IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BELCHER PHARMACEUTICALS, LLC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	C.A. No. 17-775-LPS
	:	
HOSPIRA, INC.,	:	
	:	
Defendant.	:	

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OPINION

March 31, 2020
Wilmington, Delaware

UNSEALED ON
APRIL 3, 2020

STARK, U.S District Judge:

Belcher Pharmaceuticals, LLC. ("Belcher" or "Plaintiff") sued Hospira, Inc. ("Hospira" or "Defendant") under the Hatch-Waxman Act, *see* 35 U.S.C. § 271(e), for Hospira's attempts to bring to market a bioequivalent of Belcher's Epinephrine Injection USP. (D.I. 1 at ¶ 8) Belcher alleges that Hospira's bioequivalent product infringes U.S. Patent No. 9,283,197 ("the '197 Patent") under the doctrine of equivalents. (D.I. 1 at ¶¶ 17-26; D.I. 201 at ¶ 3) Hospira contends that it does not infringe the '197 Patent and, further, that the Patent is invalid and/or unenforceable. (*See* D.I. 156) In June 2019, the Court held a two-day bench trial. (*See* D.I. 217-19) ("Tr.") Thereafter, the parties submitted post-trial briefing (D.I. 222, 225, 230, 232, 235, 236), proposed findings of fact (D.I. 223-24, 231), and notices of supplemental authorities (D.I. 240-42).

Pursuant to Federal Rule of Civil Procedure 52(a), and having considered the entire record in this case and the applicable law, the Court concludes that: (1) Hospira does not infringe the '197 Patent under the doctrine of equivalents, (2) the '197 Patent is invalid as obvious in view of the prior art and for improper inventorship, and (3) the '197 Patent is unenforceable due to inequitable conduct.

The Court's findings of fact and conclusions of law are set forth in detail below.

FINDINGS OF FACT

This section contains the Court's findings of fact ("FF") on disputes raised by the parties during trial, as well as the facts stipulated to by the parties. The Court adopts the parties' Stipulated Facts (D.I. 201-1 Ex. 1) ("SF"), which are repeated in part below. Certain findings of fact are also provided in connection with the Court's legal analysis later in this Opinion.

I. Introduction

1. This patent infringement action arises out of Hospira's submission of New Drug Application ("NDA") No. 209359 to the U.S. Food and Drug Administration ("FDA") pursuant to 21 U.S.C. § 355(b). Hospira's NDA seeks FDA approval of a 0.1 mg/mL injectable l-epinephrine formulation ("Hospira's NDA Product"). (SF ¶¶ 20-21, 28)

2. Belcher is the holder of NDA No. 205029, which was approved by FDA on July 29, 2015 for a 1 mg/mL injectable l-epinephrine formulation ("Belcher's NDA Product"). (D.I. 1 at ¶ 13; *see also* JTX-59/DTX-137)

3. The FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations – commonly referred to as the "Orange Book" – lists the '197 Patent for Belcher's NDA No. 205029. (D.I. 1 at ¶ 15; Rubin Tr. at 149)[1]

4. Hospira's NDA included a certification ("Paragraph IV certification"), pursuant to 21 U.S.C. § 355(b)(2)(A)(iv), that the claims of the '197 Patent are invalid, unenforceable, and/or will not be infringed by the manufacture, use, importation, sale or offer for sale of Hospira's NDA Product. (SF ¶ 21)

5. On June 16, 2017, Belcher sued Hospira for infringing the '197 Patent pursuant to 35 U.S.C. § 271(a), (b), (c) and (e)(2), based on the filing of Hospira's NDA and the accompanying Paragraph IV certification as to Hospira's NDA Product. (D.I. 1 at ¶¶ 22-26)

6. Belcher and Hospira stipulated that Hospira's NDA Product does not literally infringe claims 6 and 7 of the '197 Patent. (SF ¶ 35)

[1] Citations to the trial transcript are in the form of ("[Witness last name] Tr. at [page]).

7. Trial proceeded on Belcher's theory of infringement under the doctrine of equivalents and Hospira's affirmative defenses and counterclaims of non-infringement, invalidity, and unenforceability. (*See* D.I. 201 at ¶¶ 3-5)

II. Patent-in-Suit

8. The '197 Patent, entitled "More Potent and Less Toxic Formulations of Epinephrine and Methods of Medical Use," issued on March 15, 2016 from U.S. Application No. 14/460,845 ("the '845 Application"). (SF ¶¶ 3, 5; *see also* JTX-1)

9. The '197 Patent lists Jugal K. Taneja as the sole inventor. (SF ¶ 4; *see also* JTX-1)

10. The '197 Patent is assigned to Belcher. (SF ¶ 6)

11. Belcher asserts claims 6 and 7 of the '197 Patent. (D.I. 1 at ¶ 20; D.I. 201 at ¶ 2)

12. Claim 7 depends from claim 6. (JTX-1 at cl. 7)

13. Claim 6 recites:

> An injectable liquid pharmaceutical formulation of l-epinephrine sterile solution; said liquid pharmaceutical formulation having a pH between 2.8 and 3.3; said injectable liquid pharmaceutical formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine, and further including a tonicity agent; said liquid pharmaceutical formulation including no more than about 6% d-epinephrine and no more than about 0.5% adrenalone at release[2], and no more than about 12% d-epinephrine and no more than about 0.5% adrenalone over a shelf-life of at least 12 months.

(JTX-1 at cl. 6)

[2] The FDA defines "release" as the time a drug product leaves the manufacturer's possession. *See* 21 C.F.R. § 610.1 ("No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product . . . .").

14. Claim 7 recites:

> The said injectable liquid pharmaceutical formulation of claim **6** further having a concentration of 1 mg per mL l-epinephrine.

(JTX-1 at cl. 7)

15. The Court construed the claim limitation "said injectable liquid pharmaceutical formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine" as a product-by-process limitation, such that "1.0 to 1.06 mg/mL l-epinephrine" must be present in the solution after the compounding step has been completed. (D.I. 96 at 5; D.I. 97; D.I. 204 at 4-5; D.I. 205)

16. The Court construed "in an aqueous solution" to mean "in a homogenous mixture of one or more substances dissolved in a solvent that is mainly water." (D.I. 96 at 10; D.I. 97)

17. The Court construed "said liquid formulation having a pH between 2.8 and 3.3" as referring to the pH of the final product. (D.I. 204 at 2; D.I. 205)

III. Witnesses

A. Belcher's Expert Witness

18. Dr. Shyam Mohapatra earned his Ph.D. in molecular biology and genetics before joining the College of Medicine, Internal Medicine Department, at the University of South Florida, where he has earned the title of distinguished health professor. (Mohapatra Tr. at 294) Dr. Mohapatra is a named inventor on more than 39 U.S. patents, including patents related to drug development, formulation, and delivery, and has collaborated with pharmaceutical companies such as Pfizer, Merck, Bristol-Myers-Squibb, and Astra-Zeneca, to improve their pharmaceutical products. (*Id*. at 295-96)

B. Hospira's Expert Witness

19. Dr. Rodolfo Pinal earned his bachelor's degree in pharmaceutical chemistry from the National Autonomous University of Mexico. (Pinal Tr. at 225) From 1990 to 2003, he worked on pre-formulations, sterile products (including their manufacture), and solid pharmaceuticals at Hoffman LaRoche. (*Id*. at 225-26) He is currently an Associate Professor in Industrial and Physical Pharmacy at Purdue University, where he has taught parenteral products to both undergraduate and graduate students since 2004. (*Id*.)

C. Fact Witnesses

20. Brian McHugh was a program manager of several epinephrine programs at Hospira, including the Abboject project. (McHugh Tr. at 58-59)

21. Xifeng Zhang is a product manager in the Regulatory Affairs Division at Hospira and was responsible for filing the NDA for Hospira's NDA Product. (X. Zhang Tr. at 76)

22. Eric Zhang has been an employee of Hospira since 2004 and is an associate researcher fellow who worked extensively on Hospira's NDA Product. (E. Zhang Tr. at 94)

23. Jugal Taneja is the Chief Executive Officer of Belcher and the sole named inventor of the '197 Patent. (J. Taneja Tr. at 114-15) He graduated with a degree in petrochemical mining in 1966 from a university in India. (*Id.* at 115) After moving to the United States in 1972, he held a series of positions in various fields before earning his Master of Business Administration from Rutgers University in 1978. (*Id*. at 116) He subsequently worked at a series of banks involved in petrochemicals, and then joined a nutraceutical company that produced vitamins. (*Id*. at 117) In 2005, his company began producing generic drugs. (*Id*. at 117-18)

24. Darren Rubin is the Chief Science Officer of Belcher. (Rubin Tr. at 145-46) He graduated summa cum laude with a degree in biology before earning a Master's degree in

medical sciences, specializing in biochemistry and molecular biology and a Master of Business Administration, specializing in finance.[3] (*Id*. at 145) Rubin has also been referred to as the "Head of [Intellectual Property]" at Belcher and helped draft and prosecute the '197 Patent. (*Id*. at 149; *see also* M. Taneja Tr. at 218) Rubin is neither a patent agent nor patent attorney. (Rubin Tr. at 146)

25. Mihir Taneja is Belcher's Vice President of Sales and Marketing at Belcher and was involved in Belcher's interactions with Sintetica SA ("Sintetica") concerning epinephrine formulations. (M. Taneja Tr. at 209-11) He is the son of Jugal Taneja. (*Id.* at 210)

26. Fabio Lanzieri was a salesperson associated with Belcher. (Lanzieri Tr. at 384)

IV. Person of Ordinary Skill in the Art

27. A person of ordinary skill in the art ("POSA") in relation to the '197 Patent is a person with a PharmD or Ph.D. in pharmaceutical sciences or a related discipline, with at least three years of experience formulating and/or manufacturing commercial scale drug products, or a Master's or Bachelor's degree and five to eight years of experience. (D.I. 224 at ¶ 30) The POSA would also have experience in the development of parenteral (injectable) drugs, specifically including solutions for injection, formulating such solutions for human or animal use, and would have the skills necessary to perform the testing and evaluation necessary to obtain regulatory approval of such formulations.[4] (*Id.*; Pinal Tr at 250-51)

[3] Trial testimony did not reveal where Mr. Rubin earned his educational degrees.

[4] Belcher offers only Dr. Mohapatra as a definition of a POSA. (D.I. 231 at ¶¶ 40-41) While Dr. Mohapatra is certainly skilled in the art, the Court needs to describe the qualifications of a "hypothetical person" to define the POSA for purposes of deciding issues in this case. *See Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1454 (Fed. Cir. 1984) ("[The] hypothetical person is not the inventor, but an imaginary being possessing 'ordinary skill in the art' created by Congress to provide a standard of patentability."); *id*. at 1453 ("[That person]

28. Hospira's expert agreed that his opinions would be the same regardless of which definition of a POSA the Court adopts. (Pinal Tr. at 251)

V. Background

29. Parenteral drug products are drugs administered by injection. (Pinal Tr. at 251) Formulations of parenteral drugs must be sterile, free of particles, and free of pyrogens. (*Id*. at 252) To that end, special precautions are taken during their production, such as controlling the manufacturing environment (e.g., formulations are compounded and filled in "very clean air"), protecting products from degradation (e.g., by removing oxygen during compounding), and ensuring drug stability and solubility (e.g., by controlling pH). (*Id*. at 252-53)

30. Epinephrine is a grandfathered[5] drug product that has been sold since at least 1938. (Rubin Tr. at 147; Pinal Tr. at 253) By the time of the alleged invention, it was well-known that epinephrine was subject to degradation. (Pinal Tr. at 253)

31. Epinephrine may undergo three reactions: racemization, oxidation, and substitution by bisulfite. (JTX-37 at 4-8; Pinal Tr. at 254)

32. Racemization describes a change in the arrangement of molecules around a carbon "chiral center." (Pinal Tr. at 254-55) For epinephrine, racemization is the conversion of the active form, l-epinephrine, to its less potent isomer, d-epinephrine. (Pinal Tr. at 255; JTX-37 at 4; JTX-41 at 7)

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must be presumed to have, or is charged with having, knowledge of all material prior art."). Hence, the Court will adopt Hospira's definition of a POSA. (*See* D.I. 224 at ¶ 30)

[5] Grandfathered drug products are old, well-known products that are not subject to certain FDA requirements if they meet specific conditions. *See* 21 U.S.C. § 321(p)(1); *see also* Marketed New Drugs without Approved NDAs and ANDAs, FDA CPG § 440.100 (2011).

33. Oxidation describes a change in a compound's chemical composition due to molecular oxygen or other oxidizing agents. (JTX-37 at 4) For epinephrine, oxidation occurs at the catechol moiety (*id*.), and may result in degradants such as adrenalone (Mohapatra Tr. at 54).

