IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC.,	§	
	§	
Plaintiff,	§	
	§	
v.	§	**FILED UNDER SEAL**
	§	
FRESENIUS KABI USA, LLC,	§	Civil Action No. 22-985-WCB
	§	
Defendant.	§	
	§	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This is a Hatch-Waxman Act case. The plaintiff, Heron Therapeutics, Inc., has sued the defendant, Fresenius Kabi USA, LLC, for patent infringement under 35 U.S.C. § 271(e)(2). Fresenius argues that it does not infringe two of the claims at issue in the case and that the asserted claims of the two patents in suit are invalid for obviousness under 35 U.S.C. § 103 and for failure to satisfy the written description requirement of 35 U.S.C. § 112(a).

I. Procedural Background

The Hatch-Waxman Act is the name commonly used to refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360(cc) and 35 U.S.C. §§ 156, 271, 282), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066. The Hatch-Waxman Act was designed to strike a balance between two competing policy interests: (1) to induce pioneering research and development of new drugs; and (2) to enable competitors to bring low-cost generic copies of those drugs to market rapidly if those drugs are not entitled to patent

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protection. *See Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). To promote those objectives, the Hatch-Waxman Act provides for a prompt determination of whether drugs made and sold by brand-name pharmaceutical companies are protected by valid patents. If the patents are held to be infringed and not invalid, the covered drugs cannot be made and sold by generic manufacturers until the patents expire. If the patents are held to be invalid or not infringed, the Act provides a mechanism for prompt approval of the generic versions of the drugs by the U.S. Food and Drug Administration ("FDA"), which regulates the sale of pharmaceutical drugs in this country.

To obtain the necessary FDA approval to market a new drug, a pharmaceutical company must file a New Drug Application ("NDA"). That application is designed to show the FDA, through rigorous testing procedures, that the drug is safe and effective for its proposed uses. After considering the application, and often after extended negotiations with the pharmaceutical company, the FDA may grant the application and authorize the company to market the drug for particular indications. The company is restricted to marketing the drug for those indications, as dictated by FDA regulations that govern both labeling and advertising for all prescription drugs. *See* 21 C.F.R. §§ 201.1–201.327 (labeling), *id.* § 202.1 (advertising).

To speed up the approval process for generic drugs, the Hatch-Waxman Act provides that a generic drug manufacturer may submit an Abbreviated New Drug Application ("ANDA") for approval by the FDA. If the generic company intends to market a drug that is bio-equivalent to the first pharmaceutical company's approved drug, the ANDA may rely on the safety and efficacy studies previously submitted as part of the first company's NDA.

Under the Hatch-Waxman Act, NDA holders are required to notify the FDA of all patents that "claim [] the drug for which the [NDA] applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1), (c)(2). The FDA lists such patents in a publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations," which is commonly referred to as the "Orange Book." *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1318 (Fed. Cir. 2012); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045 (Fed. Cir. 2010).

The Hatch-Waxman Act creates what is referred to as an "artificial" type of infringement that allows for the adjudication of the parties' rights regarding patents that would be infringed if the ANDA were issued and the generic product made, used, or sold in this country. *See Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004). In particular, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of patent infringement to submit an ANDA for a drug claimed in a patent or the use of which is claimed in a patent if the purpose of the submission of the ANDA is to obtain approval to engage in the commercial manufacture, use, or sale of the drug claimed in the patent, or the use of which is claimed in the patent, before the patent's expiration.

Heron is the owner of U.S. Patent Nos. 9,561,229 ("the '229 patent") and 9,974,794 ("the '794 patent"), the two patents asserted in this case. Heron holds NDA No. 209296 for an injectable emulsion for intravenous use, containing 130mg/18mL aprepitant as one of the active ingredients. It markets and sells the product in the United States under the name Cinvanti®.

Cinvanti® is indicated for the treatment of emesis, also known as vomiting and nausea. The asserted patents are listed in the Orange Book as covering Cinvanti®. Fresenius filed ANDA

No. 214639, seeking approval for a product containing an injectable aprepitant emulsion. The Reference Listed Drug for Fresenius's ANDA product is Cinvanti®. Based on Fresenius's ANDA filing, Heron is accusing Fresenius of infringing several claims of the '229 patent and the '794 patent under 35 U.S.C. § 271(e)(2)(A).

II. The Asserted Claims

The asserted patents are both titled "Emulsion Formulations of Aprepitant" and are directed to pharmaceutical formulations for intravenous use developed by Dr. Thomas B. Ottoboni and Dr. Han Han.[1] The claims asserted in this case are claims 9, 10, and 21 of the '229 patent and claims 9 and 10 of the '794 patent. The priority date for both patents is September 19, 2014.

Emulsions are systems that consist of two immiscible liquid phases, such as oil and water, one of which is dispersed throughout the other in the form of fine droplets. Lipid emulsions for intravenous use consist of oil suspended in an aqueous dispersion. *See* JTX 76 at 4. The formulation typically comprises a phospholipid, such as egg yolk lecithin, glycerol, and water. Oil is mixed into the dispersion, leading to the formation of globules of triglycerides surrounded by a layer of the phospholipid. It is important that the globules remain small for purposes of intravenous injection, as larger globules can coalesce into large droplets that can result in lipid deposition in a patient's organs, with serious consequences, while smaller globules provide optimal stability and safety. *Id*.

[1] Dr. Han is identified as "Han Han" in the patents, but was frequently referred to as "Hannah Han" in the trial testimony and in some of the documents introduced into evidence at trial.

Claim 8 of the ’794 patent, from which claims 9 and 10 of the ’794 patent depend, is representative of all five asserted claims of the two patents in suit. That claim recites:

> 8. A physically stable pharmaceutical composition suitable for intravenous administration comprising:
>
> 0.7 wt/wt % aprepitant.
> 14 wt/wt % egg yolk lecithin.
> 9 wt/wt % to 10 wt/wt % soybean oil; and
> a pH modifier, wherein the pH modifier is sodium oleate.
> wherein the pH of the composition ranges from 7.5 to 9.0.

Claims 9 and 10 of the ’794 patent add additional limitations regarding the concentrations of sucrose (5 wt/wt %) and ethanol (between 2 and 6 wt/wt %), respectively. The claims of the ’229 patent largely mirror those of the ’794 patent; they differ only in that the claims of the ’229 patent do not require that the composition be “physically stable.” Claim 21 of the ’229 patent is directed to a method of treating nausea and vomiting with the claimed composition by intravenous administration. Cinvanti® is the commercial embodiment of both patents.

“Physically stable,” for purposes of the asserted patents, means, first, that the composition must satisfy the criteria set forth in chapter 729 of the United States Pharmacopeia (“USP <729>”), a reference work that contains standards for various pharmaceuticals. USP <729> requires that for oil-in-water emulsions (i.e., emulsions of oil droplets suspended in water) intended for intravenous injection, the mean droplet size in the composition must satisfy the following criteria: (1) the suspended droplets must not exceed 500 nanometers in diameter; and (2) the population of fat globules greater than five microns in diameter must not exceed 0.05% (a standard referred to as “PFAT5”). JTX 120 at 4, 6. In addition, the asserted claims require, as a measure of physical stability, that the emulsions have no aprepitant crystals that are visible when viewed at a magnification of 4x to 10x, after being stored either at 5º Celsius or at room temperature for a

period of at least one week.[2] *See* '229 patent, col. 8, ll. 5–21; '794 patent, col. 8, ll. 5–21; Dkt. No. 54 at 14–15.

III. Background of the Problem

A major problem for patients undergoing cancer treatment is the nausea and vomiting associated with chemotherapy. Chemotherapy Induced Nausea and Vomiting ("CINV") can result in treatment delays, can require dose reductions of the chemotherapy medication, and sometimes can result in patients prematurely discontinuing chemotherapy. JTX 128 at 6. It is critical that CINV be managed in the first treatment cycle, or it will continue to be problematic in subsequent cycles. *Id.*

Anti-emetic drugs designed to block the neurotransmitters associated with nausea and vomiting can prevent CINV. One category of anti-emetic drugs works on neurokinin-1 or "NK-1" receptors, which are located in the brain and the peripheral nervous system and are stimulated by peptides that are released in response to stressful or noxious stimuli. *See* Tr. 894:11–895:8. When stimulated by those peptides, the NK-1 receptors signal that the body has ingested something

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[2] The evidence at trial made clear that the references to 4x and 10x magnification in the common specification were shorthand for a total magnification of 40x and 100x, due to the fact that one magnifying component in the light path of a standard microscope (the eyepiece) has a fixed magnification of 10x, and the second magnifying component (the objective lens) has a variable magnification. The variable magnifying components referred to in the asserted patents have powers of 4x and 10x, so the total magnification of the system is 40x to 100x. *See* Tr. 22:15–23:12, 69:13–23, 71:20–72:3, 476:3–8. Although some confusion resulted from the court's initial understanding that the references to 4x and 10x in the patents represented the total magnification, the evidence at trial established that the references to 4x and 10x were shorthand for a total magnification of 40x to 100x, which is the correct understanding of the meaning of the patents' references to 4x and 10x. *See* '229 patent, col. 8, ll. 14–15; *id.*, col. 21, ll. 23–24; '794 patent, col. 8, ll. 14–15; *id.*, col. 21, ll. 12–13.

noxious, and they induce nausea and vomiting to expel the offending substance. *Id.* The NK-1 receptor pathway is one of the primary mechanisms underlying CINV.

NK-1 receptor antagonists can prevent nausea and vomiting. As the name suggests, those drugs work by inhibiting the NK-1 receptors, so as to prevent the triggering of a vomit response. The first NK-1 receptor antagonist to be discovered was aprepitant, which was developed by Merck & Co. Aprepitant is the active ingredient in both Heron's drug Cinvanti® and Fresenius's ANDA product. NK-1 receptor antagonists such as aprepitant are especially valuable in combatting CIVN because they supplement other anti-emetic drugs by preventing the recurrence of nausea and vomiting well after the initial chemotherapy session, a phenomenon referred to as "delayed emesis." Tr. 584:22–585:5.

Dr. Jeffrey Hale, one of the inventors of the aprepitant molecule, testified at trial on behalf of Heron. *See* Tr. 890:6–10. As Dr. Hale explained, aprepitant is highly effective in treating emesis. It is difficult to formulate, however, because although it has excellent biological properties, it has poor physical properties. Tr. 891:13–16. In particular, aprepitant is insoluble in either oil or water. Tr. 900:10–14. In characterizing the compound, Dr. Hale likened the physical properties of aprepitant to those of "cement dust." Tr. 901:17–902:1. Despite the challenges of working with such a compound, Merck was ultimately able to formulate aprepitant for oral ingestion. Tr. 917:3–22. Merck's solution to the problem of developing a method for oral delivery of aprepitant was to devise a capsule consisting of nanoparticles of aprepitant, each surrounded by a surfactant. Tr. 121:11–17; JTX 82. Merck's oral aprepitant product was approved by the FDA in 2003 and is sold under the brand name Emend®.

Oral administration of aprepitant, however, presented problems. A drug taken orally must go through the stomach and the liver before reaching the bloodstream and ultimately the brain. That process exposes the drug to the risks of not being fully absorbed or being metabolized in part or in whole before it reaches the bloodstream. Merck discovered that oral administration of aprepitant could result in unacceptable variations in the level of bioavailability of the drug from patient to patient. Tr. 909:15–910:8. In addition, even apart from the patient-to-patient variations in bioavailability, the oral formulation of aprepitant proved to be less than ideal. Oral administration of the drug is ineffective in cases in which the patient begins vomiting before the drug is digested. And because the oral formulation needs to be taken well in advance of a chemotherapy session, it is typically not taken under the supervision of a medical professional. As a result, the oral formulation presents problems of patient compliance. Tr. 577:23–578:16.

