IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PAR PHARMACEUTICAL, INC., PAR STERILE PRODUCTS, LLC, and ENDO PAR INNOVATION COMPANY, LLC, Plaintiffs, vs. HOSPIRA, INC., Defendant.	**1:17CV944** **UNDER SEAL** **FINDINGS OF FACT and CONCLUSIONS OF LAW**

This matter is before the Court after a bench trial from June 28, 2019, to July 3, 2019. This is a patent infringement action brought under the Hatch-Waxman Act, 21 U.S.C. § 355, *et seq.* Defendant Hospira Inc. ("Hospira") filed an Abbreviated New Drug Application ("ANDA"), No. 208908, with the Food and Drug Administration ("FDA"), seeking approval to engage in the manufacturing and sale of a generic version of the plaintiffs' Adrenalin® brand epinephrine injection 1 mg/mL product, which is indicated for emergency treatment of allergic reactions, including anaphylaxis. The plaintiffs, Par Pharmaceutical, Inc. ("Par Pharm"), Par Sterile Products, LLC ("Par Sterile"), and Endo Par Innovation Company, LLC ("EPIC") (collectively, "Par") allege that Hospira's ANDA infringes its patents, United States Patent Nos. 9,119,876 ("the '876 Patent") and 9,295,657 ("the '657 Patent"). Hospira challenges the validity of Par's patents.

I. REGULATORY BACKGROUND

The Hatch–Waxman Act was passed in 1984 to respond to two problems created by the statutes that then regulated patents and pharmaceuticals. *Eli Lilly and Co. v.*

Medtronic, Inc., 496 U.S. 661, 669 (1990). The first arose from the fact that inventors ordinarily applied for patent protection for newly discovered drugs well before securing regulatory approval, even though marketing was prohibited until regulatory approval was obtained. *Warner–Lambert Co. v. Apotex Corp*., 316 F.3d 1348, 1357 (Fed. Cir. 2003). Because the FDA generally took much longer to approve a New Drug Application ("NDA") than the Patent and Trademark Office ("PTO") took to grant a patent, the seventeen-year patent term was substantially eroded by the time the patentee could market its product obtain the benefit of his invention. *Id*.

The second problem was the requirement that a generic manufacturer obtain its own NDA—providing its own safety and efficacy data—if it wanted to market a product. *Id*. At that time, manufacturing or using a patented product solely for the purpose of conducting tests and developing the necessary information to apply for regulatory approval later was an act of infringement under 35 U.S.C. § 271(a). *Id*. Because it took a substantial amount of time for a generic manufacturer to obtain data and secure regulatory approval, requiring those manufacturers to wait until after the patent expired to begin testing and other pre-approval activities resulted in a *de facto* extension of the patent term. *Id*.

The Hatch–Waxman Act was designed to address both of these problems by restoring time lost to innovators during pre-patent testing and regulatory approval, while at the same time enabling generic manufacturers to be ready to enter the market once the patents expired. *Id*. To further the overall goal of getting generics to market faster, Hatch-Waxman authorized the filing and approval of Abbreviated New Drug Applications and provided a mechanism through which patent-holders could adjudicate

patent infringement claims prior to a product coming on the market. *Id*.; *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc*., 731 F.3d 1271, 1279 (Fed. Cir. 2013) (noting that the Hatch-Waxman framework envisions resolution of the infringement issue earlier, and generally before ANDA approval). Under Hatch-Waxman, generic manufacturers had to show bioequivalence to a patented drug, but no longer had to prove the safety and efficacy of a generic version of a drug, they could effectively "piggy-back" on the patent holder's showing of safety and efficacy. Generic manufacturers are also allowed to test and seek approval to market the generic formulation during the patent term. *Id*.

Under the infringement adjudication mechanism of the Act, patentees and NDA holders are required to list patents that claim the approved drug or its approved use in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* publication (the "Orange Book"). *Id*.; *see* 21 U.S.C. § 355(b)(1). ANDA applicants are required to either certify that no unexpired patent is listed for its proposed generic formulation, or that the listed patent is either invalid or would not be infringed by the manufacture, use, or sale of the drug by the ANDA applicant ("a paragraph IV certification"). *Id*.; 21 U.S.C. § 355(j)(2)(A)(I-IV).

The filing of an ANDA with a paragraph IV certification constitutes an act of artificial patent infringement under 35 U.S.C. § 271(e)(2)(A), which allows litigation to commence before actual sale of an accused product has occurred. *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd*., 887 F.3d 1117, 1126 (Fed. Cir. 2018); *see also Sunovion,* 731 F.3d at 1279 ("Although no traditional patent infringement has occurred until a patented product is made, used, or sold, under the Hatch–Waxman framework,

the filing of an ANDA itself constitutes a technical infringement for jurisdictional purposes"). Patent holders benefit from the Act because the patent term was extended for products subject to a regulatory review before commercial marketing or use, if the permission for the commercial marketing or use of the product after such regulatory review period was the first permitted commercial marketing or use of the product. *Id*. at 1358.

II. FINDINGS OF FACT

A. Background

The following facts are gleaned from the parties' agreed facts in the Pretrial Order and from the evidence adduced at trial. (D.I. 192-1, Pretrial Order, Exhibit ("Ex.") 1, Statement of Uncontested Issues of Fact ("Agreed Facts"); D.I. 223 to D.I. 226, Trial Transcript ("Tr.")).

The dispute between the parties involves injectable epinephrine formulations and long-standing problems of stability and shelf-life. Epinephrine is a well-known drug used to treat allergic reactions and anaphylaxis for over 100 years. Joint Trial Exhibit ("JTX") 48; D.I. 225, Tr. at 452. Older epinephrine formulations, including Par's original Adrenalin® formulation and Hospira's ampoule and Abboject® products, pre-date the current FDA regulatory regime and were sold without FDA approval under statutory "grandfather" provisions. D.I. 225, Tr. at 527. Although the "grandfathered" drugs had been sold for many years, they did not meet modern pharmaceutical standards in terms of quality, stability, and absence of impurities. D.I. 223, Tr. at 159.

In 2006, the FDA began a drug safety initiative regarding the marketing of unapproved drugs. D.I. 224, Tr. at 215-16; Filing No. 225, Tr. at 527. Under the

initiative, the FDA required registration of unapproved products for listing in the Orange Book. *Id*. Accordingly, the scientists at Par's predecessor company, JHP Pharmaceuticals LLC ("JHP"), began working to develop a product that would meet the FDA's new requirements. Plaintiff's Trial Exhibit ("PTX") 1, '876 Patent, col.1, ll. 53 to 62. Par's Adrenalin® was the first epinephrine injection product approved by the Food FDA for use in a clinical setting available in the United States. D.I. 192-1, Agreed Facts at 3. Par's NDA No. 204200 was approved by FDA on December 7, 2012 (*Id*.).

Though it approved the product, the FDA asked JHP for a post marketing commitment that it would try to reduce the levels of impurities in Adrenalin®. PTX 191 at 3. The impurities were the result of degradation, a process whereby the amount of the active ingredient, and thereby the potency, of the product decreases and the amount of potentially toxic compounds increases. The primary degradants in epinephrine products are epinephrine sulfonic acid (ESA) and D-epinephrine, an enantiomer of the active ingredient L-Epinephrine.[1] PTX 1, '876 Patent at col. 1, ll.53-56.