34. Racemization of epinephrine is inversely proportional to pH, whereas oxidation is proportional to pH. (Pinal Tr. at 255-56; JTX-37 at 4, 6) Thus, as the "rate of oxidation increases with increased pH, and since the rate of racemization decreases with increased pH, there is an optimum pH at which racemization and oxidation can be balanced to minimize loss of intact drug by these two routes; this is approximately pH 3.0-3.8." (JTX-37 at 6; *see also* Pinal Tr. at 255-56) Other studies have shown successful epinephrine formulations with a pH as low as 2.4, but such formulations were susceptible to undesirably fast racemization. (*See* JTX-41 at 7 ("To improve the shelf-life, raising the pH of the injection somewhat [from 2.4] should be considered. . . . The racemization [(as compared to oxidation)] is the limiting degradation process [to shelf-life]."); *see also* Pinal Tr. at 257-58)

VI. Belcher's NDA Product

35. Sintetica has manufactured pharmaceutical preparations of epinephrine since at least the 1930s (Rubin Tr. at 167; DTX-137 at 6), and has developed sulfite-free epinephrine formulations since the 2000s (Rubin Tr. at 168; DTX-137 at 8-9). These formulations include the use of hydrochloric acid to reach a pH of 2.8 to 3.3. (Rubin Tr. at 168; DTX-137 at 9)

36. On November 30, 2012, Belcher submitted its "original 505(b)(2) New Drug Application (NDA 205029) for Epinephrine Injection, USP 1:1000 (mg/mL)," covering 1 mg/mL epinephrine, with 1 mL of solution contained in a 2 mL ampule. (DTX-137 at 1) The proposed indication was "for use in increasing systemic arterial blood pressure in acute hypotensive stress associated with septic shock." (*Id*.)

37. Belcher's NDA was a "literature-only based submission. No nonclinical or clinical studies . . . ha[d] been conducted," except an in vitro blood compatibility study that demonstrated a lack of red cell hemolysis at the 1:1000 dilution concentration. (DTX-137 at 2)

38. Belcher's NDA details the historical development of epinephrine injection products. (*See* JTX-59) The NDA describes Sintetica's early pharmaceutical preparations of epinephrine, which included preservatives and sulfites, had pHs of 2.2-4.0, and included 10% more epinephrine (i.e., an "overage") than "the theoretical value to compensate the activity loss during manufacturing and storage." (*Id.* at 4-6; Rubin Tr. at 167)

39. Belcher's NDA further describes how market demand in the early 2000s encouraged Sintetica to produce preservative and sulfite-free formulations, which involved a "very simple" solution of increasing the concentration of the tonicity agent, and slightly increasing the overage, to account for the loss of anti-oxidant preservatives. (JTX-59 at 6; *see also* Rubin Tr. at 168) The NDA states that Sintetica's early preservative and sulfite-free formulations had a pH of 2.8-3.3 and 15% overages. (JTX-59 at 6-7) The NDA also describes a reference product manufactured by American Regent Laboratories, Inc., which had approximately the same pH and overages as Sintetica's formulations. (*Id*. at 15-18)

40. As part of its NDA, Belcher also provided data to the FDA from several batches manufactured by Sintetica. (J. Taneja Tr. at 128-30) Belcher was not involved in the production of these batches. (*See* Rubin Tr. at 168 (testifying Sintetica's products from 2000s were made "[b]efore Belcher's interaction with Sintetica"); J. Taneja Tr. at 118, 129 (testifying Belcher, Inc. (formed in 2000) was not involved with epinephrine in 2003, and Belcher, LLC (the party here) was formed in 2010); *but see* JTX-59 at 24-25 ("This positive result allowed ***us*** [(i.e. Belcher)] to produce the pilot batch 03122 (40'000 ampoules)" ***in 2003***) (emphasis added))

a. Belcher provided data to the FDA from four Sintetica batches (02149P, 030997-99) made between November 2002 and April 2003 to validate formulation stability without antioxidant agents in clear glass ampules. (JTX-59 at 18-23) The data demonstrates that, over a 24-month period, each batch had a pH ranging from 3.1-3.2, undetectable levels of adrenalone, and epinephrine overages ranging from 10-15%. (*Id*. at 19-22)

b. Belcher provided data to the FDA from one Sintetica batch (03122) made in June 2003 to validate the sterilization cycle. (*Id*. at 24-25) The data demonstrates that, over a 24-month period, the batch had a pH that ranged between 3.1-3.3, undetectable levels of adrenalone, and overages ranging from 11-14%. (*Id*. at 25)

c. Belcher provided data to the FDA from three Sintetica batches (03166-68) made between April and November 2003 to validate the manufacturing process conditions. (*Id*. at 26) The data demonstrates that each batch had a pH ranging from 3.0-3.1, undetectable levels of adrenalone, and overages ranging from 11-13%. (JTX-59 at 27-29; *see also* Rubin Tr. at 170-71)

41. As part of its NDA, Belcher sought to replace the "old" in-process pH of 2.8-3.3 with a "new" in-process pH of 2.4-2.6, and use an overage of 10-15%. (JTX-59 at 35-36; J. Taneja Tr. at 130-31)

42. On February 7, 2013, Belcher received a communication from the FDA regarding its NDA. (JTX-83; Rubin Tr. at 171-73) The FDA sought data that "support[ed the] evaluation of drug product for potential racemization from manufacturing process conditions and over the shelf life." (JTX-83 at 3; *see also* Rubin Tr. at 173) The FDA also asked Belcher to provide "justification for 10% overage of epinephrine in the manufacturing process," and whether the

stability batches from 2003 and 2004 were manufactured using an identical formulation and process as the one proposed for marketing. (JTX-83 at 3; *see also* Rubin Tr. at 173)

43. On March 8, 2013, Belcher submitted a response to the FDA's February 2013 requests (JTX-61), which (to the best of Mr. Rubin's recollection) was prepared by Sintetica. (Rubin Tr. at 174-75) In response to the racemization inquiry, Belcher stated that "[r]acemization [of l-epinephrine] is a well-known process." (JTX-61 at 10; Rubin Tr. at 175) In response to the overage inquiry, Belcher cited the United States Pharmacopeia ("USP") monograph, which allows for up to 15% overages in epinephrine products. (JTX-61 at 10; JTX-42 at 3; Pinal Tr. at 269-70) In response to the inquiry about identical formulations, Belcher insisted that while Sintetica's 2003-04 batches had a pH of 2.8-3.3, Belcher's proposed product (with a pH of 2.4-2.6) was essentially identical because all of the batches fell within the USP's allowable pH range of 2.2-5.0. (JTX-61 at 12-13; *see also id*. at 12 ("We consider the in process pH change to be a very minor change . . . to minimize oxidation of this preservative free formulation."))

44. On October 4, 2013, Belcher received a "Complete Response Letter" from the FDA, which asked Belcher to evaluate the effect of an in-process pH of 2.4 to 2.6 on racemization. (JTX-88 at 2; J. Taneja Tr. at 131-32)

45. Belcher again asked Sintetica to handle the response. (J. Taneja Tr. at 132) Sintetica thereafter provided Belcher with test results of several batches (13043, RD035, 13015-16) that had consistent pHs but varying overages (3% or 10%). (JTX-93 at 22; J. Taneja Tr. at 133-36) Sintetica's data showed that overage "made no difference in the d-epinephrine formation." (J. Taneja Tr. at 135) Instead, Belcher and/or Sintetica determined that "d-epinephrine isomer formation is mainly influenced by [the] pH." (*Id*. at 136; JTX-93 at 22)

Belcher and/or Sintetica's draft response suggested a new in-process pH of 3.2 to 3.8. (JTX-93 at 22-23)

46. On October 17, 2013, Belcher's regulatory consultants – INC Research – recommended that Belcher use the in-process pH of 2.8-3.3 presented in the original NDA and Sintetica batch data, since any changes in the process from the process used to obtain the batch data would delay approval. (J. Taneja Tr. at 138-39; JTX-94 at 1)

47. Belcher submitted its response to the FDA, stating, in part: "We have refocused our studies on determining the effect of the in-process pH of 2.8-3.3 on the formation of d-epinephrine during each step of the manufacturing process, which was used to manufacture the 3 primary stability batches (03166, 03167, 03168) provided in the NDA." (JTX-63 at 2; J. Taneja Tr. at 142-43) Belcher then sought "approval for the drug product manufacture using the same manufacturing process provided in the NDA with the exceptions of changing the pH from 2.4-2.6 back to the initial pH of 2.8-3.3 in order to significantly reduce the amount of d-epinephrine produced during the manufacturing process and on stability." (JTX-63 at 9; *see also* J. Taneja Tr. at 143)

48. The FDA ultimately approved Belcher's epinephrine product with a pH of 2.8-3.3. (*See* J. Taneja Tr. at 143)

VII. Hospira's NDA Product

49. The composition of Hospira's NDA Product (and Belcher's NDA Product, as the Reference Listed Drug ("RLD")) is presented in Table 1 of Section 3.2.P.2.2 of NDA No. 209359, reproduced below:

Table 1. Formulation Comparison

Component	Hospira Formulation Quantity per Milliliter (mL)	RLD Quantity per Milliliter (mL)
Epinephrine	0.10 mg	1 mg
Sodium Metabisulfite	0.46 mg	None
Sodium Chloride	8.16 mg	9 mg
Citric Acid, Anhydrous	2.13 mg	None
Sodium Citrate, Dihydrate	0.41 mg	None
Hydrochloric Acid	None	A.R.
Water for Injection	q.s. to 1 mL	q.s. to 1 mL
Primary Container	10 mL clear glass cartridge	1 mL clear Ampul

A.R. = as required; q.s. = quantity sufficient

(SF ¶ 26)

50. The pH, amount of d-epinephrine, and amount of adrenalone of Hospira's NDA Product at close to release is presented in Table 41 of Section 3.2.P.2.2 of NDA No. 209359, which is reproduced below:

Table 41. Comparison Data between the RLD and Hospira Product at Close to Release

Lot No.	RLD	Hospira Product			
	16163	48332SB[3]	48333SB[3]	48334SB[3]	66454SB[4]
Manufacture Date	Not available	Dec 2014	Dec 2014	Dec 2014	Jun 2016
Expiry	Nov 2017	TBD	TBD	TBD	TBD
Test Date	28Jul 2016	22Jan2015	22Jan2015	22Jan2015	02Aug2016
Months to Expiry	16	15	15	15	15
pH	3.3	3.1	3.1	3.1	3.0
Assay (%)	103.1; 102.8	109.6	110.0	109.6	98.6
d-Epi (%)	4.8; 4.9	0.5	0.5	0.5	0.5
ESA (%)	0.1	0.4	0.4	0.4	0.3
Adrenalone (%)	ND	< 0.1[2]	< 0.1	< 0.1	ND
Norepinephrine (%)	ND	ND	ND	ND	ND
Epinephrine Thiosulfonic Acid (ETA) (%)	ND	0.1	0.1	0.1	0.2
RRT 0.39 (%)	ND	ND	ND	ND	ND
Unspecified Impurity (%)	ND	ND	ND	ND	ND
Total Impurities (%) (including d-epinephrine)	4.9; 5.0	1.0	1.0	1.0	1.0

[1] ND=not detected
[2] PQL for related substances = 0.1%
[3] These three lots have 10% overage
[4] This lot does not have overage.

(SF ¶¶ 29, 31-32)

51. The pH, amount of d-epinephrine, and amount of adrenalone of Hospira's NDA Product at expiry is presented in Table 42 of Section 3.2.P.2.2 of NDA No. 209359, which is reproduced below:

Table 42. Comparison Data between the RLD and Hospira Product at Expiry

Lot No.	RLD	Hospira Product		
	15199	48332SB[3]	48333SB[3]	48334SB[3]
Manufacture Date	Not available	Dec 2014	Dec 2014	Dec 2014
Expiry	Sep 2016	Apr 2016[4]	Apr 2016[4]	Apr 2016[4]
Test Date	07 Sep2016	22Apr2016	22Apr2016	22Apr2016
pH	3.4	3.1	3.1	3.1
Assay (%)	103.5	102.3; 102.6[5]	102.3; 102.1[5]	102.5; 102.1[5]
d-Epi (%)	7.4; 7.6	3.6	3.7	3.7
ESA (%)	< 0.1	6.9	6.7	6.9
Adrenalone (%)	ND[1]	< 0.1[2]	< 0.1	< 0.1
Norepinephrine (%)	ND	ND	ND	ND
Epinephrine Thiosulfonic Acid (ETA) (%)	ND	0.3	0.3	0.4
RRT 0.39 (%)	ND	0.1	0.1	0.1
Unspecified Impurity (%)	ND	ND	ND	ND
Total Impurities (%) (including d-epinephrine)	7.4; 7.6	10.9	10.8	11.1

[1] ND=not detected
[2] PQL for related substances = 0.1%
[3] These three lots have 10% overage
[4] Proposed shelf life is 15 months.
[5] Assay was tested at 18 months as the assay testing for 15 months was missed.