For those reasons, even after developing Emend®, formulators at Merck sought to develop an aprepitant solution that could be delivered through injection or intravenous administration.[3] The scientists at Merck initially focused on maintaining the biological properties of aprepitant while improving its physical characteristics relating to solubility. Those efforts, however, were unsuccessful because of the aprepitant molecule's poor solubility characteristics. While he was employed at Merck, Dr. Hale attempted to ionize aprepitant in order to create a soluble sulfonic

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[3] An injectable drug is typically administered by syringe into the patient's muscle tissue, while a drug delivered intravenously is administered directly into the patient's bloodstream, either into a peripheral vein (such as in the patient's arm or hand) or into a vein closer to the patient's heart, typically through a "central line" or "central port" that is designed for intravenous administration of drugs during chemotherapy. *See* Tr. 613:8–616:19, 638:11–25. For convenience, I will refer to both forms of administration as types of injection.

acid salt. PTX 3 at 1. He succeeded in ionizing the aprepitant, but the drug readily precipitated out of solution, and as a result the composition did not prove sufficiently stable to be a viable pharmaceutical product.

Eventually, Merck abandoned its efforts to develop a soluble aprepitant formulation and pivoted to pursue a new molecule with better physical properties. Although Merck failed to create an intravenous formulation of aprepitant, it succeeded in creating an intravenous NK-1 receptor antagonist based on a related active ingredient called fosaprepitant. Tr. 942:7–10.

Fosaprepitant is a "prodrug" of aprepitant. That is, it is not itself pharmacologically active, but is metabolically converted into aprepitant after it is introduced into the body. Tr. 124:11–23; JTX 82 at 5. Fosaprepitant differs from aprepitant in that it contains an additional phosphate group, which renders the molecule 6000 times more soluble in water than aprepitant. *See* Tr. 938:15–21. Fosaprepitant circulates in the body in the soluble prodrug form before phosphatase enzymes in the blood and liver cleave the phosphate group and convert the fosaprepitant into aprepitant. Tr. 940:11–24. Merck markets fosaprepitant as Emend IV®. Emend IV® received FDA approval in 2008. Merck's fosaprepitant patents expired in 2019, allowing generic entry.

Although Emend IV® and the generic injectable fosaprepitant products proved effective in treating emesis, practitioners reported injection site reactions and hypersensitivity reactions in some patients taking Emend IV®. These adverse events were frequently attributed to polysorbate 80, one of the excipients in Merck's Emend IV® product. *See* Tr. 122:12–123:7 ("There were issues of allergic type of reactions" to polysorbate 80.), 235:9–18, 252:23–253:3, 469:13–470:22, 1035:6–19, 1050:2–1051:7, 1064:22–1065:5; 1428:25–1429:11.

Although there was no firm scientific consensus as of 2014 that formulations containing polysorbate 80 and fosaprepitant were responsible for the adverse reactions that clinicians had observed, concerns regarding the fosaprepitant/polysorbate 80 formulations were significant enough that the Mayo Clinic changed its guidelines in 2011 to recommend the use of oral aprepitant rather than the intravenous fosaprepitant/polysorbate 80 formulation. *See* JTX 137 at 2.

In addition to the concerns about the possible side effects of Emend IV®, the fosaprepitant-based product had the disadvantage that synthesizing fosaprepitant involved a series of complex reactions and that the cost of producing fosaprepitant was greater than the cost of producing aprepitant. Tr. 143:19–144:3; JTX 71 at 12.

IV. The Prior Art

In 2012, a group of researchers in China succeeded in creating an injectable aprepitant formulation in the form of a lipid emulsion. The group published their results in a Chinese patent application, which was introduced into evidence in this case as JTX 71. Wei Zhou, one of the inventors on the Chinese patent application, was the lead author on an article published the same year, which expanded on the work described in the patent application. The article, which was titled "Preparation of Aprepitant Emulsion for Intravenous Injection" ("Zhou" or "the Zhou article"), was introduced into evidence at trial as JTX 115. Although aprepitant is not soluble either in water or in oil, the researchers responsible for the Chinese patent application and the Zhou article were able to dissolve aprepitant in an emulsion formed at the interface between the water and oil phases of the solution to create a stable injectable aprepitant formulation that did not contain polysorbate 80.

The Chinese patent application, referred to as CN845, is titled "Aprepitant microemulsion for injection and preparation method thereof." According to Dr. Barrett Rabinow, Fresenius's expert on pharmaceutical formulations, CN845 was a "game changer" that "transformed" the state of the art for aprepitant formulations. Tr. 132:21–133:15, 326:2–4. Based on all the evidence at trial, I find that characterization to be accurate.

At the time CN845 was published, Dr. Rabinow explained, the conventional wisdom was that emulsions were appropriate only for water-insoluble drugs that were soluble in oil. Tr. 133:2–10. CN845 marked a departure from that convention by using an emulsion to create an injectable formulation containing a drug that is not soluble in either water or oil. Tr. 133:12–15. According to Dr. Rabinow, "[t]hat was not really done before." Tr. 133:15.

Dr. Rabinow explained that the abstract of CN845 "tells you exactly what classes of excipients you need." Tr. 133:19–20. In addition to the aprepitant, he explained, CN845 "specifies you need oil for injection, an emulsifier, protective agent, and water. And it also gives you concentration windows for each of those." Tr. 133:20–24. In particular, CN845 lists the following components of the injectable aprepitant emulsions and the ranges of their concentrations to be used in the composition: "0.05 to 2 percent of aprepitant, 5 to 30 percent of oil for injection, 0.5 to 10 percent of emulsifier, 1 to 10 percent of co-emulsifier, 5 to 20 percent of protective agent and 60 to 80 percent of water for injection." JTX 71 at 1. The reference also includes descriptions of eight exemplary formulations, which set forth particular amounts of each of the components falling within the above ranges. *Id.* at 14–17.

CN845 contains lists of particular compounds that can be used for each of the categories of excipients. As relevant to the patents in suit, the examples and claims of CN845 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), egg yolk phospholipid as the emulsifier (examples 1, 4, 5, 6, and 7; claim 6),[4] ethanol as the co-emulsifier (examples 1, 4, 5, 6, and 7; claim 7), glycerin as the protective agent (examples 1, 4, 5, 6, and 7; claim 8) and water for injection (all examples and claim 9). JTX 71 at 9.

In addition to listing each of the substances set forth above, the eight examples in CN845 identify substitutes that can be used in place of several of those compounds. As relevant here, in Example 2 of CN845 sucrose is substituted for the glycerin component listed as the protective agent in claims 1 and 8 of that reference. JTX 71 at 9, 15.

CN845 extolls the virtues of the disclosed aprepitant microemulsion for injection. It notes that the microemulsion features uniform particle size and low viscosity, is thermodynamically stable, and enhances the stability of otherwise unstable drugs. JTX 71 at 12. CN845 concludes that the small size of the particles and the dispersion of the drug within the emulsion makes the emulsion a suitable vehicle for direct injection into patients. JTX 71 at 12.

The Zhou article supplemented the disclosures in the CN845 application. Zhou reported the optimal concentration of ingredients in the formulation to be 0.25% aprepitant, 2.5% egg yolk phospholipid, 0.125% oleic acid, 15% soybean oil, ethanol, and water. JTX 115 at 9 (reporting

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[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. Egg yolk lecithin is the principal component in the commercial product referred to as "Lipoid E 80." *See* Tr. 537:10–19.

optimal quantities); *id.* at 11 (explaining that oleic acid is used as a co-emulsifier to improve the activity of the egg yolk phospholipid (the emulsifier), making it easier to obtain an emulsion with smaller particle sizes). Importantly, Zhou reported that the emulsion prepared according to the directions set forth in the article was stable after three months of storage and that no stratification or de-emulsification was detected. JTX 115 at 10.

In his testimony early in the trial, Dr. Rabinow provided an instructive tutorial on the chemistry involved in the creation of a stable emulsion, with reference to the components used in the two Chinese references and in the '229 and '794 patents. Tr. 133:25–137:11, ,138:16–141:8. I found his testimony on the science of emulsions to be credible and consistent with the other evidence in the case.

Dr. Rabinow explained that an emulsifier, such as the egg yolk lecithin used in CN845, is a compound that has both a hydrophilic and a lipophilic component. The hybrid nature of the lecithin molecule allows it to bind with both oil and water. Tr. 134:22–135:4. The emulsifier coats the oil globules in an oil-in-water mixture and causes an emulsion to form at the interface between the oil and water phases of the solution. The hydrophilic ends of the emulsifier molecules project into the water phase of the solution, and the lipophilic ends of those molecules project into the oil globules. As Dr. Rabinow explained, that "satisfies the solubility needs of both phases in one and the same molecule, which is situated at the interface" of the oil and water phases of the solution. Tr. 135:6–14. Although aprepitant will not dissolve in either the oil or the water, it is drawn to the emulsion interface between the two phases. Tr. 362:1–4. Dr. Rabinow testified that a POSA would understand that the process described in the CN845 reference, which led to the

formation of a clear solution, meant that the emulsifier must be solubilizing the drug. Tr. 158:11–18.

The experts for both parties agreed that emulsions can be unstable. If the components are not carefully selected and prepared, an emulsion can degrade through flocculation (in which the oil droplets form adherent masses) and coalescence (in which the interface between the individual oil droplets is lost, resulting in a layer of free oil). JTX 113 at 13.

Dr. Rabinow stated that, up to a point, adding a large amount of an emulsifier can counteract degradation and contribute to the stability of the emulsion. He explained that the emulsifier results in generating smaller oil globules, which in turn provides more total surface area for the interface between the emulsion's oil and water phases. Tr. 136:23–137:11. To stabilize the emulsion, he testified, it is necessary to have "adequate emulsifier levels to keep the oil globules separate and distinct and prevent them from first approaching each other, then merging, then coagulating, then rising to the surface." Tr. 138:8–11.

The stabilization of emulsions is enhanced, according to Dr. Rabinow, by a process known as complexation. In that process, the addition of a co-emulsifier, such as ethanol, solubilizes the emulsion. Because the aprepitant and emulsifier molecules are drawn to one another, solubilizing the composition allows the aprepitant molecules to approach the emulsifier molecules more freely, resulting in the formation of a complex between the two. Tr. 138:19–139:5, 147:24–148:3, 151:6–152:16. Although CN845 did not identify the phenomenon that resulted from the process it disclosed as "complexation," Dr. Rabinow testified that a person of ordinary skill in the art would understand that the effect of the process described in CN845 would be to facilitate the creation of a complex between the emulsifier and aprepitant molecules, which makes the composition more

stable and less likely to separate into discrete oil and water phases. *See* JTX 71 at 12; Tr. 152:25–154:15.

The components of the emulsion disclosed in CN845 are similar to the components claimed in the ’229 and ’794 patents. The emulsifier used in most of the examples in CN845 is egg yolk lecithin; the oil used in most of the examples is soybean oil; and the co-emulsifier used in most of the examples is ethanol. *See* JTX 71 at 8–10. Each of those components performs the same role in the ’229 and ’794 patents as in CN845.

