 at 3-4. Each of these claims required 0.7% (wt/wt) aprepitant and 14% (wt/wt) of an emulsifier (i.e., egg yolk lecithin). Ex. 1030 at claims 8-10, 21; Ex. 1031 at claims 8-10; Ex. 1002 ¶184. In response to a "strong showing" that the asserted claims would have been obvious (Ex. 1007 at 57-58), Heron was forced to defend the patentability of these claims by making numerous admissions concerning this amount of emulsifier that now curtail written description compliance for the Challenged Claims, which recite more than 14% (wt/wt) of emulsifier. Ex. 1002 ¶¶185-195.

For example, Heron admitted that a POSA would have had a "skeptical" and nigh "impossible" opinion regarding the development of an injectable emulsion given the history of industry failure. Ex. 1020 at 44 ("After over 20 years of industry failure, a POSA would have been skeptical of an aprepitant emulsion being stable

and safe for intravenous use."), 53 ("impossible"), 54-55 ("failure" and "not successful"); Ex. 1032 at 1270:7-23 ("[T]his is one of those tough compounds."); Ex. 1002 ¶185. With such a mindset, a POSA would need a correspondingly greater disclosure in a patent's specification for the full range of emulsifier concentration being claimed to understand that the inventors actually possessed such emulsions. *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004) ("[I]f the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus."); Ex. 1002 ¶186.

Moreover, Heron admitted that this "skeptical" POSA would have also believed that increasing the concentration of emulsifier in the aprepitant emulsion would destabilize the emulsion. Ex. 1033 at 77:16-24 (arguing that "increasing emulsifier can lead to instability"); Ex. 1020 at 36 (Heading) ("A POSA Would Not Simply Increase Emulsifier Because That Can Destabilize an Emulsion"), 44 ("[T]he prior art undisputedly showed that increasing an emulsifier could cause stability issues…."), 45 ("Fresenius is wrong that a POSA would have expected that increasing egg lecithin content beyond the 10% upper limit of CN '845 ["Zhou" (Ex. 1003] to 14% (*i.e.*, 40% more) would yield a physically stable aprepitant emulsion."); Ex. 1027 at 12, 19, 23 ("[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. 1026 at 13-14; Ex. 1032 at 1281:16-21

(increasing emulsifier content will become an "issue"), 1282:8-19 ("[Y]ou could have a stability problem if you go up…."), 1283:13-16 (increasing emulsifier content is "anything but routine"); Ex. 1002 ¶¶187-188. Indeed, Heron argued that 14% (wt/wt) emulsifier was "an unusually high amount," "unprecedented," and "a departure from all prior conventions." Ex. 1026 at 6; Ex. 1020 at 1, 7; Ex. 1002 ¶189. Once again, to now claim ranges/amounts of emulsifier that allow even more than the 14% (wt/wt) that Heron defended, the "skeptical" POSA would naturally require a greater level of disclosure to convey possession of such claims. Ex. 1002 ¶190.

Additionally, Heron admitted that changing the amount of emulsifier in the emulsion would have a cascading, unpredictable effect on the formulation that required trial-and-error experimentation to develop. Ex. 1020 at 7 ("[E]verything is important to make a stable emulsion."), 44-45 ("[E]mulsions are complex systems in which changing ingredients and their amounts could have a cascade of effects."); Ex. 1027 at 7 (referring to "the unpredictable interactivity of the components of aprepitant emulsions and the lack of success in the art."), 8 (characterizing aprepitant emulsions as containing variables that interact in an "unpredictable or unexpected way"), 20 ("[E]mulsions, in particular, were one of the more complex formulation strategies in which changing the ingredients and amounts could have a cascade of effects."); Ex. 1034 at 508:6-9 (discussing "a lot of trial-and-error experiments");

Ex. 1002 ¶¶191-192. Thus, Heron argued that the amount of emulsifier was "critical" and afforded "unexpected" stability. Ex. 1020 at 7 n.1 ("The amount of lecithin, in combination with other ingredients, was ultimately critical for the developing [sic] a stable product."), 12 ("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. 1023 at 1408:21-1409:7 (describing "unexpected" results for the 14% (wt/wt) emulsion); Ex. 1033 at 53:8-12 (arguing proof of "criticality"); Ex. 1002 ¶193. Yet again, to now claim ranges/amounts of emulsifier even more than the 14% (wt/wt) that Heron defended as falling within "unpredictable" territory, the "skeptical" POSA would require more disclosure to understand that there was possession of such emulsion. Ex. 1002 ¶194.