(SF ¶¶ 33-34)

52. Hospira's NDA Product has a concentration of 0.1 mg/mL l-epinephrine after the compounding step has been completed. (SF ¶ 28; PTX-94A at 2)

53. Hospira's NDA Product is intended to be filled into 10 mL syringes to deliver a total of 1.0 mg of l-epinephrine to patients. (X. Zhang Tr. at 78; E. Zhang Tr. at 100; Pinal Tr. at 246; Mohapatra Tr. at 325; PTX-95 at 1)

54. Hospira's NDA states that its NDA Product is "essentially similar to the approved listed drug [Belcher's NDA Product], as it has "the same active moiety and delivers the same amount of drug to the patient as both products have essentially the same concentration of Epinephrine when diluted in 1000 mL of a dextrose containing solution." (PTX-94A at 2) Hospira's NDA also states that its NDA Product "has the same route of administration, indication and method of use" as Belcher's NDA Product. (*Id.*) However, Hospira's NDA Product "contains excipients which are not present in Belcher's product." (*Id.*)

VIII. Facts Relating to Infringement

55. Concentration is an attribute of a solution; it is an objective property defined as the mass per volume. (Mohapatra Tr. at 39; Pinal Tr. at 249)

56. Concentration is different than "overage," which is defined as the excess amount of something over and above the amount that is required or desired. (Pinal Tr. at 235, 249-50; Mohapatra Tr. at 311) In the case of pharmaceutical drug products, "overage" generally means the amount of an active ingredient in a formulation that is more than the nominal amount claimed on the product label. (Pinal Tr. at 249-50)

57. Claims 6 and 7 of the '197 Patent recite a specific concentration of l-epinephrine, not a particular overage (or amount delivered to the patient) of l-epinephrine. (JTX-1 at cls. 6-7; Pinal Tr. at 235-36, 249-50)

A. Doctrine of Equivalents

58. The concentration of 0.10 mg/mL l-epinephrine in Hospira's NDA Product does not perform substantially the same function in substantially the same way to obtain substantially the same result as the claimed 1.0-1.06 mg/mL l-epinephrine in claim 6 of the '197 Patent. (Pinal Tr. at 233-39)

59. The formulation of claims 6 and 7 is compounded at 1.0-1.06 mg/mL l-epinephrine to allow for minor losses due to subsequent production steps (e.g., filling, sterilization, and/or storage) (function/way), to produce a final concentration of 1 mg/mL (result). (*See* JTX-2 at 66-67 (patentee arguing concentration of 1.0 to 1.06 mg/mL l-epinephrine "describes how the formulation is <u>compounded</u> during manufacture; a narrow concentration range during the production step of compounding; to result in a drug product of 1 mg/mL epinephrine sterile solution after the steps of filling, sterilization, and over its shelf-life") (emphasis added); Pinal Tr. at 234-36; Mohapatra at 320-23)

60. Hospira's NDA Product is compounded at a concentration 0.1 mg/mL – one-tenth that of the claimed invention – without any overages (function/way), to produce a final concentration of 0.1 mg/mL (result). (Pinal Tr. at 236-37, 364; Mohapatra at 323)

61. Claim 7 of the '197 Patent recites a concentration of 1.0 mg/mL l-epinephrine, which is intended to be the approximate concentration over the shelf life of the claimed product. (Pinal Tr. at 237-39; JTX-002 at 67)

62. Hospira's NDA Product is intended to have an approximate concentration of 0.1 mg/mL l-epinephrine over the shelf life of the NDA Product. (Pinal Tr. at 238-39)

63. Prior to FDA approval of NDA No. 205029, Belcher submitted a Request for Type C Meeting, seeking to gain approval also for "a new dosage form of Epinephrine Injection . . . containing different concentrations." (JTX-69 at 1) Belcher proposed a 1 mL formulation at a concentration of 1 mg/mL "for emergency treatment of allergic reactions (Type I), including anaphylaxis," and a separate 10 mL formulation at a concentration of 0.1 mg/mL "for increasing mean arterial blood pressure in adult patients with hypotension associated with septic shock." (*Id*. at 1-2)

64. There is a substantial, ten-fold difference between the concentration claimed in the '197 Patent (1.0-1.06 mg/mL) and the concentration of Hospira's NDA Product (0.1 mg/mL). (Pinal Tr. at 240-45; JTX-69 at 1-2)

65. Belcher's 1 mg/mL NDA Product is filled into 1 mL vials, whereas Hospira's 0.1 mg/mL NDA Product is filled into 10 mL vials. (X. Zhang Tr. at 78; E. Zhang Tr. at 100; Pinal Tr. at 246; Mohapatra Tr. at 325; PTX-95 at 1) Hence, the total amount of l-epinephrine delivered to a patient is the same for both the Belcher and Hospira NDA Products: approximately 1 mg. (X. Zhang Tr. at 78; E. Zhang Tr. at 100) There is also no substantial difference between

the products in terms of concentration of l-epinephrine after diluting for administration; both NDA Products are diluted in a 1-liter intravenous bag of 5% dextrose solution, which produces a final difference in concentration of about 1%. (Mohapatra Tr. at 306-07, 322, 325) However, neither the total amount of l-epinephrine delivered to a patient nor the diluting step are claimed in asserted claims 6 or 7.

66. The ’197 Patent envisions (but does not claim) filling 1 mL of the l-epinephrine product into a 2 mL container, which would deliver 1 mg of l-epinephrine to a patient. (JTX-1 at col. 4 ll. 6-16)

67. Hospira represented to the FDA that, when its NDA Product is diluted with dextrose for administration, its pH is 4.0 (compared to Belcher’s diluted pH of 4.5). (DTX-87 at 3; Pinal Tr. at 248-49)

B. Hypothetical Claims

68. For purposes of the doctrine of equivalents and analysis of Hospira’s ensnarement defense, Belcher proposes two hypothetical claims. For the first, the concentration of claim 6 would state: “0.1-0.106 mg/mL.” (Mohapatra Tr. at 50, 319) For the second, the concentration limitation is replaced entirely with “having an overage between 0-6%.” (*Id*. at 50-51, 319-20)

69. Hospira also proposes a hypothetical claim, wherein the concentration of claim 6 would state: “0.1-1.06 mg/mL l-epinephrine.” (Pinal Tr. at 344-45)

70. Prior to the filing date of the ’197 Patent, Hospira publicly marketed, sold, and distributed lots 79-492-DK, 73-329-DK, 70-200-DK, and 61-485-DK of the Abboject Product. (SF ¶¶ 63, 67) The Abboject Product is a sterile, nonpyrogenic solution administered parenterally, supplied as a 0.10 mg/mL l-epinephrine syringe. (SF at ¶ 64; Pinal Tr. at 345-46; JTX-3 at 97) It “‘[m]ay contain additional citric acid and/or sodium citrate for pH adjustment. pH 3.3 (2.2 to 5.0).’” (SF ¶ 66 (quoting JTX-3 at 97); *see also* Pinal Tr. at 346; Mohapatra Tr. at

419) It also includes sodium chloride as a tonicity agent. (SF ¶ 65; Pinal Tr. at 346; JTX-3 at 97) The Abboject Product is compounded at 0.11 mg/mL epinephrine. (Pinal Tr. at 347; Mohapatra Tr. at 401-02; JTX-3 at 77) Moreover, the results of impurity testing on commercial lots of Hospira's Prior Abboject show less than 6% d-epinephrine at 12 months and less than 0.5% of all impurities (including adrenalone). (SF ¶¶ 79, 81, 83, 84; JTX-3 at 80, 83; Pinal Tr. at 348-50) These results are reproduced below:

Table 6-9 Impurity Test Results for Commercial Lots of Epinephrine Injection USP Abboject® Syringe Products

Lot Number	79-492-DK	73-329-DK	70-200-DK	61-485-DK
Expiration date	04/01/2011	10/01/2011	07/01/2010	10/01/2009
List Number	4901	4921	4901	4921
Age at testing (month)	2	9	12	20
ESA[1] (%)	0.69	1.6	2.7	2.7
d-epinephrine	1.1	1.6	2.2	2.9
Unknown RRT[2] 0.28	0.08	0.13	0.40	0.09
Unknown RRT 0.50	0.60	2.2	2.6	6.9
Unknown RRT 1.18	0.18	0.16	0.62	0.36
Total[3]	1.6	4.3	5.7	11.0

1. ESA = epinephrinesulfonic acid. Result reported as Epinephrine base.
2. RRT = relative retention time.
3. Total includes all reportable impurities except *d*-epinephrine.

(JTX-3 at 83)

71. Bruss et al., U.S. Patent Application No. 2008/0269347 ("Bruss"), is prior art to the '197 Patent under 35 U.S.C. ¶ 102. (SF ¶ 111) Bruss discloses a "sterile, non-pyrogenic solution administered parenterally by the intravenous or intracardiac (left ventricular chamber) routes, or via endotracheal tube into the bronchial tree." (DTX-97 at ¶ [0009]) Bruss also teaches that "[e]ach milliliter (mL) of the 1:10,000 solution contains epinephrine 0.1 mg; sodium chloride 8.16 mg; sodium metabisulfite added 0.46 mg; citric acid, anhydrous 2 mg and sodium citrate, dihydrate 0.6 mg added as buffers, [and may] contain additional citric acid and/or sodium

citrate for pH adjustment. pH 3.3 (2.2 to 5.0)." (*Id.*) Bruss does not disclose any properties over the shelf life of the product. (*See generally* DTX-97)

IX. Facts Relating to Invalidity

72. Hospira has failed to show by clear and convincing evidence that claims 6 and 7 of the '197 Patent are anticipated by the prior art. (FF ¶¶ 75-89; Mohapatra Tr. at 402-06)

73. Hospira has failed to show that either JHP's Adrenalin Product or Hospira's Ampul Product contain an anticipatory concentration of l-epinephrine after the compounding step. (*See* Mohapatra Tr. at 402-06) Instead, both of these products have post-compounding concentrations that exceed the claimed concentration range. (*See id.*)

74. Hospira has shown by clear and convincing evidence that claims 6 and 7 of the '197 Patent are invalid as obvious in view of the prior art. In particular, a POSA would have been motivated, at the time the invention was made, to minimize the overages of JHP's Adrenalin Product and/or Hospira's Ampul Product, in order to comply with ICH Guidelines and FDA standards, and would have had a reasonable expectation of success she could do so. (FF ¶¶ 75-103; Pinal Tr. at 230, 338-39)

A. Prior Art

1. JHP's Adrenalin Product

75. JHP's Adrenalin Product is prior art to the '197 Patent under 35 U.S.C. § 102. (SF ¶ 103; *see also* Pinal Tr. at 259-60) JHP manufactured, marketed, sold, and distributed in the United States lots 682476, 682480, 682489, 590839, 590845, and 682478 of its Adrenalin Product prior to the filing date of the '197 Patent. (SF ¶¶ 85, 90; Pinal Tr. at 260)

76. JHP's Adrenalin Product is an injectable liquid pharmaceutical formulation of l-epinephrine sterile solution. (SF ¶ 86; Pinal Tr. at 260; JTX-035 at 8) It has a concentration of 1 mg/mL l-epinephrine, and is supplied in a 1 mL vial single-dose container. (SF at ¶ 86) JHP's

Adrenalin Product was approved by the FDA on December 7, 2012, and has a shelf life of 18 months. (SF ¶¶ 88-89; Pinal Tr. at 260, 264)

77. Hospira acquired and tested lots 682476, 682480, and 682489 of JHP's Adrenalin Product. (SF ¶¶ 91-94; Pinal Tr. at 262; JTX-3 at 173) During their shelf lives, lots 682476, 682480, and 682489 each had a pH of between 2.8 and 3.4, no more than 0.5% adrenalone, less than 6% d-epinephrine at release, and less than 12% d-epinephrine over the shelf life, as shown in the table below:

Table 19. Adrenalin Testing Data Summary

Lot No.	**682476**		**682480**		**682489**	
Expiry	**31Oct 2014**		**31Dec 2014**		**30Jun 2015**	
Test Date	**02Dec2013**	**02Dec2014**	**03Feb2014**	**02Feb2015**	**10Mar2014**	**14Jul2015**
pH	3.1	2.9	2.8	3.0	3.4	3.2
Assay (%)	109.5	104.3	110.3	104.2	113.4	100.4
d-Epi (%)	1.8	5.3	1.8	6.5	0.9	4.5
ESA (%)	2.9	8.8	3.2	8.2	0.9	18.3
Adrenalone (%)	<PQL*	0.14	<PQL	0.12	<PQL	0.1
Norepinephrine (%)	<PQL	<PQL	<PQL	<PQL	<PQL	<PQL
Unspecified Impurity	0.14 (RRT0.30)	0.52 (RRT0.48)	0.15 (RRT0.30)	0.69 (RRT0.48)	<PQL	0.3 (RRT0.39)

*PQL=Practical quantitation limit=0.1%

(JTX-3 at 173; SF ¶¶ 95-97; Pinal Tr. at 262-66) Each of the second tests occurred within approximately one month after expiry. (JTX-3 at 173; Pinal Tr. at 262-63)

78. Belcher also purchased three of JHP's Adrenalin Product lots (590839, 590845, 682478) during the development of its NDA Product and sent them to Sintetica for testing. (SF ¶¶ 98-99) Sintetica e-mailed Belcher the results. (JTX-107) Sintetica's analysis showed that all three lots had a pH between 2.8 and 3.3, no more than 0.5% adrenalone, and less than 6% d-epinephrine at release, as demonstrated in the table below:

Attribute	Batch 590839 Expiration Date 03/14 Analysis Date 12/13	Batch 590845 Expiration Date 07/14 Analysis Date 12/13	Batch 682478 Expiration Date 11/14 Analysis Date 01/14
pH	2.9	2.9	3.1
Epinephrine assay (HPLC)	105.1%	106.2%	108.2%
Related substances (HPLC)			
Adrenalone	0.1%	0.1%	0.1%
Adrenaline ß-Sulfonate	5.0%	4.2%	3.0%
d-Epinephrine assay (HPLC)	5.16%	2.57%	1.70%

(JTX-107 at 1; SF ¶¶ 100-02; Pinal Tr. at 266-67) Batch No. 590839 was analyzed three months before expiry, and was therefore about 15 months old. (SF ¶ 100; Pinal Tr. at 268) At that time, it contained less than 12% d-epinephrine. (*Id.*)

79. JHP's Adrenalin Product used sodium chloride as a tonicity agent. (SF ¶ 87; JTX-35 at 8; Pinal Tr. at 260-61)

80. Hospira's testing showed that JHP's Adrenalin Product included overages between 9.5 and 13.4%. (Mohapatra Tr. at 405; FF 77) In other words, a product labeled as having 1 mg/mL l-epinephrine may actually have had between 1.095 and 1.134 mg/mL l-epinephrine at release. (Mohapatra Tr. at 405; FF 77)

81. JHP's Adrenalin Product does not expressly teach, nor has it been shown to inherently possess, a concentration of 1.00-1.06 mg/mL between compounding and release. (Mohapatra Tr. at 405-06)

2. Hospira's Ampul Product

82. Hospira's Ampul Product is prior art to the '197 Patent under 35 U.S.C. § 102. (SF ¶ 62; Pinal Tr. at 333) It was publicly marketed, sold, and distributed prior to the filing date of the '197 patent. (SF ¶ 36; Pinal Tr. at 333)

83. Hospira's Ampul Product is a sterile, injectable liquid pharmaceutical formulation of 1 mg/mL l-epinephrine, which is supplied in a 1 mL ampule single-dose container. (SF ¶ 37)

84. Hospira manufactured, sold, and distributed four commercial lots of Hospira's Ampul Product, Nos. 100103A, 100603A, 120303A, and 120853A, prior to the filing date of the '197 Patent. (SF ¶ 39) At testing, each lot had a pH between 2.8 and 3.3, no more than 0.5% adrenalone, and less than 12% d-epinephrine after approximately 24 months, as shown below:

Table 1. Summary data for pH and Epinephrine assay.
(Note: epinephrine assay is the summation of *l*-epinephrine and *d*-epinephrine.)