Dr. Rabinow stated that as of the priority date for the two asserted patents, a person of ordinary skill in the art (a “POSA”) considering emulsifier and oil options would prefer egg yolk lecithin and soybean oil, which had been used in other drugs that had been given to tens of millions of patients, and thus had “a huge track record.” Tr. 146:16–25. Dr. Rabinow characterized egg yolk lecithin as being in a “class by itself” compared with other candidate emulsifiers, as it was commercially available and did not present risks of side-effects of the sort presented by other known emulsifiers. Tr. 147:1–12. And he explained that among the candidate co-emulsifiers, ethanol had the lowest boiling point, which made it an attractive option, as it could be evaporated from the composition without needing a high temperature that could risk oxidizing the emulsifier and oil. Tr. 147:19–148:13.

For the protective agent, Dr. Rabinow explained, a person of ordinary skill would consider various options, including glycerin or sucrose. Tr. 148:20–149:7. CN845 provides for the inclusion of a protective agent in amounts between 5% and 20% and reports that the protective agent can be one of eight compounds, including glycerin and sucrose. JTX 71 at 13. Claim 9 of the ’229 and claim 9 of the ’794 patent recite the use of a 5% concentration of sucrose.

Although the CN845 patent application set forth a concentration range for the emulsifier of 0.5% to 10%, it described the preferred concentration of emulsifier as falling at the high end of that range, between 8% and 10%. *See* JTX 71 at 13 ("The preferred mass percentage of each component is. . . .8% - 10% of emulsifier"), *id.* at 9 (claim 9); *id.* at 16 (Example 5 containing 10% egg yolk lecithin); *id.* at 17 (Example 7 containing 9.8% egg yolk lecithin); *id.* at 15 (Example 2 containing 10% poloxymer, identified as an alternative emulsifier).

At trial, Dr. Rabinow testified that CN845 "transformed" the state of the art in 2012 by teaching how to formulate an aprepitant emulsion. Tr. 132:21–133:15. CN845 began with standard emulsion ingredients, including oil, water, an emulsifier, a co-emulsifier, and a protective agent. *See* JTX 71; Tr. 134:6–18. CN845 deviated from the prior art, however, in that it used a significantly higher level of emulsifier than other formulations—up to as much as 10%. That amount, Dr. Rabinow stated, was "something like eight times what the conventional levels of emulsifier are in commercially available emulsions." Tr. 155:20–156:3.

According to Dr. Rabinow, a POSA familiar with the prior art regarding emulsions would immediately have understood from CN845 that aprepitant dissolved at the interface of the oil and water; in other words, a POSA would have understood "exactly what is happening [in CN845], what the result is, and why." Tr. 171:2–3.

CN845 and Zhou reported success in creating an injectable aprepitant formulation with each of the examples they described, and Zhou tested one of the formulations for stability and found it stable. However, the Zhou reference tested that emulsion under a standard referred to as K_e. That standard differs from the applicable USP standard for stability, which is the minimum standard that the FDA expects all medications to satisfy when submitted for approval. Tr. 208:9–

209:11. When testing the formulations approximating those described in Zhou and CN845, Heron determined that neither the "optimal" formulation in Zhou nor the examples in CN845 were stable enough to satisfy the needs of a commercial product. *See* Tr. 406:4–8, 409:2–410:25, 490:24–491:10, 541:9–542:7.

At trial, Fresenius relied on several other prior art references to show what a POSA would know about making an injectable aprepitant emulsion as of the 2014 priority date for the two patents in suit. The principal references that Fresenius relied on, other than CN845 and Zhou, were a 1996 article by Washington, titled "Stability of Lipid Emulsions for Drug Delivery," JTX 113; a 2011 article by Liu, titled "Progress in Research of Injectable Microemulsion," JTX 93; and a 2011 review article by Khan, titled "Basics of Pharmaceutical Emulsions: A Review," JTX 91.

The Washington reference discussed emulsion systems for drug delivery generally and noted that although emulsions had been used with oil-soluble drugs, they had not been used with water-soluble drugs or drugs not soluble in either oil or water. JTX 113 at 2. Washington noted that phospholipid emulsifiers are especially suitable for pharmaceutical formulations, *see* JTX 113 at 3, a point reiterated by Dr. Rabinow, *see* Tr. 222:21–25 (discussing the low incidence of adverse reactions, high biological compatibility, and strong safety profiles of phospholipids). Washington noted that drugs that are poorly soluble in both water and oil (such as aprepitant) "can only be loaded into an emulsion by adsorbing to the [oil] droplet interface," and that "it is often necessary to post-load emulsions with them, in order to have a large surface area available for loading." JTX 113 at 9.

Dr. Rabinow pointed to the Washington article as support for his conclusion "that you can only load such drugs onto the droplet interface. So, if you want to have a good chance of loading

the drug onto the interface, you've got to have a large interface." Tr. 174:8–12. Dr. Rabinow continued, "[Y]ou want to have a large surface area, which means you need to have more emulsifier to stabilize that increased surface area. So, the implication is you need a lot more emulsifier to generate the increased surface area so that you can situate your drug at that interface." Tr. 176:21–177:2. Dr. Rabinow concluded that a POSA would recognize that the solubility problems with the formulations in CN845 could be overcome by increasing the amount of egg yolk lecithin in those formulations. *See* Tr. 177:10–178:1.

Fresenius relied on the Liu reference principally for the proposition that the amounts of surfactants (including phospholipids) that are used in microemulsions can be between 5% and 30%. JTX 93 at 10–11. That range encompasses both the 10% maximum emulsifier concentration disclosed in CN845 and the 14% emulsifier concentration set forth in Heron's asserted claims. Based on Liu, Dr. Rabinow testified that a POSA would consider working in an "operative range" of emulsifier concentration from "5 to 30 percent." Tr. 228:15–20; *see also* Tr. 219:24–220:4, 223:1–8.

Fresenius looked to the Khan reference to show that it was known at the time that "the amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability." JTX 91 at 5. Based on a prior study, Kahn explained that emulsifier concentration "has a great impact on emulsion stability." Kahn added that there is a "concentration window" outside of which emulsion stability declines. If the emulsifier concentration is too low, Kahn explained, the emulsion becomes unstable because of the agglomeration of oil droplets that are not kept apart from one another by the emulsifier. If the emulsifier concentration is too high, "emulsion instability occurs because of rapid coalescing." *Id.*; Tr. 168:11–169:13.

While acknowledging the risk of using too much emulsifier, Dr. Rabinow noted that the inventors of CN845 had "tested a broad dynamic range" of emulsifier concentrations, and "[i]t seemed as though everything they tried worked. . . . [I]t was a robust process and manufacturing procedure." Tr. 169:17–170:1; *see also* Tr. 166:11–15 (The examples in CN845 show "[y]ou're dealing with a very robust process. It works with a lot of different combinations.").

According to Dr. Rabinow, in light of what was disclosed in CN845 and Zhou, all that would be left for a POSA to do would be to "come up with a commercializable formulation, which means it would have to comply with USP guidelines in order to be submitted to FDA. So, what he would do is start with the formulations that were specified in the patent" and "employ routine optimization to ensure that they would comply with USP." Tr. 167:8–15.

Dr. Steven Little, Heron's formulation expert, noted that Zhou regarded an emulsifier concentration of 2.5% as optimal. He found no sound support in the prior art for Fresenius's contention that a POSA would select on a much higher concentration such as the 14% emulsifier concentration set forth in the asserted claims as a matter of routine optimization of the formulations described in CN845 and Zhou. Tr. 1288:17–1289:6.

V. Development of the Patented Invention

Dr. Ottoboni joined Heron in 2012, and began researching ways to formulate an aprepitant-based product that would not have the adverse side effects associated with Emend IV®. Tr. 548:12–18, 548:21–549:2. Initially, he sought to use cosolvents and surfactants in an effort to solubilize aprepitant, but those approaches proved unsuccessful. Tr. 520:10–21.

In early 2014, Dr. Ottoboni and Dr. Han began researching other efforts to formulate aprepitant emulsions. Dr. Ottoboni testified that "the goal of the project was to develop a product

that we hoped would be safer than Emend for injection when administered to people." Tr. 548:24–549:2. Dr. Han explained that the ultimate objective was "to develop an emulsion system that contains safe excipients for patients, including not containing polysorbate 80." Tr. 470:20–22.

Dr. Ottoboni and Dr. Han (who conducted much of the experimental work) began their work on the emulsion project with the Chinese patent application, CN845, and the related journal article by Zhou, both of which had announced the successful solubilization of aprepitant by use of an emulsion.[5] *See* Tr. 474:15–475:6, 488:24–489:11, 490:21–491:5, 501:7–505:20, 545:3–546:21. Dr. Han testified that the project marked the first time she had ever made an emulsion formulation and the first time she had ever tested and evaluated the stability of emulsion formulations. Tr. 467:13–23. She said that she educated herself on how to make an emulsion formulation by "looking to review articles to help me understand emulsion stability," Tr. 467:24–468:2, and that she educated herself on testing the stability of the resulting formulations by looking to the USP, which contains the standards for stability that the FDA requires such formulations to meet, Tr. 468:5–469:3.

Dr. Han started with the disclosures in the CN845 patent application. In her laboratory notebook, she wrote at the time that "[t]he initial formulation process of the oil-in-water emulsion containing aprepitant was adapted from patent CN 102,379,845," *i.e.*, the Chinese patent application CN845. *See* Tr. 474:20–23; DTX 262 at 11 (same statement in the Formulation Development Report prepared for the project); *see also* Tr. 549:10–18. That initial formulation,

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[5] The Heron team obtained a translation of the CN845 patent application in late March of 2014. Tr. 538:13–24. The provisional application from which the two patents in suit derived was filed on September 19 of the same year.

however, showed visible aprepitant crystals under polarized light at 10x magnification after 24 hours, and therefore did not satisfy the Heron team's objectives regarding stability. Tr. 475:2–18. Dr. Han spent several months attempting to create an aprepitant formulation based on the ranges disclosed in CN845, hoping to discover a formulation that would prove to be physically stable under USP standards. *See* Tr. 491:15–25. After failing to develop a formulation in which aprepitant did not crystallize within the first week, Dr. Han concluded that "[t]he compositions in [CN845] resulted in an unstable emulsion." Tr. 492:15–16.

After determining that the formulations described in CN845 and the optimized formulation in Zhou were not sufficiently stable to satisfy the requirements for a marketable drug, Drs. Han and Ottoboni experimented with different formulations to optimize the emulsion for stability. *See generally* DTX 259; Tr. 465:1–6, 542:15–543:2. They were unsuccessful until they began experimenting with emulsifier concentrations higher than the range of concentrations disclosed in CN845. Through what Dr. Han described as "trial-and-error," she and Dr. Ottoboni eventually succeeded in developing the stable aprepitant emulsion that was the subject of the '229 and '794 patents. Tr. 465:1–6, 508:9–11. Their emulsion contained 14% egg yolk lecithin, a concentration four percentage points above the concentration range set forth in the 2012 Chinese patent application. That emulsion formed the basis for the first intravenous aprepitant product that was approved by the FDA for administration to patients in the United States. Tr. 506:5–12. Heron now markets that formulation as Cinvanti®.