Filtering compliance with the written description requirement through Heron's own description of the facts concerning a lesser amount of emulsifier, the "skeptical" POSA would not understand that the inventors possessed the subject matter of the Challenged Claims in the absence of evidence that such emulsions—reciting an amount of emulsifier now greater than the already "unprecedented" amount of 14% (wt/wt)—were actually prepared. Indeed, experimental results were a component of Heron's requirements for demonstrating obviousness. Ex. 1020 at 45 ("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. 1023 at 1439:17-25 ("A. [The CN '845 reference] 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. 1033 at 66:5-9 ("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. 1002 ¶¶194-195. As discussed in further detail, *see* Sections VII.B-C, *infra*, the '254 patent's disclosure fails to rise to the level needed to satisfy Heron's litigation admissions.

B. The Breadth of the Challenged Claims Exceeds The "Critical" Emulsifier Content that Heron Alleged During Prosecution

Until the '254 patent, Heron had been content with prosecuting claims that were directed to formulations containing an emulsifier in an amount of no more than 15% (wt/wt) or having an emulsifier to aprepitant ratio centered on 20:1. *See* Ex. 1035 at claim 1 ("11 wt/wt % to 15 wt/wt % of an emulsifier"); Ex. 1036 at claim 1 ("11 wt/wt % to 15 wt/wt % of an emulsifier"); Ex. 1037 at claim 1 (ratio of "about 18:1 to 22:1 (wt/wt %)"); Ex. 1038 at claim 1 (ratio of "about 18:1 to 22:1 (wt/wt %)"); Ex. 1002 ¶196. Heron's rationale for doing so was crystal clear—it argued

that an emulsion's stability was "unpredictable" even when using 15% (wt/wt) or less emulsifier:

> 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, the 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 at 45; *id*. 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***."); Ex. 1040 ¶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."); Ex. 1002 ¶197.

Not only did Heron receive allowance of the '742 patent on the basis of such "surprising and unexpected" properties (*see* Ex. 1039 at 70-71), the allowance of the '850 patent received the same rationale. Ex. 1041 at 44-45; Ex. 1002 ¶199. Indeed, by the allowance of the '074 patent, the Examiner had been persuaded that "the amount of emulsifier is critical in the claimed emulsion." Ex. 1042 at 37; Ex. 1002

¶199. For each allowance, the claims focused on the 11%-15% (wt/wt) amount of emulsifier and/or a narrow ratio of emulsifier to aprepitant surrounding the 20:1 ratio.

Heron's reliance on "criticality" and "unexpected results" for the 11%-15% range of emulsifier content and ratio of emulsifier to aprepitant was also consistent with its patentability arguments for its other patent family directed to emulsions—U.S. Patent Nos. 9,561,229 (Ex. 1030), 9,808,465 (Ex. 1043), 9,974,793 (Ex. 1044), 9,974,794 (Ex. 1031), and 10,500,208 (Ex. 1045). Ex. 1046 at 23 ("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 at 25 ("An emulsifier present in a range of 13 – 15 wt/wt% unpredictably and unexpectedly results in a pharmaceutical emulsion which is more stable…."); Ex. 1046 at 36 ("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…."); Ex. 1040 at ¶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…."); Ex. 1046 at 61 ("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. 1047 at 49 ("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) and an emulsifier:aprepitant ratio ranging from 18:1 to 22:1 demonstrates an unexpected and unpredictable advantage of the aprepitant emulsions…."); Ex. 1047 at 88-89 ("Applicant has demonstrated unexpected results in regard to physical stability of the instantly claimed composition."); Ex. 1048 at 38 ("Applicant demonstrated unexpected results in regard to the physical stability of the instantly claimed composition…."); Ex. 1049 at 44 ("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 at 56 ("[A]s argued by Applicant, the instantly claimed composition exhibits unexpected results in terms of physical stability…emulsifier weight percentages falling within the range of 11 – 15 wt. %...."); Ex. 1002 ¶¶199-201. Thus, by the time Heron prosecuted the '254 patent, the Examiners had been utterly convinced that the range of 11%-15% (wt/wt) emulsifier was crucial to patentability.