Sample Name	Expiry	Testing date	pH (Limit 2.2 to 5.0)	Assay (%) (Limit 90.0 to 115.0)
HSP Lot 100103A	10/1/2013	12/13/2013	2.8	101.1
HSP Lot 100603A	10/1/2013	12/13/2013	2.8	100.7
HSP Lot 120303A	12/1/2013	12/13/2013	2.8	100.2
HSP Lot 120853A	12/1/2013	12/13/2013	2.8	100.5

Table 2. Summary data for epinephrine product impurities.
(Note: there is no specification for impurities for the Hospira epinephrine product.)

Sample Name	d-Epi (%)	ESA* (%)	Adrenalone (%)	RRT 0.30 (%)	RRT 0.39 (%)	RRT 0.53 (%)
HSP Lot 100103A	10.5	13.50	0.03	ND	0.06	ND
HSP Lot 100603A	11.4	14.39	0.05	ND	0.11	ND
HSP Lot 120303A	10.4	13.49	0.07	ND	0.13	ND
HSP Lot 120853A	8.9	13.64	0.05	ND	0.08	ND

* ESA: epinephrine sulfonic acid; ND: not detected.

(JTX-34 at 4-5 (Tables 1 and 2 cropped to reflect relevant batch data); SF ¶¶ 37, 52-56; Pinal Tr. at 333-37)

85. Dr. Pinal testified that lot 100103A had less than 6% d-epinephrine at release based on a linear conversion of l-epinephrine to d-epinephrine. (Pinal Tr. at 336-37) For instance, although lot 100103A contained 10.5% d-epinephrine after a 26-month shelf life, it may be presumed that lot 100103A had "roughly half" (5.25%) as much d-epinephrine after 13 months. (*Id.*)

86. Dr. Mohapatra testified that although the combined l- and d-epinephrine in Hospira's Ampul Product comprised 0.2-1.1% overage at the time of testing (i.e., 1.002-1.011 mg/mL epinephrine), if epinephrine sulfuric acid ("ESA") were included, it would be 10-15% overages. (Mohapatra Tr. at 403)

87. Hospira's Ampul Product included sodium chloride as a tonicity agent. (SF ¶ 38; Pinal Tr. at 334; JTX-33)

88. Hospira also tested commercial lots 69-190-DD, 66-555-DD, 60-025-DD, and 57-145-DD of its Ampul Product, which it provided to the FDA. (SF ¶ 57) Lot 69-190-DD was tested after 11 months and contained 4.7% d-epinephrine. (*Id.* ¶ 58) Lot 66-555-DD was tested after 14 months and contained 4.5% d-epinephrine. (*Id.* ¶ 59) Lot-60-025-DD was tested after 20 months and contained 8.3% d-epinephrine. (*Id*. ¶ 60) Since d-epinephrine is expected to increase over time, Hospira's Ampul Product thus contained less than 6% d-epinephrine at release. (*Id.* ¶¶ 58-59; *see also* Pinal 263-64)

89. Hospira's Ampul Product does not expressly teach, nor has it been shown to inherently possess, a concentration of 1.00-1.06 mg/mL l-epinephrine between compounding and release. (Mohapatra Tr. at 402-04)

3. General Knowledge for Purposes of Obviousness

90. In 1986, Kenneth A. Connors et al., CHEMICAL STABILITY OF PHARMACEUTICALS: A HANDBOOK FOR PHARMACISTS 438 (John Wiley & Sons, 2d. ed. 1986) ("Connors"), taught that there is an inverse relationship between racemization and pH, and a proportional relationship between oxidation and pH, for epinephrine formulations. (JTX-37 at 4, 6; Pinal Tr. at 255-56; *see* FF ¶ 34) That is, when pH is decreased, racemization is promoted, and when pH is increased, oxidation is promoted. (JTX-37 at 4, 6) Connors taught that "there is an optimum pH at which racemization and oxidation can be balanced to minimize

loss of intact drug by these two routes; this is approximately pH 3.0-3.8." (JTX-37 at 6; Pinal Tr. at 256) Connors also taught manufacturing conditions that may reduce the risk of oxidation, such as removal of oxygen or packing ampules under nitrogen (JTX-37 at 6; Pinal Tr. at 256), and that epinephrine products may be sterilized by filtration or heating (JTX-37 at 10; Pinal Tr. at 257).

91. In 1990, Fyllingen et al., *Racemisation and oxidation in adrenaline injections*, ACTA PHARM. NORD. 2(5) 355-362 (1990) ("Fyllingen"), published a study on the effects of pH on epinephrine stability. (JTX-41; Pinal Tr. at 257) Fyllingen studied racemization and oxidation of epinephrine by evaluating a large number of commercial products. (Pinal Tr. at 257) Fyllingen noted that "[l]-adrenaline is easily racemized in acidic solutions" (JTX-41 at 1), and that decreased pH or increased temperature lead to increased racemization (*id*. at 7). Fyllingen concluded that racemization is a greater limiting factor than oxidation in epinephrine formulations, and "[t]o improve the shelf-life, raising the pH of the injection somewhat should be considered. The pH in the injections is 2.4, which is supposed to be the pH at which both oxidation and racemization are at a minimum. A rise in pH may increase the oxidation rate, but it would at the same time reduce the racemization rate. In this way, the shelf-life for military storage could possibly be prolonged." (JTX-41 at 7; Pinal Tr. at 258)

92. In 2004, 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) ("Stepensky"), published a study detailing rates of degradation in contemporary epinephrine formulations. (JTX-38 at 1) In particular, Stepensky discussed epinephrine bitartrate formulations having a pH of 3.25-3.70. (*Id*. at 5) The formulations studied contained 5.6% d-epinephrine after two years of storage. (*Id*. at 10) While

epinephrine bitartrate is not the same as l-epinephrine, the '197 Patent covers both forms of epinephrine. (Rubin Tr. at 158, 206)

93. In 2010, Kerddonfak et al., *The Stability and Sterility of Epinephrine Prefilled Syringe*, 28 ASIAN PAC. J. OF ALLERGY AND IMMUNOLOGY 53 (2010), discussed the effect of pH on epinephrine stability. (JTX-39; Pinal Tr. at 257) Kerddonfak conducted a study in which commercial epinephrine products were filled into syringes and observed for a period of three months. (Pinal Tr. at 258) The Kerddonfak study was conducted "under laminar flow hood (sterile technique) and open air." (JTX-39 at 2; Pinal Tr. at 259) Kerddonfak studied formulations where "[t]he pH was 3.17-3.23 (acceptable range 2.8-3.6)" (JTX-39 at 3; *see also* Pinal Tr. at 258-59), and found the product was stable under these conditions (Pinal Tr. at 259).

94. The USP monograph for epinephrine permits injections to have real values between 90% and 115% of the nominal amount of epinephrine claimed on the label. (JTX-42 at 3; Pinal Tr. at 269-70) In other words, a 1 mg/mL formulation meets the USP monograph if it has 0.9-1.15 mg/mL epinephrine. (Pinal Tr. at 269-70; Mohapatra Tr. at 417-18)

95. The International Conference on Harmonisation ("ICH"), an initiative which sets standards for pharmaceutical development, noted in revised guidelines ("ICH Guidelines") issued in August 2009 that "use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged. Any overages . . . should be justified . . . ." (Pinal Tr. at 338-40; DTX-103 at 8) The FDA and U.S. Pharmaceutical Association are part of the ICH conference. (Pinal Tr. at 339)

96. At some point after the ICH Guidelines were released, the FDA began demanding reduced epinephrine overages (or justification for overages) despite historically having allowed overages of up to 15%, as permitted by the USP. (McHugh Tr. at 62-63, 72; X. Zhang Tr. at 79,

89-90; E. Zhang Tr. at 96-97; Rubin Tr. at 148, 150-51; PTX-94A at 3) In one instance, the FDA would not approve the Sintetica Cura Product in part because it had overages the FDA considered to be too high. (J. Taneja Tr. at 121-22; Rubin Tr. at 150-51; M. Taneja Tr. at 211-12)

97. A POSA would have known, at the time of the invention of the '197 Patent,[6] that for l-epinephrine formulations, the concentration of l-epinephrine decreases as it racemizes into d-epinephrine over a reasonable shelf life, and oxidation increases the concentration of adrenalone. (Pinal Tr. at 336; Rubin Tr. at 185-87, 199; Mohapatra Tr. at 54; JTX-101 at 6; JTX-41 at 5) However, it is also possible for a formulation to reach equilibrium, at which point racemization stops, or reverses slightly before reaching a different equilibrium. (Rubin Tr. at 187, 189; JTX-101 at 6)

98. A POSA would have known that both l-epinephrine and d-epinephrine can convert to epinephrine sulfonate ("ESF"). (Mohapatra Tr. at 403)

99. A POSA would have known that temperature impacts degradation/racemization; degradation of l-epinephrine will be faster at higher temperatures, and slower at lower temperatures. (E. Zhang Tr. at 102; DTX-149 at 19)

100. A POSA would have known that pH impacts degradation/racemization; as pH decreases, formation of d-epinephrine increases and ESA decreases (and vice versa). (Pinal Tr. at 258, 341; JTX-41 at 1, 7)

101. A POSA would have known that differences in the concentration of epinephrine in a compounded solution do not necessarily result in a difference in the amount of l-epinephrine

[6] All references to what a POSA would have known or done are directed to the time the invention was made.

in the finished products. (Pinal Tr. at 271) The difference between the concentration after compounding and that of the finished product depends on several factors, such as the sterilization technique. (*Id*.) For instance, a formulation subjected to heat sterilization may lose about 4% l-epinephrine, whereas a formulation sterilized by sterile filtration will not undergo such degradation. (Pinal Tr. at 271-73; *see also* JTX-1 at col. 4 ll. 36-37)

102. A POSA would have expected that changing the concentration of an epinephrine formulation would not substantially impact the relative degradation/racemization rate of epinephrine. (Pinal Tr. at 340-42; *see also* JTX-37 at 4 (describing racemization rate by pH and temperature, not concentration); JTX-149 at 19; JTX-29 at 8)[7] Instead, a POSA would have expected changing concentration to impact primarily the shelf life (i.e., more overages mean more l-epinephrine is available to degrade/racemize before falling below the nominal amount claimed on the label). (*See* Pinal Tr. at 340-41; DTX-103 at 8 (stating overages are used to compensate for degradation "to extend shelf life"); *see also* McHugh Tr. at 61-63; DTX-149 at 19/JTX-193 at 22; J. Taneja Tr. at 135)

103. A POSA would have known she could reduce the epinephrine concentration without modifying other aspects of the formulation. (Pinal Tr. at 339-40) A POSA would have also known that a slight reduction in the concentration of l-epinephrine after compounding would not substantially affect the safety and efficacy of a composition (presuming the same nominal epinephrine concentration). (Pinal Tr. at 343)

[7] JTX-29 does not appear to be prior art, as it is dated December 9, 2016, which is after the filing date of the '197 Patent. Nor has DTX-149 been proven to be prior art, as it is an internal and confidential document produced by Belcher. Dr. Pinal relied upon JTX-29 to "confirm" a general principle (that concentration does not substantially affect the degradation rate), rather than to serve as the basis of an opinion (Pinal Tr. at 340-41), and the Court's finding is appropriately based on that principle.