The record shows there are three epinephrine degradation pathways—oxidation, racemization, and sulfonation. D.I. 223, Tr. at 165, 173, 179. Patrick Irish, a scientist at JHP, testified it was very difficult to come up with a set of components in a formulation that could minimize one degradation pathway without exacerbating another degradation pathway. D.I. 223, Tr. at 163. The difficulty was that there were unintended

[1] Enantiomers are two molecules with identical atoms arranged as mirror images of each other, like a person's hands. (D.I. 225, Tr. at 453-54). Enantiomers often have distinct physical properties. *Sunovion*, 731 F.3d at 1274. Epinephrine degrades from the active ingredient L-epinephrine, into D-epinephrine, an enantiomer that has insignificant therapeutic activity (JTX 1, '876 Patent at col. 1, ll. 55-56).

consequences of the experiments—solving one issue would create another problem. D.I. 225, Tr. at 452-56

Par's efforts to improve the 2012-FDA-approved product eventually led to a supplemental NDA, No. 204200-04, that was approved on September 12, 2016, and to the two patents that are the subject of this case. D.I. 223, Tr. at 69; D.I. 192-1, Agreed Facts at 2-3. Par's predecessor, JHP, filed Application Serial No. 14/657,990 with the PTO on March 13, 2015, and it issued as the '876 Patent on September 1, 2015. D.I. 192-1, Agreed Facts at 2. JHP filed Application Serial No. 14/818,121 with the PTO on August 4, 2015, and it issued as the '657 Patent on March 29, 2016. *Id.* at 3. The '657 Patent is a continuation of the application that issued as the '876 Patent. *Id.* at 2-3. Both patents are titled "Epinephrine Formulations." *Id.* The '657 Patent and the '876 Patent share a common specification. *Id.* Vinayagam Kannan, Patrick Irish, and Michael Bergren are the named inventors of the '657 and '876 Patents. *Id.* The '876 Patent covers the composition of the inventive formulations and the improved impurity profile (JTX 1). The '657 Patent covers using those formulations to treat patients (JTX 2).

The improved formulation of Adrenalin® is the embodiment of the asserted claims of the patents at issue and has a shelf life of twenty-four months. D.I. 192-1, Agreed Facts at 3; JTX 7, FDA correspondence at 2. The '876 and '657 Patents are listed in the Orange Book for the listing for Adrenalin® brand epinephrine injection. *Id.* at 4.

Hospira had also committed to the FDA in 2007 that it would remediate its unapproved products—Epinephrine Injection USP Ampul and Epinephrine Injection

USP Abboject. JTX 95, 2015 Epinephrine Injection USP Project Technical Review ("2015 PTR") at 2. Dr. Zhang was the main formulation scientist responsible for the generic product and he testified that Hospira began developing its ANDA Product sometime in 2009. D.I. 223, Tr. at 215, 318: JTX 95, 2015 PTR at 6. After several unsuccessful efforts, Hospira submitted ANDA No. 208908 to the FDA in 2017, seeking approval to engage in the commercial manufacture and sale of a generic version of Adrenalin® epinephrine injection, 1 mg/mL ("Hospira's ANDA Product") prior to the expiration of the '876 and '657 Patents.[2] D.I. 192-1, Agreed Facts at 5.

B. Infringement

Par asserts that Hospira's ANDA product infringes claims 1-3, 5, and 10-19 of each patent ("the asserted claims") Independent claim 1 of the '876 Patent claims:

1. A composition comprising:

in the range of about 0.5 to 1.5 mg/mL of epinephrine and/or salts thereof,

in the range of about 6 to 8 mg/mL of a tonicity regulating agent,

in the range of about 2.8 to 3.8 mg/mL of a pH raising agent,

in the range of about 0.1 to 1.1 mg/mL of an antioxidant,

in the range of about 0.001 to 0.010 mL/mL of a pH lowering agent, and

in the range of about 0.01 to 0.4 mg/mL of a transition metal complexing agent, wherein the antioxidant comprises sodium bisulfite and/or sodium meta bisulfite.

[2] Pfizer purchased Hospira midway through the development effort, and Hospira is now part of Pfizer. The Court will continue to refer to the defendant as Hospira.

D.I. 1-1, '876 Patent, col. 28, ll. 1-14. The remaining asserted claims are dependent claims.[3]

In claim construction, the parties agreed to the following claim construction: the word "about" should be given its ordinary meaning, which is "approximate." D.I. 67, Joint Claim Construction Chart, Appendix A. A "pH raising agent" is a "component to raise the composition's pH, which may comprise a buffer system." *Id.* A "buffer system" is a "component present in a composition or solution which may provide a resistance to significant change in pH caused by a strong acid or base; may comprise a single agent or more than one agent, such as a weak acid and its conjugate base." *Id.* A pH lowering agent" is a "component to lower the composition's pH." *Id.* A "transition metal complexing agent" is a "component to complex with transition metals, such as a chelating agent." *Id.*

The parties agree that Hospira's ANDA Product is a composition and is indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis. D.I. 192-1, Agreed Facts at 6. Hospira's ANDA describes the composition of Hospira's ANDA Product, including the target amounts of each component and Hospira's stated function of each component. *Id.* at 4-5. The parties also agree that Hospira's ANDA Product contains: in the range of about 0.5 to 1.5 mg/mL of epinephrine and in the range of about 0.1 to 1.1 mg/mL of sodium metabisulfite. *Id.* at 5. Further, they agree that sodium metabisulfite is an antioxidant; sodium chloride is a tonicity regulating agent;

[3] Asserted claim 2 claims the "composition of claim 1, wherein the tonicity regulating agent comprises sodium chloride. Asserted claim 3 claims the "composition of claim 1, wherein the pH raising agent comprises a buffer system comprising at least two compounds. Asserted claim 5 claims the "composition of claim 1, wherein the pH lowering agent comprises hydrochloric acid." Asserted claims 10 and 11 claim the composition of claim 1 and a solvent comprising water. Asserted claims 12 to 19 claim the composition of claim 1 and recite limitations on percentage amounts of impurities after eighteen months of storage at certain temperatures and levels of humidity. (JTX 1, '876 Patent)

citric acid and sodium citrate are a pH raising agent; citric acid and sodium citrate are a buffer system; hydrochloric acid is a pH lowering agent; and water for injection is a solvent. *Id*. Also, the parties agree that Hospira's ANDA Product contains a solvent comprising water and contains about 11% or less of ESA after 18 months of storage at 23° C to 32° C and 55% to 70% relative humidity and about 3% or less of D-Epinephrine after 18 months of storage at those temperature and humidity levels. *Id*. at 6.

Par contends that Hospira's ANDA product contains amounts of the specified agents in the ranges that are claimed in at least one asserted claim in each of the patents at issue. Hospira contends that its ANDA product does not infringe Par's patents, arguing that Par and Hospira took fundamentally different approaches to remediating their former products.[4]

There is no dispute that Hospira's ANDA product contains the active ingredient epinephrine and an antioxidant wherein the antioxidant comprises sodium bisulfite and/or sodium metabisulfite. D.I. 192-1, Agreed Facts at 5, Table 13. There is also no dispute that Hospira's ANDA product meets the improved impurity profile that is specified in the claims. In support of its contention of noninfringement, Hospira points to

[4] Hospira contends that its ANDA Product is based on Par's original Adrenalin® product (that had been approved in 2012) and therefore differs from the formulation claimed by Par's patents. Although Hospira states that its ANDA is directed at Par's 2012-approved formulation, the evidence shows that the reference listed drug ("RLD") for Hospira's ANDA is the Par drug that was approved in 2016. (JTX 7, FDA correspondence at 12) Karen Becker testified as an expert on FDA regulations for drug product approval and labeling. D.I. 225, Tr. at 432. She testified that the FDA identified reformulated Adrenalin as the reference listed drug for Hospira's ANDA. *Id*. at 432-33. The record shows the FDA denied Hospira's request that the FDA maintain a listing for the original 2012-approved Adrenalin formulation, stating that "an ANDA seeking approval of a product that duplicates the original formulation Adrenalin® may rely on reformulated Adrenalin® as the basis of submission." JTX 7 at 12. The FDA indicated that if the formulation varies beyond what is indicated in the regulations, the applicant duplicating the original formulation of Adrenalin® could request a waiver of requirements for inactive ingredients. D.I. 225, Tr. at 434. Hospira did so and provided supporting information to the FDA to identify and characterize the differences between its formulation and reformulated Adrenalin® and to demonstrate that those differences don't affect the safety or efficacy of its proposed product. *Id*. at 434-35; JTX 10, Request for Waiver; JTX 49, Pharmaceutical Development document at 15.

different concentrations of 1) a tonicity regulating agent; 2) a pH raising agent and 3) absence of a transition metal complexing agent in its proposed product.