The '254 patent and the Challenged Claims, in contrast, are now directed to weight percentages of emulsifier that were outside of, and much broader than, what Heron perceived as the "critically" ascribed range of 11%-15% (while also expanding the emulsifier:aprepitant ratio well-beyond the previous limits). Ex. 1001 at claims 1-30; Ex. 1002 ¶202. Despite this shift, the Examiner provided the same

"criticality" rationale that had been previously given for the different, narrower emulsifier range. Ex. 1022 at 39 ("***It appears that the amount of emulsifier is critical in the claimed emulsion***. . . ."). Ex. 1002 ¶203. Inexplicably, the Examiner never questioned the Challenged Claims' satisfaction of the written description requirement—particularly for claimed values that now departed from the exemplified emulsions of the specification.[4] *See* Section VII.C, *infra*. Given Heron's prior allegations of "criticality" and "unexpected results" for the emulsifier amount of 11%-15% (wt/wt), and the Examiner's adoption of these allegations, such "criticality" and "unexpected results" for a different, narrower range were relevant to whether the newly claimed amounts (and the claims as a whole) satisfied the written description requirement. *In re Glob. IP Holdings LLC*, 927 F.3d 1373, 1378 (Fed. Cir. 2019). The '254 patent's description needed to convey the possession of emulsions that were now beyond the "critical" and "unexpected" values—and do so under the impossible standards that Heron articulated during trial with Fresenius.

[4] Perhaps due to the Examiner's mistaken belief that the claims of the '254 patent were commensurate in scope with the claims of the earlier patents in view of the Examiner incorrectly stating that "[i]n order to arrive at the claimed composition, [a POSA] would have to modify [the prior art to increase the emulsifier:aprepitant ratio] to about 18:1 to 22:1 (wt/wt%)." Ex. 1022 at 39-40.

Ex. 1002 ¶¶204-221. Yet there are no examples of preparing such emulsions in the '254 patent—and no indication of possession in the disclosure. Ex. 1002 ¶¶207-221.

C. The Breadth of the Challenged Claims Greatly Exceeds The Exemplified Emulsions

Nothing about the '254 patent or, importantly, its exemplified emulsions would have informed a skilled artisan that the inventors possessed emulsions having 15% or more emulsifier or even a ratio of emulsifier to aprepitant of more than 20:1. Ex. 1002 ¶¶207-221. In all instances, the ratio of the one species of emulsifier utilized (i.e., Lipoid E80) to aprepitant was either exactly 20:1 or less. Ex. 1001 at Examples 1-6; Ex. 1002 ¶¶207-209, 212. And each of these examples utilized less than 15% (wt/wt) of the solely exemplified Lipoid E80 emulsifier. Ex. 1001 at Examples 1-6; Ex. 1002 ¶¶210-211. While "the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described," it should be a prominent consideration here. *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011). Especially so, given the high bar that Heron alleged concerning unpredictability, criticality, and unexpectedness for a lesser-claimed amount. *See* Sections VII.A-B, *supra*. The purportedly "skeptical" POSA would not have understood the inventors to have possessed emulsions containing 15% or more emulsifier as now claimed—particularly in the absence of experimental evidence. Ex. 1002 ¶211.

Indeed, the '254 patent provides a reason for the "skeptical" POSA to be wary of any deviation from the exemplifications—it afforded an unstable emulsion that was unsuitable for injection. Ex. 1001 at Examples 4-5; Ex. 1002 ¶210. For example, each of Examples 1-3 and 6 recite a ratio of one species of emulsifier (i.e., Lipoid E80) to aprepitant of exactly 20:1. Ex. 1001 at Examples 1-3, 6; Ex. 1002 ¶¶210-212. Those emulsions were specifically called out in the written description for their purported stability. Ex. 1001 at Example 7 and Table 7. Even then, not all of these emulsions were stable over the full range of testing as only Example 3 exhibited "enhanced stability" that was attributed to "a large concentration of sucrose." Ex. 1001 at Example 8; Ex. 1002 ¶210. In contrast, emulsions containing a ratio of either 14.8:1 or 10:1 Lipoid E80 to aprepitant (and concomitantly reduced weight percentages of Lipoid E80 along with lesser amounts of sucrose) exhibited crystallization "[w]ithin 4 days post-preparation at room temperature." Ex. 1001 at Examples 4-5; Ex. 1002 ¶210. Not only do these examples fail to convey what may happen upon increasing the emulsifier content (which Heron has argued may be detrimental to stability), but they suggest a fragile nature for the exemplified 20:1 ratio. Ex. 1002 ¶¶213-214. In view of Heron's admissions, compliance with the written description requirement for differing and greater emulsifier amounts/ratios necessitates much more than silence in view of this experimentation. Ex. 1002 ¶214.