B. Facts Related to Inventorship

104. Jugal K. Taneja ("Mr. Taneja" or "J. Taneja") is the sole named inventor on the '197 Patent. (J. Taneja Tr. at 125; JTX-1) Mr. Taneja is a businessman, not a scientist. (J. Taneja Tr. at 117-18, 125-26) Mr. Taneja does not have a background in pharmaceutical chemistry or organic chemistry and is not a pharmaceutically-trained individual. (*Id.* at 115-19)

105. Mr. Taneja testified that he suggested to Sintetica using a pH of 2.8-3.3, and that Mihir Taneja and Darren Rubin participated in the discussion. (J. Taneja Tr. at 123-24, 126) Mihir Taneja ("Mihir" or "M. Taneja") has limited recollection of a discussion with his father about whether to use an in-process pH of 2.4-2.6 or 2.8-3.3, but has no recollection of a discussion with anyone else. (M. Taneja Tr. at 214-15) ("I recall my father wanting to adjust the pH after we failed the formulation.") The only basis Mihir had for believing his father was the inventor of the pH modification was because Mr. Taneja told him so. (*Id*. at 216) Mr. Rubin stated that he only had "secondhand information, not firsthand" of any conversation Mr. Taneja had with Sintetica regarding the pH. (Rubin Tr. at 190-91)

X. Facts Related to Inequitable Conduct

A. Rubin's Knowledge

106. Rubin was a consultant for Belcher from 2010 to 2014 and has been Belcher's Chief Science Officer since 2014. (Rubin Tr. at 145-46) Rubin was also referred to as the "head of IP" for Belcher in a 2012 email. (M. Taneja Tr. at 217-18; DTX-173)

107. As Belcher's Chief Science Officer, Rubin's job responsibilities include overseeing Belcher's products at various stages of regulatory approval and development, and helping with IP work, such as patent drafting, prosecution, and litigation. (Rubin Tr. at 146)

108. Rubin is neither a patent attorney nor agent. (*Id.*)

109. Rubin helped draft the ’845 Application, which became the ’197 Patent, including the specification and claims. (Rubin Tr. at 149, 165) He also served as the liaison between Jugal Taneja, Michael Colitz (Belcher’s patent prosecution attorney), and the Patent Office. (*Id.*) As liaison, Rubin “facilitated an office action,” and “project-managed everything. It all led to [him].” (*Id.* at 149-50) On November 3, 2015, Rubin sent a copy of the response to an Office Action concerning the’197 Patent to Vikas Khurana (Belcher’s Chief Medical Officer), Mihir Taneja, Jugal Taneja, and Mandeep Taneja, stating “please find a copy of my response for the epi patent office action that you wanted to see. I dug into case law on this.” (*Id.* at 151-52; JTX-115) On April 21, 2017, Rubin claimed in an e-mail that he “made sure [he got claim 6 of the ’197 Patent] allowed” without a “preservative-free/sulfite-free” limitation. (JTX-120 at 1)

110. Rubin asserts that, by claiming in claim 6 “compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine,” he “meant to say [that there] was no more than 6 percent overage because the whole premise of the patent was to have a product with a low overage and that everything else in the past had a high overage.” (Rubin Tr. at 165)

111. Rubin was involved in the development of Belcher’s epinephrine product. His job responsibilities included “writing new drug applications,” and “[t]he first drug product that [he] got approved was epinephrine.” (Rubin Tr. at 146) Rubin was “a technical writer and [he] was very familiar with the regulatory process with epinephrine.” (*Id*. at 150)

112. Rubin acknowledged that he knew of Sintetica’s epinephrine formulations, which had a pH of 2.8-3.3, which were cited in Belcher’s NDA as an “old” pH. (Rubin Tr. at 152, 193-94; FF ¶ 41) However, according to Rubin, the product Belcher initially submitted for FDA approval had a pH of 2.4-2.6 and high overages. (Rubin Tr. at 152) It was Mr. Taneja that “wanted [Sintetica] to go back up to 2.8 to 3.3 and lower the overage.” (*Id.*) In Rubin’s view,

Sintetica resisted these changes, and recommended other pHs, such as 3.5, and other epinephrine forms such as a bitartrate. (*Id*. at 153)

113. Rubin knew of Stepensky prior to the filing of the '197 Patent. (*Id.* at 175) Stepensky was cited in two of Belcher's FDA responses. (*Id.* at 174-75, 188; JTX-61 at 10 (quoting Stepensky to assert "[r]acemization of the enantiomerically pure L-Epinephrine isomer in injectable formulations of epinephrine is a well-known process"); JTX-63 at 10-11) Rubin also sent an e-mail to Belcher's regulatory consultant quoting portions of Stepensky and providing the reference as an attachment. (Rubin Tr. at 177-78, 202-04; JTX-101 at 1) Specifically, Rubin's e-mail quoted (and emphasized) Stepensky as saying:

> the lowest acceptable limit (90% as a sum of L- and D- isomers) was attained after 2.0 years of storage, whereas the L- adrenaline content in the formulation at that time point was notably lower and equal only to 85%. ***The 5.6% racemization of adrenaline during a 2 -year storage period*** is consistent with the results of previous studies showing 10% racemization into the D- isomer after years of storage at pH 2.4 (Fyllingen 1990) or after 3 years at pH 3.0-3.5 (Aligire 1985).

(JTX-101 at 1; *see also* Rubin Tr. at 174-75, 177)

114. Rubin was unsure if all formulations cited in Stepensky related to epinephrine bitartrate or l-epinephrine, but knew that, at the very least, Stepensky tested equivalents to a 1 mg/mL l-epinephrine product. (Rubin Tr. at 179-80) He also knew the formulations studied in Stepensky included sodium chloride as a tonicity agent. (*Id.* at 180-81; JTX-101 at 4, 6)

115. By October 29, 2013, Rubin possessed the label for JHP's Adrenalin Product. (JTX-98; Rubin Tr. at 181-82) The label taught a 1 mg/mL epinephrine formulation with a pH range of 2.2-5.0, and included sodium chloride as a tonicity agent. (JTX-98 at 9; Rubin Tr. at 182) By January 2014, Rubin also knew that JHP's Adrenalin Product had a shelf life of 18 months. (JTX-105; Rubin Tr. at 183-84)

116. Sintetica tested batch 590839 of JHP's Adrenalin Product, which at that time was about 3 months from expiration and had undergone a 15-month shelf life. (Rubin Tr. at 184) The testing showed batch 590839 had a pH of 2.9, with an adrenalone content of 0.1%. (*Id.*) Rubin understood that the product would have had less than 0.1% adrenalone after release and after 12 months of storage. (*Id.*) He also understood that Batch 590839 had a d-epinephrine concentration of 5.16% after 15 months. (*Id.* at 185)

117. Rubin also knew of Sintetica's prior epinephrine products (batches 03166-68) that were included in Belcher's NDA, which had a pH of approximately 3.0 and undetectable levels of adrenalone over 12 months. (*Id.* at 169-71, 193-94; *see* JTX-59 at 27-29; FF ¶ 40)

118. Rubin may also have known of the existence of Fyllingen as of November 7, 2013, as it was cited as part of Stepensky in Rubin's e-mail. (Rubin Tr. at 177; JTX-101 at 1; *but see* Rubin Tr. at 204 (stating he did not "have Fyllingen in my possession until this litigation"))

119. Rubin was aware of, but did not disclose to Belcher's prosecuting attorney or the Patent Office, the Stepensky reference, the JHP Adrenalin Product, and Sintetica's epinephrine products. (Rubin Tr. at 197-99) Rubin testified he considered the references "irrelevant" because they were either not directed to l-epinephrine or contained "high" overages. (*Id.* at 157-62, 190, 192, 197-99, 206-07)

120. Stepensky, the JHP Adrenalin product, and/or Sintetica's epinephrine products are but-for material to the patentability of the '197 Patent. (Pinal Tr. at 230-31, 352-53)

B. Statements Made to the Patent Office

121. The '845 Application specification submitted to the Patent Office stated:

> Producing an epinephrine drug product with a high l-epinephrine content, such as greater than 90%, throughout its shelf-life of over one year seemed impossible in a preservative-free, sulfite-free

> solution, and had never been accomplished before. Increasing overages above 10% was not a viable solution. . . . The thought of ***raising the in-process pH above the 2.2-2.6*** of previous methods, and allowing for additional oxidation in an antioxidant-free solution, ***was contradictory to one skilled in the art***.

(JTX-2 at 19-20 (emphasis added); Rubin Tr. at 191-92) At the time this application was submitted, Rubin knew that Sintetica had previously produced a preservative-free formulation with a pH of 2.8 to 3.3 – and he also knew that formulation had high overages. (Rubin Tr. at 192-94)

122. The application specification also stated:

> Inadvertently, ***increasing the in-process pH to 2.8-3.3, unexpectedly reduced the racemization*** of l-epinephrine to d-epinephrine at release by approximately two-thirds, from 14% to 5%, respectively. To the contrary, these results led to the discovery that in a preservative-free, sulfite-free, l-epinephrine solution, racemization was a more significant problem than expected, even more so than oxidation. This discovery led to new methods of manufacturing sulfite-free, l-epinephrine solution with an in-process pH of 2.8 to 3.3, approximately 3.0, ***which was a nonobvious solution to the problem of racemization***. Most importantly, with these new methods, overages could greatly be reduced.

(JTX-2 at 20 (emphasis added); Rubin Tr. at 191-92) At the time the application was submitted, Rubin knew that Sintetica had previously produced a preservative-free formulation with a pH of 2.8 to 3.3 – and he also knew that formulation had high overages. (Rubin Tr. at 192-94)

123. During prosecution, the examiner rejected the claims over Canadian Patent Application No. 2002643A ("Helenek"), which taught an epinephrine formulation with a pH of 2.2-5.0. (JTX-2 at 40-41; Rubin Tr. at 194) Belcher responded (and Rubin agreed): "Helenek et al. also does not make obvious the Applicant's ***pH range of 2.8 and 3.3, which was unexpectedly found to be critical by the Applicant*** to reduce the racemization of 1-epinephrine," as Helenek provides several examples with pHs varying widely from 2.2 to 7.1. (JTX-2 at 71-72

(emphasis added); Rubin Tr. at 194-95) At the time this statement was made to the PTO, Rubin knew about both Stepensky and the JHP Adrenalin Product, both of which taught a pH in the range of 2.8 to 3.3. (FF ¶¶ 113-16)

124. In the Notice of Allowance, the Examiner wrote: "The claims are allowable over the closest cited prior art, Helen[e]k et al. in view of Gherzghiher et al., because the cited prior art does not teach, disclose, nor render obvious[] the instantly claimed liquid pharmaceutical formulations of 1 mg per mL l-epinephrine ***in view of Applicant's demonstration of criticality of a pH range between 2.8 and 3.3***." (JTX-2 at 86 (emphasis added); *see also* Rubin Tr. at 196) The Examiner concluded: "Thus, there [is] nothing in the prior art that would teach or suggest the instantly claimed pH range of between 2.8 and 3.3 would result in the limited racemization and impurities as instantly claimed." (JTX-2 at 86; *see also* Rubin Tr. at 196-97) There is no express reference to overage in the Examiner's reasons for allowance. (Rubin Tr. at 197)

LEGAL STANDARDS

I. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in deciding infringement. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly-construed claims to the accused infringing product. *See id.* If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a [dependent] claim." *Id.* at 1552.

The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). A patent owner may prove infringement under two theories: literal infringement or the doctrine of equivalents. Literal infringement occurs when "every limitation in a patent claim is found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal JG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). Infringement under the doctrine of equivalents occurs when the accused product embodies every element of a claim either literally or by an equivalent. *See id.* This doctrine "allows the patentee to claim insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002).

II. Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original). A defendant's burden to prove invalidity based on prior art (e.g., anticipation or obviousness) is "especially difficult when the prior art [on which it relies] was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lamb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

III. Anticipation

A claim is anticipated under 35 U.S.C. § 102(a)(1) if "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to

the public before the effective filing date of the claimed invention." For a patent claim to be invalid due to anticipation, each and every limitation must be found, either expressly or inherently, in a single prior art reference. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Whether a claim is anticipated is a question of fact. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006).

IV. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (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 considerations of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal citation and quotation marks omitted); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007).

Obviousness determinations cannot rely on hindsight. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon ex post reasoning"). To protect against the improper use of hindsight in a determination that an invention would have been obvious, the Court is required to consider objective (or "secondary") considerations of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g.*, *Leo Pharm. Prods., Ltd v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Objective considerations "may often be the most probative and cogent evidence in the record" relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

DISCUSSION

I. Infringement

Belcher seeks judgment that Hospira's NDA Product infringes claims 6 and 7 of the '197 Patent under the doctrine of equivalents ("DOE"). (D.I. 222 at 5-10) Belcher has failed to prove infringement.

A. Doctrine of Equivalents

The Supreme Court has explained that 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., Ltd.*, 535 U.S. 722, 732 (2002). Two frameworks are available for application of DOE: (1) the "function-way-result test," which asks whether the accused product performs "'substantially the same function in substantially the same way to obtain the same result'" as the patented invention; and (2) the "insubstantial differences test," which asks "whether the accused product or process is substantially different from what is patented." *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 866-67 (Fed. Cir. 2017) (quoting *Graver Tank & Manufacturing Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950)).

"[T]he 'all elements' rule informs a DOE analysis by requiring that equivalence be assessed on a limitation-by-limitation basis, rather than from the perspective of the invention as a whole, and that no limitation be read completely out of the claim." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1017 (Fed. Cir. 2006). A determination of infringement under the doctrine of equivalents is a question of fact. *See Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009).

But the DOE analysis does not stop there, for the ensnarement doctrine works to limit the breadth of DOE. Under the ensnarement doctrine, the patentee may not assert "a scope of equivalency that would encompass, or ensnare, the prior art." *DePuy Spine*, 567 F.3d at 1322 (internal quotation marks omitted); *see also Tate Access Floors v. Interface Architectural Res.*, 279 F.3d 1357, 1366-67 (Fed. Cir. 2002) (noting there can be no infringement under DOE when practicing prior art). "Hypothetical claim analysis is a practical method to determine whether an equivalent would impermissibly ensnare the prior art." *Intendis GMBH v. Glenmark Pharm. Inc., USA*, 822 F.3d 1355, 1363 (Fed. Cir. 2016). This is a two-step process. "The first step is to construct a hypothetical claim that literally covers the accused device. Next, prior art introduced by the accused infringer is assessed to determine whether the patentee has carried its burden of persuading the court that the hypothetical claim is patentable over the prior art." *Id*. (internal citations and quotation marks omitted). "In short, [the Court] ask[s] if a hypothetical claim can be crafted, which contains both the literal claim scope and the accused device, without ensnaring the prior art." *Id*.