VI. Infringement by Fresenius's ANDA Product

I previously granted Heron's motion for partial summary judgment of infringement of claims 1–11 of the '229 patent. Dkt. No. 150. Then, shortly before trial began, the parties

stipulated to a finding that Fresenius's ANDA product infringes claim 21 of the '229 patent. Dkt. No. 174 at ¶ 5. In view of the summary judgment order, the parties further stipulated that "the sole remaining infringement dispute for claims 9 and 10 of the '794 patent is whether Fresenius's ANDA product meets the 'physically stable' claim limitation" that applies to dependent claims 9 and 10 through dependent claim 8. *Id.* at ¶ 6. That issue was litigated at trial.

Heron presented several theories of infringement. Heron's first theory as to why Fresenius's product meets the "physically stable" limitation is that Fresenius's request for approval of a product not containing aprepitant crystals is sufficient to prove infringement under *Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 731 F.3d 1271, 1279 (Fed. Cir. 2013). Heron's theory, however, mischaracterizes the law under *Sunovion*.

In *Sunovion*, the Federal Circuit held that where "an ANDA specification defines a compound such that it meets the limitations of an asserted claim," the ANDA product infringes, regardless of whether there is evidence that the ANDA product will be manufactured in a way that does not meet one of those limitations. *See* 731 F.3d at 1280. "When an ANDA is silent with respect to infringement," however, *Sunovion* is inapplicable. *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1382, 1387–88 (Fed. Cir. 2014). I do not doubt that, as Heron argues, Fresenius's goal is to avoid the formation of aprepitant crystals in its ANDA product. But the ANDA itself does not explicitly say that Fresenius's product meets the particular microscopy test for visible particles set forth in the asserted claims, as would be required to infringe the claims under this theory. *Sunovion* is therefore inapplicable to this case.

Rather than *Sunovion*, the correct infringement analysis in this case is dictated by *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997). In *Glaxo*, the Federal Circuit

explained that "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Id.* Although Heron's *Sunovion*-based argument is unpersuasive, I find that Heron has carried its burden of proving that Fresenius's ANDA product will more likely than not meet the physical stability limitation of claims 9 and 10 of the '794 patent.

As noted, the '794 patent defines a "physically stable" emulsion as one that satisfies not only the criteria of USP <729> (requiring a mean droplet size not exceeding 500 nanometers and a PFAT5 not exceeding 0.05%), but also Heron's microscopy test (requiring that the formulation exhibit no visible aprepitant crystals when viewed at magnification of 4x to 10x after being stored either at 5º Celsius or at room temperature for a period of at least one week). '794 patent, col. 8, ll. 5–21. At trial, Dr. Little testified that Fresenius's ANDA product has a mean droplet size between 45 and 75 nanometers and a PFAT5 of not more than 0.05%. *See* Tr. 32:15–33:4. That testimony was unrebutted, and I credit it. Dr. Little also testified that Fresenius's ANDA product would not be likely to contain visible aprepitant crystals when viewed at a magnification of 4x to 10x after being stored either at 5º Celsius or at room temperature for a period of at least one week.

To be sure, Heron did not actually use the microscopy test on Fresenius's ANDA product. Instead, Dr. Little explained that Fresenius's product satisfied the "ultracentrifugation test," which Dr. Little explained was a more exacting test for detecting aprepitant crystals than the crystal visibility test at 4x to 10x magnification. *See* Tr. 36:22–37:12; *see also* JTX 33 at 2 (Fresenius's regulatory filing to the FDA asserting that no crystals were observed after ultracentrifugation); JTX 34 at 14 ("no crystals observed after ultracentrifugation"); Tr. 103:17–104:20 (confirming that no crystal content had been observed in any of Fresenius's exhibit batches during testing).

Based on the results of the ultracentrifugation test, Dr. Little concluded that Fresenius's product would necessarily contain no visible aprepitant crystals when viewed at magnifications of 4x to 10x after being stored either at 5º Celsius or at room temperature for a period of at least one week. *See* Tr. 33:16–37:15.

Dr. Little's conclusion was consistent with Fresenius's own submission to the FDA reporting that Fresenius's ANDA product contained no crystals after ultracentrifugation. *See* JTX 33 at 2. Furthermore, Dr. Little's testimony at trial that Fresenius's ultracentrifugation test is more stringent than the test set forth in the '794 patent for stability was unrebutted. *See* Tr. 36:22–37:12. I credit Dr. Little's testimony that a product that forms no crystals under Fresenius's ultracentrifugation test would also form no observable crystals under the microscopy test set forth in the asserted claims of Heron's patents. *See id.*; JTX 33 at 2; JTX 28 at 9; JTX 34 at 14.

Dr. Little's conclusion is further supported by the undisputed fact that Cinvanti® itself meets the '794 patent's physical stability requirement. *See* Tr. 21:2–22:21; JTX 49 at 41–43 (showing that no crystals were observed by microscopy in Cinvanti® at storage conditions between 2 and 8 degrees Celsius after six months); *id.* at 47–49 (showing the same at 25 degrees Celsius). Fresenius asserts that its ANDA product is identical to Cinvanti®. *See* JTX 192 at 2. If Fresenius is correct that the two products are identical in composition, then Fresenius's ANDA product should meet the same physical stability criteria as Cinvanti®, including that the product contains no visible aprepitant crystals when viewed at magnifications of 4x to 10x (i.e., 40x to 100x of actual magnification). And in fact, the evidence at trial showed that Fresenius's ANDA represented that the composition of Fresenius's product had the same components in the same amounts as Cinvanti®. Tr. 23:23–27:15, 85:5–87:20, 88:7–89:19, 95:8–99:11; JTX 33; JTX 26 at

9; JTX 38 at 25–26 (Fresenius's drug product "uses the same formulation as the [Reference Listed Drug] product, Cinvanti®.").[6]

In sum, based on Dr. Little's analysis of the physical stability of Fresenius's ANDA product and the compositional features of that product, Tr. 38:25–39:7, I find as a factual matter that Fresenius's ANDA product satisfies the "physical stability" limitations in claim 8 (and thus dependent claims 9 and 10) of the '794 patent. I therefore find that Fresenius's ANDA product infringes claims 9 and 10 of the '794 patent.

VII. Obviousness of the Asserted Claims

The principal disputed issue in this case is whether Heron's asserted claims would have been obvious in light of the prior art in existence as of the September 19, 2014, priority date of the '229 and '794 patents.

Obviousness under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The underlying factual considerations "include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations" bearing on obviousness. *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736 (Fed. Cir. 2013) (citing *Graham*, 383 U.S. at 17–18, and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)). "The obviousness analysis should not be conducted 'in a narrow, rigid manner,' but should instead focus

[6] The fact that Fresenius concedes that its ANDA product is identical to Cinvanti® may not be sufficient by itself to prove that the ANDA product will satisfy the physical stability limitation in the '794 patent, but it supports the other evidence in the case indicating that Fresenius's ANDA product meets that limitation.

on whether a claimed invention is merely 'the result [] of ordinary innovation,' which is not entitled to patent protection." *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 595 (D. Del. 2018) (quoting *KSR*, 550 U.S. at 427–28), aff'd sub nom. *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019).

An obviousness determination "requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so." *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347 (Fed. Cir. 2024) (quoting *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019), and *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018)). The party in a district court proceeding challenging the validity of issued claims bears the burden of proving that the asserted claims would have been obvious and must do so by clear and convincing evidence. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014).

A. Summary of the Parties' Positions

In brief summary, Fresenius's theory of obviousness is that the Chinese patent application, CN845, disclosed an emulsion consisting of essentially the same components and prepared by the same process as the emulsion disclosed in Heron's '229 and '794 patents. Fresenius argues that the only significant difference between the two is that CN845 disclosed a range in the emulsifier concentration between 0.5% and 10% (with an optimal level at 8% to 10%), while the '229 and '794 patents recited an emulsifier concentration of 14%. According to Fresenius, a POSA would have been motivated to use the slightly higher concentration of emulsifier as a matter of routine

optimization and would have had a reasonable expectation of success in obtaining a stable emulsion using that higher emulsifier concentration.

A POSA would have been motivated to consider the higher emulsifier concentration, according to Fresenius, based on other prior art and the POSA's knowledge. Specifically, the POSA would have known from the Zhou article that the method used in CN845 produced an aprepitant emulsion that was stable, as measured by a standard somewhat less demanding than the applicable USP standard, *see* JTX 115 at 10, giving rise to a motivation to improve the stability of the formulation to meet the USP standard. The POSA would also have known from the Liu reference that for certain stable emulsions (referred to as microemulsions) the emulsifier concentration can be as high as 30%, *see* JTX 93 at 10, inviting optimization of the CN845 formulations by using emulsion concentrations slightly higher than the range set forth in CN845. Finally, the POSA would have known that to solubilize drugs such as aprepitant that are not soluble in either oil or water, the drug must be adsorbed into the interface between the oil and water phases of the solution, JTX 113 at 9, and for that mechanism to be effective, a larger amount of the emulsifier is required than would be required to dissolve a drug that is insoluble in water but is soluble in oil, *see* Tr. 228:25–229:8, 229:22–230:6.

Heron's theory of the case for nonobviousness begins with the fact that the 14% concentration of emulsifier in the asserted claims is not within the 0.5% to 10% range set forth in CN845, and therefore is not subject to the principle that a claim that falls within a range disclosed in the prior art is presumed obvious. In addition, Heron points out that the 2012 Zhou article suggested that the optimal concentration for the emulsifier disclosed in CN845 was 2.5%, which is toward the lower end of the 0.5% to 10% range set forth in CN845. According to Heron, the

work of Zhou and his collaborators, as reflected in both CN845 and the Zhou article, does not suggest to a POSA that emulsions containing an emulsifier concentration above the maximum 10% level set forth in CN845 would be likely to be stable.

Heron also notes that the claims of the '229 and '794 patents recite the use of sodium oleate as a pH modifier, whereas the CN845 application does not specify a particular agent for pH modification, but merely instructs "adjusting the pH" of the composition. JTX 71 at 14. The evidence at trial, according to Heron, did not show that the use of sodium oleate as a pH adjuster would have been obvious to a POSA as of the priority date of the patents in suit.

B. Person of Ordinary Skill in the Art

The parties in this case do not materially disagree about the qualifications of a POSA. Fresenius's position is that a POSA would have "an advanced degree in pharmaceutical formulation, pharmaceutical chemistry, medicinal chemistry, or a related field and experience with intravenous emulsions." Tr. 129:19–130:6. Such a person would also have access to a physician with experience treating cancer patients. *Id.* Heron's position is that a POSA could have a lower level of education, such as a bachelor's degree in a relevant field, provided that the individual has a "commensurate degree of experience in the real world." Tr. 1212:24–1214:3. Despite the minor differences between those definitions, the parties' definitions are functionally equivalent. Both parties' experts agreed that their respective opinions on the issue of obviousness would be the same under either definition of "a person of ordinary skill." *See* Tr. 130:15–17, 1214:6–14. I therefore do not regard it as necessary to decide which party's definition of a person of ordinary skill in the art to accept.

C. Framing of the Obviousness Question

The parties disagree about the proper framing of the obviousness question. In particular, they disagree about how to characterize the problem to be solved facing a POSA as of the patents' priority date. Fresenius argues that the problem was to develop a stable intravenous aprepitant formulation. Heron argues that the problem to be solved was to develop an intravenous NK-1 receptor antagonist without the negative side effects associated with fosaprepitant.

The framing of the problem to be solved is a question of fact. *See Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("Whether a person of ordinary skill in the art would narrow the research focus to lead to the invention depends on the facts."). I agree with Fresenius and find that a POSA would have identified creating a stable intravenous aprepitant formulation as the problem to be solved.