Outside of the examples, the '254 patent's written description fares little better concerning possession of an aprepitant emulsion having more than 15% (wt/wt) emulsifier or a ratio of emulsifier to aprepitant greater than 20:1. A laundry list of potential emulsifier weight percentages can be found (although not in conjunction with any guidance that such percentages would lead to an emulsion). Ex. 1001 at 3:49-58; Ex. 1001 at 11:51-60; Ex. 1002 ¶¶215-217. Yet this is clearly not sufficient here—precedent is replete with holdings that *ipsis verbis* generic statements and laundry lists of values do not satisfy the written description requirement. *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021); *FWP IP ApS v. Biogen MA, Inc.*, 749 F. App'x 969, 972, 974-976 (Fed. Cir. 2018); *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1126 (Fed. Cir. 2008) ("To satisfy the written description requirement in the case of a chemical or biotechnological genus, more than a statement of the genus is normally required."); *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) ("An *ipsis verbis* disclosure of a claimed genus … is not *per se* sufficient to meet the written description requirement."); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("Clearly, however, just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a "laundry list" disclosure of every possible moiety for every possible position would constitute a written

description of every species in the genus. This cannot be….”). Such statements truly fail the test here in view of Heron’s admissions and the absence of any examples illuminating the scope of the Challenged Claims.

This same rational applies to the ’254 patent’s statement concerning the ratio of emulsifier to aprepitant. Ex. 1001 at 4:63-5:3. Again, such generic statements do not necessarily convey possession. *Bos. Sci. Corp.*, 647 F.3d at 1364; *Fujikawa*, 93 F.3d at 1571. That is particularly true in view of Heron’s admissions and when its own examples significantly question the ability to obtain an emulsion that deviates from the 20:1 ratio. Ex. 1002 ¶¶218-219.

The ’254 patent contains no guidance or even positive affirmation for a POSA to consider whether any or all of the generically provided emulsifier percentages and ratios with aprepitant would afford an aprepitant emulsion. Ex. 1002 ¶220. This is in stark contrast to other ratios and amounts that the inventors focused on for the “surprising” production and stability of the disclosed emulsions. Ex. 1001 at 12:43-49 (referring to the oil to aprepitant ratio), 12:56-67 (referring to the ratio of emulsifier to oil); Ex. 1002 ¶220. Thus, Heron certainly understood how to ascribe significance to certain parameters in the disclosed emulsions, but failed to do so concerning the weight percentage of emulsifier or even the ratio of emulsifier to aprepitant. Ex. 1002 ¶221. Such silence, and even the criticality Heron attributed to the lesser amounts of emulsifier, further suggests that the inventors did not have

possession of the now claimed ranges/ratios. *Glob. IP Holdings*, 927 F.3d at 1378 ("[T]he criticality or importance of the expressly disclosed species may be relevant to whether an inventor had possession of a claimed genus."); *Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1382 (Fed. Cir. 2019) ("Here, there is no similar hook or disclosure in the specification that an ordinarily skilled artisan can rely on to understand that the inventor possessed effective uncoated PPI."); *Carnegie*, 541 F.3d at 1125 (discussing the description indicated as being "critical to the claimed invention").

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"Critical," "unprecedented," "unexpected," "surprising," and "unpredictable"—each of these are Heron's adjectives characterizing emulsions and emulsifier concentrations for claims that require less than the concentration of emulsifier that the Challenged Claims now permit. The '254 patent needed to demonstrate possession, within its four corners, of the full scope of emulsions now claimed to an admittedly "skeptical" POSA that allegedly believed that increasing the concentration of emulsifier would result in failure. The '254 patent failed the test—there is no evidence within for a POSA to understand that the inventors possessed the full scope of the newly claimed ranges. As such, the Challenged Claims fail to comply with the written description requirement.