At trial, Dr. Edmund Elder testified on behalf of Par (D.I. 223, Tr. at 59 to 149). He has a Ph.D. in Pharmaceutical Sciences, spent 16 years in the pharmaceutical industry, and is an expert in pharmaceutical formulations, including injectables. *Id*. at 63; JTX 113, Curriculum Vitae ("C.V."). He is director of the Zeeh Pharmaceutical Experiment Station in the School of Pharmacy, University of Wisconsin-Madison, where he oversees formulation development activities, including for injectable products. *Id*. at 60. Dr. Elder teaches drug development and formulation and sits on a committee that oversees the University's FDA-regulated research. *Id*. at 60-61. He also sits on the compounding expert committee of the United States Pharmacopeia and is an editor for peer-reviewed journals. *Id*. at 62-63.

Dr. Elder reviewed Hospira's ANDA submission. D.I. 223, Tr. at 70-71; JTX 110, Hospira ANDA, overall summary; JTX 50, specification; and JTX 86, PTX 387, PTX 388, PTX 389, batch records. He testified that Hospira's ANDA product infringes claim 1 of the '876 Patent, both literally and under the doctrine of equivalents. *Id*. at 90-91. He first stated that Hospira's ANDA product contains 8.55 to 9 mg/mL of sodium chloride, which is a tonicity regulating agent. D.I. 223, Tr. at 73-74.

The record shows that the target amount of sodium chloride in Hospira's ANDA Product is 9 mg/mL. JTX 110, Hospira ANDA at 18. The amount of sodium chloride in commercial batches of Hospira's ANDA Product will vary from the target concentration of 9 mg/mL. *Id*. at 72. The release specification for the first three exhibit batches was as low as 8.55 mg/mL. *Id.* at 75. The measured amount in the exhibit batches was

between 8.91 and 9.27 mg/mL. *Id*. at 75; JTX 86 at 13, 19, 24; PTX 387 at 13, 19, 24; PTX 388 at 10, 17, 22. Dr. Elder expressed the opinion that the amount of sodium chloride in Hospira's ANDA product literally meets the claim limitation of "about 8 mg/mL." *Id*. at 77-78.

The patent specification describes the purpose of the tonicity regulating agent is to "maintain the tonicity of the composition in a physiologically acceptable range." D.I. 223, Tr. at 77; JTX 1, '847 Patent at col. 8, ll. 46-53. "Physiologically acceptable" means that the product will not have a negative impact on the cells that are exposed to it—it will be in an isotonic range. D.I. 223, Tr. at 79; PTX 165 at 3, PTX 173 at 6. Dr. Elder stated that tonicity is osmotic pressure, explaining that when a blood cell is in an isotonic environment, the concentration of dissolved species in solution matches that inside the cell, creating an equilibrium of water exchange between the cell and the solution. *Id*. In a hypertonic solution, a higher concentration of dissolved particles in the surrounding solution causes water to flow out of the cell, resulting in cell shrinkage. *Id*. In a hypotonic solution, the fluid surrounding the cell has a lower concentration of dissolved particles, causing water to move into the cell, resulting in cell swelling and eventually bursting. *Id*. at 78-79. He also testified that a physiologically acceptable range of tonicity reported in the literature is between 225 and 350 milliosmoles per kilogram (mOsm/kg.) and formulations within that range are considered isotonic. *Id*. at 79.

Hospira's ANDA similarly states that the purpose of the 9 mg/mL sodium chloride in Hospira's ANDA Product is to provide "isotonicity" to the composition. *Id*. at 80. That function is identical to the function for the claim limitation of "about 6 to 8 mg/mL of a

tonicity regulating agent" in the patents in suit. *Id.* Also, Dr. Elder testified that the osmolality of Hospira's ANDA Product with 8.55 mg/mL sodium chloride would be slightly lower than the 323 or 324 mOsm/kg reported for the target of 9 mg/mL, which would also be well within the physiological acceptable range. *Id.* at 81-82. He concluded that Hospira's ANDA product, which contains 8.55 mg/mL to 9 mg/mL of sodium chloride as a tonicity regulating agent, meets the claimed limitation of *about* 6 to 8 milligrams per milliliter. *Id.* (emphasis added).

Dr. Elder also testified that 8.55 to 9 mg/mL sodium chloride meets the limitation "about 8 mg/mL" in the '847 Patent under the doctrine of equivalents. *Id.* at 84. He evaluated the amount of sodium chloride in Hospira's ANDA Product under the function-way-result test and found it was equivalent: the function of the claimed range of tonicity regulating agent is to regulate tonicity; the way it does that is by providing dissolved particles; and the result is a physiologically acceptable tonicity. *Id.* at 83-85. He concluded that the sodium chloride concentration in the product is insubstantially different from the claimed range, because both provide a physiological acceptable tonicity. *Id.* at 83-84.

Dr. Elder also noted that Hospira represented to FDA that the "calculated osmolality of 308 mOsm/kg for the reformulated Adrenalin is comparable to the measured values for the proposed product . . . the minor differences are not expected to affect safety and efficacy of epinephrine injection." *Id.* at 81; JTX 49 at 16. Hospira's lead chemist on its ANDA project, Dr. Eric Zhang, confirmed Hospira's representations as to the osmolality of Hospira's ANDA product. D.I. 224, Tr. at 273, 299.

The record also shows that during the development of its ANDA product, Hospira varied the sodium chloride concentration between 6 and 9 mg/mL without ever testing its impact. D.I. 224, Tr. at 262; Tr. at 82; (JTX 94, 2014 Hospira Product Technical Review at 18. Hospira never measured the osmolality of its formulations with 6 mg/mL sodium chloride and did not test for any difference between 6 and 9 mg/mL concentrations. D.I. 224, Tr. at 270. There was no suggestion or discussion within Hospira or Pfizer that such a variation would affect the safety of the drug product. *Id*. at 265.

With respect to the limitations "a pH raising agent," "a pH lowering agent" and "a transition metals complexing agent," Hospira acknowledged to the FDA that Par's reformulated Adrenalin and Hospira's ANDA product have a difference in pH buffer, noting that the reformulated Adrenalin® includes a pH buffer formed by tartaric acid and sodium hydroxide, whereas the pH buffer in the Hospira's proposed drug contains sodium citrate and citric acid. JTX 49 at 15. Par argues that functionally Hospira's ANDA product meets the limitations of "about 2.8 to 3.8 mg/mL of a pH Raising Agent," and "about 0.001 to 0.010 mL/mL of a pH Lowering Agent" in Par's '876 Patent.

Dr. Francisco Dean Toste testified on behalf of Par. D.I. 224, Tr. 319-423. He is the Gerald E. K. Branch Distinguished Professor at the University of California, Berkeley. *Id*. at 320. His research focuses on transition metal catalysts used in chemistry and pharmaceuticals. *Id*. at 320-21. Dr. Toste has consulted with pharmaceutical companies for 15 years. *Id*. at 321-22. Dr. Toste is a fellow of the American Academy of Arts and Sciences and the Royal Society of Canada. *Id*. at 322-

23. He is an expert in chemistry including acid-base chemistry and transition metal chemistry. *Id*. at 323; JTX 196, C.V.

He opined on the claim limitations of "in a range of about 2.8 to 3.8 milligrams per milliliter of a pH raising agent," "in the range of about 0.001 to 0.010 milliliters per milliliter of a pH lowering agent," and "in the range of about 0.010 to 0.4 milligrams per milliliter of a transition metal complexing agent." D.I. 224, Tr. at 325. He also looked at whether the composition in the Hospira ANDA also contained a buffer system comprising at least two compounds. *Id*.

He stated that he interpreted the patent claims from the viewpoint of a person of ordinary skill in the art of the patents-in-suit, that is, a person with a bachelor's or master's degree in pharmacy, pharmaceutical sciences, chemistry or a related field, with at least five years' experience in developing pharmaceutical products, including products for injection, or a Ph.D. in a relevant field, such as chemistry. D.I. 224, Tr. at 325-26. Dr. Toste reviewed and followed the Court's claim construction, noting that a "pH raising agent" could be a component of the buffer and a buffer was defined as a component which may provide a resistance to a significant change in pH caused by a strong acid or base and may comprise a single agent or more than one agent. D.I. 224, Tr. at 326-27, 361. He also applied the following claim construction for "transition metals complexing agent": "A transition metal complexing agent is a component to complex transition metals, such as a chelating agent." *Id*. at 334.

The '876 Patent claim limitation for a transition metals complexing agent is a range of about .01 to 0.4 mg/mL. JTX 1, '876 Patent at col. 28, ll. 12-13. Dr. Toste testified that Hospira's ANDA product contains a transition metals complexing agent

(D.I. 224, Tr. at 339) and components derived from citric acid such as sodium citrate (*Id*.).

Dr. Toste first explained that transition metals are found in the middle of the periodic table of elements and include iron, copper and gold. *Id*. at 334. He used the analogy of a crab with claws to explain that a complexing agent bonds with a transition metal. *Id*. at 335. An interaction between a molecule and a transition metal is analogous to one of a crab's claws grabbing the transition metal. The molecule would form a complex with that transition metal, a coordinating bond (*Id*. at 335, 337). If the transition metal is grabbed by two claws, it would be said to be a special form of complexation called chelation. *Id*. If a crab with multiple claws grabs the transition metal, there will no longer be sites on that transition metal for a further reaction to occur, for example, in an oxidation reaction. *Id*. at 338. In that context, the chelating agent is also acting as an antioxidant, preventing further oxidation reactions from occurring. *Id*. A "polydentate ligand" is analogous to a crab with more than one claw. *Id*. at 337. A textbook explains that "[c]helating agents act in an antioxidant capacity by binding metal ions, thus removing them, thermodynamically speaking, from solution. The most effective chelating agents used pharmaceutically are ethylenediaminetetraacetic acid (EDTA), citric acid, [and others]." *Id*. at 339; PTX 107 at 25.

Dr. Toste testified that "citric acid is a very, very well-known transition metal complexing agent" that is present in Hospira's ANDA product. D.I. 224, Tr. at 339. Dr. Toste also explained that elemental impurities include transition metals. D.I. 224, Tr. at 349. Hospira's ANDA includes a specification requiring that the elemental impurities in the ANDA Product meet International conference on Harmonisation of Technical

Requirements for Registration of Pharmaceuticals for Humane Use ("ICH") Q3D guidelines. D.I. 224, Tr. at 348-49, 405; JTX 128, ICH Guidelines; JTX 50, ANDA at 2. The Guidelines establish permitted daily exposure ("PDE") to transition metals such as copper, iron, or cadmium. The control threshold is defined as a level that is 30 percent of the established PDE in the drug product. *Id*. at 349; JTX 128 at 12. Dr. Toste used the ICH limit as the amount of transition metals to be complexed because "the ANDA says they could have up to that amount and still be able to sell it." D.I. 224, Tr. at 405; JTX 91, Pfizer Risk Assessment at 13.

To determine the amount of citric acid available to complex with transition metals in Hospira's ANDA product, Dr. Toste applied the concept of equilibrium, and the law of thermodynamics, using a swimming pool analogy. D.I. 224, Tr. at 341. He found stability constants for cadmium, mercury, cobalt, nickel, palladium, and copper as measured by the National Institutes of Standards and Technology. *Id*. at 353; JTX 129; JTX 78, Critical Stability Constants. He could not find reliable stability constants for chromium, vanadium, gold, osmium, rhodium, ruthenium, silver, molybdenum, iridium, and platinum, so he devised a model for a representative range, assigning all those metals a stability constant that was less or weaker than that for the weakest transition metal element that had been measured, which was cadmium. D.I. 224, Tr. at 354. He applied a mathematical formula to determine the amount of citric acid required to bind to the transition metals. *Id*. at 356-57. For example, he found the citric acid/citrate to bind nickel would be 0.00140 mg/mL. *Id.* His calculations resulted in the conclusion that the amount of citric acid to complex with these transition metals is 0.02 to 0.18 mg/mL,

which meets the patent limitation of contains "about 0.01 to 0.4 mg/mL of a Transition Metal Complexing Agent." D.I. 224, Tr. at 348-49, 360, 405; D.I. 226, Tr. at 594.

The '876 Patent identifies citric acid as a preferred transition metal complexing agent. JTX 1 at col. 7, l. 51 to col. 8, l. 17. The term "chelating agent" in the '876 Patent refers to "a substance capable of chelation, i.e., the formation or presence of two or more separate coordinate bonds between a polydentate ligand and a single central atom." PTX 1, '876 Patent at col. 7, ll. 11-14; D.I. 224, Tr. at 337. The purpose of the transition metal complexing agent, as identified in the '876 Patent is to "reduce the catalytic activity of trace metals present in the composition," and the Patent notes that "[i]n some embodiments that transition metal complexing agent may chelate trace metals in the composition that may otherwise increase and/or accelerate the degradation of components in the composition." *Id.*, '876 Patent at col. 7, ll. 15-20; Tr. at 337.

Dr. Toste's testimony is buttressed by Dr. Zhang, who conceded that it is general chemical knowledge that citric acid is a chelating agent in complexes with metals. Hospira Rule 30(b)(6) Deposition at 127. Also, Hospira represented to the FDA in its Pharmaceutical Development Report that "EDTA is a well-known and widely used chelating agent which forms complexes with metallic cations. Similarly, the citrate ion also forms complexes with metallic cations so the citric acid buffer in the Hospira product has similar chelating effect. . . . As such, the Hospira product does not need an additional chelating agent for its formulation." JTX49 at 16-17; D.I. 224, Tr. at 340-41. Further, Dr. Elder agreed that that citric acid is a multi-functional excipient. D.I. 223, Tr. at 88-89.

Dr. Toste also stated that Hospira's ANDA product has a pH raising system and buffer system, as claimed in the '876 Patent. D.I. 224, Tr. at 327. Hospira's ANDA product contains 2.01 mg/mL of citric acid and 0.58 of sodium citrate, with the stated function of a "buffering agent"), as well as and hydrochloric acid "q.s." as a Ph adjustment. *Id*. He testified that the pH raising agent/buffer system in the Hospira's ANDA product is the citric acid and its derivative, sodium citrate. *Id*. He explained that pH is a function of proton concentration and chemical reactions to the addition of an acid or a base agent. *Id*. at 328. Dr. Toste stated that buffers resist changes to pH caused by the addition of basic or acidic agents, by both lowering the pH and raising the pH relative to its absence. *Id*. at 327-329.

He testified that citric acid and sodium citrate are very well known buffer systems (*Id*. at 329). He further testified that the Hospira's ANDA product has a pH lowering system in that it has citric acid and hydrochloric acid to lower the composition's pH (*Id*. at 331; JTX 110 at 18). He testified that a pH lowering agent could consist of more than one component and the patent identifies citric acid and hydrochloric acid as potential pH lowering agents. D.I. 224, Tr. at 332.

He explained that the nominal amount of buffering agent (citric acid and sodium citrate) in Hospira's ANDA product is 2.59 mg/mL. *Id*. at 411;JTX 110 at 18. He stated that what is important to consider is "how the buffer functions, not the exact amount" to determine whether it falls within "in the range of about" a certain amount of excipient. *Id*. 363-64. The term "about" considers the fact that buffer systems do not have the same effectiveness at the same mass amounts. D.I. 224, Tr. at 363. For example, 10 mM of sodium citrate and 10 mM of potassium citrate will behave the same, even

though sodium citrate is present at 2.6 mg/mL and potassium citrate at 3.1 mg/mL due to their molecular weights. *Id*. Even though the mass amounts are different, and one is above 2.8 and the other is below 2.8, "they behave exactly the same because they have the same number of moles to do the job." *Id*.

Dr. Toste conducted experiments to determine whether the amounts of citric acid and sodium citrate in Hospira's ANDA product serve the same purpose as the amounts of claimed pH raising agent. *Id*. at 364. To do this, he measured buffering capacities, adapting the teaching of the Patent to develop a titration protocol. *Id*. at 365, JTX 63, Titration Protocol. The result of the experiments showed that the buffering capacity of 2.41.mg/mL citrate, 2.57 mg/mL citrate and 2.80 mg/mL citrate are roughly the same. *Id*.; JTX 63, Titration Protocol at 8. Accordingly, after accounting for and subtracting the amount of citric acid and sodium citrate attributable to complex transition metals, Dr. Toste concluded Hospira's ANDA contains 2.41 to 2.57 mg/mL citric acid and sodium citrate as a pH raising agent/buffer system. D.I. 224, Tr. at 360-362 (noting that citric acid and sodium citrate molecules "cannot be in two places at once") which meets the limitation "in the range of about 2.8 to 3.8 mg/mL of a pH raising agent" in the '876 Patent.

He also compared the purpose of the pH raising agent in the '876 Patent to the purpose of the pH raising agent in Hospira's ANDA product. *Id*. at 367. He found that Hospira represents that the pH raising agent is there to control the formulation pH and to stabilize the formulation pH, to lower the amount of sodium metabisulfite required to serve as an antioxidant, and to minimizes D-epinephrine formation. *Id*. at 367-38; JTX-49 at 15; JTX-119 at 13; JTX 102 at 1. The '876 Patent states the purpose of the

formulation is to resist significant changes in pH, to require less antioxidant, and to reduce D-epinephrine formation. *Id*.; JTX 1. He concluded that Hospira's ANDA product "absolutely" meets the claim requirement in the range of about 2.8 to 3.8 milligrams per milliliter of a pH raising agent. *Id*. at 368 (stating "that 2.41 to 2.5 milligrams per milliliter of citric acid and sodium citrate in the ANDA are about 2.8 to 3.8 mg/mL that is claimed in the patent at JTX-1 at 19").

With respect to the doctrine of equivalents, he testified that 2.41 to 2.57 mg/mL of citric acid and sodium citrate in the ANDA product is insubstantially different from the about 2.8 mg/mL of a pH raising agent limitation of the '876 Patent. *Id*. at 369. He determined that the function, way, and result of the pH raising agent in Hospira's ANDA product was exactly the same as that of the '876 Patent. *Id*. at 371. Dr. Elder also testified that the pH raising agent/buffer system in Hospira's ANDA product also infringes under the doctrine of equivalents. D.I. 223, Tr. at 90.

Dr. Toste testified there are two pH lowering agents in the Hospira's ANDA product—citric acid and hydrochloric acid. *Id*. Hospira's ANDA product identifies hydrochloric acid for pH adjustment. *Id*. at 331. The amount of citric acid is set forth in Hospira's ANDA, and the amount of hydrochloric acid is added to Hospira's ANDA Product "q.s." (quantity sufficient) to pH 2.9-3.3, to account for variability in different batches. *Id*. at 371-72; JTX 110, Hospira ANDA at 18; JTX 30, Response to Information Request.

Dr. Toste testified that hydrochloric acid is a very strong acid and is specifically identified in the patent as a pH lowering agent. *Id*.; JTX 1 at col. 8, ll. 37-45. To obtain the amount of citric acid functioning as a pH lowering agent in Hospira's ANDA product,

Dr. Toste subtracted the amount of citric acid that would be used to complex transition metals. D.I. 224, Tr. at 371-74. He calculated the mass (grams) divided by the density of the excipients to determine volume, and found a range of 0.001 milliliters per milliliter (mL/mL) to 0.0012 mL/mL of citric acid acting as a pH lowering agent in the Hospira exhibit batches. *Id*. at 373. He then added the amount of citric acid to the amount of hydrochloric acid resulting in a range of 0.0014 mL/mL to 0.0015 mL/mL of pH lowering agent. *Id*. at 374. He concluded "that 0.0014 to 0.0015 mL/mL per of hydrochloric acid and citric acid present in Hospira's ANDA falls within the claimed range of 0.001 to 0.010 mL/mL of a pH lowering agent in the patent-in-suit." *Id*. at 374. He noted that the patent specifically provides that the pH lowering agent comprises one or more of citric acid, hydrochloric acid, both are listed as pH lowering agents. *Id*.; JTX 1, '876 Patent at col. 8, ll. 37 to 45.

Based on Dr. Toste's calculations, Dr. Elder agreed that Hospira's ANDA product meets the limitations of "about 2.8 to 3.8 mg/mL of a pH Raising Agent," and "about 0.001 to 0.010 mL/mL of a pH Lowering Agent" in Par's '876 Patent. D.I. 223, Tr. at 85-86.

Hospira presented the testimony of Dr. Rodolpho Pinal on both infringement and invalidity. He has a bachelor's degree in pharmaceutical chemistry from the National University of Mexico and a Ph.D. in Pharmaceutical Sciences from the University of Arizona. He is Associate Professor of Industrial and Physical Pharmacy at Purdue University in Indiana. D.I. 225, Tr. at 445. He expressed the opinion that Hospira's ANDA product does not meet the tonicity agent limitation because 1) the Hospira ANDA product is a hypertonic solution while the claim limitations make it an isotonic solution so

those belong to two different categories; and 2) the 9 milligrams per milliliter of sodium chloride, which is the concentration in Hospira's ANDA product, is disclosed but not claimed in the patents. *Id*. at 449.

Dr. Pinal's testimony is not materially at odds with the testimony of Dr. Elder and Dr. Toste. D.I. 225, Tr. 444 to 646. He testified he agrees that the reformulated Adrenalin® is isotonic and that difference in osmolality between the proposed product and the RLD as negligible. *Id*. at 567, 574. He conceded, however, that, if the tonicity of Hospira's ANDA product were not in the physiologically acceptable range, it could not be safely administered to patients. *Id*. at 567. He stated however, that hydrochloric acid is the pH lowering agent in the Hospira's ANDA product. *Id*. at 511. He acknowledged that citric acid has antioxidant capability, but denied that it is functioning as an antioxidant in Hospira's ANDA product. *Id*. at 514. Further, he stated that there is no reasonable basis for Par's theory that citric acid could count as a pH raising agent, a pH lowering agent, and a transition metal complexing agent but not as an antioxidant. *Id*. at 515. He contended that in order to be consistent with itself in terms of the theory posed by Par as well as with the teachings in the patent-in-suit, the function of antioxidant would need to be included as part of the analysis. *Id*. at 514.

Hospira's expert, Dr. George Gokel, a professor at the University of Missouri - St. Louis and an expert on organic chemistry and complexing transition metal ions, also agreed with Dr. Toste on certain points. He stated that that at varying pH, including the pH of Hospira's ANDA Product, citric acid acts as a complexing agent. D.I. 225, Tr. at 676-77 (stating that Dr. Toste "knows what he's talking about" and "he's absolutely correct that you can eventually get more interactions in complexation, and at different

pHs that will happen and so on"). Though he acknowledged citric acid is a transition metal complexing agent, although not as effective as EDTA, he stated citric acid was not performing that function in the Hospira ANDA product. *Id*. at 678. Rather than analyzing the amount of transition metals complexing agent represented to the FDA in Hospira's ANDA, Dr. Gokel looked at specific amounts in the three exhibit batches. D.I. 224, Tr. at 350; D.I. 226, Tr. at 712-13. Dr. Toste stated the batch amounts were very small and highly variable and did not assess the entire claim potential to infringe on the claim. D.I. 224, Tr. at 350.

C. Invalidity

In its challenge to the validity of the patents, Hospira contends that the asserted claims of the '876 Patent would have been obvious to a person of ordinary skill in the art as of the priority date in light of several combinations of prior art references. Drs. Elder and Toste both testified that a person of ordinary skill in the art of the patents-in-suit has a bachelor's or master's degree in pharmacy, pharmaceutical science, chemistry, or a related field, with at least five years of experience developing pharmaceutical products, including products for injection, or a Ph.D. in a relevant field, such as chemistry. D.I. 223, Tr. at 67-68; D.I. 224, Tr. at 325-326. The relevant time frame is the period leading up to Par's patent filing in 2015.

The parties agree that certain references were published, publicly available, and/or effectively filed before the effective filing date of the '876 and '657 Patents, including :

a. U.S. Patent Application Publication No. 2008/0269347 ("Bruss") (JTX 44)

b. U.S. Patent Application Publication No. 2015/0246009 ("Gupta") (JTX 47)

c. International Patent Publication No. WO 2014/127015

d. International Patent Publication No. WO 2014/057365

e. Label for Adrenalin® 1 mL, revised December 2012 (JTX 48)

f. Lloyd V. Allen Jr., THE ART, SCIENCE, AND TECHNOLOGY OF PHARMACEUTICAL COMPOUNDING, 4th ed. (2012) ("Allen") (JTX 56)

g. Michael P. Boquet and Dawn Wagner, Injectable Formulations of Poorly Water-Soluble Drugs, in FORMULATING POORLY WATER SOLUBLE DRUGS, R.O. Williams III, *et al*., eds., 1st ed. (2012) ("Boquet") (JTX 55)

h. Kenneth A. Connors et al., Epinephrine in CHEMICAL STABILITY OF PHARMACEUTICALS: A HANDBOOK FOR PHARMACISTS, 2nd ed. (1986)

i. Takeru Higuchi and Louis C. Schroeter, Kinetics and Mechanism of Formation of Sulfonate from Epinephrine and Bisulfite, 82 J. AM. CHEM. SOC. 1904 (1960)

j. B. Grubstein and E. Milano, Stabilization of Epinephrine in a Local Anesthetic Injectable Solution Using Reduced Levels of Sodium Metabisulfite and EDTA, 18 DRUG DEVELOPMENT AND INDUS. PHARM. 1549 (1992) (JTX 31)

k. Ludwig Hoellein and Ulkrize Holzgrabe, Ficts and facts of epinephrine and norepinephrine stability in injectable solutions, 434 INT'L J. PHARMACEUTICS 468 (2012) (JTX 52)

l. Louis C. Schroeter and Takeru Higuchi, A Kinetic Study of Acid-Catalyzed Racemization of Epinephrine, 47 J. AM. PHARM. ASSOC. 6, 426 (Jun. 1958)

m. David Stepensky *et al*., Long-Term Stability Study of L-Adrenaline Injections: Kinetics of Sulfonation and Racemization Pathways of Drug Degradation, 93 J. PHARM. SCIS. 4, 969 (Apr. 2004) (JTX 139)

D.I. 192-1, Agreed facts at 6-7. Hospira relies on the following combinations of references: A publication by Gupta in combination with a publication by Boquet and a publication by Allen; the publication by Gupta in combination with the publication by Bruss and the publication by Allen; and the Prior Adrenalin® Label in combination with publications by Boquet, Bruss, and Allen. D.I. 225, Tr. at 450.

Dr. Pinal stated the opinion that the asserted claims of Par's patents are invalid over the above stated combinations of the prior art. *Id*. He also expressed the opinion that the impurity limitations described in claims 12 through 19 of the '876 Patent recite the natural result of formulating the composition that is taught by the prior art. *Id*. Dr. Pinal further testified that if not the natural result, they were disclosed but not claimed in the 876 Patent. *Id*. at 643-44.

The record shows the Bruss reference is actually Hospira's Abboject® formulation. Dr. Zhang's testimony shows that the Abboject® product had 6.9 percent of unknown impurities, and it took Par several years to figure out what the impurities were. The testimony of the inventors of the patents at issue, as well as that of Hospira's lead chemist Dr. Zhang, shows that formulating the composition that is the subject of the asserted Patents required extensive experimentation and many failures.

Dr. Pinal testified that a person of ordinary skill in the art would have been motivated to add EDTA to the formulation in the label, as taught by the Bruss reference, a patent application. D.I. 225, Tr. at 538-539. He testified that based on the teachings of Boquet, Bruss and Allen, a person of ordinary skill would be motivated to incorporate a buffer and a chelator into the formulation disclosed in the prior Adrenalin® label. *Id*. at 540. The record shows however, that the FDA communication to Par about reducing

impurities for the product approved in 2012 under the prior label would not have been known to the public. *Id*. at 618.

Dr. Schöneich is Chair of the Department of Pharmaceutical Chemistry at the University of Kansas. He has a Ph.D. in Chemistry with honors from the Technical University in Berlin and has with parenteral formulations for many years.[5] JTX 193, CV. He was asked by Par to evaluate Dr. Pinal's opinions that the asserted claims are invalid based on obviousness, lack of enablement and indefiniteness. D.I. 226, Tr. at 727. He testified about the complications of Hospira's attempts to come up with a stable product to submit to the FDA and stated that that the evidence presented by Hospira does not show that the subject matter of the asserted patents would have been obvious to a person of ordinary skill in the art. *Id*. at 740. He also opined that the asserted claims are fully enabled to practice, and that asserted claim 19 was not invalid for indefiniteness. *Id.*

Dr. Schöneich testified that Dr. Pinal's analysis: 1) failed to consider the totality of the art and 2) offered no motivation for the combination, and no rationale for any reasonable expectation of success. *Id*. at 743. He also stated that Dr. Pinal used hindsight in his analysis, failed to show a prima facie case, and used references that did not account for all the degradants. *Id*. He testified that prior art taught away from use of metabisulfite and would not provide a motivation to add metabisulfite to formulations. *Id*. at 751, 774. He testified specifically with regard to the Boquet and Allen references, and stated "they provide laundry lists, they are very general references, they're not teaching us how much of the metal complexing agent or buffer I should add in order to

[5] Parenteral is defined as "[b]y some other means than through the gastrointestinal tract; refers particularly to the introduction of substances into an organism by intravenous, subcutaneous, intramuscular, or intramedullary injection. Stedmans Medical Dictionary 653710 (Westlaw 2014).

obtain the stability which is required, so clearly they don't give us any guidance." *Id*. at 774. He stated that no exemplary formulation contained all the elements that would have guided a person of ordinary skill in the art to combine and thus they provided no motivation to do so. *Id*. With respect to the prior Adrenalin® label, he noted that a person of ordinary skill in the art would not see much need to improve on a product that was FDA-approved. *Id*. at 775. Prior art evidence also taught away from the use of a metal chelating agent and a buffer because a buffer could negatively influence some degradation pathways. *Id*. Hindsight means that without the combination that is part of the asserted independent claim, a person of ordinary skill in the art would not have arrived at the formulation just by routine optimization. *Id*. at 775.

He stated that neither the Boquet or Allen references or the prior label taught the missing elements, nor did they provide any long-term stability data. *Id*. at 778. He also stated that his opinions on obviousness in view of prior art were equally applicable to the asserted dependent claims as to claim I of the '876 Patent. *Id*. at 777. Further, he added that claims 12 through 19 are directed towards certain stability indicating data, impurities, especially Impurities A, B, or Unknown C, and these are not addressed at all by the reference Allen, Boquet, or Bruss, nor does any of them have any long-term stability data, for example, on the formation of D-epinephrine over 18 months. *Id*. at 778. He noted the Gupta prior art was an abandoned application. *Id*. at 780. It teaches that increasing epinephrine content reduces degradants and taught away from metabisulfite. *Id*. Because the Gupta reference had only three months of stability data there was no motivation to reduce the levels of impurities and no expectation of success. *Id*. at 779. Further, he testified that there was no government standard with

respect to impurity levels in epinephrine that would have been known to a person of ordinary skill in the art in 2015. *Id*. He formed the same conclusion with respect to whether the asserted claims of the '657 Patent would have been obvious in light of the combinations testified to by Dr. Pinal. *Id*. at 782.

Dr. Schöneich also testified that there had been an enduring need for stable epinephrine solutions for at least 60 years and the Par patents satisfied the need. *Id*. at 784. There had not been any big improvement until the prior Adrenalin© Label was approved in 2012. *Id*. Impurities A, B, and C were unknown until first described in the '876 when the applicants used and identified the correct methodology to analyze for those impurities. *Id*. at 785. The prior art as a whole taught away from the use of metabisulfite, the use of transition metal complexing agent was not straightforward, and the prior art suggested numerous different solutions, none of them suggesting the claimed combinations of the excipients. *Id*.

Dr. Schöneich testified that to meet the enablement requirement the patent disclosure must teach a person of ordinary skill in the art how to make and use the claimed invention without undue experimentation. *Id*. at 786. He stated the teaching of the '876 Patents clearly do that. *Id*. He also stated that the subject matter of claims 12 to 19 is fully enabled. *Id*. at 787.

Dr. Schöneich applied the standard that "a patent is invalid for indefiniteness only if its claims read in light of the specification and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention. *Id*. at 788. He stated there was USP standard for color and have artisans been able to figure out compliance with that USP standard through easy experiments. *Id*. at 789.

III. CONCLUSIONS OF LAW

A. Legal Standards

1. Infringement

Infringement is a fact question. *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1275 (Fed. Cir. 2013). First, the claims must be appropriately construed, and, second, the accused product must be compared to the properly-construed claims. *PSC Computer Prods., Inc. v. Foxconn Int'l*, 355 F.3d 1353, 1360 (Fed. Cir. 2004) .

The filing of an ANDA is a technical act of infringement. 35 U.S.C. § 271(e)(2). If "a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." *Sunovion*, 731 F.3d at 1278-79. What a generic applicant "has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur." *Sunovion,* 731 F.3d at 1278. Moreover, an ANDA applicant should not be permitted to liken their product to the claimed composition to support their bid for FDA approval, yet avoid the consequences of such a comparison for purposes of infringement. *Intendis GMBH v. Glenmark Pharm. Inc., USA*, 822 F.3d 1355, 1366–67 (Fed. Cir. 2016).

The word "about" does not have a universal meaning in patent claims, and its meaning depends on the technological facts of the particular case. *Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008). When "about" is used as part of a numeric range, its use "avoids a strict numerical boundary to the specified parameter." *Id*. The range of the specified parameter "must be interpreted in its

technologic and stylistic context." *Id*. To determine how far beyond the claimed range the term "about" extends, the Court "must focus on the criticality of the numerical limitation to the invention." *Id*. (citation omitted). Courts must look to the purpose and function of the claim limitation, to determine whether an amount can still serve that purpose. *Id*.

"The scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*., 535 U.S. 722, 731 (2002). Equivalency under the doctrine of equivalents is determined by "evidence that the accused device contains an element that is not 'substantially different' from any claim element that is literally lacking, or that the claimed limitation and the accused component perform substantially the same function in substantially the same way to achieve substantially the same result." *Kraft Foods, Inc. v. Int'l Trading Co*., 203 F.3d 1362, 1371 (Fed. Cir. 2000).

The fact that a claim recites numeric ranges does not, by itself, preclude a party from relying on the doctrine of equivalents. *Abbott Labs. v. Dey, L.P.*, 287 F.3d 1097, 1108 (Fed. Cir. 2002); *see also Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1170-71 (Fed. Cir. 2012) (when claimed range is given a specific "quantitative definition," then "the doctrine of equivalents is not foreclosed").

2. Invalidity

A patent is presumed valid. 35 U.S.C. § 282. "'The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.'" *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011) (quoting 35 U.S.C. § 282). An invalidity defense must be proved by clear and convincing evidence. *Id*.

A patent is only invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. Obviousness is a question of law based on underlying fact findings on: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). "[O]bjective indicia 'may often be the most probative and cogent evidence' of nonobviousness." *Liqwd, Inc. v. L'Oreal USA, Inc.*, No. 2018-2152, 2019 WL 5587047, at *2 (Fed. Cir. Oct. 30, 2019) (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000)). Objective indicia are essential safe-guards that protect against hindsight bias. *Id*. The objective indicia analysis is, therefore, a fundamental part of the overall § 103 obviousness inquiry. *Id*. Courts must consider all evidence of obviousness and non-obviousness before reaching a determination. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012). The burden of showing obviousness is "especially difficult" when "the infringer attempts to rely on prior art that was before the patent examiner during prosecution." *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004).

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). A party seeking to invalidate a patent on obviousness grounds must demonstrate that "a skilled artisan

would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1271 (Fed. Cir. 2018). It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does—a reason for combining disparate prior art references is a critical component of an obviousness analysis; "this analysis should be made explicit." *KSR*, 550 U.S. at 418 (noting that this is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known).

Extensive experimentation and failure is evidence of a lack of reasonable expectation of success. *Endo Pharm., Inc. v. Actavis LLC*, 922 F.3d 1365, 1373 (Fed. Cir. 2019) (finding that no reasonable expectation of success "is further supported by the fact that the inventors . . . engaged in extensive experimentation, involving much failure, to ultimately produce . . . the Asserted Claims"). Charting a path to the claimed compound by hindsight is not enough to prove obviousness. *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc.*, 933 F.3d 1367, 1375 (Fed. Cir. 2019). "'Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious.'" *Id*. (quoting *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019)). "The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of

ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

Enablement requires that "the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A claim is not enabled when, "at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Whether a claim satisfies the enablement requirement is a question of law based on factual underpinnings. *Tr. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1361 (Fed. Cir. 2018).

A "patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

3. Dedication-Disclosure

"[W]hen a patent drafter discloses but declines to claim subject matter . . . this action dedicates that unclaimed subject matter to the public." *Johnson & Johnston Assocs. v. R.E. Servs. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002). The inquiry requires a showing that "one of ordinary skill in the art can understand the unclaimed disclosed teaching upon reading the written description." *PSC Computer Prods., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1360 (Fed. Cir. 2004); *see also Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1378 (Fed. Cir. 2005). Only subject matter that is "disclosed, but not claimed" in a patent will be deemed "dedicated to the public" and consequently,

ineligible for re-capture under the doctrine of equivalents. *Johnson & Johnston Assocs.*, 285 F.3d at 1054. A disclosure must be "of such specificity" that a person of ordinary skill in the art could immediately "identify the subject matter that had been disclosed and not claimed." *Id*.

B. Discussion

1. Infringement

The Court first finds that the person of ordinary skill in the art of the patents-in-suit has a bachelor's or master's degree in pharmacy, pharmaceutical science, chemistry, or a related field, with at least five years of experience developing pharmaceutical products, including products for injection, or a Ph.D. in a relevant field, such as chemistry. The Court agrees with the definition propounded by Drs. Elder and Toste and finds other proposed definitions of the person of ordinary skill are too limiting. The patents in suit would not require a person of ordinary skill in the art to have experience with large-scale manufacturing or regulatory approval.

The '876 Patent claims are directed to compositions comprising: (1) epinephrine, (2) a tonicity regulating agent, (3) a pH raising agent, (4) an antioxidant comprising sodium bisulfite and/or sodium metabisulfite, (5) a pH lowering agent, and (6) a transition metal complexing agent, in certain ranges. The Court finds Par has shown by a preponderance of the evidence that Hospira's ANDA product infringes each of the asserted claims of the patents-in-suit.

Hospira argues that because the sodium chloride in its ANDA product exceeds the patent's limitation of "in the range of about 6 to 8 mg/mL," it cannot literally infringe that limitation. Par, on the other hand argues that the modifier "about" encompasses

the range set out in Hospira's ANDA and literally meets the claim limitation "about 8 mg/mL." The Court agrees with Drs. Elder and Toste that the sodium chloride in Hospira's ANDA product meets the patent claim's limitation. The parties agreed that "about" means approximate (D.I. 67). In an earlier order the Court noted that scope of "about" "is not a strict numerical boundary to the specified parameter," but rather "must be determined using a functional approach" and "requires a factual inquiry as to the purpose of the limitation." D.I. 197 at 5.

That functional approach and factual inquiry leads to the conclusion that the limitation, qualified as it is to "about 6 to 8 mg/mL of sodium chloride, covers Hospira's ANDA product. There is no dispute that the sodium chloride in the Hospira ANDA product is a tonicity regulating agent, the main dispute is how much is required. Par's expert testimony was uniformly targeted to address the technological context, the criticality of the range, and the purpose of the limitation, whereas Hospira's experts focused largely on linguistics and semantics. The Court credits Dr. Elder's testimony on this topic over Hospira's experts. Dr. Pinal did not provide a meaningful analysis of the technologic context or the function of the claimed amount of tonicity regulating agent. Instead, he imposed a strict numerical boundary on the claim scope. His opinion effectively changes the claim construction. His approach is contrary to the Court's construction of "about" and the Court's recognition that the scope of "about" "is not a strict numerical boundary to the specified parameter," but rather "must be determined using a functional approach" and "requires a factual inquiry as to the purpose of the limitation." *See* D.I. 197 at 5.

Also, tonicity regulating is not the crucial issue. The product must be clinically isotonic or it could not be injected safely. The function of the tonicity regulating agent is that it is present in the composition to maintain the tonicity of the composition in a physiologically acceptable range. The Court agrees with Par's position that the difference in osmolality that's produced by the amount of 9 mg/mL of sodium chloride in Hospira's formulation, is functionally equivalent to the tonicities produced by the ranges set out in the '876 Patent because it is physiologically acceptable.

A more critical component is the pH raising/lowering limitation. There is really no dispute that that citric acid and sodium citrate are a buffering agent which it fits within the definition of "pH raising agent" in the Court's claim construction. There is no dispute that it was added to Hospira's ANDA product to control the PH within an optimal range throughout the product's shelf life. Dr. Toste's testimony on the scientific results from testing that was done through Dr. Elder showed that the buffer capacity provided by the differing numerical values showed that the slight difference between 2.41 to 2.57 mg/mL and the numerical value at the low end of the range (2.8 mg/mL) of the limitation of the '876 Patent made little difference from a functional perspective. The variance comes within the parameters of "about" in the context of the purposes of the excipient in the formulation. Hospira's evidence demonstrates that the lower the pH, the more d-epinephrine will form (JTX 102 at 1). Therefore, the citrate buffer keeps the pH in a reasonably stable range to minimize D-epinephrine formation. The amount of pH raising buffer system in Hospira's product meets those functional requirements as Dr. Toste testified at length.

To the extent that Hospira's ANDA Product does not literally meet the claim limitations "about 6 to 8 mg/mL of a tonicity regulating agent" or "about 2.8 to 3.8 mg/mL of a pH raising agent," Hospira's ANDA Product meets those claim limitations under the doctrine of equivalents. The evidence shows that the amount of 8.55 and 9 mg/mL sodium chloride is equivalent to "about 8 mg/mL" of a tonicity regulating agent, and the amount of 2.41 and 2.57 mg/mL is equivalent to 'about 2.8 mg/mL" pH raising agent under a function-way-result analysis.

The Court also credits Dr. Toste with respect to his transition metals complexing agent analysis. The evidence shows that the sodium metabisulfite quantity is enough for all the oxidation expected. Metals are a catalyst for unknown A, B, & C, and Hospira admitted to the FDA that it has a chelating agent. There are clearly metals in the Hospira's ANDA product, though below ICH Q3D limits. Hospira's expert acknowledges that transition metals are variable and not subject to control.

Dr. Gokel's testimony does not refute Dr. Toste's methodology or analysis. Dr. Gokel's results were based on trace metals in experimental batches, which did not reflect the full scope of the ANDA request. The Court finds the relevant comparison is to the product that an ANDA applicant seeks permission to sell, not to its representative batches. Hospira represented to the FDA that the citrate ion in their proposed product performs the very function described in the '876 Patent specification.

2. Invalidity

Hospira has not shown, by clear and convincing evidence, that a person of ordinary skill in the art would have had a motivation to combine or modify the teachings of the combinations of references relied upon by Hospira's expert to arrive at the subject

matter claimed in the asserted claims and would have had a reasonable expectation of success in doing so. Nor did it prove that evidence of objective indicia of non-obviousness, including long-felt need, failure of others, recognition of the problem, teaching away, skepticism of others, and unexpected results, support the non-obviousness of the asserted claims.

The long-standing failure of others to develop similar epinephrine formulations with long-term stability supports a finding that the patented formulation was not obviousness. The record shows that there was a need for a stable formulation as recently as 2013, despite the fact that epinephrine degradation had been studied since the 1960's. Both Par and Hospira engaged in lengthy development efforts with repeated failures and scientists at both companies expressed the unexpected difficulty of developing long-term stable epinephrine formulations.

Hospira failed to prove by clear and convincing evidence that the asserted claims of the Patents-in-Suit are invalid. Dr. Pinal essentially presumed the patent to be invalid, and applied hindsight bias to pick out pieces from the prior art, when nothing in the prior art as a whole suggested the desirability of making the claimed combination. Importantly, the prior art cited by the defendant in trial was included in the prior art presented to the patent examiner. Dr. Pinal's testimony also was not directed to the time of the invention—March 2015—and thus his testimony cannot have shown that the asserted claims were invalid as obvious. Dr. Pinal's testimony was vague and did not articulate reasons why a person of ordinary skill in the art at the time of the invention would combine these references.

The Court credits Dr. Schöneich's testimony that the prior art teaches away from the combination and agrees that a person of ordinary skill in the art would not be motivated to improve on a product that had already been approved. The motivation provided to Par in the FDA's request was not public, nor is there evidence that the fact was known to Hospira scientists at the time no motivation to combine. Prior art teaches away from essentials of the formula.

The Court also rejects Hospira's reliance on the disclosure-dedication rule. Hospira has not shown that the subject matter of Hospira's ANDA was surrendered to the public by the patentee because it is disclosed in the specifications of the patents-in-suit but is not encompassed in the claim language. The Court finds Dr. Pinal's testimony on that subject was not credible and credits the experts' testimony to the contrary.[6]

[6] Hospira argues that the patent specification discloses, but does not claim, 9 mg/mL of a tonicity regulating agent and 2.59 mg/mL of a pH raising agent (which are the concentrations claimed in Hospira's ANDA product), and therefore Hospira's ANDA product cannot infringe under the doctrine of equivalents. It contends Par cannot write claims that are narrower than what is disclosed in the specification and attempt to broaden the claims using the doctrine of equivalents. Par argues that the disclosure-dedication doctrine does not apply because the specification provides ranges of tonicity regulating agents generally, not specifically sodium chloride.

The Court finds the claim limitation is to a range of "about 6 to 8 mg/mL" of a functional group of tonicity regulating agents—not a single "target concentration" of sodium chloride. The Court rejects Hospira's argument that 9 mg/mL is an alternative unclaimed concentration. The claim construction of "about" is dispositive of the issue. The Court discounts Dr. Pinal's testimony on the issue. In order to adopt Dr. Pinal's analysis, one would have to reject the agreed claim construction of "about" and limit the claim to a discrete numerical limitation. Contrary to Hospira's contention, the Court finds the subject matter "9 mg/mL of a tonicity regulating agent," specifically sodium chloride, is within the limitation of the claim and is not a distinct alternative to what is claimed. Similarly, as Dr. Toste testified, the amount of in the range of about 2.59 mg/mL of a pH raising agent, a citrate buffer, is encompassed within the claimed limitation of the patent. The Court finds the subject matter of these concentrations of excipients is claimed in the patent and is not dedicated to the public so as to be ineligible for re-capture under the doctrine of equivalents.

Hospira has not shown that the disclosure in the specification is "of such specificity" that a person of ordinary skill in the art could immediately "identify the subject matter that had been disclosed and not claimed." *Johnson*, 285 F.3d at 1054. The Court credits the testimony of Par's experts that a person of ordinary skill in the art would view the subject matter as claimed in the patent. In any event, based on the

Accordingly, the Court rejects defendant Hospira's invalidity defense and finds in favor of plaintiff Par on its claim of infringement.

A judgment in conformity with these Findings of Fact and Conclusions of Law will issue this date.

SO ORDERED this 13th day of November 2019.

BY THE COURT:

s/ Joseph F. Bataillon
Senior United States District Judge

testimony of Par's experts, the Court finds the Hospira's ANDA product literally infringes Par's patents and resort to the doctrine of equivalents is superfluous.