The prior art would have provided a POSA with a clear motivation to develop an intravenous aprepitant product. The evidence introduced at trial showed that it was well known at the time of the invention that aprepitant had excellent biological properties but that its physical properties made it difficult to formulate for intravenous administration. *See, e.g.*, Tr. 891:13–16. The evidence also showed that formulators have sought to create a soluble aprepitant formulation since aprepitant was first discovered. *See, e.g.*, PTX 3 at 1 (Dr. Hale's research publication stating, "Since the availability of both an oral and an intravenous formulation of [aprepitant] was deemed to be necessary in order to provide maximum clinical flexibility with this compound, we sought ways to overcome the solubility issues associated with it.").

After learning that CN845 and Zhou had success with solubilizing aprepitant in an emulsion suitable for intravenous injection, a POSA would recognize that the next step toward

commercializing an intravenous aprepitant emulsion would be to modify the formulation to meet regulatory requirements in the United States, including the USP guidelines. *See* Tr. 208:17–19, 209:12–17 (Dr. Rabinow testifying that a POSA would be familiar with the USP guidelines and would know that an injectable aprepitant emulsion would need to comply with the USP<729> standard to gain FDA approval).

Heron argues that a POSA would have experimented with intravenous formulations for other NK-1 receptor antagonists, such as the compounds rolapitant and netupitant. *See* Tr. 944:17–945:11. Even if that assertion is true, it does not negate the evidence that there was a motivation to create an intravenous aprepitant product. *See PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014) ("Our precedent . . . does not require that the motivation be the best option, only that it be a *suitable* option from which the prior art did not teach away" (citing *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d at 738, and *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013)); *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). But the incentive to seek an aprepitant-based solution rather than experimenting with other NK-1 receptor antagonists would have been strong, as aprepitant had been shown to be safe and highly effective in the course of years of clinical experience. Tr. 128:13–129:11. Thus, I agree with Fresenius that a POSA would have been motivated to overcome aprepitant's inherent solubility problems to develop an intravenous formulation.

Heron also accuses Fresenius of relying on hindsight in framing the obviousness question. As Heron notes, the Federal Circuit has repeatedly cautioned against defining the problem to be solved in terms of the patented solution. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998) ("Defining the problem in terms of its solution reveals

improper hindsight in the selection of the prior art relevant to obviousness."); *see also Insite*, 783 F.3d at 859 (explaining that "an overly narrow statement of the problem can represent a form of prohibited reliance on hindsight, because often the inventive contribution lies in defining the problem in a new revelatory way." (cleaned up)); *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (Using the invention "to define the problem that the invention solves" is "a form of prohibited reliance on hindsight.); *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Heron's argument, however, is refuted by the position taken by scientists working in the field that it was desirable to develop a way to dissolve aprepitant so that it could be formulated for intravenous administration. *See, e.g.*, PTX 3 at 1 ("[T]he availability of both an oral and an intravenous formulation of [aprepitant] was deemed to be necessary in order to provide maximum clinical flexibility with this compound."). Such expressions would have provided sufficient reason for a POSA to pursue the claimed formulations. *See Bayer Pharma AG v. Watson Lab'ys, Inc.*, 874 F.3d 1316, 1324 (Fed. Cir. 2017) ("Here, the motivation to formulate an ODT [oral disintegrating tablet] version of vardenafil is plainly evident from the face of multiple prior art references disclosing ODT formulations of ED [erectile dysfunction] drugs. No further rationale for developing vardenafil ODT was necessary.").

In summary, a POSA would have envisioned the problem to be developing an intravenous formulation of aprepitant. The question in this case, therefore, is whether it would have been obvious, based on the prior art, to devise a stable aprepitant formulation suitable for injection that would satisfy the limitations of the asserted claims of the '229 and '794 patents. *See KSR*, 550 U.S. at 419–20 (explaining that claims are invalid as obvious where "there existed at the time of

invention a known problem for which there was an obvious solution encompassed by the . . . claims.”). Thus, as to the framing of the problem to be solved, I agree with Fresenius.

D. Differences Between the Claims and the Prior Art

The parties dispute whether the formulations recited in the asserted claims were more stable than the formulations in CN845 and Zhou. I find that the patented formulations were shown to have superior physical stability as compared to aprepitant emulsions similar to those disclosed in CN845 and Zhou. Examples 4 and 5 in the common specification of the asserted patents were prepared in a manner generally consistent with the formulations set forth in CN845 and Zhou. While the optimized formulation set forth in Zhou satisfied the K_e test for stability, the corresponding formulations in Examples 4 and 5 of the ’229 and ’794 patents did not satisfy the microscopy test for stability that Drs. Ottoboni and Han used and that was incorporated into the asserted claims. In both of those formulations, crystal formation was observed within four days after preparation. *See* ’229 patent, col. 18, line 16, through col. 19, line 26; ’794 patent, col. 18, line 16, through col. 19, line 23. By contrast, the formulations in Examples 1, 2, 3, and 6 of the asserted claims, which were based on the formulations set forth in the asserted claims of those patents, were found to pass the microscopy test and also to satisfy the requirements of USP<729>.

The recited features of the asserted claims are similar to those set forth in CN845 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 CN845 specification (0.05% to 2%), JTX 71 at 13, and is close to

the concentration set forth in several of the examples in CN845.[7] The concentration of soybean oil in the asserted claims is 9% to 10%, which falls well within the range set forth in the CN845 specification (5% to 30%) and includes the concentration of soybean oil in Example 7 of CN845, which is 9.5%. *Id.* at 17. And the pH of the composition in the asserted claims ranges from 7.5 to 9.0, which overlaps with the 6.0 to 8.0 pH value of the emulsion in CN845. *Id.*

According to Heron, there are two important differences between the claimed formulations and the Chinese prior art references. First, the concentration of egg yolk lecithin differs: CN845 recommends a concentration of egg yolk lecithin emulsifier of 0.5% to 10% (with a preferred concentration of 8% to 10%), while the asserted claims recite a concentration of 14% egg yolk lecithin. Second, CN845 refers to the use of a pH modifier to produce the appropriate pH levels for its formulations, but it does not disclose the use of any specific pH modifier, while the claims of the asserted Heron patents recite the use of sodium oleate as a pH modifier.

E. Evidence as to the Motivation to Increase Lecithin Concentration

At the time of the invention, a person of skill in the art would have recognized that the Chinese formulators had successfully solubilized aprepitant in an emulsion by using up to eight times as much emulsifier as had been used in conventional emulsions. In addition, the Zhou article showed that at least one formulation achieved a degree of stability, as measured by the K_e centrifugation test. A POSA also would have recognized that CN845 recommended the use of an emulsifier at the top of the 0.5% to 10% range disclosed in that publication, and that nothing in the

[7] Examples 1, 4, and 6 of CN845 contain 0.5% of aprepitant, while Example 8 contains 1% of aprepitant. JTX 71 at 14–17.

publication indicated that a concentration any higher than 10% would cause the emulsion to fail. More generally, a POSA would have known that, up to a point, increasing the concentration of the emulsifier in the aprepitant emulsion would increase the surface area of the interface between the oil and water phases of the emulsion, thus potentially increasing the stability of the composition. And a POSA would be aware that the Liu review article published in 2011 had characterized the concentration of surfactants (including phospholipids) used in microemulsions as being between 5% and 30%.

On the other hand, Heron points to evidence that would not have encouraged a POSA to consider an emulsifier concentration as high as 14%. In his testimony, Dr. Little focused on the Zhou article, which was published in 2012, shortly after CN845. Tr. 1253:2–9. Dr. Little explained that a POSA confronted with CN845's broad range of emulsifier concentrations would look to the inventors' other work—namely, the results reported in the Zhou article—for further guidance when picking the concentration within CN845's range to focus on. *See* Tr. 1254:4–1255:25. Dr. Little noted that the Zhou article disclosed that the "optimal formulation" of an aprepitant emulsion would contain only 2.5% egg yolk lecithin, in contrast to the 8% to 10% concentration level suggested in CN845. JTX 115 at 1, 6, 7; *see also* Tr. 1257:10–14 (Little), 349:2–7 (Rabinow).

Dr. Little further testified that there was no general rule that increasing the concentration of the emulsifier component would result in a more stable emulsion; to the contrary, he testified that high levels of emulsifier would have a destabilizing effect. *See* Tr. 1286:14–1288:13. He added that "a formulation scientist . . . [is] trying to decrease [the emulsifier] 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." Tr. 1288:7–13. Dr. Rabinow agreed in part, acknowledging that there is a point at "which the amount of the emulsifier clearly becomes counterproductive." Tr. 249:18–252:1.

Fresenius relies on the Khan reference, JTX 91, which stated that the "amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability." *Id*. at 5. But Kahn added that "[a]t high emulsifier concentration emulsion instability occurs because of rapid coalescence." *Id.* That disclosure is consistent with the undisputed expert testimony that, above a certain level, increasing the emulsifier level will not further improve stability. *See, e.g.*, Tr. 1286:24–1287:20.

Dr. Little pointed out that as of 2014 other products using lecithin as an emulsifier employed concentrations of lecithin in the low single digits,[8] and he stated his opinion that "going up to 14 percent is not what a person of ordinary skill in the art would even be thinking about doing." Tr. 1282:13–19. That opinion, Heron argues, is consistent with Zhou's characterization of the emulsifier concentration level of 2.5% as optimal.

Heron also challenges the applicability of the Liu reference to the technology at issue in this case on the ground that Liu referred to "microemulsions," not "emulsions." Heron argues that microemulsions are quite different from conventional emulsions of the sort recited in the asserted

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[8] For example, the aprepitant emulsion disclosed in the Hingorani patent application publication relied on by Fresenius, JTX 21, contained only 1.2% lecithin. Tr. 262:131–21, 327:25–328:8, 1284:17–1286:7. Similarly, the emulsions described in the Washington reference, JTX 113, also relied on by Fresenius, contained only 1.2% lecithin. Tr. 364:8–365:24; JTX 113 at 2.

claims, and that the range of 5% to 30% for microemulsions referred to in Liu has no application to the emulsions at issue in this case.

In support of that position, Dr. Little testified that even though CN845 used the term "microemulsion" to describe the emulsion in that reference, a POSA, reading CN845, would "understand that it's talking about an emulsion." Tr. 1375:16–1376:7. He explained that microemulsions are thermodynamically stable, while classical emulsions are not, and that the two have very different properties. Tr. 1240:19–1241:16, 1295:10–1296:3.

Dr. Rabinow agreed that under the "technical, classical definition" of an emulsion, making an emulsion requires energy to be put into the system, whereas making a microemulsion does not. Tr. 162:2–24, 340:4–16. As Dr. Rabinow put it, in the case of a microemulsion, "you don't add energy . . . you just bring the ingredients together, and miraculously you form your microemulsion." Tr. 162:14–16. Dr. Rabinow therefore agreed with Dr. Little that under the classical definition of an emulsion, the emulsions created by the inventors on the CN845 application would be considered emulsions, not microemulsions, because they required the input of energy to formulate. *See* Tr. 162:9–24, 1240:21–1241:16. The inventors of the CN845 application, according to Dr. Rabinow, appear to have referred to their emulsions as "microemulsions" simply because the particles were much smaller than the particles that would be present in an ordinary emulsion. Tr. 161:3–14.