VIII. GROUND 3: LACK OF ENABLEMENT

To the extent that Heron contends that the Challenged Claims are not obvious, then they are invalid for lack of enablement. Ex. 1002 ¶222. The '254 patent's "specification must enable the full scope of the invention as defined by its claims"—which includes emulsifier concentrations of 15% or more and ratios of emulsifier to aprepitant greater than the exemplified 20:1 ratio utilized in the examples. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023); Ex. 1002 ¶¶222-223. Much of the discussion in Section VII, *supra*, concerning Heron's admissions of criticality, unpredictability, unexpected and surprising results, the unprecedented amount of emulsifier being claimed, the complexity of emulsions, and the absence of any working examples demonstrating the preparation of emulsions having such higher emulsifier content and ratios to aprepitant are applicable here. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (identifying factors such as "(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."). Because of the interrelatedness of their legal criteria, "written description and enablement often rise and fall together." *Ariad*, 598 F.3d at 1352; *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005). Thus, Petitioner has already addressed many of the factors that

support a finding of lack of enablement for the full scope of the Challenged Claims when setting forth Heron's failure to satisfy the written description requirement.

Moreover, if not obvious, it would necessarily be the epitome of "undue experimentation" for the allegedly "skeptical" POSA to engage in the trial-and-error experimentation needed to increase the emulsifier content, its ratio to aprepitant, and any other unidentified variable in an effort to obtain an emulsion falling within the greater limits of the Challenged Claims. Ex. 1002 ¶¶224-225; Ex. 1020 at 7; Ex. 1034 at 508:6-11; Ex. 1032 at 1283:13-16. Increasing the concentration of emulsifier was admittedly "anything but routine" experimentation according to Heron's prior expert. Ex. 1032 at 1283:13-16; Ex. 1002 ¶225. Even a named inventor and the same expert admitted that changing anything in the emulsion is rife with failure. Ex. 1034 at 508:6-11 ("A. 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."); Ex. 1032 at 1288:7-13 ("[W]hat you're doing is you're trying to decrease it, to get the lowest amount that you can for it to be stable. Because if you add any more than that, you're going to cause problems with other design parameters that you have and potentially cause instabilities."); Ex. 1020 at 44-45 ("[C]hanging ingredients and their amounts could have a cascade of effects."); Ex. 1027 at 7-8 (discussing "unpredictable interactivity").

However, there is no guidance in the specification for making the adjustments needed to obtain emulsions amongst the outer scope of the Challenged Claims. Ex. 1002 ¶¶227-228; *In re McLeay*, No. 2023-2338, 2025 WL 516809, at *3 (Fed. Cir. Feb. 18, 2025). No working examples of the '254 patent utilize any concentration of emulsifier in the realm of 15% or more. Ex. 1002 ¶¶229-230. Despite this, Heron has repeatedly professed the "difficulty," "complexity," "specificity," "criticality," and "unprecedented" 14% by weight emulsifier content that was needed to obtain an emulsion of aprepitant. Ex. 1020 at 1, 7 n.1, 44, 54-55; Ex. 1026 at 6; Ex. 1002 ¶¶231-232. Enablement of the Challenged Claims, which are not limited to this specificity, is severely compromised by these admissions and the alleged "skepticism," "lack of expectation," and "failures" that came before. Ex. 1020 at 4, 7, 44-45, 53-55; Ex. 1002 ¶¶233-234. As compared against the '254 patent and its shortcomings in disclosure, the rubric for enablement of the Challenged Claims that Heron has created is insurmountable considering the degree of "unpredictability" for preparing an aprepitant emulsion only containing 14% emulsifier by weight. Ex. 1033 at 77:2-8; Ex. 1020 at 7, 44-45; Ex. 1027 at 8, 20; Ex. 1039 at 45; Ex. 1002 ¶¶235-240.

What remains is for a POSA to engage in the same trial-and-error approach of the inventors to determine the parameters that will allow the greater amounts of emulsifier to be utilized. Ex. 1002 ¶¶241-244. If it is not obvious to do so as

Petitioner alleges, the full scope of the Challenged Claims is simply not enabled. *Amgen*, 598 U.S. at 614-615; *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1366-67 (Fed. Cir. 2023). Enablement is nowhere close in view of Heron's admissions.

IX. INSTITUTION IS WARRANTED

This petition should not be subject to discretionary denial under the Board's §314(a) or §325(d) tests.