B. Analysis

The parties agree that only one claim limitation is at issue and, thus, "[t]he only dispute is whether Hospira's [0.1 mg/mL] NDA Product is equivalent to a formulation 'compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine.'" (D.I. 222 at 5) (quoting '197 Patent)

Belcher argues the two are equivalent because both are intended to use low (0-6%) overages and to deliver the same total amount (1 mg) of epinephrine to a patient. (*See id*.) Hospira responds that the claims are directed to concentrations, not overages or amounts, and the concentrations of the claim and the Hospira NDA Product are, indisputably, not equivalent. (D.I. 232 at 4-5) The Court agrees with Hospira.

Central to the parties' dispute is whether the Court, in applying DOE, should look to the claimed concentration itself, or the intended purpose of that concentration. (*Compare* D.I. 222 at 6 (Belcher arguing function of Hospira's infringing concentration is "to achieve a product as close as possible to the desired label claim by using an overage between 0-6%") *with* D.I. 232 at 6 (Hospira arguing "function of the claimed concentration range in the compounded solution is to achieve a 1 mg/mL final product")) In the Court's view, the all-elements rule mandates that the Court look only at the claimed concentration – "compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine" (JTX-1 at cl. 6) – and not the intended overage, amount, or use of the formulation as a whole, ***as none of those features are claimed***. *See DePuy Spine*, 469 F.3d at 1017.

The disputed claim limitation is directed to concentration, so to prove infringement Belcher was required to prove that the accused product practices the claimed concentration, either literally or by equivalents. Having failed to do so, the Court cannot find infringement.

Belcher's desire to look past the text of the claims is improper, as it would essentially require redrafting or reading additional limitations into the claims. DOE does not provide Belcher that opportunity. *See Streamfeeder, LLC v. Sure-Feed Sys., Inc.*, 175 F.3d 974, 983 (Fed. Cir. 1999) (stating DOE analysis "is not an opportunity to freely redraft granted claims"); *see also Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999)

("[The Court] must construe the claims based on the patentee's version of the claim as he himself drafted it."). Although the specification provides an example of a 1 mL, 1 mg, low-overage epinephrine product (JTX-1 at col. 5, ll. 4-26), the claims as written might cover ***any amount*** (or volume)[8] of l-epinephrine at ***any overage***, so long as the formulation has a particular concentration. (JTX-1 at cls. 6, 7; *see also* Mohapatra Tr. at 324-25 (conceding that example with 15% overage would literally infringe claim 6); *i4i Ltd. Partn. v. Microsoft Corp.*, 598 F.3d 831, 843 (Fed. Cir. 2010), *aff'd*, 564 U.S. 91 (2011) (stating claims not limited to embodiments in specification unless "clear intention to limit the claim's scope") (internal quotation marks omitted)) Those involved in prosecuting the '197 Patent knew that concentration is not the same as amount, volume, or overage, yet they chose to claim (in the disputed limitation) by concentration. (*See, e.g.*, JTX-2 at cols. 3-4 (discussing overages, volumes, amounts, and concentrations separately and accurately); col. 5, ll. 36-41 (noting that while formulation "can be produced having any desirable concentration . . . they are preferably compounded [at] 1.0 to 1.06 mg/mL"); *see also Iridescent Networks, Inc. v. AT&T Mobility, LLC*, 933 F.3d 1345, 1352 (Fed. Cir. 2019) ("The written description demonstrates that the inventor knew how to describe [an unclaimed feature].")

Throughout its post-trial briefing and proposed findings of fact (*see* D.I. 222 at 5-10; D.I. 231 at ¶¶ 29-36, 43-44), Belcher repeatedly emphasizes the specification's focus on low overages, and Hospira's representations to the FDA that the Belcher and Hospira NDA Products are equivalent. Belcher particularly draws attention to the testimony of Hospira's McHugh, who testified (and represented to the FDA) that the two NDA Products are "quantitative and

[8] Belcher relies on the "filling step" to read a 1 mg ***amount*** (as compared to concentration) of l-epinephrine into the claim. (D.I. 222 at 4, 9-10) The Court is unpersuaded; the claims do not recite any specific filling volume from which a total amount of l-epinephrine could be derived.

qualitative equivalen[ts]." (McHugh Tr. at 62) But, as already explained, the DOE analysis is not performed at the high level Belcher envisions. One does not prove infringement by pointing to general characteristics, or even bioequivalency, between two products, or even between claims and an accused product. *See Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476 (Fed. Cir. 1984) ("Infringement is not determined . . . by comparison between commercial products sold by the parties."). Instead, the analysis proceeds claim by claim, and here Belcher has failed to show that the Hospira NDA Product practices (even by equivalence) the concentration limitation. It is immaterial if the commercial embodiments share similar overages or total amounts of l-epinephrine, since those aspects of the commercial embodiments are not captured by the claims.

The '197 Patent is, at its core, directed at a formulation with a specific and narrow concentration range, which Hospira's Product is substantially (i.e., ten-fold) below. (JTX-2 at 66; D.I. 232 at 6; FF ¶ 59) Throughout the entire Patent, that range is provided for one reason: to produce a formulation with a specific ***concentration*** of 1 mg/mL l-epinephrine. (*See generally* JTX-1; *see also* JTX-2 at 66 (noting claim 6 is directed to a "narrow concentration range . . . to result in a drug product of 1 mg/mL epinephrine"); FF ¶ 59; SF ¶ 14 (stating in Office Action response that "[t]he importance of the current invention is that the concentration of 1 mg per mL l-epinephrine is maintained as best as possible")) Belcher has provided no evidence (let alone a preponderance of the evidence) that l-epinephrine concentrations of 0.1 mg/mL and 1.0 mg/mL are equivalent under either DOE framework. (FF ¶¶ 58-60, 64)

Even if the Court were to find equivalency, any properly-construed hypothetical claim would ensnare the prior art. Belcher proffers two alternative hypothetical claims for the ensnarement analysis: (1) the concentration of claim 6 would state "0.1-0.106 mg/mL" (in other words, allowing up to a 6% overage to a 0.1 mg/mL formulation); or (2) the concentration

limitation is replaced entirely with "having an overage between 0-6%." (FF ¶ 68) Hospira offers its own hypothetical claim, in which the concentration of claim 6 would state: "0.10-1.06 mg/mL." (FF ¶ 69) The Court will adopt Hospira's proposed claim.

Belcher's hypothetical claims fail for two reasons. First, they improperly attempt to substantially redraft the claims. Belcher cannot use DOE to import a specific overage or amount limitation when it failed to include any such limitations during the Patent's prosecution. *See Streamfeeder*, 175 F.3d at 983. Second, Belcher's hypothetical claims fail to encompass "both the literal claim scope ***and*** the accused device." *Intendis*, 822 F.3d at 1363 (emphasis added); *see also Abbott Laboratories v. Dey, L.P.*, 287 F.3d 1097, 1100, 1105 (Fed. Cir. 2002) (finding claimed range of 68.6-90.7% and accused product of 94.5% results in a hypothetical claim covering 68.6-94.5%); *Merck & Co., Inc. v. Mylan Pharm., Inc.*, 19 F. Supp. 2d 334, 343 (E.D. Pa. 1998), *aff'd*, 190 F.3d 1335 (Fed. Cir. 1999) ("Because Merck's formulation has 5-25 mg of HPC and Mylan's generic uses 29.3 mg of HPC, the hypothetical must cover a range of 5-29.3 mg of HPC"). Belcher's first option (0.1-0.106 mg/mL) does not include the claimed range (1.0 to 1.06 mg/mL). Belcher's second option (0-6% overage) does not include ***any*** concentration range; instead, it requires reference to an unclaimed (and likely unknown) desired (e.g., label) amount of drug, with respect to which overages are calculated. Belcher has failed to meet its burden to articulate an appropriate hypothetical claim, so its infringement claims must be denied for this reason as well.

Hospira has presented an acceptable hypothetical claim, as its proposal covers both the accused product and claimed invention. A further deficiency in Belcher's proof is that Hospira's claim also ensnares at least Hospira's prior art Abboject Product. (FF ¶¶ 70-71) Hospira has met its burden on this point. Belcher does not really dispute these facts, instead opting to attack

the appropriateness of Hospira's hypothetical claim and challenging the prior art on other grounds, none of which is persuasive.[9]

For all of these reasons, Belcher has failed to prove, by a preponderance of the evidence, that Hospira's NDC Product infringes claim 6 of the '197 patent under the doctrine of equivalents. Because Belcher has not proven infringement of independent claim 6, it also cannot prove infringement of dependent claim 7. Accordingly, judgment of non-infringement will be entered for Hospira.

II. Invalidity

Hospira seeks to invalidate claims 6 and 7 of the '197 Patent on three independent bases: (1) the prior art anticipates the claims; (2) the prior art renders the claims obvious; and (3) the Patent fails to list all of the correct inventors. (D.I. 225 at 4-17) Hospira has failed to meet its burden of clear and convincing evidence with respect to anticipation, but has proven that the prior art renders claims 6 and 7 obvious and that the '197 Patent is invalid for improper inventorship.

A. Anticipation

Hospira argues the '197 Patent is invalid based on two pieces of anticipatory prior art: (1) JHP's Adrenalin Product; and (2) Hospira's Ampul Product. (D.I. 225 at 4-11) Belcher

[9] Belcher argues Hospira's hypothetical claim "vitiate[s] the role" of limitations in claim 6, as it would cover overages from 0-1060%. (D.I. 222 at 11-12) As has already been discussed repeatedly, claim 6 concerns a specific concentration range, not overages. Thus, there is no vitiation. Belcher also argues that the Abboject prior art, with its 10% overage, would have been rejected by the FDA and, thus, does not meet an inherent "medicinal use" limitation. (D.I. 222 at 13-14; D.I. 235 at 16-20) Nothing in the record suggests that an inherent "medicinal use" limitation means "FDA approval" (nor did Belcher propose such a construction during any of the claim construction proceedings), so the Court rejects Belcher's contention. (*See* D.I. 232 at 26 n.2) Lastly, Belcher attacks Bruss because it does not disclose the compounding concentration or post-release stability (D.I. 222 at 14), but these arguments, too, are unpersuasive (*see* D.I. 232 at 27).

contends that neither is prior art, and both have overages 0-6% (which is how Belcher reads the 1.0 to 1.06 mg/mL concentration limitation). (D.I. 230 at 8-11) The Court concludes that the Ampul and Adrenalin Products (hereinafter collectively referred to as the "Products") are prior art, but do not anticipate the claimed invention.

Prior to trial, Belcher and Hospira stipulated that the Products are prior art. (*See* SF ¶¶ 62, 103) Belcher now seeks to escape from these stipulations, contending they were "legal conclusions, not facts" and that, at trial, Hospira's Dr. Pinal opened the door to second-guessing the Products' prior art status. (D.I. 230 at 9-10) Despite being publicly sold, Belcher argues that the Products are prior art because their manufacturing instructions were not public, they are not available for purchase today, and Hospira did not show that "one highly skilled in the art" tested the Products' properties. (D.I. 230 at 10-11)

The Court sees no reason why Belcher should be relieved of its stipulations. *See Waldorf v. Shuta*, 142 F.3d 601, 610, 616 (3d Cir. 1998) ("Allowing parties easily to set aside or modify stipulations would defeat this purpose, wasting judicial resources and undermining future confidence in such agreements. Thus, it is a well-recognized rule of law that valid stipulations entered into freely and fairly, and approved by the court, should not be lightly set aside."). In any event, Belcher's challenges to the prior art status of the Products are baseless. Even if the Court were to consider Belcher's arguments, the unrestricted sale of the Ampul and Adrenalin Products renders both prior art. *See Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1570 (Fed. Cir. 1997) (finding public sale constitutes prior art, even if not enabling or certain parts of invention undisclosed); *see also Pronova Biopharma Norge AS v. Teva Pharm. USA, Inc.*, 549 F. App'x 934, 943 (Fed. Cir. 2013) ("Where, as here, . . . a compound is provided without restriction to one highly skilled in the art, that compound's formulation is disclosed in detail, and

the formulation subject to confirmatory testing, no other activity is needed to render that use an invalidating one."); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."). Belcher cannot now credibly argue that Hospira's proof of the Products' prior art status was deficient in light of Belcher's own stipulations. (D.I. 236 at 2-3)

Nevertheless, neither JHP's Adrenalin Product nor Hospira's Ampul Product anticipates the claimed invention, as neither teaches a "formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine."[10] '197 Patent, cl. 6. The Court construed this limitation as a product-by-process limitation (*see* D.I. 204), which means that, "[f]or validity purposes, the 'invention' . . . is the product." *Medicines Co. v. Hospira, Inc.*, 827 F.3d 1363, 1374 (Fed. Cir. 2016).[11]

Hospira argues there are no structural differences between the claimed invention and JHP's Adrenalin Product or Hospira's Ampul Product, as all constitute a 1 mg/mL epinephrine product according to the USP. (D.I. 225 at 7-8, 10-11) The test for anticipation, however, is not

[10] Both Products teach every other claim limitation. (*See* FF ¶¶ 75-79, 82-85, 87, 88) The only other limitation even open to dispute is the level of d-epinephrine of the Ampul Product at release, which Dr. Pinal estimated. (FF ¶ 85) However, Belcher does not contest anticipation of the d-epinephrine limitation. (*See, e.g.*, D.I. 230 at 8-13; D.I. 231 at ¶¶ 74-77) (challenging only status as prior art and anticipation of compounding limitation))

[11] Hospira points to *Amgen v. F. Hoffman-La Roche Ltd.*, 589 F.3d 1340, 1370 (Fed. Cir. 2009), for the proposition that a "product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitations," and, therefore, JHP's 1mg/mL epinephrine formulation necessarily anticipates claims 6 and 7. (*See* D.I. 225 at 6-7) While the Court generally agrees that an old product is not patentable even if it is made by a new process, this principle does not eliminate the relevance of non-anticipatory material evidence of structural/functional differences attributable to the process. *See Amgen*, 589 F.3d at 1370.

whether two substantially similar (but not necessarily identical) structures can be used for the same purpose and in compliance with some standard (such as the USP). Rather, the Court looks only at whether the prior art references anticipate the structure that would result from the claimed process. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006) ("If those product-by-process claims produced a different product than that disclosed by the [prior art] patent, there would be an argument that the [prior art] patent disclosure did not anticipate.").

To anticipate the claimed invention, the prior art must have a post-compounding l-epinephrine concentration between 1.0 and 1.06 mg/mL. This does not mean at ***any*** time after compounding (like Hospira's Ampul Product, which arguably had 1.002-1.01 mg/mL l-epinephrine at testing, FF ¶¶ 84, 86), but some time relatively immediately thereafter. For if the concentration soon after compounding were any higher than that claimed, a structural difference would exist – that is, a larger initial quantity of l-epinephrine (assuming constant volume). The purported prior art and claimed invention would, in effect, have different starting points from which they would degrade, which would produce different expected shelf-lives. (*See* FF ¶ 102) The Products have higher post-compounding overages and concentrations (e.g., 1.095-1.134 mg/mL for JHP's Adrenalin Product and approximately 1.1 mg/mL for Hospira's Ampul Product) than the claimed invention (*see* FF ¶¶ 77, 84; D.I. 225 at 7-8, 10-11).[12] This structural difference precludes a finding of anticipation.

[12] It appears undisputed that JHP's Adrenalin Product has an overage between 9.5 and 13.4% (FF ¶ 80), but the record contains no similarly clear number for Hospira's Ampul Product. While Hospira provided data showing overages ranging from 0.2-1.1%, that was at the time of testing, not post-compounding. (FF ¶¶ 84, 86) Belcher argued the Ampul Product was compounded with a 10% overage, but mistakenly cited to Hospira's 0.1 mg/mL Abboject Product. (*See* D.I. 231 ¶ 77) (citing McHugh Tr. at 60) Neither Dr. Mohapatra's (Mohapatra Tr.

B. Obviousness of the '197 Patent

While neither JHP's Adrenalin Product nor Hospira's Ampul Product anticipate the claims due to their higher post-compounding concentrations, it would have been obvious to a POSA to reduce those Products' overages (and, thereby, their concentrations) in light of the ICH Guidelines and general knowledge (as represented by Connors, Stepensky, Fyllingen, and/or Kerddonfak).

The record shows that the FDA historically approved (or permitted through grandfathering) the sale of epinephrine products that complied with the USP monograph, which set the upper limit on overages at 15%. (FF ¶ 94; Rubin Tr. at 161; Pinal Tr. at 269-71; *see also, e.g.*, FF ¶¶ 75, 80) At some point, however, the FDA began rejecting products that were otherwise USP-compliant, and demanded justifications for overages in accordance with ICH Guidelines. (FF ¶¶ 95-96; *see also, e.g.*, FF ¶ 42)

Due to the FDA's enforcement of the ICH Guidelines, a POSA would have been motivated to minimize the overage in any epinephrine product in order to obtain FDA approval. A POSA would have known that reducing overages would not negatively impact other relevant properties, such as racemization rate or safety. (FF ¶¶ 102-03) Instead, as a POSA would know, reducing overages would predominantly impact shelf life, for there would be less epinephrine available to oxidize or racemize before reaching the 90% floor set by the USP.[13] (*Id.*; *see also* McHugh Tr. at 61 ("So typically the overage is there to promote shelf life."); *id*. at 63) Both

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at 403; *see also* D.I. 230 at 12 (highlighting ESA in table) nor Dr. Pinal's (*see* D.I. 225 at 8) opinions on this point were persuasive.

[13] It does not appear that the ICH Guidelines impacted the permissible floor set by the USP. (*See generally* DTX-103; *see also* Mohapatra Tr. at 404 ("[T]hey are looking at not ICH guideline alone, they're looking at what's USP guideline."))

JHP's Adrenalin Product and Hospira's Ampul Product had ample shelf life to spare. (*See* FF ¶¶ 75, 84 (showing JHP's allowable[14] shelf life at 18 months, and Hospira's near-allowable shelf life at 24 months, compared to claimed 12 months); McHugh Tr. at 63 (stating 12-month shelf life is minimum for commercial viability)) For these reasons, it would have been obvious to minimize the approximately 10-15% overages of the Products, including to between 0 and 6%, while balancing allowable shelf life. That, in turn, means it would have been obvious to compound JHP's Adrenalin Product or Hospira's Ampul Product at 1.0-1.06 mg/mL to produce a 1 mg/mL product, in accordance with the ICH Guidelines. A POSA would have had a reasonable expectation of success in pursuing this obvious modification of one or both of the Products. (*See* Pinal Tr. at 230, 338-41)

As for secondary considerations of nonobviousness, Belcher has failed to show that its NDA Product (which is an embodiment of claims 6 and 7 of the '197 Patent) is an unexpected solution to a long-felt need for preservative-free, low-overage epinephrine products. It is, instead, an obvious and inevitable response to FDA policy.[15] That policy, which was applied industry-wide, demanded a reduction in overages, or a justification for such overages, in epinephrine products. This at least partially explains why Belcher's NDA Product and '197

[14] By "allowable," the Court refers to the limits of l-epinephrine, d-epinephrine, and adrenalone of claims 6 and 7.

[15] Belcher points out in its nonobvious arguments that the ICH Guidelines came out in 2009, JHP's Adrenalin Product was approved in 2012, and Hospira did not know of the FDA's position on overages until 2015. (D.I. 230 at 14) Thus, Belcher continues, if it were obvious to reduce overages, Hospira would have done so in 2015, without the FDA's direction. (*Id*.) The obviousness inquiry, however, does not look at the invention from Hospira's point-of-view but from that of a POSA, who is presumed to have known exactly when the FDA began rejecting high-overage epinephrine formulations, and would thereafter have been motivated to reduce overages. This conclusion is corroborated by Belcher's actual experience of initially seeking overages of 10-15% until directed otherwise by the FDA. (FF ¶¶ 41, 42)

Patent were able to be conceived by Mr. Taneja, who, by his own admission, does not possess any skill or experience in drug formulation and (the Court finds) does not meet the definition of a POSA. Belcher's contention that the prior art taught away from the claimed invention is also unavailing, as it is based entirely on its own internal deliberations and communications with Sintetica, which would not have been available to the public or, therefore, considered by a POSA.

For these reasons, the Court is persuaded by clear and convincing evidence that claims 6 and 7 of the '197 Patent are invalid as being obvious in view of either JHP's Adrenalin Product or Hospira's Ampul Product, combined with the ICH Guidelines and general knowledge.

C. Improper Inventorship

Under 35 U.S.C. § 102(f), one cannot obtain a valid patent if "he did not himself invent the subject matter sought to be patented." This provision requires that a patent accurately name the correct inventors of a claimed invention. *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1349 (Fed. Cir. 1998); *see also* 35 U.S.C. § 101 ("***Whoever*** invents . . . may obtain a patent."); 35 U.S.C. § 115 ("An application for patent . . . shall include . . . the name of the inventor."). "Determining 'inventorship' is nothing more than determining who conceived the subject matter at issue, whether that subject matter is recited in a claim in an application or in a count in an interference." *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994). Conception is a question of law premised on underlying factual findings. *See In re VerHoef*, 888 F.3d 1362, 1365 (Fed. Cir. 2018). "If nonjoinder of an actual inventor is proved by clear and convincing evidence, a patent is rendered invalid." *Pannu*, 155 F.3d at 1349.

In this case, Hospira contends that Mr. Taneja – the sole named inventor – "neither conceived of nor reduced to practice the alleged invention of the '197 Patent," as his sole contribution was to suggest a pH of between 2.8 and 3.3, which was known in the prior art. (D.I.

225 at 15) The Court agrees. Hospira has proven by clear and convincing evidence that Mr. Taneja is not properly named as an inventor of the '197 Patent.

Before explaining why the Court has reached this conclusion, the Court first notes that it is ***not*** because of Mr. Taneja's relative lack of technical experience: he is a CEO, not a scientist, who directed others to test his general hypotheses. (D.I. 255 at 15-16) As Hospira readily concedes, epinephrine products are extremely old and well-known in the art, and the relative properties of its formulations are substantially predictable. (FF ¶¶ 30-34, 90-93) Given these circumstances, it is not a necessary condition for the inventor of an epinephrine product to possess all of the skills of an advanced pharmaceutical formulator. Nor does the law require that the inventor actually reduce the invention to practice. *See In re DeBaun*, 687 F.2d 459, 463 (CCPA 1982) ("[T]here is no requirement that the inventor be the one to reduce the invention to practice so long as the reduction to practice was done on his behalf."). There is nothing *per se* improper about the prospect of Mr. Taneja being the sole inventor, even if he only made high-level judgment calls and directed Sintetica's scientific teams to create the formulation on his behalf.

Nonetheless, Hospira has proven, by clear and convincing evidence, that Mr. Taneja is an improper inventor because he only contributed the idea for the pH limitation, and nothing else. As Mr. Taneja testified:

> I was the person who was making decisions on every step, working with . . . Sintetica; and when we got from the FDA some hints [to lower our overages], we sat down with our scientific team and started discussion. And at that time I came up with some ideas to let's try a different approach and use the 2.8 to 3.3 pH and see what kind of results we [get] . . . .

(Taneja Tr. at 123-24; *see also* Rubin Tr. at 152 ("Mr. Taneja wanted them to go back up to 2.8 to 3.3 and lower the overage.")) While the burden to prove invalidity always rests with Hospira,

Hospira's arguments do not improperly shift the burden to Belcher by simply pointing out that there is no evidence – even from the purported inventor himself – that Mr. Taneja conceived of any other limitation of claim 6 or 7. Further, and importantly, the record is devoid of reliable corroborating evidence to support Mr. Taneja's claim that he conceived of the pH range limitation and communicated it to Sintetica. *See generally Apator Miitors ApS v. Kamstrup A/*S, 887 F.3d 1293, 1295 (Fed. Cir. 2018) ("It is well established . . . that when a party seeks to prove conception through an inventor's testimony the party must proffer evidence, in addition to [the inventor's] own statements and documents, corroborating the inventor's testimony.") (internal quotation marks omitted). No documentary evidence to corroborate Mr. Taneja's claim was introduced. (*See* Taneja Tr. at 123-24) Both Mr. Rubin and Manir Taneja testified that they had only second-hand information – i.e., Mr. Jugal Taneja's statement – that Jugal Taneja conceived of and communicated the claimed pH range. (*See* Rubin Tr. at 190-91; M. Taneja Tr. at 216) "[T]he inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). The record here on this point is lacking.

Additionally, as Mr. Taneja himself testified, he was aware that "[a]s early as 2003 Sintetica manufactured 1 milligram per milliliter epinephrine products having a pH in the range of 2.8 to 3.3," so in fact even he recognized that he was not the first to conceive of using the claimed pH range in epinephrine formulations. (Taneja Tr. at 127)

Even if all of this were incorrect, and even taking Mr. Taneja's testimony in the best possible light, all he had was a "hope, or wish" that his pH would be successful, which is insufficient to constitute conception. *See Hitzeman v. Rutter*, 243 F.3d 1345, 1356-57 (Fed. Cir. 2001) ("[T]he critical deficiency is that [the alleged inventor] specifically claimed the result of a

biological process . . . with no more than a hope, or wish, that yeast would perform this assembly process that had never before been achieved in yeast. Such a bare hope is insufficient to establish conception."). Mr. Taneja's account is that he "sat down with [the] scientific team" and proposed a "different approach," that is to "use the 2.8 to 3.3 pH and see what kind of result we can get." (Taneja Tr. at 123-24) This is not conception, which requires more than "just a general goal or research plan," and instead requires a "definite and permanent idea of an operative invention, including ***every feature*** of the subject matter to be patented." *In re VerHoef*, 888 F.3d 1362, 1366 (Fed. Cir. 2018) (internal quotation marks omitted).

III. Unenforceability of the '197 Patent

Hospira has proven, by clear and convincing evidence, that the '197 Patent is unenforceable because Mr. Rubin purposefully withheld "but-for" material prior art from the Patent Office and did so with the requisite intent. (D.I. 225 at 17-24)

A. Inequitable Conduct

"Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent." *Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011). To prevail on a claim of inequitable conduct, the accused infringer must prove by clear and convincing evidence that the patentee: (1) "acted with the specific intent to deceive the PTO" and (2) made a material misrepresentation or omission. *Id.* at 1290 (Fed. Cir. 2011). "In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant ***made a deliberate decision*** to withhold a ***known*** material reference." *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1181 (Fed. Cir. 1995)

"Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence. However, to meet the clear and convincing evidence standard, the specific intent to deceive must be 'the single most reasonable inference able to be

drawn from the evidence.'" *Therasense*, 649 F.3d at 1290 (quoting *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008)). When the evidence may support multiple reasonable inferences, it cannot result in a finding of deceptive intent. *Id*. "Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive." *Id*.

For a misrepresentation or omission to be "material," it must be "but-for" material. *Therasense*, 649 F.3d at 1290. That is, the accused infringer must prove that "the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id*. The Court must, therefore, "determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference," applying the preponderance of the evidence standard and giving the claims their broadest reasonable interpretation. *Id*. at 1291-92. Patentability determinations may be congruent with validity; that is, in a particular case, if the claim has been invalidated by the Court based on a reference the Court finds was deliberately withheld from the PTO, that reference is necessarily material, as the Court applies a higher evidentiary burden for validity than the PTO does for patentability. *See id*. at 1292. Ultimately, however, unenforceability due to a material misrepresentation or omission is an equitable remedy and "should only be applied in instances where the patentee's misconduct resulted in the unfair benefit of receiving an unwarranted claim." *Id*.; *see also Star*, 537 F.3d at 1366 ("Just as it is inequitable to permit a patentee who obtained his patent through deliberate misrepresentations or omissions of material information to enforce the patent against others, it is also inequitable to strike down an entire patent where the patentee committed only minor missteps or acted with minimal culpability.").

B. Analysis

As Chief Scientific Officer of Belcher and an active participant in the prosecution of the '197 Patent, Mr. Rubin owed a duty of candor and good faith to the Patent Office. (*See* FF

¶¶ 106-108) (finding Rubin wrote parts of '845 Application (leading '197 Patent) and served as liaison between Mr. Taneja and prosecution attorney, Mr. Colitz); *see also Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995) (discussing duty of candor and good faith). That includes the duty to inform the Patent Office of any information material to patentability. *See id.*; *see also* 37 C.F.R. § 1.56(a) ("Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section."); 37 C.F.R. § 1.56(c)(3).

Despite this duty, Rubin admits that he withheld information from Belcher's patent prosecution attorney and the Patent Office, including Stepensky, JHP's Adrenalin Product, and the 2003 Sintetica Products,[16] at least some of which the Court has found to be but-for material to patentability. (*See* FF ¶¶ 106-20; *see also* D.I. 230 at 24 (Belcher post-trial brief admitting that what "was proven at trial was that Mr. Rubin knew about the references and decided not to submit them to the USPTO")) Rubin testified that he withheld these references because he considered them (and others) irrelevant, as they were directed to formulations that contained preservatives, used epinephrine bitartrate base, or had "high" overages. (FF ¶ 119) Hence, the specification – which Rubin helped write – summarily dismissed all prior art with preservatives and/or high overages, and provided only a single, nonspecific example of a preservative-free

[16] The record does not establish whether the 2003 Sintetica Products produced on behalf of Cura constitute public prior art. Either way, there was still an obligation to disclose them to the Patent Office. *See* 37 C.F.R. §1.56(b) ("Information is material to patentability when . . . [i]t refutes, or is inconsistent with, a position the applicant takes in: (i) [o]pposing an argument of unpatentability relied on by the Office, or (ii) [a]sserting an argument of patentability."); *see also* MPEP § 724 ("It is incumbent upon patent applicants, therefore, to bring 'material' information to the attention of the Office. It matters not whether the 'material' information can be classified as a trade secret, or as proprietary material, or whether it is subject to a protective order. The obligation is the same.").

formulation that used 10% overages with a pH between 2.2 and 2.6. (*See* JTX-2 at 3-6; Rubin Tr. at 208 ("I wanted the blanket statements in the specification to cover all the prior references. . . . I indirectly described all the prior references.")) While the specification adequately disclosed the range of high-overage prior art products, the specification failed to disclose prior art that had pHs above 2.6, despite their indisputable existence and Rubin's knowledge of them.

After the specification ***implicitly*** limited all subsequent statements to "preservative-free, sulfite-free solution," the specification then espoused the novelty of having a pH between 2.8 and 3.3. (*See* FF ¶¶ 121-22) For example, the specification stated that "increasing the in-process pH to 2.8-3.3, ***unexpectedly*** reduced the racemization . . . [and] ***was a nonobvious solution*** to the problem of racemization." (FF ¶ 122; JTX-2 at 20) This statement may have been true in the context of preservative-free, low overage formulations, but it was not true as a general principle. In fact, it was neither unexpected nor nonobvious that raising pH reduced racemization, and – most importantly – epinephrine formulations with a pH of 2.8-3.3 were not new. (FF ¶¶ 112-13, 115-17) Rubin testified that he knew of Stepensky before filing for patent; and Stepensky taught an epinephrine formulation with a pH of 3.25-3.70. (*Id.*; *see also* FF ¶ 92) In an e-mail dated November 7, 2013 (the patent application was filed on August 15, 2014), Rubin quoted a portion of Stepensky that cited to Fyllingen – and Fyllingen expressly taught that raising the pH above 2.4 would reduce racemization. (FF ¶ 113) That same quoted portion of Stepensky also cited to Aligire, which likewise showed that formulations with higher pHs took longer to racemize. (*Id.*) Yet Rubin deliberately withheld Stepensky, Fyllingen, and Aligire from the PTO.

At trial, Rubin claimed that he did not carefully examine Stepensky or any of the references cited in it, but his repeated efforts to evade questioning and inject attacks of the prior

art into his answers raised serious questions as to his credibility. (*See, e.g.*, Rubin Tr. at 184 (repeatedly conditioning answers on "these high overage products"); *id*. at 186-87, 190, 192-94, 196-97 (evading question); *id*. at 192-93, 198 (dismissing relevance of prior art as "high overage"); *id*. at 194 (attacking Sintetica's 2003 batches); *id*. at 198, 204 (calling Stepensky "nonrelevant" and "flawed," for unspecified reasons).

The Court did not find Rubin's testimony about why he did not disclose the prior art references to the PTO to be credible or plausible.[17] That, in combination with express statements made during prosecution, persuade the Court by clear and convincing evidence that Rubin engaged in inequitable conduct. In the non-final rejection of the '845 Application, the Examiner relied on Helenek, which taught an epinephrine formulation with a pH range of 2.2-5.0. (FF ¶ 123) In pushing back on Helenek's pH, Rubin and Belcher knew that pH would be critical to persuading the Examiner to approve the patent. Certainly by this point in the prosecution, Rubin and Belcher had an unambiguous duty to disclose any material information pertinent to the claimed pH, and not just prior art limited to preservative-free or low overage formulations. Yet Rubin approved the following response from Belcher: "Helenek et al. [] does not make obvious the Applicant's pH range of 2.8 and 3.3, which was ***unexpectedly found to be critical*** by the Applicant to reduce the racemization of 1-epinephrine." (*Id*.) (emphasis added)

The statement that Belcher's claimed pH was "unexpected" was false. At the time this statement was made, Rubin knew about Stepensky, the JHP Adrenalin Product, and the 2003

[17] On April 21, 2017, Rubin wrote an email to Messrs. Jugal and Mihir Taneja expressly touting that their Patent "has an independent claim 6 that ***does not mention preservative-free/sulfite free***. I made sure I got that allowed." (JTX-120) (emphasis added) It is clear that Rubin did not view the '197 Patent as limited to formulations that contained preservatives and/or sulfites. Therefore, it is not plausible that his decision to withhold references from the PTO was because they were directed to formulations with preservatives and/or sulfites.

Sintetica Products, all of which taught a pH in the range of 2.8 to 3.3. (*Id*.) The Examiner, not knowing of these references, accepted Belcher's representations as true and was persuaded by them to approve the Patent. The "Notice for Allowance" states that the '845 Application was patentable "***in view of Applicant's demonstration of criticality of a pH range between 2.8 and 3.3***." (FF ¶ 124) (emphasis added) The Examiner added: "Thus, there [is] nothing in the prior art that would teach or suggest the instantly claimed pH range of between 2.8 and 3.3 would result in the limited racemization and impurities as instantly claimed." (JTX-2 at 86; *see also* Rubin Tr. at 196-97) Belcher and Mr. Rubin did not correct the Examiner's misunderstandings.

While there is no direct evidence of deceptive intent, the above-referenced facts, taken together, persuade the Court, clearly and convincingly, that this is the only reasonable inference that can be drawn. *See Therasense*, 649 F.3d at 1290. Rubin was an active participant in Belcher's entire process to market its l-epinephrine product, from filing the NDA to seeking patent protection. (Rubin Tr. at 145-46, 149, 152-54, 161) He knew the '197 Patent sought to protect a literature-based NDA Product (FF ¶ 37), meaning the NDA was based substantially on prior formulations. He knew Sintetica had created epinephrine formulations with the claimed pH range as far back as 2002 to 2004, and that Belcher considered a pH of 2.8-3.3 as "old." (FF ¶¶ 40-41) He also knew that Belcher did not raise the pH of its NDA Product from 2.4-2.6 to 2.8-3.3 based solely on an inventive epiphany by Mr. Taneja, but also because Belcher's outside consultants thought that would expedite FDA approval. (FF ¶¶ 41, 46) In addition, he knew that Belcher had disclosed to the FDA some of the very same references it withheld from the PTO. (*See* Rubin Tr. at 166, 174-75, 188-89; JTX-059 at 20 (disclosing Sintetica Product Testing data in NDA); JTX-061; JTX-063)) And he knew that Stepensky and JHP's Adrenalin Products taught epinephrine formulations in the claimed pH range. (FF ¶ 119)

In spite of all of this knowledge, Mr. Rubin helped create a fiction throughout the specification that the pH was an inventive feature. At the same time, he unilaterally decided that any information that undermined that fiction was irrelevant, and refused to share it with Belcher's own attorney and the Patent Office.

The Court agrees with Hospira that the record clearly and convincingly demonstrates all of the following:

> Mr. Rubin knew (1) that each of the three references [Stepensky, Sintetica's prior epinephrine products, and JHP's Adrenalin Products] disclosed the allegedly critical pH range of 2.8 to 3.3; (2) that epinephrine products with such a pH range resulted in levels of impurities that fell squarely within the claimed limits; and (3) that the Examiner specifically allowed the '197 patent claims based on the alleged criticality of the pH range in reducing impurities. . . . Belcher's *post-hoc* justification of Mr. Rubin's conduct falls apart under scrutiny. Nothing in the prosecution history suggests that either the Examiner or Mr. Rubin believed epinephrine overages to be so critical to the invention that all epinephrine products with a high overage – even products that met the claimed pH range and levels of impurities – were "immaterial."

(D.I. 236 at 18)[18]

Based on the totality of the evidence, this was not a situation where Mr. Rubin "knew of a reference, should have known of its materiality, and decided not to submit it to the PTO," *Therasense*, 649 F.3d at 1290, but, rather, one in which Mr. Rubin made "misleadingly incomplete, if not plainly inaccurate" statements combined with active omission of relevant information, *Apotex, Inc. v. UCB, Inc.*, 763 F.3d 1354, 1362 (Fed. Cir. 2014). This was an

[18] Belcher's added attempts to justify the intentional withholding of material prior art references – including that Rubin did not want to "bury things" and "burden the examiner" (Rubin Tr. at 25; *see also* D.I. 230 at 25-26) and that the withheld references would not have made a difference to the PTO – are also implausible and do not undermine the Court's finding of deceptive intent, for reasons including those stated by Hospira (*see, e.g.*, D.I. 236 at 18-19).

inequitable breach of his duty of candor and good faith that warrants an equitable solution. Accordingly, the Court finds the ’197 Patent unenforceable.

CONCLUSION

Belcher has not proven by a preponderance of the evidence that Hospira infringes claims 6 or 7 of the ’197 Patent. Hospira, however, has proven by clear and convincing evidence that claims 6 and 7 are invalid for obviousness, that Mr. Taneja is an improper inventor, and that the ’197 Patent is unenforceable for inequitable conduct. An appropriate Order follows.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BELCHER PHARMACEUTICALS, LLC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	C.A. No. 17-775-LPS
	:	
HOSPIRA, INC.,	:	
	:	
Defendant.	:	

ORDER

At Wilmington this **31st** day of **March**, **2020**, for the reasons set forth in the Opinion issued this date, **IT IS HEREBY ORDERED** that:

1. Plaintiff has not proven by a preponderance of the evidence that Defendant infringes claims 6 or 7 of U.S. Patent No. 9,283,197 ("the '197 Patent").

2. Defendant has proven by clear and convincing evidence that claims 6 and 7 of the '197 Patent are invalid for obviousness, that Jugal Taneja is an improper inventor, and that the '197 Patent is unenforceable due to inequitable conduct. Defendants have failed to prove that claims 6 and 7 of the '197 Patent are invalid due to anticipation.

3. The parties shall meet and confer and submit, no later than **April 3, 2020**, a proposed order consistent with the Opinion, to enter final judgment **FOR** Defendant and **AGAINST** Plaintiff and to close this case.

4. Because the Opinion has been issued under seal, the parties shall meet and confer and, no later than **April 2, 2020**, submit a proposed redacted version, as well as a supporting memorandum justifying any redactions they propose. Should the parties fail to comply, or fail to

persuade the Court any portion of the Opinion should be redacted, the Court will unseal the Opinion.

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT JUDGE