While acknowledging the differences between emulsions and microemulsions, Tr. 161:3–14, 338:18–19, Dr. Rabinow testified that the differences between the two are irrelevant to the range of emulsifier concentrations disclosed by Liu, because "[b]iocompatibility and safety are similar for microemulsions or emulsions," and the concentration of the emulsifier is "a safety,

biocompatibility consideration." Tr. 339:3–4, 12–13. For that reason, he concluded, a POSA would have understood Liu's reference to a suitable emulsifier concentration of between 5 and 30% in microemulsions to be equally applicable to classical emulsions. Tr. 338:23–339:13.

I agree with Fresenius that a person of skill in the art would consider the Liu reference to have at least some application to an emulsion such as the emulsions in CN84 and Zhou, in which the particles were much smaller than in classical emulsions. That is not to say, however, that Liu provides convincing evidence that a POSA would be motivated to use an emulsifier concentration as high as 14%. Dr. Little pointed out a number of other reasons that a POSA would not find the information in Liu to be of use in optimizing either CN845 or Zhou. Tr. 1289:13–17. First, Dr. Little explained that Liu was directed to emulsions in which the oil component consisted of medium-chain triglycerides, not long-chain triglycerides, such as the soybean oil used in Zhou and CN845. Tr. 1292:8–1293:7. Second, Dr. Little noted that Liu is principally concerned with water-in-oil emulsions, not oil-in-water emulsions such as the emulsions in Zhou and CN845. Tr. 1291:2–20, 1299:15–1300:21. Third, Dr. Little testified that Liu is not directed solely to the use of phospholipids such as egg yolk lecithin, but refers to a wide range of surfactants; thus, the Liu reference does not teach the use of concentrations of up to 30% of egg yolk lecithin. Tr. 1295:10–24. Finally, Dr. Little noted that Liu does not discuss aprepitant emulsions at all. Tr. 1293:21–1294:7. Based on those observations, Dr. Little concluded that a POSA would not look to the statement in Liu about surfactant concentrations "in order to get surfactant concentrations to apply to an emulsion like CN '845, Zhou, and the patents-in-suit." Tr. 1300:22–1301:5. In view of those differences, I discount the relevance of Liu to establishing motivation for a POSA to use an emulsifier concentration above 10%. That conclusion is further bolstered by the fact that Liu's

reference to an emulsifier concentration of 5 to 30% is made in passing and the fact that Liu does not offer any disclosures as to how the specific concentration would be selected from that range, which Liu itself describes as "relatively large." *See* JTX 93 at 10.

Consistent with Dr. Little's critique that Liu does not discuss egg yolk lecithin, Dr. Rabinow admitted that he "did not identify a single prior art document that disclosed a formulation containing more than 10 percent egg lecithin." Tr. 338:2–9. And the evidence showed that as of 2014, all FDA-approved emulsions based on egg yolk lecithin used concentrations of 1.2% or less. Tr. 327:5–9. Dr. Rabinow pointed out that the Washington reference "says you need to expand the surface area of the interface, which would necessarily imply additional emulsifiers required," Tr. 365:15–21, but the example formulations discussed in the Washington reference contain only 1.2% lecithin, *see* Tr. 364:21–365:1. Moreover, the only reference dealing specifically with aprepitant used a concentration of only about 1% egg yolk lecithin. *See* JTX 21 at 8; Tr. 327:25–328:5 (Rabinow); Tr. 1286:2–7 (Little). In short, the other prior art references taught emulsifier concentrations at the low end of the 0.5% to 10% range disclosed in CN845 and close to or below the 2.5% concentration disclosed in Zhou. Those references would therefore suggest to a POSA that formulators should focus on emulsifier concentrations well below 10% rather than concentrations in excess of 10%. And the fact that all these emulsions used concentrations of egg yolk lecithin below the minimum recommended concentration in Liu further supports discounting the reference in Liu to emulsifier concentrations between 5 and 30%.[9]

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[9] During his testimony, Dr. Rabinow identified several references that use high concentrations of egg yolk lecithin: a 2014 article by Agarwal, JTX 67; a 1991 European patent application, JTX 74; and a 2009 article by Yue, JTX 114. I find those references not to be probative

I find unpersuasive Dr. Rabinow's testimony that, even absent an applicable reference, a POSA would have been motivated to increase the concentration of egg yolk lecithin above the range disclosed in CN845 and up to as much as 14%. Fresenius contends that a POSA would be able to derive a 14% concentration of egg yolk lecithin as the appropriate emulsifier concentration as a matter of "routine optimization." But this is not a case involving routine optimization within a range of values disclosed in the prior art. *See Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.3d 1341, 1347–49 (Fed. Cir. 2024); *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1005–10 (Fed. Cir. 2018). The 14% lecithin concentration in the '229 and '794 patents was not within the 0.5% to 10% range discussed in CN845. For that reason, the analysis in cases dealing with routine optimization within a range disclosed in the prior art is inapplicable here.

Heron challenges Dr. Rabinow's testimony about complexing and his conclusion that a POSA would have considered increasing the emulsifier concentration in order to facilitate complexing between the aprepitant and emulsifier molecules, but, as explained above, I find Dr. Rabinow's testimony about the phenomenon of complexing to be credible. Moreover, what is important about Dr. Rabinow's testimony about complexing is not whether there were actual

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of the issues in this case because (1) they do not discuss aprepitant, Tr. 357:15–17; (2) they do not discuss intravenous formulations, Tr. 357:18–358:5; and (3) they disclose a lecithin-to-active-ingredient ratio of 3:1 or less, while the asserted claims recite a ratio of 20:1, Tr. 356:10–14, 330:10–13. In view of those differences, those references are not analogous to the formulations in the asserted patents, so I credit Dr. Little's testimony that a POSA would not understand those references to indicate that the concentration of egg yolk lecithin should be increased above the levels suggested in the CN845 or Zhou references. *See* Tr. 1304:4–1305:19. In any event, Fresenius relies on those references only as examples of complexation, and not to show that a POSA would use a high concentration of lecithin in an aprepitant emulsion.

complexes formed in the aprepitant emulsion, but that a POSA at the time of the invention would have understood that complexes can form between emulsifier and aprepitant molecules if enough emulsifier is present, and that the consequence of the complexation is to increase the stability of the emulsion. Therefore, I credit his testimony that the possibility of complexation—and the resulting increase in the stability of the emulsion—would be a factor encouraging a POSA to consider using an increased concentration of the emulsifier.

Nonetheless, I also credit Dr. Han's explanation that "[t]he emulsion is very complex. The ratio of lecithin to aprepitant, oil to aprepitant, sodium oleate used, everything is important to make a stable emulsion." Tr. 508:1–16. I also find credible Dr. Han's testimony that the claimed invention was developed through "a lot of trial-and-error experiments." *Id.* As Dr. Little testified, a person seeking to improve on the formulation set forth in CN845 would not necessarily modify the concentration of the emulsifier in the first instance, but "may modify something else from the Zhou formulation." Tr. 1281:22–1282:7.

The fact that the Heron group was able to develop its formulation in only about six months after focusing on the Chinese patent application as a starting point for its emulsion experiments—particularly in light of Dr. Han's lack of prior experience working with emulsions—provides some support for Fresenius's obviousness argument. It is not enough, however, to justify the conclusion that a POSA would be motivated to increase the level of emulsifier concentration as high as 14% and that the POSA would have a reasonable expectation of success in producing a stable emulsion with an emulsifier concentration that high. In view of the general consistency of the references in disclosing emulsifier concentrations well below 10%, I find that a POSA would not have had a motivation to increase the concentration of lecithin above 10%, including a concentration of at

least 14%, and would not have had a reasonable expectation of success with an emulsifier level that high.

Accordingly, based on the evidence summarized above, I find that Fresenius has not shown by clear and convincing evidence that a POSA would have had a motivation to modify Zhou's formulation by increasing the amount of egg yolk lecithin to concentrations well above the range disclosed in CN845, especially when the person would be working within the ranges disclosed in CN845 for every other ingredient. *See* Tr. 227:18–228:14, 224:8–20. Nor would a POSA have had a reasonable expectation of success with such a formulation.

F. Evidence as to the pH Modifier

Claim 8 of both patents includes a pH modifier as one of the components of the injectable pharmaceutical emulsion. The claims specify sodium oleate as the pH modifier, although they do not state what amount of sodium oleate should be used; instead, the claims simply say that the pH of the emulsion must fall within the range between 7.5 and 9.0. Fresenius argues that the use of sodium oleate as a pH modifier in the formulation would have been obvious to a POSA in light of the prior art.

CN845 disclosed adjusting the pH in its formulations to between 6.0 and 8.0, JTX 71 at 10, 13, 14, but it did not identify a specific pH modifier or an amount of such modifier to be used. While Dr. Little testified that the most common basic pH modifier is sodium hydroxide, Tr. 1219:2–18, 1309:9–25, Dr. Rabinow testified that as of the priority date it was not "considered a big deal" to use sodium oleate in an emulsion especially in view of the fact that "oleate was already used in commercialized emulsions," Tr. 425:3–8.

When Dr. Ottoboni was asked whether Heron was the first company to use sodium oleate as a pH adjuster, he responded that sodium oleate "was present in one other pharmaceutical formulation that I'm aware of." Tr. 551:4–8. In addition, during the examination of the application that led to the asserted patents, the examiner found that it would have been obvious to one of ordinary skill in the art to use sodium oleate to adjust the pH of the claimed formulations. The examiner observed that CN845 (which the examiner referred to as "Zhou et al.") did "not recite any particular agent as preferred for adjusting the pH, therefore any suitable compounds may be used. In the absence of unexpected results or other evidence to the contrary, the selection of sodium oleate is the mere selection of a material suitable for the intended use." JTX 2 at 88.

Heron has not suggested that there is any special reason that the asserted claims called for sodium oleate as the designated pH adjuster, as opposed to a more common pH adjuster such as sodium hydroxide. In fact, the common specification of both patents in suit states that although sodium oleate is used in examples 1, 2, and 3 to adjust the pH of the emulsion, "[o]ther pH modifiers that may be used include but are not limited to sodium hydroxide, potassium hydroxide, magnesium hydroxide, Tris, sodium carbonate and sodium linoleate." '229 patent, col. 11, ll. 63–66; '794 patent, col. 11, ll. 63–66.[10] I therefore find that a POSA would have been aware that a

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[10] Heron argues that it would not have been obvious to use sodium oleate as a pH adjuster because of concerns that sodium oleate could cause hemolysis (rupturing of red blood cells). The evidence at trial, however, showed it was known that in an emulsion formulation sodium oleate migrates to the emulsion and enters the emulsion membrane where it is sequestered from interfering with red blood cells. *See* Tr. 383:22– 385:2; JTX 88 at 1. Dr. Rabinow explained why the concern expressed about hemolysis in one of the references introduced at trial, JTX 112, was unwarranted, particularly in light of the evidence that sodium oleate was commonly used in emulsion formulations. *See* Tr. 207:13–208:1; JTX 76 at 4. Heron did not rebut Dr. Rabinow's testimony on that point, and I credit that testimony.

number of compounds could be used as pH adjusters, including sodium oleate, and that in the absence of any reason to believe sodium oleate would have been superior to other similar compounds, such as those listed as suitable substitutes in the specification, the choice of sodium oleate would have been obvious. *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (finding a strong case of obviousness when claim recited "a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known cooling agent [i.e., component] for another").