A. Azurity will submit a *Sotera* stipulation upon institution

If the PTAB decides to institute this petition, then Azurity will enter a stipulation in the parallel district court litigation that is consistent with *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 18–19 (PTAB Dec. 1, 2020) (precedential as to § II.A). Accordingly, discretionary denial under 35 U.S.C. §314(a) should not be exercised here. *See* Katherine K. Vidal, "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation" (June 21, 2022) ("*Fintiv* Memo") at 3 (footnote omitted), 7 ("[T]he PTAB will not discretionarily deny institution of an IPR or ***PGR*** in view of parallel district court litigation where a petitioner stipulates not to pursue in a parallel district court proceeding the same grounds as in the petition or any grounds that could have reasonably been raised in the petition.") (emphasis added); *see also Samsung Elecs. Co., Ltd. v. Cardware Inc.*, PGR2023-00013, Paper 14 at 21-23 (PTAB Aug. 11,

2023); *Cosentino S.A.U. & C & C N. Am. Inc. v. Cambria Co. LLC*, PGR2021-00010, Paper 11 at 13-16 (PTAB May 18, 2021).

B. *Advanced Bionics* Does Not Favor Denial

In determining whether to exercise discretion to deny institution under §325(d), the Board applies *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469 (PTAB Feb. 13, 2020) (Paper 6) (precedential) ("(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.").

1. Step 1 is largely inapplicable

There were no rejections for lack of written description or lack of enablement during prosecution of the '254 patent. *See* Ex. 1022 at 8-24. Accordingly, this petition's Grounds 2 and 3 are not the same or substantially the same arguments previously presented. Moreover, no claims were rejected for obviousness during prosecution. *Id*. Although Zhou (Ex. 1003) was cited in an IDS and in the Examiner's Reasons for Allowance as "[t]he closest prior art" (Ex. 1022 at 39), the PTAB has rejected arguments that an Examiner's acknowledgement of an IDS is a sufficient basis for discretionary denial. *Bowtech, Inc. v. Mcp Ip, LLC*, IPR2019-

00382 Paper 12 at 12 (P.T.A.B. Aug. 6, 2019) ("*Becton, Dickinson* expressly distinguished the situation 'where the prior art was simply listed in an IDS during prosecution.'").

2. *Advanced Bionics* favors institution

Upon considering Grounds 1-3, the Examiner plainly erred by relying solely on a theory of obviousness-type double patenting to reject the claims. Ex. 1022 at 8-24. Moreover, for Grounds 2-3, the Examiner did not have the benefit of Heron's admissions and expert's statements regarding the complexity of the broadly claimed emulsions or the "critical," "unprecedented," "unexpected," "surprising," and "unpredictable" results afforded by a range of emulsifier that is only a sliver of the amounts now recited by the Challenged Claims.

Accordingly, the two-step *Advanced Bionics* test does not disfavor institution.

X. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(A)(1)

Pursuant to 37 C.F.R. §42.8(a)(1), the mandatory notices identified in 37 C.F.R. §42.8(b) are provided below as part of this Petition.

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

Azurity Pharmaceuticals, Inc., Azurity Pharma India LLP, and Slayback Pharma LLC are the Petitioners and real-parties-in-interest. Slayback Pharma LLC is a wholly-owned subsidiary of Azurity Pharmaceuticals, Inc.

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

Petitioner is aware of the following judicial or administrative matters that would affect, or be affected by, a decision in the proceeding:

- PGR2025-00036
- *Heron Therapeutics, Inc. v. Azurity Pharmaceuticals, Inc. et al*. (DDE-1-24-cv-01363)
- *Heron Therapeutics, Inc. v. Azurity Pharmaceuticals, Inc. et al.* (DDE-1-24-cv-00830)
- *Heron Therapeutics, Inc. v. Mylan Pharmaceuticals Inc.* (DDE-1-24-cv-00043)
- *Heron Therapeutics, Inc. v. Mylan Pharmaceuticals Inc.* (DDE-1-23-cv-01015)
- *Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al.* (DDE-1-22-cv-00985)

Petitioner is aware of the following patents and patent applications related to the ’254 patent:

- U.S. 9,974,742
- U.S. 10,624,850
- U.S. 11,173,118
- U.S. 11,878,074

- U.S. 12,115,255
- U.S. Application Serial No. 18/885,125
- U.S. 9,561,229
- U.S. 9,808,465
- U.S. 9,974,793
- U.S. 9,974,794
- U.S. 10,500,208
- U.S. 10,953,018
- U.S. 11,744,800.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

Petitioners provide the following designation of counsel, all of whom are identified in Petitioners' Power of Attorney.

Lead Counsel	Back-up Counsel
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D. Service Information (37 C.F.R. §42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsel at the addresses shown above. Petitioners also consent to electronic service by email to AzurityIPRs@windelsmarx.com.

XI. PAYMENT OF FEES

The undersigned authorize the Office to charge the §42.15(a) review fee and any additional fees to Deposit Account No. 603243. Review of 30 claims is requested.

XII. ADDITIONAL REQUIREMENTS UNDER 37 C.F.R. §42.204

The '254 patent issued on October 15, 2024 and Petitioners have timely filed this Petition no later than nine months after the date of the grant of the patent. 35 U.S.C. §321(c); 37 C.F.R. §42.202. Petitioners certify that the '254 patent is available for PGR and that Petitioners are not barred or estopped from requesting PGR challenging the claims on the identified grounds.

XIII. CONCLUSION

Claims 1-30 of the '254 patent are unpatentable and should be canceled.

Respectfully submitted,

WINDELS MARX LANE & MITTENDORF, LLP

Dated: February 28, 2025 By: /Andrew E. Morrell/

Andrew E. Morrell (Reg. No. 63,737)
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APPENDIX 1

Listing of claims from U.S. 12,115,254
Claim 1
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 %).
Claim 2
2. The emulsion of claim **1,** wherein the emulsifier is a phospholipid.
Claim 3
3. The emulsion of claim **2,** wherein the phospholipid is present in the emulsion at about 16 wt/wt %.
Claim 4
4. The emulsion of claim **2,** wherein the phospholipid is present in the emulsion at about 17 wt/wt %.
Claim 5
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 **1,** further comprising an osmotic agent.
Claim 14
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.
Claim 15
15. The emulsion of claim **14,** wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.
Claim 16
16. The emulsion of claim **1,** further comprising a pH modifier.
Claim 17
17. The emulsion of claim **16,** wherein the pH modifier is oleic acid or a salt thereof.
Claim 18
18. The emulsion of claim **1,** wherein the emulsifier is egg lecithin.
Claim 19
19. The emulsion of claim **1,** wherein the co-surfactant is ethanol.
Claim 20
20. The emulsion of claim **1,** further comprising sucrose.
Claim 21
21. The emulsion of claim **1,** further comprising sodium oleate.

Claim 22
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 %).
Claim 23
23. The emulsion of claim **22,** wherein the emulsifier is a phospholipid.
Claim 24
24. The emulsion of claim **23,** wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.
Claim 25
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 % aprepitant; an emulsifier; an oil; a co-surfactant; and water, wherein the ratio of the emulsifier to aprepitant 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.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that foregoing **PETITION FOR POST GRANT REVIEW OF U.S. PATENT 12,115,254** complies with the type-volume limitation of 37 C.F.R. §42.24(a)(1). According to Microsoft Office Word 2016's word count, this Petition contains 16729 words, exclusive of the parts exempted as provided in 37 C.F.R. §42.24(a).

Respectfully submitted,

WINDELS MARX LANE & MITTENDORF, LLP

Dated: February 28, 2025

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITION FOR POST GRANT REVIEW OF U.S. PATENT 12,115,254** and **EXHIBITS 1001-1009, 1011-1020, and 1022-1050** are being served on February 28, 2025, via Federal Express overnight delivery at the correspondence address for U.S. 12,115,254 as identified in Patent Center:

Attn: Paul Devinsky
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

Service is also being effected by sending a true and correct copy of the foregoing **PETITION FOR POST GRANT REVIEW OF U.S. PATENT 12,115,254** and **EXHIBITS 1001-1009, 1011-1020, and 1022-1050**, via Federal Express overnight delivery to the address of Heron Therapeutics, Inc.:

Craig Collard
Chief Executive Officer
100 Regency Forest Drive, Suite 300
Cary, NC 27518

A courtesy copy of the foregoing **PETITION FOR POST GRANT REVIEW OF U.S. PATENT 12,115,254** and **EXHIBITS 1001-1009, 1011-1020, and 1022-1050** are being sent via Federal Express overnight delivery to the address of Heron's counsel of record in *Heron Therapeutics, Inc. v. Azurity Pharmaceuticals, Inc. et al.* (DDE-1-24-cv-01363):

Azurity v. Heron
PGR Petition – U.S. 12,115,254

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