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To summarize my findings on the issues of obviousness, I find that all but two of the limitations found in the asserted claims of the '229 and '794 patents fall within the ranges of components identified in CN845. The two "missing" limitations are the concentration of 14% egg yolk lecithin and the use of sodium oleate as a pH modifier. 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. However, I find that the limitation requiring a 14% concentration of egg yolk lecithin was a substantial departure from what was taught in the relevant prior art and what a POSA would have been motivated to use in such an emulsion with a reasonable expectation of success. For that reason, I conclude that the asserted claims of the two patents in suit would not have been obvious.

G. Objective Considerations

Even though I have concluded that Fresenius has not shown that the asserted claims would have been obvious based on an analysis of the prior art references from the perspective of a person of ordinary skill in the art, I will address the issue of how the "objective considerations" bear on

the issue of obviousness, as those considerations serve as a "fundamental part of the overall § 103 obviousness inquiry." *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1077–79 (Fed. Cir. 2012). The objective considerations on which the parties focused at trial were the alleged (1) long-felt unmet need for an injectable form of aprepitant; (2) failure of others to satisfy that need and the unexpected nature of the invention; (3) industry skepticism regarding the invention, praise from others in the industry, and copying of the invention by others; and (4) commercial success of the product based on the invention. *See Apple Inc. v. Samsung*, 839 F.3d 1034, 1052–53 (Fed. Cir. 2016 (en banc).

1. Long-Felt Unmet Need

Heron's expert on medical oncology, Dr. Eric Roeland, testified that prior to the inventors' work that led to the patents at issue in this case, "there was a long-felt unmet need for an NK-1 receptor antagonist that was equally as efficacious [as fosaprepitant] with fewer related side effects." Tr. 1058:23–1059:2. He added that oncologists preferred intravenous formulations of such drugs because of concerns about bioavailability and patient compliance with oral formulations. Tr. 1017:12–1018:7, 1020:15–1021:16 (explaining that patients frequently experience problems adhering to instructions for taking oral medications, and that oral delivery of drugs is not as direct as intravenous delivery, resulting in lower bioavailability of the drug); *see also* JTX 137 at 1–2. Dr. Roeland concluded that Cinvanti® satisfied that unmet need "[b]ecause it was equally as efficacious [as fosaprepitant] and had fewer related infusion site reactions." Tr. 1060:9–1061:2.

Dr. Maurie Markman, Fresenius's expert on cancer treatment, including preventing emesis and CINV, disagreed with Dr. Roeland on the issue of long-felt need. He testified that the industry had developed workarounds designed to solve the problems associated with the use of fosaprepitant in anti-emetic drugs such as Emend IV®. Those workarounds included diluting the dosage of fosaprepitant, *see* Tr. 730:14–731:18, and using a "central line" or "port" to administer the fosaprepitant, i.e., a subcutaneous device through which drugs can be administered directly into the patient's veins, *see* Tr. 614:22–616:19.

Fresenius argues that the fact that such workarounds could minimize the risks associated with Emend IV® indicates that there was no unmet need for Heron's invention. To the contrary, I find, however, that the evidence shows there was pressure in the industry to find a solution to the problems that were associated with oral aprepitant formulations and injectable fosaprepitant formulations that were eventually solved by Cinvanti®. Moreover, the evidence shows that workarounds such as the use of a central line or port were not available or advisable in all cases, so the risk of adverse reactions to the fosaprepitant-based drugs remained a concern in at least some instances.

In pushing back on the issue of long-felt unmet need, Fresenius points to a survey conducted by Heron prior to the launch of Cinvanti® in which Heron concluded that healthcare professionals were "generally satisfied with IV Emend safety and indicate low level of concern regarding [injection site reactions] and hypersensitivity." JTX 177 at 30. The survey further concluded that there was a "[l]ow level of stakeholder awareness of [polysorbate 80] and lower awareness of [polysorbate 80] in IV Emend." *Id.* In addition, the survey found that there was a "perceived lack of clinical differentiation of Cinvanti vs. Emend IV (e.g. Cinvanti's Polysorbate

80 free characteristic was viewed as only impacting a small patient population, which would not be a differentiator vs. Emend IV)." *Id.* at 98.

Based on Dr. Markman's testimony and a 2022 study of the safety and efficacy of injectable NK-1 receptor antagonist formulations, Fresenius argues that the safety and efficacy of Emend IV® and Cinvanti® were "the same." Tr. 653:9–654:23 (citing JTX 127 at 5). In fact, however, the study cited by Dr. Markman concluded that although there were relatively few infusion site events with either Cinvanti® or Emend IV®, patients who received Emend IV® had a slightly higher risk of infusion site reactions, but the small number of events reported meant that the incremental risk was not deemed statistically significant. JTX 127 at 6–7. The study concluded that to reduce the risk of infusion site adverse events with a fosaprepitant-based emetic, physicians should either use a workaround with a central port line or substitute Cinvanti® as the emetic of choice.

Heron's evidence showed that the side effects from the available fosaprepitant formulations, which included the surfactant polysorbate 80, were a matter of some concern to practitioners.[11] *See* Tr. 1203:15–23 (prior to launch, "health care providers view[ed] surfactant-

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[11] Although Fresenius argues that the evidence did not prove that the polysorbate 80 in Emend IV® was responsible for the increased number of side effects, Heron introduced a number of publications that reached the opposite conclusion. *See* JTX 139 at 1, 16; JTX 150 at 2; JTX 148 at 2; JTX 155 at 10; JTX 142 at 28; Tr. 1035:6–12, 1046:20–1054:20 (Dr. Roeland). Dr. Markman analyzed those studies at length and pointed out methodological weaknesses in the studies that undercut Heron's contention that the adverse reactions in patients receiving Emend IV® were attributable to the polysorbate 80 in that formulation. Tr. 607:10–660:12. In any event, however, with one exception those studies were published after the 2014 priority date for the two patents in suit and therefore contribute little if anything to the risks associated with Emend IV® that were perceived as of the time of the filing of the provisional application on which the patents are based. The one exception, JTX 146, was a Japanese study that Dr. Markman regarded as irrelevant

free formulation as a worthwhile benefit versus Emend IV, although modest," and that "there was some modest view that the polysorbate 80-free formulation was of a benefit"). For example, as noted above, after switching from oral aprepitant to intravenous fosaprepitant as an anti-emetic, a Mayo Clinic study reported that "infusion site adverse events were a prominent and substantial problem for a significant number of patients." JTX 137 at 2. In light of that experience, the Mayo Clinic in 2011 changed its guidelines, recommending the use of oral aprepitant rather than fosaprepitant with certain forms of chemotherapy treatment. *Id*. Moreover, the FDA-approved labels for Emend IV® and Cinvanti® both contained a warning regarding hypersensitivity, but only the label for Emend IV® contained a warning for infusion site reactions, indicating that the infusion site reactions were a known risk associated with Emend IV®. *Compare* JTX 129 at 1 (label for Emend IV®) *with* JTX 51 at 1 (label for Cinvanti®).

Taken as a whole, the evidence supports a finding that although healthcare providers were aware of the risk of adverse reactions from the polysorbate 80 in fosaprepitant products such as Emend IV®, the level of concern was moderate and could be minimized by countermeasures, such as the use of a central port for administering the drug. I therefore find that while at the time of the invention there was some degree of interest in developing an aprepitant formulation that would avoid the side effects of the fosaprepitant treatments, the motivation to do so was not an urgent or compelling one. Thus, I find that the "long-felt, unmet need" factor weighs in Heron's favor, but only moderately.

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because, among other issues, the concentration of fosaprepitant given to the patients in that study was much higher than is permitted in the United States. Tr. 641:10–645:12.

2. Failure of Others and Unexpected Results

Dr. Little explained at trial that the formulations disclosed in CN845 and the Zhou article formed crystals within four days, and thus were not sufficiently stable for commercial use, while the formulations recited in the claims were shown to have long-term stability. *See* Tr. 1344:20–1346:5. He based his opinion on a comparison of Cinvanti® with the formulations set forth in Examples 4 and 5 of the common specification of the asserted patents, which approximate the formulations described in CN845 and Zhou. The difference, he testified, is a difference in kind, not just in degree. Tr. 1346:10–14. Long-term stability is critical to commercialization, Dr. Little explained, because if a formulation is not stable for at least one week, "it becomes almost impossible to commercialize." *See* Tr. 541:23–542:7. I credit that testimony, especially in view of the fact that it was essentially unrebutted.[12]

There was also testimony at trial that the aprepitant molecule had been known for 20 years before Cinvanti®, yet no intravenous aprepitant formulation had been brought to market at any point during that period. The absence of a marketable intravenous or injectable aprepitant formulation is notable in view of the fact that during the same period an injectable fosaprepitant formulation was available. *See* Tr. 1322:25–1323:7. It is also significant that Merck was unsuccessful in its efforts to develop an injectable aprepitant formulation. *See* Tr. 914:18–919:1. Dr. Hale, who was employed by Merck while Merck was attempting to develop such a formulation,

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[12] Fresenius asserts that the ability to commercialize a product is irrelevant. I find that argument entirely unpersuasive. It is readily apparent that a drug that cannot be commercialized is of reduced value and does not represent success for an industry that is focused on bringing new pharmaceutical products to market.

testified that his reaction upon learning about Heron's product was surprise that "someone had cracked this problem that we [*i.e.*, Merck] weren't able to solve" in the "20 years previously, or anyone else between then and the time that Heron did this." Tr. 955:23–956:5. As Dr. Hale put it, his reaction at the time was "surprise[], but kudos, good job." *Id*. I find that testimony credible and corroborated by the publications introduced at trial stating that the "sparing water solubility of [aprepitant] precludes its formulation in a vehicle acceptable for intravenous administration in humans." *See* PTX 3 at 1; JTX 82 at 5. Thus, the secondary considerations of the failure of others and the unexpected results achieved by the inventors weigh in Heron's favor.

A significant mitigating factor in that regard is that the inventors had the advantage of starting their project with the CN845 application in hand, and were able to file their provisional application within about six months of beginning work on the project. There was no evidence at trial that others who had access to the CN845 application had tried and failed to formulate an emulsion stable enough to satisfy the USP standards, and there was no evidence that others in the field regarded Heron's success as unexpected after the groundbreaking work had been done by the Chinese scientists. The "failure of others" and "unexpected results" factors thus favor Heron, but only moderately.

3. Industry Skepticism, Praise, and Copying

There was little evidence at trial bearing on whether the patented invention was met by skepticism within the industry or was greeted by praise. Although Dr. Hale regarded the invention of a stable aprepitant formulation suitable for injection or infusion to be a breakthrough, Heron did not introduce evidence that the industry as a whole was skeptical that such a formulation could be

made, nor did Heron offer evidence that there was widespread praise for the invention in the industry. Those related objective considerations are therefore not at issue in this case.

The presence of copying, although recognized as bearing on nonobviousness in many instances, is also not a relevant consideration in this case. Because an ANDA filer must demonstrate bioequivalence to the branded NDA product in order to obtain FDA approval, Tr. 283:5–22, copying is not ordinarily regarded as probative of nonobviousness in a Hatch-Waxman Act case. *Adapt Pharma Operations Ltd. v. Teva Pharms. USA*, *Inc.*, 25 F.4th 1354, 1374 (Fed. Cir. 2022) (quoting *Bayer*, 713 F.3d at 1377); *see also* Tr. 1349:12–15.

Heron argues that copying is a relevant secondary consideration in this case because Fresenius could have avoided copying Cinvanti® by changing the formulation of its ANDA product and seeking FDA approval for its product by filing what is known as a "section 505(b)(2) application." *See* 21 U.S.C. § 355(b)(2). A section 505(b)(2) applicant may seek approval for a product that is not identical to the NDA product. If the applicant does so, the applicant must demonstrate that the proposed drug is safe and effective, but the applicant is permitted to rely at least in part on clinical studies previously submitted to the FDA. As a result, that course of action can be easier than beginning from scratch with an original NDA, but it is still considerably more burdensome than filing an ANDA based entirely on the NDA application filed by the original applicant. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1046 (Fed. Cir. 2010); *Takeda Pharms., U.S.A., Inc. v. Burwell*, 78 F. Supp. 3d 65, 71–72 (D.D.C. 2015), *aff'd in part and vacated in part on other grounds*, 691 F. App'x 634 (D.C. Cir. 2016). Fresenius's choice to file an ANDA rather than a section 505(b)(2) application is therefore not persuasive evidence of nonobviousness.

The factors of industry skepticism, praise, and copying thus provide no significant support for Heron on the issue of nonobviousness and must be regarded as neutral.

4. Commercial Success

Finally, Heron points to the commercial success of Cinvanti® as a further indication of the nonobviousness of the claimed invention. Heron points out that Cinvanti® enjoys a substantial share of the market for intravenous NK-1 receptor antagonists. That share reached a high of 43% in 2019 before generic fosaprepitant entered the market. Cinvanti®'s share of the market has since stabilized at 25% to 28%. Fresenius acknowledged that Cinvanti® is "doing exceedingly well in the market," which has motivated Fresenius to develop a generic version of Cinvanti®. JTX 186 at 5.

The critical question on this issue is what is responsible for Cinvanti®'s commercial success. Heron contends that Cinvanti® has proved successful because it provides the benefits of intravenous delivery, while being free of polysorbate 80, and thus, unlike the injectable fosaprepitant products, it does not come with the risk of side effects in the form of injection-site adverse reactions. In addition, Heron contends that Cinvanti® is more convenient to use than the competing fosaprepitant drugs. Heron notes that Cinvanti® can be administered in a two-minute intravenous "push," rather than an extended 20- to 30-minute infusion process. Tr. 1066:19–1071:5. Moreover, Cinvanti® can be stored at room temperature for up to 60 days, and in refrigeration for 12 months. Tr. 779:3–9, 1339:8–1340:8. And Cinvanti® comes in a vial and does not have to be reconstituted by a medical professional at the time it is administered. Tr. 1068:9–1069:1.

On the other hand, Fresenius introduced evidence that the success of Cinvanti® has been attributable to Heron's pricing strategy rather than to the advantages of the patented formulation. *See, e.g.*, Tr. 836:12–841:14. It is true that Heron priced Cinvanti® below Emend IV® when Cinvanti® launched. *See* Tr. 1188:15–1189:3. And, as Heron acknowledges, the attractive price of the product was a factor motivating customers to move from Emend IV® to Cinvanti®. JTX 158 at 94; *see also* Tr. 824:25–825:19. Weighing the competing evidence, I conclude that the commercial success of Cinvanti® has been at least partly attributable to its properties compared to the competing products, but that the pricing strategies followed by Heron have had a significant role to play in giving Cinvanti® as large a market share as it has. On balance, then, I find that the commercial success factor favors Heron, but only slightly.

* * * * *

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

VIII. Written Description

In addition to obviousness, Fresenius argues that the asserted claims are invalid for failing to provide an adequate written description of the claimed inventions. According to Fresenius, the

specification does not demonstrate that the inventors were in possession of the full range of the claimed subject matter when the applications for the asserted patents were filed.

Section 112(a) of the Patent Act provides, in pertinent part, that the specification "shall contain a written description of the invention." 35 U.S.C. § 112(a). The purpose of the written description requirement is to ensure that the "inventor actually invented the invention claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The specification's disclosure is sufficient when it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art," *id.*, and it is "highly dependent on the facts of each case," *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1342 (Fed. Cir. 2021). As with other invalidity issues, the patent challenger bears the burden of proof on this issue, and "must establish by clear and convincing evidence that the written description requirement was not met, in light of the presumption of validity." *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003).

The presentations of the parties at trial relating to the written description issue were quite brief. In slightly more than one page of testimony, Dr. Rabinow noted that the claimed pH range for each of the asserted claims was pH 7.5 to pH 9. He contended that the specification did not support a range that broad because the "examples that were alleged to be found to be viable, stable formulations [were] all done in a very narrow pH range of something like 8.7 to 8.8," and a POSA would not "believe that the named inventors of the [two asserted patents] possessed the range 7.5 to 9.0 for the claimed formulations." Tr. 306:25–307:20.

The common specification of the two asserted patents showed that in the pertinent examples of operative embodiments of the inventions, the formulations had pH values of between 8.74 and 8.92. *See* '229 patent, col. 20, line 57, through col. 21, line 11; '794 patent, col. 20, ll. 54–67. Fresenius's argument is that the inventors failed to show that they had possession of the full claimed pH range (7.5 to 9.0) because there were no examples showing formulations with a pH between 7.5 and 8.74.

Heron responds that the common specification discloses that "[i]n one embodiment, the composition has a pH of about 6 to 9, 7 to 9, 7.5 to 9, 7.5 to 8.5, 8 to 9, 6 to 8, 7 to 8, or 6, 7, 8, or 9." '299 patent, col. 4, ll. 65–67; '794 patent, col. 4, ll. 65–67. Those references in the common specification, however, simply list pH ranges between 6 and 9 and thus add little to the written description provided by the original claims themselves, which include a somewhat narrower range of pH values of 7.5 to 9.0.

The more pertinent portion of the specification is the passage that describes the aqueous phase of the formulation as including "a pH-modifying agent," and notes that sodium oleate is used in Examples 1, 2, and 3 of the specification "to adjust the pH of the emulsion to about 6 to 9, depending on the desired emulsion formulation." '229 patent, col. 11, ll. 58–61; '794 patent, col. 11, ll. 58-61. That passage of the specification then continues as follows:

> The aqueous phase is produced by mixing water with the tonicity agent and sodium oleate as the pH modifying agent. Other pH modifiers that may be used include but are not limited to sodium hydroxide, potassium hydroxide, magnesium hydroxide, Tris, sodium carbonate and sodium linoleate. The pH modifier used is effective for adjusting the pH of the emulsion to a preferred pH of about 6 to 9, or about 6, 7, 8, or 9.

’229 patent, col. 11, line 61, through col. 12, line 2; ’794 patent, col. 59, line 61, through col. 12, line 2.

Although the specification reported that Examples 1, 2, 3, and 6, as tested, had pH values of between 8.74 and 8.80, *see* ’794 patent, col. 20, ll. 54–67, the statement in the specification refers to the permissible pH values for those examples as being between pH 6 and pH 9 and explains how those pH values are obtained, thus providing support for the claimed pH range of 7.5 to 9.0.

The question presented by this issue is whether Fresenius has proved, by clear and convincing evidence, that the inventors have failed to show that they had possession of the claimed compositions with pH values of between 7.5 and 9.0. With respect to the ’229 patent, the answer is straightforward. Claim 8 of the patent, from which the asserted claims depend, merely sets forth the components of a composition; it does not contain any requirement of efficacy or stability. Therefore, the mere recitation of the range of pH values in the specification and in the claims is sufficient to satisfy the written description requirement of 35 U.S.C. § 112.

The issue is less clear-cut with respect to the ’794 patent, because claim 8 of that patent, from which the asserted claims depend, requires that the composition be “physically stable.” Thus, the written description requirement demands that the patent establish that the inventors had possession not just of compositions with pH values between 7.5 and 9.0, but also of compositions with pH values between those two values that are physically stable.

“There is no rigid requirement that the disclosure contain ‘either examples or an actual reduction to practice.’” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting *Ariad*, 598 F.3d at 1352; *see also Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366

(Fed. Cir. 2006) ("[E]xamples are not necessary to support the adequacy of a written description."). To the contrary, the written description requirement is satisfied if, for example, the specification provides enough representative embodiments to show that the inventor was in possession of the full scope of the claim. *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019). All that is required to satisfy the written description requirement is that the patent disclosure "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 1350; *see also Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018) (same); *Allergan*, 796 F.3d at 1308 ("[T]he proper inquiry is whether the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail that a person of ordinary skill would understand that the inventor had made the invention at the time of filing."), *quoting Ariad*, 598 F.3d at 1352.

It is true that none of the examples in the common specification of the two patents in suit explicitly shows that the claimed compositions of the '794 patent are physically stable at a pH of between 7.5 and 8.74. But the burden of showing lack of an adequate written description falls on Fresenius, and Fresenius has not shown that the examples set forth in the specification for compositions having a pH of 8.74 and above would not be representative of compositions with a pH as low as 7.5. To the contrary, the discussion in the specification of using a pH modifying agent to adjust the pH of the emulsion to a preferred pH of between 6 and 9 indicates that the inventors understood that their invention would be operative over a wide pH range. Because Fresenius has not suggested any reason to believe that the exemplary composition, which was shown to be stable at a pH of 8.74 would not also be stable at a pH of 7.5, the lower end of the

claimed pH range, Fresenius has failed to show by clear and convincing evidence that the asserted claims of the ’794 patent lack adequate written description.

The specification’s disclosures distinguish this case from *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 (Fed. Cir. 2000), relied on by Fresenius. In that case, the limitation claimed a characteristic that was “not discussed even in passing in the disclosure.” 230 F.3d at 1327. That is not the case here, given the explicit disclosure covering the full range of the challenged claim limitation regarding pH values and examples covering at least a portion of the range of that challenged claim limitation. Accordingly, I find that Fresenius has not shown by clear and convincing evidence that the claims are invalid for failing to satisfy 35 U.S.C. § 112(a).

IX. Conclusion

For the foregoing reasons, I hold that Heron has proved by a preponderance of the evidence that Fresenius’s ANDA product infringes claims 9 and 10 of the ’794 patent, in addition to claims 1–11 and 21 of the ’229 patent, which were previously determined to be infringed. I further hold that Fresenius has not proved by clear and convincing evidence that the asserted claims are invalid for obviousness under 35 U.S.C. § 103 or for the lack of adequate written description under 35 U.S.C. § 112.

The issue of obviousness in this case is a close one. The case was skillfully presented by both sides, and the expert witnesses for both sides were knowledgeable and helpful to the court. In the end, the dispositive factor was the burden of proof. Clear and convincing evidence is a high standard, and even though Fresenius made a strong showing in various respects in support of its claim that the asserted claims would have been obvious, in the end I concluded that Fresenius’s

showing was not clear and convincing, and that Fresenius therefore did not satisfy that demanding standard of proof.

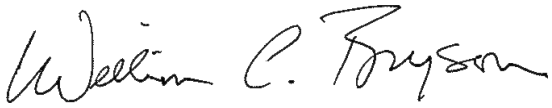
Heron is directed to file a proposed form of judgment in accordance with these Findings of Fact and Conclusions of Law within five days of the issuance of this order.

* * * * *

The briefs that Fresenius submitted in support of its proposed findings of fact and conclusions of law in this case were both submitted under seal. For that reason, I have filed this opinion under seal. Within ten business days of the issuance of this order, Fresenius is directed to advise the court by letter whether any portions of this order should remain under seal, and if so which portions. Any request that portions of the order remain under seal must be supported by a particularized showing of need to limit public access to those portions of the order.

IT IS SO ORDERED.

SIGNED this 3rd day of December 2024.



WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE