2020-1799

In The

United States Court Of Appeals

For The Federal Circuit

BELCHER PHARMACEUTICALS, LLC,

Plaintiff-Appellant,

v.

HOSPIRA, INC.,

Defendant-Appellee.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE
Case No. 1:17-cv-00775-LPS

BRIEF OF APPELLANT BELCHER PHARMACEUTICALS, LLC

August 13, 2020

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2020-1799

Short Case Caption Belcher Pharmaceuticals, LLC v. Hospira, Inc.

Filing Party/Entity Belcher Pharmaceuticals, LLC

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 8/13/2020

Signature: /s/ Peter M. Lancaster

Name: Peter M. Lancaster

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☐ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☑ None/Not Applicable
Belcher Pharmaceuticals,LLC	Belcher Pharmaceuticals,LLC	

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Stefan V. Stein GrayRobinson, P.A.	William Stein GrayRobinson, P.A.	
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Stephen B. Brauerman BAYARD, P.A.		

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☑ None/Not Applicable ☐ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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GLOSSARY OF TERMS USED IN THIS BRIEF

Degradation*:*	Epinephrine may degrade by three reactions: racemization, oxidation, and sulfonation (substitution by bisulfite).
Epinephrine:	Also called adrenaline, the principal blood-pressure raising hormone secreted by the adrenal glands, prepared from adrenal extracts or made synthetically; this catecholamine has many physiologic functions, including stimulating the heart.
Oxidation*:*	A change in a compound's chemical composition due to molecular oxygen or other oxidizing agents. Epinephrine may oxidize into degradants such as adrenalone.
Racemization*:*	A change in the arrangement of a molecule around its "chiral center," such that the molecule cannot be superimposed on its mirror image notwithstanding being rotated and translated. The active form of epinephrine, l-epinephrine, racemizes into its less potent isomer, d-epinephrine.
Sulfonates*:*	Degradation products of both l-epinephrine and d-epinephrine that form in the presence of sulfites, which are added as antioxidants to epinephrine formulations. Examples include epinephrine sulfonate and adrenaline beta sulfonate.
Tonicity agent:	Sodium chloride may be included to reduce osmotic shock upon injection.

STATEMENT OF RELATED CASES

1. There are no other appeals to this or any other appellate court from the District of Delaware proceedings in this case.

2. There are no cases known to counsel to be pending in this Court or in any other court that will directly affect or be directly affected by this Court's decision in the pending appeal.

JURISDICTIONAL STATEMENT

The District Court had original subject matter jurisdiction under 28 U.S.C. §§1331 and 1338. This Court has appellate jurisdiction pursuant to 28 U.S.C. §1295(a)(1), because the appeal is from a final decision of the District Court in a civil action arising under the Patent Act.

STATEMENT OF THE ISSUES

1) Whether the district court correctly found inequitable conduct where the prior art on which it based its conclusion fails the materiality standard established by *Therasense v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (*en banc*)?

2) Whether the district court correctly found inequitable conduct where intent to deceive is not the most plausible explanation of the patent applicant's actions?

INTRODUCTION

Although the technology can be complex, at its core Belcher's appeal is simple: Did the district court err in finding Belcher's patent unenforceable due to inequitable conduct? Clear errors of fact pervade the court's inequitable conduct analysis, eliminating the foundation upon which the district court made both its materiality and intent determinations. These clear errors require reversal of the district court's inequitable conduct holding.

Belcher was the first to develop and patent a stable epinephrine formulation that retained safety and efficacy over at least a 12-month period following release, despite having low-to-no overage of its active ingredient. Belcher accomplished this through a counterintuitive combination of variables that included two key features, among others, that distinguished its invention from the prior art: a pH range between 2.8 and 3.3, and a low "overage" between 0 and 6% of its active ingredient upon release.

In finding inequitable conduct, the district court committed a *first* clear error by misinterpreting the prosecution history of Belcher's patent to construct an incorrect and unduly narrow conception of patentability. The court selected one argument from thirteen pages of amendment and argument distinguishing the prior art and determined that this particular argument—that the claimed pH range for Belcher's epinephrine formulation was an unexpected advance over the art—was the

sole patentable distinction between Belcher's patent claims and the prior art. But Belcher made the argument in a context disregarded by the court, and Belcher described multiple other distinctions between its claimed invention and the cited art. The examiner did not base allowance on a single Belcher argument, but rather on Belcher's "*arguments*." The district court provides no defensible basis for its unduly narrow view of patentability.

Based on this incorrect understanding of the prosecution history, the court concluded that Belcher engaged in inequitable conduct by not submitting three pieces of prior art, even though:

- One reference, Stepensky, teaches only high overage formulations, and discloses no formulations tested at both release and 12 months later, let alone any formulations within the claimed pH *and* time range. Its statement regarding racemization and pH relied on by the district court cites two sources, one of which teaches using pH well *below* Belcher's claimed range, while the other does not relate to a plain epinephrine solution.

- The second reference, 2003 Sintetica products, also high overage products, was not shown to be prior art, as was conceded by the district court.

- The third reference, JHP's high overage Adrenaline Product, included information that Mr. Rubin lacked during prosecution.

- A fourth reference, which *was* before the Patent Office and which was the basis for an obviousness rejection, disclosed an epinephrine pH range that overlapped with the range claimed in Belcher's patent.

These references, along with all other prior art references of record, have the same shortcoming: every one is a "high-overage" epinephrine product, a product released with an excessive amount of the active ingredient to permit degradation of that

ingredient over the product's shelf life. The court committed a *second* clear error in assuming that the materiality conclusions of its obviousness analysis—determinations built upon references, testing, and testimony not available to Belcher during prosecution—have equal application in the inequitable conduct context. The district court clearly erred in concluding that the three withheld references were but-for material where none disclosed a low-to-no overage product, and where the sole reference—certain generalized pharmaceutical guidelines—that the district court used in its obviousness conclusion to supply that missing limitation was *not* part of the inequitable conduct case. Materiality in this context is determined with reference to *known* references, and no reference known to Belcher supplied the central low-to-no overage feature of Belcher's patent. Even had generalized pharmaceutical guidelines been part of the but-for materiality analysis, it would have been clear error for the court to find that they would have provided a reasonable expectation of success where undisputed trial evidence established that the major industry players with decades of epinephrine formulation experience struggled and/or failed to make a low-to-no overage product like that claimed by Belcher.

Belcher's lead technical witness testified that he did not disclose high-overage references because Belcher's patent distinguished itself from and improved upon the high-overage art. His testimony supplied an explanation at least as plausible as the court's conclusion that he deliberately intended to deceive the PTO by not disclosing

the three references. His testimony was corroborated by evidence relating to development of the product described in Belcher's patent, the patent application itself, and Belcher's prosecution arguments. The district court committed a *third* clear error in disregarding this objective corroboration of plausible testimony demonstrating that intent to deceive the PTO is not the single most reasonable inference to be drawn from the evidence.

The district court paired its third clear error with a *fourth* clear error to find intent to deceive the PTO, based on the ground that Belcher knew its pH-based argument made in prosecution was not true in all circumstances. But Belcher made the criticized argument with specific regard to sulfite-free epinephrine formulations, the very context in which the court acknowledges the arguments to be credible. Again, the court ignored this crucial context, and in so doing, clearly erred in finding intent to deceive the PTO.

STATEMENT OF THE CASE

BACKGROUND

I. BELCHER'S EPINEPHRINE PRODUCT AND PATENT

Belcher Pharmaceuticals, LLC is a pharmaceutical company focused on the development and manufacture of specialty prescription drug products. One such drug, Belcher's New Drug Application No. 205029 ("Belcher's NDA Product"), was approved by the FDA on July 29, 2015, for a 1 mg/mL injectable l-epinephrine formulation. Appx3. The product's proposed indication was "for use in increasing

systemic arterial blood pressure in acute hypotensive stress associated with septic shock." Appx1559; Appx9.

Belcher's NDA Product is an advancement on the nearly century-old art of injectable epinephrine products. Epinephrine was known to suffer degradation from three primary reaction pathways: racemization, oxidation, and sulfonation (substitution by bisulfite). Appx1338-1342; Appx784; Appx8. For epinephrine, *racemization* is the conversion of the active form, l-epinephrine, to its less potent isomer, d-epinephrine. Appx8; Appx785; Appx1338; Appx1370. This degradation leads, over time, to a less potent product. *See* Appx784-785. *Oxidation* describes a change in a compound's chemical composition due to molecular oxygen or other oxidizing agents. Appx1338. Oxidation of epinephrine may result in discoloration and degradation into adrenalone. Appx9; Appx682. Sulfites are used in epinephrine products as stabilizers to combat oxidation, but *sulfonation* also provides a third means of degradation. *See* Appx1341.

These degradation pathways are problematic for epinephrine manufacturers and patients. As the active ingredient degrades, the product becomes less potent and less effective in delivering its intended therapeutic benefit. Appx785. Before Belcher's invention, epinephrine manufacturers addressed degradation simply by adding excess epinephrine above product label levels—called "overage"—to the package to accommodate degradation and extend the product's shelf life. Appx765.

Degradation is not harmful just because of loss of potency; it also results in degradants, which may cause unwanted health results for a patient. *See* Appx927-928. Belcher was the first to address racemization for epinephrine injection drug products, such as by setting strict limits on d-epinephrine content. *See* Appx928-929; Appx 935-936. It also was the first to set strict overage limits. *See* Appx928; Appx932.

Belcher's NDA product departed from conventions in the art to achieve a shelf-stable product that minimized unwanted degradation from these pathways. Unlike many prior art products, Belcher's NDA Product contains no sulfites, thereby avoiding sulfonation. Appx950; Appx1021-1022. And, unlike *all* prior injectable epinephrine products of record, Belcher's NDA Product has little-to-no overage. Appx928. Despite these significant departures from the art, and contrary to the expectation of persons of skill in the art ("POSAs"), Belcher found that its formulation, when compounded with little-to-no overage at a pH level between 2.8 and 3.3, minimized degradation through racemization and oxidation and achieved commercially acceptable shelf life, despite its little-to-no overage and lack of sulfites.

A. BELCHER'S '197 PATENT CLAIMS A NOVEL EPINEPHRINE FORMULATION

Appreciating that its product was a departure from and advance in the art, Belcher sought and received a patent: U.S. Patent No. 9,283,197, the patent in

dispute on this appeal. The '197 patent addresses at least two problems in the art, by providing an epinephrine formulation without sulfites or high overage of the active ingredient:

> Drug manufacturers try to deal with the problem of oxidation by adding bisulfite antioxidants and increasing overages, both of which have the potential to cause harm to patients... . [B]isulfites, can cause mild to severe, life-threatening allergic reactions ... . Most formulations also use overages of active pharmaceutical ingredient to compensate for degradation of epinephrine content and activity over the course of the product's shelf-life. This results in epinephrine drug products released after manufacturing with a higher than expected activity, which could be hazardous to patients …, increasing side effects such as tachycardia.
>
> ***
>
> There exists a great need for a liquid formulation of l-epinephrine that is both preservative-free and sulfite-free, with minimal overage, if any, and with minimal levels of degradants, including d-epinephrine, while maintaining a sterility guarantee. The present invention fulfills this great medical need... .

Appx999 (2:15-58).

Claims 6 and 7 of the '197 patent, the only claims asserted at trial, are similar to the other claims of the '197 patent in claiming an l-epinephrine formulation having certain recited chemical qualities and time-bound limitations on certain chemical impurities:

> 6. 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, 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.
>
> 7. The said injectable liquid pharmaceutical formulation of claim 6 further having a concentration of 1 mg per mL l-epinephrine.

Appx1002.

The district court construed "said injectable liquid pharmaceutical formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine" to require that "1.0 to 1.06 mg/mL l-epinephrine" be present in the solution after the compounding step[1] but before product release. Appx5. In addition to the post-compounding pH level, the claims recite maximum adrenalone and d-epinephrine levels at release (referred to as "time zero") and again at least 12 months later. *See* Appx1002.

B. pH LEVELS IN PRIOR ART EPINEPHRINE PRODUCTS VARIED WIDELY

The pH of an aqueous solution describes the solution's level of acidity or basicity. It was known before the '197 invention that pH affects both racemization and oxidation of epinephrine in solution. *See* Appx24-25.

[1] "Compounding" is the mixing step of the formulation's manufacture. Appx762.

Racemization is ordinarily *inversely proportional* to pH of the epinephrine solution; ordinarily, lower pH means increased racemization. Appx1340. Oxidation, on the other hand, is *proportional* to pH—as pH rises, ordinarily so will unwanted oxidation. Appx785-786; Appx1340. Both of these reactions, over time, render epinephrine formulations less fit for their intended uses. *See* Appx927-928.

Based on this understanding in the art and evidence presented at trial, the district court held that "there is an optimum pH at which racemization and oxidation can be balanced to minimize loss of intact drug by these two routes." Appx9. The court concluded that this pH level is "approximately pH 3.0-3.8." *Id.*, *see also* Appx1340.

While the need to select a pH in an epinephrine solution to balance racemization and oxidation was known before the '197 invention, the record evidence shows, contrary to the district court's finding, that there was no clear conception in the art of an "optimum" pH level in epinephrine products to manage racemization and oxidation, and certainly no understanding of an optimal pH in a low-to-no overage, sulfite-free l-epinephrine formulation. Each of the references discussed *infra* was presented at trial and comprise the foundation for the court's understanding of the general knowledge of persons of ordinary skill in this art. *See* Appx47.

The USP monograph, "which serves as the quality standard for epinephrine pharmaceutical formulations" (Appx1071-1072), lists a required pH in the range 2.2-5.0. Appx12; Appx1378. The Connors reference, a 1986 handbook for pharmacists relating to the chemical stability of pharmaceutical products, discloses 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*." Appx1340 (emphasis added); *see* Appx24-25. Despite this express pH range, Connors discloses no testing at a pH of 2.8 to 3.3, the pH range in the asserted claims of the '197 patent. *See* Appx905.

The Fyllingen reference, entitled "Racemisation and oxidation in adrenaline[2] injections," recites that "[t]he pH in the injections is *2.4, which is supposed to be the pH at which both oxidation and racemization are at a minimum*." Appx1370 (emphasis added); Appx25; Appx939. Kerddonfak's 2010 study, "The Stability and Sterility of Epinephrine Prefilled Syringe," concludes that syringes should not be kept for more than three months and describes the "acceptable range" for epinephrine as 2.8-3.6. Appx1361; Appx26. The 2004 Stepensky reference is a study on the long-term stability and degradation of "epinephrine bitartrate formulations having a pH of 3.25-3.70." *See* Appx25; Appx1347; Appx1351.

[2] "Adrenaline" and "epinephrine" refer to the same drug. *See, e.g.*, Appx787.

Despite this stated pH range, Stepensky discloses no testing of any formulation with a pH at or below 3.3 within a commercially reasonable period (*e.g.*, two years or less). *See* Appx941-942. None of those references was shown at trial to reach any conclusion as to pH levels for low-overage, sulfite-free formulations of injectable epinephrine. *See* Appx24-26.

C. BELCHER'S LOW-TO-NO LOW OVERAGE, STABLE EPINEPHRINE FORMULATION WAS A KEY ADVANCE IN THE ART

Overage is not a panacea. Excessive active ingredient can be harmful, "increasing side effects such as tachycardia." Appx999; *see also* Appx686; Appx927-928. Increasing overage also causes greater degradant levels as the active ingredient degrades, whether through racemization or oxidation. Appx913. While overage is sometimes expressed in terms of concentration (Appx890), concentration is different from overage because "overage" is the amount of active ingredient that exceeds the product label's stated amount. Appx765; Appx779-780.

Claims 6 and 7 of the '197 patent recite a specific concentration of l-epinephrine, not a specific overage. Appx1001-1002. But the parties' expert witnesses agreed that the importance of the concentration limitation of claim 6 is to define a 0-6% overage to achieve a final product with a concentration of 1.0 mg per mL, as specified in dependent Claim 7. Appx891-892; Appx926-929. These

opinions are buttressed by those of inventor Darren Rubin,[3] Belcher's Chief Science Officer and a primary drafter of the patent. *See*, *e.g.*, Appx30; Appx695. Mr. Rubin testified that by claiming that the formulation was "compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine," he meant 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." Appx695; Appx30.

1. The Failure of Earlier Epinephrine Marketers to Achieve a Stable, Low-to-No Overage Epinephrine Formulation

Belcher's claimed l-epinephrine concentration limitation—which contemplated a 0 to 6% overage—was a departure from and improvement over prior art epinephrine formulations, which all had high overages. *See* Appx695; Appx894. Indeed, at the time Belcher began developing its claimed product, grandfathered epinephrine products[4] *all* had overages exceeding 6%, some as high as 15%. Appx1394-1397. No prior art epinephrine product had an overage between 0 and 6

[3] The district court determined that Belcher improperly named its CEO, Jugal Taneja, as the sole inventor of the '197 patent. During trial, Belcher sought and received a certificate of correction to add Mr. Rubin as a co-inventor. *See* Appx1888. After trial, the PTO issued a second certificate of correction to remove Mr. Taneja. Because this certificate of correction was sought and issued after this appeal's institution, it is not in the district court record.

[4] "[O]ld, well-known products … are not subject to certain FDA requirements if they meet specific conditions." Appx8 n.5.

percent.[5] Appx678; Appx928; *see also* Appx905. As Belcher pointed out to the PTO, "[t]he importance of the current invention is that the concentration of 1 mg per mL 1-epinephrine is maintained ... *without using high overages during manufacturing which would result in increased side effects and inaccurate dosing to patients*." Appx1069 (emphasis added). The record establishes that the Belcher NDA product was the first of its kind, and it took other sophisticated participants in the field several more years to achieve Belcher's advance in the art.

2. The Resistance of Belcher's Own Epinephrine Manufacturer Resisted Belcher's Attempts to Formulate its Low-to-No Overage Product

Before creating its NDA Product and seeking patent protection, Belcher arranged with Sintetica, a contract pharmaceuticals manufacturer, to manufacture a new formulation. Sintetica had been Europe's leading epinephrine manufacturer for decades (Appx1564; Appx697; Appx741), but its epinephrine products all had high overages. Appx678. Sintetica's prior epinephrine preparations had preservatives and sulfites, pH levels of 2.2-4.0, and 10% overages to compensate for manufacturing and storage losses. Appx1562-1565; Appx697; Appx10. In the early 2000s Sintetica began producing preservative- and sulfite-free epinephrine formulations, which required an increased concentration of the tonicity agent and

[5] The lowest overage product identified by the district court was the JHP Adrenalin Product, with an overage of at least 9.5%. *See* Appx22.

even more overage to account for the loss of the sulfite anti-oxidant preservatives. Appx1564; *see also* Appx698. These early preservative and sulfite-free formulations had a pH of 2.8 to 3.3 and *15%* overages. Appx1564-1565; *see* Appx10. This overage increase—from 10% to 15%—was made "to prevent the possible further activity loss during manufacturing process due to the elimination of the antioxidant." Appx1566.

Against this historical context, and in collaboration with Sintetica, Belcher initially formulated its NDA product with a pH of 2.4-2.6 and an overage of 10-15%. Appx11. The FDA asked for justification of this overage. Appx1483; *see also* Appx703. Following testing by Sintetica, Belcher decided to "refocus[] 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." Appx1464; Appx672-673. Belcher directed Sintetica to manufacture a sulfite-free epinephrine formulation having a pH between 2.8 and 3.3 and an overage between 0 and 6%. Appx679; Appx682-684; Appx1487-1488.

Sintetica resisted Belcher's directives. Appx682-683. Sintetica's doubt was not unfounded. Sintetica had previously manufactured high-overage, sulfite-free epinephrine formulations at varying pH levels, including in the 2.8 to 3.3 range. Appx1564-1565; Appx10. But these formulations were pink, because of unacceptably high oxidation. Appx682; Appx684; Appx690; Appx724; *see*, *e.g.*,

Appx1378 (USP monograph teaching that epinephrine solutions should not be "pinkish"). Sintetica observed that, the higher the pH of the formulation, the more significant the coloration. Appx682; Appx1591.

Despite Sintetica's experience that high-overage products required low pH, and its resistance to manufacturing a formulation in the 2.8-3.3 range, Belcher persisted and had Sintetica prepare a low-overage, sulfite-free, 2.8 to 3.3 pH epinephrine product. Contrary to expectations, the formulation worked, leading to the unexpected discovery of reduced racemization and acceptable oxidation in a low-overage formulation, one with no sulfites or preservatives. Appx683-684; Appx999.

It was this formulation that eventually achieved FDA approval and patent protection. Appx672-673. At the time of its FDA approval, Belcher's NDA epinephrine product was the only sulfite-free, low-overage epinephrine product on the market. *See, e.g.*, Appx22; Appx24 (district court finding no anticipatory product on the market).

3. The Lengthy Period That Market Leaders Were Unable to Achieve Belcher's Invention

Sintetica was not the only experienced epinephrine manufacturer to demonstrate the nonobviousness of Belcher's patented formulation. Hospira's own development of low-overage epinephrine products evidences the difficulty of achieving—let alone *conceiving*—Belcher's invention. Hospira, a subsidiary of pharmaceutical giant Pfizer, has at least 30 years of epinephrine product experience.

Appx593. In 2007, it promised the FDA it would remediate its grandfathered, high-overage Ampul and Abboject syringe epinephrine products. It began working on its revised product by 2009. Appx1841-1842; Appx624-625. Hospira's remediation efforts did not go quickly or smoothly, suffering "several unsuccessful efforts" during its remediation research and testing. Appx1842-1843; Appx625-626. The FDA required Hospira to eliminate its 10% overage to gain approval (Appx884) at least partly because Hospira was unable to show potency loss during manufacturing to justify such an overage. Appx609. Hospira testing and research in this time showed that Hospira struggled with formulations in the pH 2.7 to 2.9 range, concluding that it caused more d-epinephrine formation through racemization. *See* Appx602.

Hospira claimed at trial that, by 2013, it possessed oxidation and racemization data for epinephrine products within claim 6's pH range, *see* Appx20-21 (Hospira 2013 test data for JHP product), Appx23 (Hospira 2013 test data for its own Ampul Product); Appx1281; Appx1330-1331, but even with this data supposedly in hand, Hospira did not submit its remediated low-overage products to the FDA until *2017*, Appx625—10 years after the FDA requested it, at least 8 years after Hospira began working on the project, and years after Belcher submitted its NDA. Hospira admits that this was a remediation period that "[n]obody [at Hospira] thought [] would take that long." Appx625-626.

JHP Pharmaceuticals (now Par Pharmaceutical), another multi-decade epinephrine product manufacturer, maintained epinephrine products with overages between 9.5 and 13.4% for years. Appx22; Appx1281. Though the FDA approved JHP's high-overage Adrenalin product in 2012, it asked JHP to commit to reducing degradants. Appx1840-1841. But reformulation was no simple task for JHP, either. Appx1841-1842. JHP scientist Patrick Irish testified that it was very difficult to come up with a set of components in a formulation that could minimize one degradation pathway without exacerbating another degradation pathway. Appx1840. JHP's reformulated product was not submitted to the FDA until 2015. *See* Appx1841.[6]

This development timeline counsels strongly against obviousness, as a sister court held in siding with JHP:

> The long-standing failure of others to develop similar epinephrine formulations with long-term stability supports a finding that the patented formulation was not obvious[]. The record shows that there was a need for a stable formulation as recently as 2013, despite the fact that epinephrine degradation had been studied since the 1960's. Both Par and Hospira engaged in lengthy development efforts with repeated

[6] The citations in this section are to a supplemental authority describing Par/JHP's reformulated NDA, not the NDA itself or the testimony referenced in the supplemental authority, which is not a part of the district court record. Whether or not the Court accepts the factual premises in this document, it may take judicial notice of the district court's finding of a longstanding failure to develop low overage epinephrine with long-term stability even as of Par's March 2015 invention date, because if the district court could view the evidence that way, surely it was reasonable for Mr. Rubin to do so as well.

> failures and *scientists at both companies expressed the unexpected difficulty of developing long-term stable epinephrine formulations*."

Appx1874 (emphasis added).

D. THE '197 PATENT PROSECUTION HISTORY EVIDENCES MANY DISTINCTIONS OVER CITED ART

Mr. Rubin, who helped draft and prosecute the '197 patent, is neither a patent agent nor a patent attorney. Appx7. His prosecution efforts likely exceeded the role his limited legal and patent experience qualified him; he even "dug into the case law" in working on an office action response. Appx681-682. Mr. Rubin's lack of prosecution experience is evident from his having pursued product-by-process claims, which experienced patent prosecutors eschew because product-by-process language is limiting for infringement but not validity. *See* Appx45.

1. Overview of Prosecution

The application that matured into the '197 patent was filed with nine claims, of which three, application claims 1, 5, and 8, were independent. *See* Appx1025-1026. Initially, independent application claims 1 and 5 recited no maximum pH, but rather "a pH above 2.6." Appx1025. Application independent claim 8 was directed at low overage formulations, and had no pH limitation at all. Appx1026. Application dependent claim 2 depended from application claim 1, and recited "a pH preferably between 2.8 and 3.3." Appx1025. Application claim 6 depended from application claim 5, and recited the same pH limitation. Appx1026.

In an August 11, 2015, office action, the examiner rejected each claim. Appx1040-1045. Among other reasons, each claim was rejected as obvious in view of Helenek, Gherezghiher, and MSDS references. Appx1041-1045.

In a November 5, 2015, amendment, the applicant presented several arguments against the obviousness rejection. *See* Appx1065-1077. With reference to *dependent* application claims 2 and 6, the applicant argued, "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 l-epinephrine... . Helenek's formulations vary from highly acidic to neutral with no regard for epinephrine degradation." Appx1076.

On December 16, 2015, the examiner issued a Notice of Allowance, withdrawing prior §112 rejections and crediting the applicant's arguments with respect to the prior art under §103. The examiner stated, "[i]n view of Applicant's arguments and the Examiner's amendment presented infra, the rejection of claims 1-9 under 35 U.S.C. 103(a) ... is herein withdrawn." Appx1086.

The examiner did not merely rubber-stamp the applicant's proposed amended claim language. In the Notice of Allowance, the examiner made several amendments to the application claims, including cancellation of application dependent claims 2 and 6, replacement of the phrase "pH above 2.6" in application independent claims 1 and 5 (issued claims 1 and 4) by "pH between 2.8 and 3.3";

and the addition in another independent claim (application claim 8; issued claim 6) of the phrase "said liquid pharmaceutical formulation having a pH between 2.8 and 3.3." Appx1087.

2. Prosecution Arguments Distinguishing Prior Art

While the patent applicant made a pH-based argument to the examiner, the argument related exclusively to dependent claims having the 2.8-3.3 pH level limitation. *See* Appx1073, *compare* Appx1066-1067 (then-pending claims 2 and 6 having the pH limitation). The argument is just one paragraph of a 13-page response. *See* Appx1065-1077.

The applicant's response to the rejection clearly stated that the invention was distinct from the prior art not merely because of its pH range, but because of its low overages and production processes as well:

> [T]here are considerable dynamics taking place during production and throughout the product's shelf-life. The l-epinephrine isomer is subject to racemization, oxidation, heat damage, and loss during production, including during sterilization, and over time while being stored. *The Applicant's preparation has tolerances and limits in production steps, such as the narrow 1.0 to 1.06 mg/mL 1-epinephrine concentration range during the compounding step*. Other considerations include *slight overages to accommodate for loss during production, and degradation over the product's shelf-life*. So while the drug product's name and approximate concentration is 1 mg per mL 1-epinephrine sterile solution, the actual concentration varies from when production is completed and over time throughout the product's shelf life. For instance, the actual concentration of the drug product may be slightly higher

> than 1 mg per mL 1-epinephrine at production release, and slightly lower than 1 mg per mL 1-epinephrine after over 1 year of this drug product sitting on the shelf.

Appx1068-1069 (emphases added).

Belcher also made other arguments unrelated to pH to distinguish the cited art:

- "[T]here is no teaching nor enablement by Helenek et al. for producing a sterile formulation of epinephrine, let alone a sterile formulation of epinephrine without preservatives and antioxidants." Appx1074.
- "Helenek also … fails to teach about, or even disclose, epinephrine degradants and impurities, such as adrenalone." *Id*.
- "Helenek provides no information about levels of epinephrine and its impurities at product release, nor any shelf-life stability information." *Id*.

The applicant stressed to the examiner that the invention was distinct from the prior art in that it was able to maintain efficacy without incurring the risks of high overages:

> The importance of the current invention is that the concentration of 1 mg per mL 1-epinephrine is maintained as best as possible in a drug product that has been made sterile for injection (a process that would degrade 1-epinephrine considerably), while maintaining at least 90% 1-epinephrine over its shelf-life, *without using high overages during manufacturing which would result in increased side effects and inaccurate dosing to patients*.

Appx1069 (emphasis added). This prosecution statement is consistent with the application:

- "Drug manufacturers try to deal with the problem of oxidation by adding bisulfite antioxidants and increasing overages, both of which have the potential to cause harm to patients." Appx1018;

- "Most formulations also use overages of active pharmaceutical ingredient to compensate for degradation of epinephrine content and activity over the course of the product's shelf-life. This results in epinephrine drug products released after manufacturing with a higher than expected activity, which could be hazardous to patients as causing higher infusion and injection doses, thereby increasing side effects such as tachycardia." Appx1019.

- "There exists a great need for a liquid formulation of 1-epinephrine that is both preservative-free and sulfite-free, with minimal overage, if any, and with minimal levels of degradants, including d-epinephrine, while maintaining a sterility guarantee." *Id*.

While the examiner, in its Reasons for Allowance, did not expressly cite or reference Belcher's concentration limitation, overage arguments, or arguments related to degradation or impurity limitations, the examiner was explicit that allowance was not *solely* based on Belcher's pH level argument:

- "In view of Applicant's *arguments* and the Examiner's amendment presented *infra*, the rejection of claims 1-9 under 35 U.S.C. 103(a) ... is herein withdrawn." Appx1086 (emphasis added).

- "While Helenek et al. teach epinephrine compositions very similar to the instantly claimed compositions ... 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. Appx1088.

Thus the examiner did not rely solely on Belcher's pH level *argument*; instead, the examiner allowed the patent claims in view of Belcher's multiple "*arguments*," and unexpected management of "*impurities as instantly claimed*" (*i.e*.,

d-epinephrine *and* adrenalone), not merely the d-epinephrine that is managed through reduced racemization at the claimed pH level.

II. THE DISTRICT COURT'S OBVIOUSNESS AND INEQUITABLE CONDUCT DETERMINATIONS

At trial, Hospira alleged that two references anticipated the '197 patent: JHP's adrenalin 1 mg/mL epinephrine formulation approved by the FDA on December 7, 2012 (the "JHP Adrenalin Product"), and Hospira's 1 mg/mL l-epinephrine ampul product (Hospira's "Ampul Product"). *See* Appx1709-1716. Hospira also alleged that the '197 patent was obvious under §103 in view of these two products and ICH Guidelines, a set of guidelines having application across multiple pharmaceutical classes. *See* Appx1716-1720.

A. NO ASSERTED ART ANTICIPATES THE ASSERTED CLAIMS

The district court rejected Hospira's anticipation arguments. The court found that—based on testing conducted by Hospira—the JHP Adrenalin Product has a pH level 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 its shelf life. Appx1281; Appx792-796; Appx21.

The court also found that Belcher acquired the JHP Adrenalin Product and had Sintetica perform qualitative testing of the product. Appx21-22; Appx1523. Sintetica's analysis, not as exhaustive as Hospira's, showed the following chemical composition:

In the following table please find the data from the JHP Adrenalin batch 682478.

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%

Appx1523; Appx21-22. The court also found JHP's Adrenalin Product used sodium chloride as a tonicity agent. Appx22. Mr. Rubin possessed only the information from Sintetica's testing of the JHP Adrenalin Product, and not from Hospira's, before the patent issued. *See* Appx21 (detailing Mr. Rubin's knowledge of Sintetica testing but not Hospira testing).

Even Hospira's own testing showed, however, contrary to claims 6 and 7 of the '197 patent, that JHP's Adrenalin Product included high overages between 9.5 and 13.4%. Appx935; Appx21; Appx46 n.12. In other words, while the JHP Adrenalin Product is labeled as having 1 mg/mL l-epinephrine, it may have had between 1.095 and 1.134 mg/mL l-epinephrine at release. Appx935; Appx22. Because of these overages, the district court found that the JHP Adrenalin Product did not anticipate the concentration limitation of claims 6 and 7. Appx22; Appx45-46; *see* Appx935-936.

The district court also found that Hospira's Ampul Product did not anticipate the asserted claims, finding that Hospira's expert Dr. Pinal's "linear conversion

analysis" was inadequate evidence to support anticipation of claim 6's concentration limitation. *See* Appx23-24; Appx45-46; *see* Appx932-934.

B. THE DISTRICT COURT'S OBVIOUSNESS DETERMINATION

While the district court found that both the JHP and Hospira Products failed to anticipate claim 6, it considered both references in view of ICH Guidelines[7] and the general knowledge of a POSA. Appx47-49. The court credited Hospira's contention that a POSA would have been motivated by the ICH Guidelines and general knowledge to reduce the overage of either or both of the JHP Adrenalin Product and the Hospira Ampul Product, and further that a POSA would reasonably have expected success:

> [I]t 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.

[7] The ICH Guidelines are non-binding guidelines for pharmaceutical development, relating to pharmaceutical products generally, not epinephrine products specifically. *See* Appx26. They state: "In general, 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." Appx1538.

These guidelines were published and available at the same time as the USP Monograph, which allows as much as a 15% overage, Appx1378; Appx799-800. A POSA would consult both to understand industry norms. *See* Appx934.

Appx48.

Real-world evidence that Sintetica, Hospira, and JHP all struggled to prepare low-to-no overage formulations shows that the district court's conclusion as to the "reasonable expectation of success in pursuing this obvious modification of one or both of the Products" by lowering overage, Appx48, was clearly erroneous. Nevertheless, Belcher does not appeal the obviousness finding. But it is important to appreciate that the district court's obviousness finding was built on a larger universe of information than that possessed by Mr. Rubin during prosecution, and it was legal error to charge Mr. Rubin with inequitable conduct based on that larger universe. Notably, the court relied on testing of the JHP Adrenalin Product conducted by Hospira, the results of which were not available to Mr. Rubin before Belcher commenced this case. Similarly, Mr. Rubin had no access to a linear conversion analysis performed by Hospira's expert. The ICH Guidelines were not alleged to have been known to Mr. Rubin or improperly withheld from the PTO as part of Hospira's inequitable conduct theory or the court's decision.

For those reasons, it was clear error for the district court to assume that its anticipation and obviousness analyses established a basis for analyzing Mr. Rubin's alleged inequitable conduct. Mr. Rubin and Belcher may be held to account only for a failure to disclose *known* material information from the PTO, and this universe

is substantially smaller than the one used by the district court to make its obviousness decision.

C. THE DISTRICT COURT'S INEQUITABLE CONDUCT DECISION

Hospira alleged, and the district court agreed, that Mr. Rubin breached his duty of candor to the PTO in failing to disclose three references: Sintetica's prior epinephrine products, JHP's Adrenalin Product, and the Stepensky reference (collectively, the "Inequitable Conduct References"). *See* Appx1724; Appx54. The court found these references to be but-for material (Appx32) because each disclosed data inconsistent with a representation Belcher made to the PTO during prosecution:

> Belcher knew that pH would be critical to persuading the Examiner to approve the patent. … 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 l-epinephrine."

Appx56 (citing Appx1073-1074).

The district court found this representation, paired with the omission of the Inequitable Conduct References disclosing epinephrine formulations within this range, to amount to inequitable conduct in view of the examiner's notice of allowance:

> 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.

Appx57.

Without reservation or an express foundation, the court adopted Hospira's argument that the omitted references "resulted in levels of impurities that fell squarely within the claimed limits," and "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.'" Appx58; *see* Appx1828.

1. <u>JHP Adrenalin Product</u>

The JHP Adrenalin Product was discussed *supra*, in Background Section II.A.

2. <u>Stepensky</u>

Stepensky is a 2004 prospective study that did not discuss l-epinephrine. Instead, it tested 42 different syringe batches of "bitartrate salts" of epinephrine (Appx1347; Appx1349), *i.e.*, epinephrine bitartrate—an active pharmaceutical

ingredient different from epinephrine. Epinephrine bitartrate is related to but meaningfully distinct from l-epinephrine. *See, e.g.*, Appx688-689. Conversion factors must be used to translate measured d-epinephrine values and other degradant levels such that they may be understood with reference to the values recited in claim 6 of the patent. *Id.* Such conversions may increase the impurity and overage values disclosed in Stepensky. Appx710; Appx735-736.

The batches tested by Stepensky were manufactured at different dates and therefore stored for different lengths of time before testing. *See* Appx25-26; Appx1347. No products were tested at either the compounding step or the manufacturing release time ("time zero"). *See* Appx1348-1349. Stepensky does not disclose an epinephrine formulation having a pH between 2.8 and 3.3, let alone a concentration between 1.0 and 1.06 mg/mL product after the compounding step is complete. *See* Appx940-942.

Stepensky teaches away from the shelf life stability of formulations at a pH of 2.8 to 3.3, as claimed in the independent claims of the '197 patent. For instance, while Stepensky states that "[t]he measured pH values of the studied samples are presented in Figure 5" and that "[t]he pH values of all the studied samples were in the 3.25-3.70 range," Appx1351, Figure 5 does not show values at or adjacent to 3.25—and Hospira's expert admits that he cannot see any "data points at that 3.25 pH value." Appx906-907. Instead, the study discloses only formulations having a

pH between 3.3 and 3.7 during a commercially reasonable shelf life, Appx1353; Appx1797; Appx941-942, as shown in the following version of Stepensky Figure 5 that Belcher expert Dr. Mohapatra annotated to show 15-month shelf life (area to left of vertical red line) and a pH of 3.3 (area above horizontal red line). The two formulations in this range *both had a pH of about 3.4. See* Appx1353; Appx942; *see also* Appx730; Appx731. The closest measured value to the pH range claimed in claim 6 that also was measured near a commercially reasonable storage period has a pH at or slightly above 3.3 at around two years. *See id.*

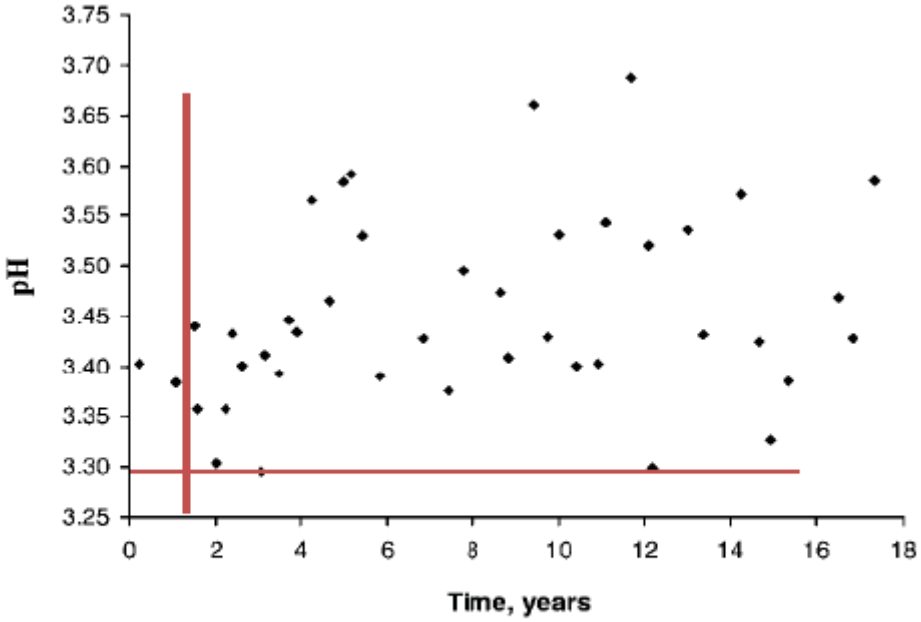

Figure 5. The pH values of the injections as a function of storage period.

Appx1353 (annotated); Appx1768; Appx941-942.

Stepensky further teaches, contrary to Hospira's expert's linear analysis, that l-epinephrine does not necessarily degrade linearly to d-epinephrine through

racemization until an equilibrium is reached between l-epinephrine and d-epinephrine. Appx27; Appx717; Appx719; Appx1351; Appx1368. Instead, "it is also possible for a formulation to reach equilibrium, at which point racemization stops, or reverses slightly before reaching a different equilibrium." Appx27; Appx716-717; Appx719; Appx733; Appx1351. This reversal of racemization (*i.e.*, conversion of d-epinephrine back to l-epinephrine) can be substantial: "At extended storage periods when D-adrenaline is present in significant concentrations, the rate of the reverse optical isomerization (conversion of D-adrenaline to L-adrenaline) becomes substantial, resulting in a distortion from the assumed first order." Appx1356.

A final distinction between Stepensky's disclosures and the claimed invention is that Stepensky analyzes epinephrine products with high overages ranging from 10.1% to 15%. Appx1354. Hospira expert Pinal admitted that Stepensky provides "no analysis ... as to what the concentration [of l-epinephrine] after the compounding step was." Appx906.

3. Sintetica Products

Hospira alleged that certain Sintetica Products—epinephrine products manufactured by Sintetica in the 2000s—were prior art to the '197 patent. Appx1724. But the district court explicitly found that record evidence does not

support this conclusion: "The record does not establish whether the 2003 Sintetica Products produced on behalf of Cura constitute public prior art." Appx54 n.16.

Even if these products *were* prior art, they do not disclose multiple limitations of the asserted claims. For example, it is undisputed that the Sintetica Products had high overages, up to and including 14%. *See* Appx1578 (showing 1.14% adrenaline concentration); Appx731-732; Appx944. Moreover, the Sintetica Products do not disclose d-epinephrine levels either at release or at 12 months. Appx882; *see also* Appx1398.

D. MR. RUBIN'S LACK OF KNOWLEDGE ABOUT SOME OF THE MATERIAL UNDERLYING THE DISTRICT COURT'S OBVIOUSNESS DECISION

As discussed *supra*, the district court was presented with substantial evidence related to Hospira's obviousness theory that cannot properly form the basis of an inequitable conduct finding. First, the only product or reference that was part of both the obviousness and inequitable conduct determinations was the JHP Adrenalin Product. *See* Appx20. Evidence regarding the Hospira Ampul Product and the ICH Guidelines, each of which informed the court's conclusion that it would be obvious to modify the prior art to achieve the invention of the '197 patent, were not alleged to have been improperly withheld from the PTO. *See* Appx1687. These generic ICH Guidelines were not shown to be known to Mr. Rubin at any time during prosecution of the '197 patent application; nor were they part of the inequitable

conduct case against Mr. Rubin. Nor was any of the data related to the Hospira's Ampul Product shown to be known to Mr. Rubin. That includes Dr. Pinal's argument using a linear conversion analysis through which Dr. Pinal and the trial court extrapolated chemical levels of the Hospira Ampul Product at release (time zero) based on measured values well after product release, Appx23, despite the applicability of such a linear analysis being in tension with Stepensky's explanation that racemization can reverse before equilibrium is reached.

The sole prior art overlapping Hospira's obviousness and inequitable conduct allegations is the JHP Adrenalin Product. The evidentiary foundation on which the court determined obviousness based in part on that product, however, is broader than that known to Mr. Rubin during prosecution. Evidence was presented at trial showing that Mr. Rubin was made aware of testing performed by Sintetica on the JHP Adrenalin Product showing the following information:

In the following table please find the data from the JHP Adrenalin batch 682478.

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%

Appx1523; *see* Appx691-692. This testing was conducted on batches that were three, seven, and ten months from expiration, respectively. *See* Appx1523. The JHP

Adrenalin product is listed as having an 18-month shelf life (Appx790; Appx794; Appx713-714), so the "freshest" batch tested was manufactured about eight months before testing. *See* Appx714 (extrapolating age of batches based on expiration). As is relevant to the claims of the '197 patent, this testing does not show:

- the concentration of l-epinephrine of the JHP Adrenalin Product between compounding and release;
- the level of d-epinephrine at release;
- the level of adrenalone at release; or
- the presence of a tonicity agent.

Appx1523.

Trial evidence also shows that Mr. Rubin forwarded via email a product label for the JHP Adrenalin product to a colleague. *See* Appx1495; Appx711-712; Appx727-728. But cross-examination regarding this reference did not show what, if anything, Mr. Rubin understood this reference to disclose at that time. *See* Appx711-712. The label does not disclose the pre-release levels of l-epinephrine, d-epinephrine, or adrenalone, nor levels of those compositions 12 months after manufacture. *See id.* The label also discloses that the product contains bisulfites. Appx1498.

The district court was presented with other evidence related to the JHP Adrenalin Product, as well as portions of the evidence in Mr. Rubin's possession but which were not shown at trial to be studied and understood by Mr. Rubin. For

example, Dr. Pinal discussed the contents of the JHP Adrenalin Product label without regard to whether that content was known to Mr. Rubin. *See* Appx790-791 (discussing sterility and tonicity properties of JHP Adrenalin Product). The Court relied on this same information in its invalidity opinions. Appx22. As discussed, record evidence does not establish Mr. Rubin's understanding of the substance of this label.

Hospira also presented the court with JHP Adrenalin Product testing *conducted by Hospira*, which was established to be *not* known to Mr. Rubin before trial. *See* Appx131; Appx792-796; Appx1281. The court also relied on this information in making its obviousness and inequitable conduct determinations. *See* Appx21; Appx47 (first sentence of court's obviousness opinion demonstrating that it was relying on the findings of its anticipation analysis).

ARGUMENT

I. INEQUITABLE CONDUCT STANDARD OF REVIEW

To prove inequitable conduct, an accused infringer must provide evidence that a patent applicant (1) misrepresented or omitted material information, and (2) did so with specific intent to deceive the PTO. *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1334 (Fed. Cir. 2011); *Therasense*, 649 F.3d at 1290-92 (Fed. Cir. 2011). Under the heightened inequitable conduct standard established in *Therasense*, the materiality required to establish inequitable conduct is, in general,

but-for materiality. *Therasense*, 649 F.3d at 1290-92. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art. *Id*.

As this Court has explained, "[t]o be guilty of inequitable conduct, one must have intended to act inequitably." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc*., 863 F.2d 867, 872 (Fed. Cir. 1988) (*en banc*) (citation omitted). "Mistake or negligence, even gross negligence, does not support a ruling of inequitable conduct." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1353 (Fed. Cir. 2008) (citation omitted). Intent must be proved by clear and convincing evidence. *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008). When intent is inferred, any predicate facts "must still be clear and convincing." *Id.* And deceptive intent must be "the single most reasonable inference able to be drawn from the evidence." *Id*. "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." *Therasense,* 649 F.3d at 1291 (citation omitted; emphasis in original). "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996).

This Court reviews a district court's determination of inequitable conduct under a two-tiered standard. First the Court reviews underlying factual

determinations of materiality and intent for clear error. *Star Scientific*, 537 F.3d at 1365. Then the Court reviews the ultimate decision as to inequitable conduct for an abuse of discretion. *Id.* But within the abuse of discretion analysis, the clear error standard continues to play a role, because an abuse of discretion occurs when (1) the trial court's decision is clearly unreasonable, arbitrary, or fanciful, (2) the court's decision is based on an erroneous construction of the law, (3) the court's factual findings are clearly erroneous, or (4) the record contains no evidence upon which the court rationally could have based its decision. *Larson Mfg. Co. of S.D. v. Aluminart Prods.*, 559 F.3d 1317, 1327 (Fed. Cir. 2009).

II. THE COURT'S OBVIOUSNESS ANALYSIS INAPPROPRIATELY CONTAMINATES ITS INEQUITABLE CONDUCT DETERMINATION

The court's inequitable conduct finding is narrow: Mr. Rubin violated his duty of candor when he failed to disclose Stepensky, JHP's Adrenalin Product, and the Sintetica Products, which the court found to be but-for material to patentability. Appx32; Appx54-59. But none of those references is, in fact, but-for material.

A primary reason the court committed this clear error is its incorporation of its obviousness analysis into its inequitable conduct decision. For example, the Court discusses the "JHP Adrenalin Product" in the context of its inequitable conduct determination (Appx54) without stating whether that term refers to the actual product or some combination of it and the JHP Adrenalin Product label, the

Sintetica testing of that product, Hospira's testing of the product, or Dr. Pinal's testimony relating to the product. *See* Appx20-22 (relying on all of these sources in making validity findings). Mr. Rubin can be charged only with withholding information he possessed during prosecution, not later information, test data, or analysis produced at trial by Hospira.

In the section entitled "Facts Related to Inequitable Conduct," the court states: "Stepensky, the JHP Adrenalin product, and/or Sintetica's epinephrine products are but-for material to the patentability of the '197 patent." Appx32. In the inequitable conduct legal analysis section, this is the court's entire analysis: "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," where the court's footnote 16 concedes that "[t]he record does not establish whether the 2003 Sintetica Products produced on behalf of Cura constitute public prior art," but still asserted that "there was still an obligation to disclose them to the Patent Office" under the Rule 56 standard. Appx54. The testimony of Dr. Pinal relied on by the court stated only that "those three prior art references [would] have been material to the patentability of the '197 patent," because "they teach two aspects covered in the claims. One of them is the pH range and the other one is the impurities." Appx760-761. Dr. Pinal also conclusorily

asserted that "had those references been before the Examiner, the claims would not have been allowed." Appx882-883. This testimony did not establish but-for materiality based on the information Mr. Rubin had but did not submit, because (1) it did not purport to disclose all claim elements, including low overage, since all the Inequitable Conduct References had high overages, Appx737-738; (2) it did not distinguish information produced at trial (*e.g.*, based on Hospira's testing) that Mr. Rubin did not have; and (3) the court relied on the ICH guidelines to supply the low overage element in its obviousness analysis, even though those guidelines were not alleged to have been withheld by Mr. Rubin.

Instead, it appears that the district court relied on the entire record with respect to the JHP Adrenalin Product, not merely the materials known to Mr. Rubin. In rendering its inequitable conduct decision, the court concluded that "*the record* clearly and convincingly demonstrates ... JHP's Adrenalin Products ... disclosed the allegedly critical pH range of 2.8 to 3.3; [and] ... resulted in levels of impurities that fell squarely within the claimed limits ...." Appx58 (emphasis added). But the court could not reach that conclusion based only on the JHP Adrenalin Product materials known to Mr. Rubin, and thus necessarily relied on information from its obviousness analysis that Mr. Rubin did *not* have to find the information that Mr. Rubin *did* have but-for material. For example, neither the Sintetica testing of the JHP Adrenalin Product nor the product label itself discloses the product's d-epinephrine or

adrenalone levels at product release. *See* Appx1523. Nor do they disclose the post-compounding, pre-release concentration of l-epinephrine of that product. *See id*; Appx22. While Mr. Rubin seemed to acknowledge that one might extrapolate adrenalone levels at release based in the Sintetica testing (Appx714), the court offers no basis for concluding that Mr. Rubin or the patent examiner knew that d-epinephrine levels at release would have been less than 6 percent. *See* Appx32 (providing no basis, based on Sintetica testing, to conclude that the JHP product had the claimed d-epinephrine value at release). Indeed, Stepensky (Appx1351), Mr. Rubin (Appx717; Appx719), and other evidence of record (Appx1368) establish that d-epinephrine levels go both up and down over time, making such extrapolation insufficient to establish that the elements were present even inherently in the prior art. Indeed, even inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981); *see also Bettcher Indus. v. Bunzl USA*, 661 F.3d 629, 639 (Fed. Cir. 2011). "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation." *Transclean Corp. v. Bridgewood Servs.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original). Moreover, Mr. Rubin testified that the Sintetica testing showed high levels of adrenaline sulfonates, indicating that much of the d-epinephrine content that existed in the JHP Adrenalin

Product had been absorbed by added sulfites, further obscuring the historical levels of d-epinephrine in the product. Appx715-716.

This failure to distinguish between the JHP Adrenalin Product information known to Mr. Rubin and that contained in the entire trial record is significant because, as explained *infra*, the information known to Mr. Rubin would not have prevented issuance of any claim in the '197 patent, and it is therefore not but-for material in the inequitable conduct context.[8] Thus, it was clear error to conclude that the court's obviousness determination—based on more JHP Adrenalin Product information that Mr. Rubin did not possess, and combined with ICH Guidelines that were neither before the patent examiner nor alleged to have been improperly withheld—requires a finding of materiality. *See Therasense*, 649 F.3d at1292 ("*Often* the patentability of a claim will be congruent with the [district court] validity determination ... because a finding of invalidity in a district court requires clear and convincing evidence, a higher evidentiary burden than that used in prosecution at the PTO.") (emphasis added).

[8] It is unclear whether other record evidence of the obviousness case—including Hospira Ampul product testing, Dr. Pinal's linear conversion testing related to such products, and teachings from the ICH Guidelines—factored into the court's inequitable conduct reasoning.

III. NONE OF THE INEQUITABLE CONDUCT REFERENCES IS BUT-FOR MATERIAL

For its materiality finding, the district court distilled thirteen pages of applicant amendment and argument (Appx1065-1077) and four pages of examiner response into a two-part supposedly false premise: the patent applicant's distinction over the cited art being based entirely on the criticality of its claimed pH range of 2.8-3.3 and the examiner's supposed allowance solely on this basis. *See* Appx56-58. The court found Stepensky, the Sintetica Products, and JHP to disclose this pH range, and on that basis found them to be but-for material to issuance of the patent claims. Appx54-56. But the court disregarded the applicant's arguments and the examiner's statements in arriving at this incorrect understanding of the record.

A. THE APPLICANT SUBMITTED MULTIPLE PROSECUTION ARGUMENTS BEYOND PH LEVELS

While Belcher made a pH-based argument to the examiner, the argument related only to two *dependent* claims, each distinct from the independent claim on which it depended only in that each claimed the pH range of 2.8-3.3. *See* Appx1066-1067; Appx1073-1074 (citing examiner's rejection of application claim 5). This argument was just one paragraph of a 13-page response. *See* Appx1065-1077. This limitation was ultimately imported into the independent claims, each of which was distinguished over the art on multiple bases independent of pH levels, including low overage.

For example, Belcher argued that prior art did not disclose a low-overage (1 mg per mL) preservative- and sulfite-free[9] formulation that was shelf-life stable. Appx1071. Nor did the cited art disclose epinephrine degradants and impurity levels, such as adrenalone. Appx1074. And none of the prior art cited by the examiner disclosed "information about levels of epinephrine and its impurities at product release, nor any shelf-life stability information." *Id.* The applicant could hardly have been more explicit that its formulation was distinct from the art in that its "preparation has tolerances and limits in production steps, *such as the narrow 1.0 to 1.06 mg/mL 1-epinephrine concentration range* …. Other considerations include *slight overages* to accommodate for loss during production, and degradation over the product's shelf-life."[10] Appx1068-1069 (emphases added). These distinctions over the art are entirely consistent with the specification, which states that "[t]here exists a great need for a liquid formulation of 1-epinephrine that is both preservative-free and sulfite-free, *with minimal overage, if any*, and with minimal levels of

[9] Unlike claims 1-5, claims 6 and 7 do not contain a preservative- or sulfite-free limitation. A patentee is, of course, entitled to claim some or all of the invention described in the specification. *In re Johnson*, 558 F.2d 1008, 1018 (C.C.P.A. 1977) ("It is for the inventor to decide what bounds of protection he will seek.") (emphasis omitted). Hospira did not allege or prove that the '197 patent disclosure is insufficient to support claims for sulfite-free formulations.

[10] Mr. Rubin explained that the concentration claim limitation was intended to give effect to the invention's low-overage advance over the art. Appx695; Appx30; *compare* Appx1022. Both parties' expert witnesses agreed. Appx891-892; Appx926-929.

degradants, including d-epinephrine, while maintaining a sterility guarantee. The present invention fulfills this great medical need ….. Appx1019 (emphasis added); Appx1781.

While the examiner, in the Reasons for Allowance notice, did not expressly cite or reference Belcher's concentration, overage, preservative, or its arguments related to degradation or impurity limitations, the examiner did state specifically that the allowance was not in view of Belcher's pH level argument standing alone: "In view of Applicant's *arguments* and the Examiner's amendment presented *infra,* the rejection of claims 1-9 under 35 U.S.C. 103(a) ... is herein withdrawn." Appx1086 (emphasis added). "While Helenek et al. teach epinephrine compositions very similar to the instantly claimed compositions ... 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*." Appx1088 (emphasis added). Thus, the examiner did not rely solely on Belcher's pH level *argument*; instead, the examiner allowed the patent claims in view of Belcher's multiple "*arguments*," and unexpected management of "*impurities as instantly claimed*" (*i.e.*, d-epinephrine *and* adrenalone), not merely the d-epinephrine that is managed through reduced racemization at the claimed pH level. *See id* (emphases added). In any event, the examiner's reason(s) for allowance need not limit a district court's factual findings regarding differences between cited art and application

claims. *See, e.g.*, M.P.E.P. §1302.14 (9th ed., June 2020) (providing examiner discretion to include a reason for allowance statement and the content of such a statement, if included; instructing that "[w]here the examiner has a large number of reasons for allowing a claim, it may suffice to state only the major or important reasons [for allowance].")

The district court erroneously framed its but-for materiality analysis when it relied simply on a reference known to Mr. Rubin that disclosed an epinephrine formulation having a pH of 2.8-3.3. But, as shown *supra*, neither the patentee's arguments nor the examiner's reasons for allowance were so limited.

That litmus test for but-for materiality cannot stand in view of other undisputed evidence of record. The record establishes that it is not enough to simply adjust the pH and/or reduce the overage of existing formulations to achieve Belcher's invention. *See* Appx1755. Sintetica tried and failed in just such an effort. Sintetica's high-overage, sulfite-free formulations in the pH range claimed by Belcher resulted in unacceptable oxidation, requiring lowering of the pH well below the range claimed by Belcher. Hospira had its own high-overage epinephrine formulation on the market in Belcher's claimed pH range, but the FDA requested remediation of the product's high overage. Appx1841-1842; Appx884. Hospira's own scientist admitted that its nearly decade-long effort lower the overage without introducing other, unacceptable considerations was a vexing undertaking, Appx624-

662, that included failure at the pH level claimed by Belcher. Appx602. So, too, with JHP, which had its own formulation in Belcher's pH range but which also contained high overage, preservatives, and degradant levels for which the FDA requested remediation. Appx1840-1841; Appx1755. But reformulation was no simple task for JHP, who in its years-long remediation effort found it very difficult to come up with a formulation that could minimize one degradation pathway without exacerbating another. Appx1840.

Belcher, then, was entirely justified in its argument to the PTO—"[i]f the Applicant's inventive formulation and methods were that obvious over" art disclosing a pH range of 2.8-3.3, "why has it taken roughly 25 years to produce [Belcher's] product?" Appx1071. An epinephrine reference with a pH in Belcher's claimed range, standing alone, does not make Belcher's invention obvious.

B. BECAUSE SINTETICA'S CITED EPINEPHRINE PRODUCTS ARE NOT SHOWN TO BE PRIOR ART, THEY CANNOT BE MATERIAL

It is black-letter law that a reference cannot be but-for material to the patentability of an invention if it is not prior art to a patent application. *Northern Telcom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940 (Fed. Cir. 1990) (because the device in question "was not prior art, it was not material to patentability"); *Environmental Designs, Ltd. v. Union Oil Company of California*, 713 F.2d 693, 698 (Fed. Cir. 1983) (same); *Specialty Composites v. Cabot Corp.*, 845 F.2d 981,

990 n.9 (Fed. Cir. 1988) ("it is not inequitable conduct to fail to disclose [alleged but unestablished 102(b) prior art] to the [PTO] during prosecution").

The district court explicitly found that the "record does not establish whether the 2003 Sintetica Products ... constitute public prior art." Appx54 n.16.

Even though the court was unable to determine whether the Sintetica Products are prior art, it nevertheless declared them but-for material. *See* Appx32. The court erred in that conclusion, because it held that, under 37 C.F.R. §1.56(b), Mr. Rubin had an obligation to disclose information that, under the terms of that section, might be "material to patentability." Appx54 n.16. But the materiality standard of Rule 56 is different from and lower than the but-for materiality standard of *Therasense*, and *Therasense* expressly held that violation of the PTO rule does not constitute violation of the *Therasense* rule. *See Therasense*, 649 F.3d at 1293-95.

Because the Sintetica Products were not established to be prior art, they cannot be but-for material to the patentability to the '197 patent, and the district court's reliance on this omitted reference in finding inequitable conduct is clear error.

In any event, the Sintetica Products lack multiple limitations of the '197 patent claims and would not have prevented issuance of the '197 patent claims. For example, the Sintetica Products had high overages of up to and including 14%, indicating that they cannot meet the '197 patent's pre-release l-epinephrine concentration limitation. *See* Appx1578; Appx731-732; Appx944; Appx1769.

They also do not disclose d-epinephrine levels either at release or at 12 months. Appx882; *see also* Appx1398.

C. THE STEPENSKY REFERENCE Does Not SUPPORT HOSPIRA'S CLAIMS

A comparison of the limitations of asserted claims and undisputed evidence at trial demonstrates that the Stepensky reference is not material:

Claim 6 limitation	Disclosed in Stepensky?	Record Cite
An injectable liquid pharmaceutical formulation of l-epinephrine sterile solution;	No. Stepensky discloses epinephrine bitartrate products, which are distinct from l-epinephrine solutions.	*See, e.g.*, Appx25-26; Appx1347; Appx1349; Appx688-689; Appx736; Appx1767.
said liquid pharmaceutical formulation having a pH between 2.8 and 3.3;	No. No product tested in Stepensky had a pH level between 2.8 and 3.3 during a commercially reasonable storage period.	*See, e.g.*, Appx1353; Appx940-942; Appx1767; Appx1797.
said injectable liquid pharmaceutical formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine,	No. Stepensky disclosed high-overage products. These products had overages as high as 10.1% (*i.e.*, 1.101 mg/mL); no compounding step tested or disclosed.	*See, e.g.*, Appx1354 (Table 1); Appx708; Appx1756; Appx1767; Appx1796-1797.
and further including a tonicity agent;	Not established in the record.	*See* Appx710-711.
said liquid pharmaceutical formulation including no more than about 6% d-epinephrine and no more than about 0.5% adrenalone at release,	No. Stepensky does not disclose degradant levels before release.	*See, e.g.*, Appx1348-1349 (discussing testing after controlled storage).

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	No. Stepensky does not disclose adrenalone levels at release or after a twelve month period. Stepensky's racemization data is suspect on its face.	*See, e.g.*, Appx1356; Appx733; Appx1768.

The chart demonstrates that Stepensky could not have prevented issuance of the '197 patent. It fails nearly every limitation grouping of asserted independent claim 6. Even if the court's improper framing of the materiality analysis were accepted—that any epinephrine product disclosing a pH level between 2.8 and 3.3 would have prevented issuance of patent claims—Stepensky fails to meet the requirements of that low bar.

While Stepensky states that it relates to epinephrine products having a pH between 3.25 and 3.7 (Appx1351), Hospira's expert admitted that the study discloses no formulations measured at or directly adjacent to a pH level of 3.25. Appx906-907; *see* Appx1353; Appx1797; Appx941-942.

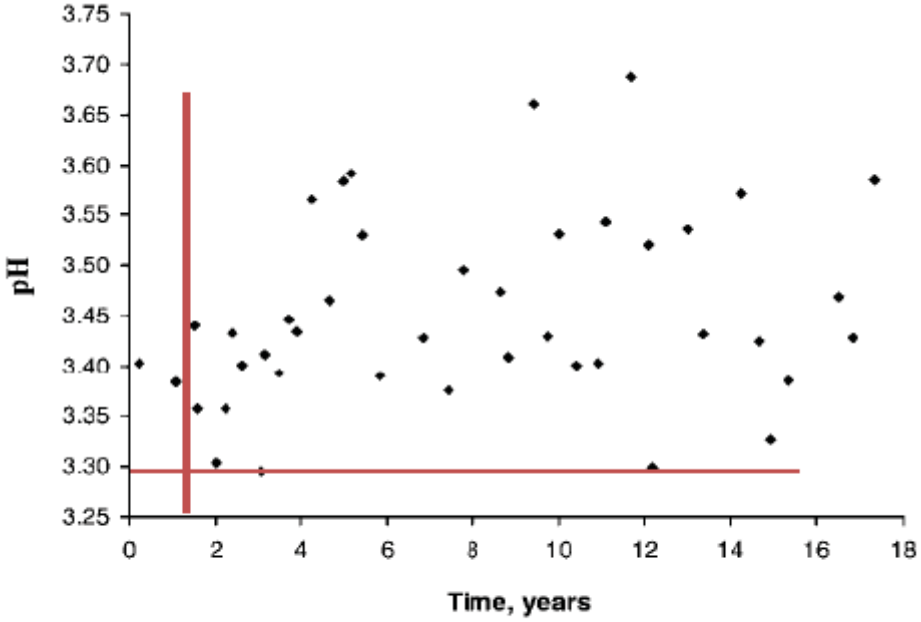

Figure 5. The pH values of the injections as a function of storage period.

Appx1353 (annotated); Appx1768; Appx941-942.

Even if the dots intersecting the horizontal red line of annotated Figure 5 were at or below the 3.3 pH level claimed by Belcher, it is unclear how this information—three out of 42 tested epinephrine products with a pH near 3.3 *at two, three, and twelve* years after manufacture, respectively—makes anything stated in prosecution false or material. Indeed, that nearly all of the formulations tested by Stepensky were well above pH 3.3 shows that Stepensky teaches *away* from the pH range in Belcher's claims, especially because Stepensky does not identify any benefits to having a pH in the 2.8-3.3 range.

The pH level that the district court found pivotal to its inequitable conduct conclusion was before the patent examiner: Belcher's patent issued over Helenek,

which disclosed epinephrine formulations with pH between 2.2 and 5.0, including epinephrine solutions with a pH range of 3.0 to 4.0. Appx1042; Appx1054-1055. A pH of 3.0, of course, is squarely within the range of the Belcher claims, yet Belcher's claims were found patentable over such art. *See Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020) ("we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness'") (quoting *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)). Additional prior art within the claimed range would have been merely cumulative. *See, e.g., Lazare Kaplan Int'l, Inc. v. Photoscribe Techs., Inc.*, 628 F.3d 1359, 1380-81 (Fed. Cir. 2010) (vacating lower court finding of inequitable conduct based on a failure to disclose reference teaching a recited range where examiner was already aware of reference disclosing claimed values); *Regeneron Pharms., Inc. v. Merus N.V.*, 864 F.3d 1343, 1350 (Fed. Cir. 2017) ("A reference is not but-for material ... if it is merely cumulative. A reference is cumulative when it 'teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO.'") (citations omitted).

Belcher argued that Helenek failed to disclose the critical importance of the 2.8-3.3 range in managing racemization (Appx1073-1074), and nothing in Figure 5 or other features of Stepensky point to the significance of Belcher's claimed pH range to manage racemization at the levels claimed by the '197 patent. Indeed,

Stepensky Figure 5 supports Belcher's argument, because it indicates that those in the art did not find the range at or below 3.3 critical to manage epinephrine degradation.

Stepensky's closest disclosure of d-epinephrine levels over time is a statement cited by Hospira and the court that "[t]he 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 ~4 years of storage at pH 2.4[8] [citing Fyllingen] or after 3 years at pH 3.0-3.5[19] [citing Allgire]." Appx31; Appx1356. This sentence suggests that a low pH of 2.4 is better for reducing or slowing racemization than a higher pH of 3.0-3.5, because stability at 4 years is better than stability at only 3, but the statement is in fact incorrect, because the opposite is true: racemization is inversely proportional to pH. Further, neither Fyllingen nor Allgire was asserted as part of Hospira's inequitable conduct theory (or even obviousness challenge) or the court's materiality findings. Indeed, Fyllingen teaches *away* from the pH range in Belcher's claims, stating that *at pH 2.4*, "both oxidation and racemization are at a minimum." Appx1370. Allgire was not introduced or discussed in any substantive way at trial; in any event, even by its title the reference relates to "lidocaine-epinephrine local anesthetics," Appx1358, quite different products from plain epinephrine solutions.

Another shortcoming of Stepensky is that Stepensky tested each batch at a single time point only, and never tested a batch at release (time zero). *See* Appx1349. That is because Stepensky neither produced the tested batches nor taught compounding. *See id.* Stepensky merely gathered a single sample of product from 42 different batches produced by different manufacturers spanning nearly two decades. *Id*. Without testing any batch at two or more separate time points, Stepensky does not speak to racemization change over time.[11]

D. THE JHP ADRENALIN PRODUCT WAS NOT BUT-FOR MATERIAL

The district court applied a clearly erroneous standard of but-for materiality to Belcher's prosecution arguments and the examiner's responses to those arguments. It also took an unduly broad view of what constitutes the "JHP Adrenalin Product" reference that was allegedly improperly withheld from the PTO. *See supra*.

Three pieces of information relating to the JHP Adrenalin Product were known to Mr. Rubin: the product itself, Sintetica test data, and the JHP Adrenalin Product label. It is undisputed that these materials (in addition to Hospira's own testing and expert testimony) fail to anticipate Belcher's patent claims (Appx22; Appx45-46), since they do not disclose all claim elements, and it is clear error to

[11] Stepensky's testing is akin to evaluating a diet by asking 42 different people to try the program while measuring their body weight only once during the program without knowing their starting weight.

conclude that these materials would have prevented issuance of the '197 claims as part of a combination.

First, the JHP Adrenalin Product—*i.e.*, the physical product itself—if submitted to the PTO, would not have changed the examiner's allowance. Such a disclosure would merely have disclosed an aqueous solution of epinephrine, and no more. That such prior art products existed was not disputed during prosecution. Inherent characteristics of the product, as evidenced at trial through the Hospira testing or testimony of Dr. Pinal, would not have been conveyed to the examiner through disclosure of the JHP Adrenalin Product. *See* Appx1751; *see, e.g.*, *In re Spormann*, 53 C.C.P.A. 1375, 1380 (C.C.P.A. 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

The Sintetica testing of the JHP product did not contain several limitations argued by Belcher during prosecution to be missing from the prior art. For example, Belcher reminded the examiner (Appx1074) that the prior art did not disclose the claimed level of impurities at release (*e.g.*, d-epinephrine), another limitation that the JHP Adrenalin Product references known to Mr. Rubin do not disclose. *See* Appx1523. After amending the claims, Belcher argued that its invention has tolerances and limits in production steps, such as the narrow 1.0 to 1.06 mg/mL l-epinephrine concentration range during the compounding step. Appx1068-1069. The lower court correctly concluded that the JHP Adrenalin Product test data

indicates that the JHP product cannot satisfy Belcher's pre-release concentration limitation. Appx22; Appx45. It is also undisputed that the JHP Adrenalin Product, unlike Belcher's claimed invention, was a high-overage product. Appx46 n.12; Appx935; Appx1069; Appx1752-1753. Belcher also argued that its invention, unlike the prior art, lacked "preservatives and antioxidants," another limitation of some claims that the JHP Adrenalin Product cannot meet. Appx1074; *see* Appx1523 (showing significant levels of sulfonated adrenalin, which results from sulfite (*i.e.*, a preservative) absorbing epinephrine (*see* Appx691-692; Appx715)). The examiner allowed claim language in view of all of Belcher's "arguments."

All of the disclosures of the three JHP Adrenalin Product references known to Mr. Rubin were already before the examiner. For example, the examiner found that Helenek in view of Gherezghiher disclosed a 1.0 mg/ml concentration of epinephrine, pH in the range claimed by Belcher, and sodium chloride as a tonicity agent. Appx1042-1043. Gherezghiher disclosed use of l-epinephrine and, according to the examiner, a person of skill in the art would be motivated to combine the teachings of these references to achieve a formulation having l-epinephrine for ophthalmic purposes. Appx1043-1044. The examiner also found that this combination would not necessarily have impurity levels exceeding the limits claimed by Belcher. Appx1045.

E. THE COMBINED INEQUITABLE CONDUCT REFERENCES DO NOT ACCOMPLISH WHAT THE INDIVIDUAL REFERENCES FAIL TO ACCOMPLISH

The Inequitable Conduct References, taken separately or together, fail to disclose all elements of claim 6. None discloses a low-to-no overage product, and the ICH Guidelines, the generalized pharmaceutical guidelines that the court used in its obviousness analysis to bridge this overage gap, were not part of the inequitable conduct allegations or analysis. *See* Appx47; Appx1764; Appx1801. Indeed, even had they been, reliance on the ICH Guidelines to supply the missing low-to-no overage limitation, and the district court's conclusion in its obviousness analysis that "[a] POSA would have had a reasonable expectation of success" in making a low-to-no overage product, Appx48, would have been clear error in view of the Sintetica, Hospira, and JHP failures in developing such a product. Applicant was not trying merely to create a product at pH 2.8-3.3; he was trying to be the first to develop a stable, low-to-no overage formulation, one that was also sulfite- and preservative-free. The Inequitable Conduct References, in contrast, all provide conventional wisdom, high-overage products. *No* reference that was part of the inequitable conduct analysis teaches or suggests a low-to-no overage product.

Because each of the Inequitable Conduct References lacks multiple limitations of the '197 patent claims, the district court clearly erred in adopting Hospira's argument that "Mr. Rubin knew (1) that each of the three references …

disclosed the allegedly critical pH range of 2.8 to 3.3; [and] (2) that epinephrine products with such a pH range resulted in levels of impurities that fell squarely within the claimed limits ….” Appx58. Disclosure of the Inequitable Conduct References would not have prevented issuance of ‘197 patent claims, and it was clear error to hold otherwise.

IV. INTENT TO DECEIVE THE PTO IS NOT THE MOST PLAUSIBLE EXPLANATION FOR MR. RUBIN’S PROSECUTION ARGUMENTS

The district court’s inequitable conduct intent finding rested on its erroneous conclusion that the Inequitable Conduct References—each allegedly satisfying the ’197 patent’s pH limitation—were highly material to prosecution of the patent. In view of this determination, the court refused to accept Mr. Rubin’s explanation for omitting them from prosecution: that he believed high-overage epinephrine references lacking multiple limitations of the application claims did not require disclosure because they were not material to Belcher’s invention. *See* Appx1796-1801; Appx691-692; Appx698; Appx708; Appx728-729. The court’s rejection of this explanation was clear error because the explanation is corroborated by undisputed evidence, and it is a more plausible explanation for Mr. Rubin’s conduct than a specific intent to deceive the PTO.

The district court inferred intent from its finding of the materiality of known references, Belcher’s prosecution statement related to criticality of pH levels, and its rejection of Mr. Rubin’s explanations for failing to supply the PTO with the

Inequitable Conduct References. *See* Appx54-58. But, as discussed *supra*, the references are not but-for material, and in any event, the materiality of a reference cannot substitute for a failure to show specific intent to deceive the PTO as the single most reasonable inference based on the proffered evidence. *Therasense*, 649 F.3d at 1290.

The court committed clear error in adopting without qualification Hospira's post-trial argument about Mr. Rubin's explanation for omitting the Inequitable Conduct References from prosecution:

> 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."

Appx58 (citing Appx1828).

This attorney argument, elevated to a judicial finding of fact by the district court, is inconsistent with the record. The common thread running through Belcher's NDA product, its patent application, its prosecution statements, and Mr. Rubin's trial testimony is the fact that Belcher's invention was a low-to-no overage product, and that feature makes it different from, and superior to, predecessor products. *See* Appx1764-1765. On this point there is no plausible dispute: Each of the Inequitable Conduct References is a high-overage product.

Despite its manufacturer's doubts, Belcher and Mr. Rubin found a way to create a sulfite-free, low-overage epinephrine formulation that managed both racemization and oxidation. Appx672-673; Appx1464; Appx1769. Mr. Rubin drafted and submitted a patent application touting the crucial advance of Belcher's invention over the high-overage art. *See* Appx1018-1019; Appx1022. When the application claims were initially rejected, Belcher clarified the importance of Belcher's invention over the art, stating "[t]he importance of the current invention is that the concentration of 1 mg per mL l-epinephrine is maintained as best as possible in a drug ... without using high overages during manufacturing which would result in increased side effects and inaccurate dosing to patients." Appx1069; Appx1784-1785. The examiner granted the pending claims in view of this and other Belcher prosecution arguments. Appx1086.

Mr. Rubin's trial testimony, then—that he believed the "importance of the invention described in the '197 patent" was to provide the public with a safe alternative to "sloppy" high-overage epinephrine products (Appx686), and that he did not submit such art to the examiner because "it was not relevant because it all had high overage" (Appx691)—is consistent with the record. These three independent sources of corroborating evidence—the NDA materials, the patent application, and the arguments made in prosecution—are the support the Court requires in circumstances like these—where a patent applicant "might be tempted to

describe his actions in an unjustifiably self-serving manner in order to ... maintain an existing patent." *Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003). When presented with such evidence, it is a court's duty to make an "evaluation *of all pertinent evidence* ... so that a sound determination of the credibility of the inventor's story may be reached." *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993) (emphasis added).

But the district court disregarded these facts corroborating Mr. Rubin's testimony when it concluded that "*[n]othing* in the prosecution history suggests that ... Mr. Rubin believed epinephrine overages to be [] critical to the invention." Appx58 (emphasis added). This is clear error. Indeed, the court faulted Mr. Rubin for repeatedly characterizing prior art references as "high overage" references."[12] Appx55-56. "When examining intent to deceive, a court must weigh all the evidence, including evidence of good faith." *Akron Polymer Container Corp. v. Exxel Container*, 148 F.3d 1380, 1384 (Fed. Cir. 1998); *Scanner Techs. Corp. v. Icos Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1376 (Fed. Cir. 2008) ("Whenever evidence proffered to show either materiality or intent is susceptible of multiple reasonable inferences, a district court clearly errs in overlooking one inference in favor of

[12] *See also* Appx714 (Mr. Rubin characterizing JHP Adrenalin Products as "these high overage products'); Appx728 (responding to question about omission of JHP Adrenalin Product from prosecution with "I don't believe we provided any high overage product data ….")

another equally reasonable inference."). The court did not consider the plausibility of Mr. Rubin's testimony in view of its consistency with the prosecution history and product development evidence, and in so doing committed clear error.

The district court's disagreement with Mr. Rubin that the Inequitable Conduct References were, despite their high overage, nevertheless required to be produced to the examiner (Appx54-55), does not support finding specific intent to deceive the PTO. "[I]nequitable conduct requires … intent to deceive. Intent to deceive cannot be inferred simply from the decision to withhold the reference where the reasons given for the withholding are plausible." *Dayco Prods., Inc. v. Total Containment*, Inc., 329 F.3d 1358, 1367 (Fed. Cir. 2003). Mr. Rubin's explanation is supported by the prosecution history and vindicated by the court's finding that the JHP Adrenalin Product has too high a concentration (and, as a result, too high an overage) to invalidate claim 6. *See* Appx46. Mr. Rubin's testimony is plausible, and specific intent to deceive therefore cannot be the single most reasonable explanation for omission of the Inequitable Conduct References.

Despite Mr. Rubin's plausible, corroborated testimony, the court found that Mr. Rubin's "repeated efforts to evade questioning and inject attacks of the prior art into his answers raised serious questions as to his credibility." Appx55-56. But the attempts of an inexperienced witness—inexperienced in both patent prosecution and testifying—to defend himself from personal attacks on his honesty, however

inelegant and unlawyerly, do not establish that he deliberately intended to deceive a government agency. *See Am. Calcar*, 651 F.3d at 1334 (reversing a finding of intent despite the trial court's characterization of testimony as "evasive and self-contradictory"). A finding that testimony is "lacking in credibility ... is insufficient to find specific intent to deceive under the knowing and deliberate standard." *Id*. at 1335.

The district court also took issue with Mr. Rubin's testimony that the '197 patent is related to sulfite-free formulations as further justification for not disclosing the Inequitable Conduct References. *See* Appx54-56. In the court's view, because claim 6 has no such limitation, a failure to submit these references for inclusion of sulfites was inexcusable. *See id.* But every *other* independent claim of the '197 patent has a sulfite-free limitation (Appx1001), demonstrating that his explanation was not baseless, but rather incomplete. The stated purpose of the '197 patent was to claim an innovation first achieved by Belcher: "a liquid formulation of 1-epinephrine that is both preservative-free and sulfite-free, with minimal overage, if any, and with minimal levels of degradants, including d-epinephrine ...." Appx999 (2:15-58). That Mr. Rubin's explanations do not have uniform application across claims is no reason to infer specific intent to deceive the PTO when each of the Inequitable Conduct References lacks multiple limitations of claim 6.

Finally, a central pillar of the district court's erroneous finding of intent is its conclusion that Mr. Rubin, through his patent prosecution counsel, made a statement he knew to be untrue: "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." Appx1057; *see* Appx56. The court reasoned that this proposition "may have been true in the context of preservative-free, low overage formulations, but [] it was not true as a general principle." Appx55.

But Mr. Rubin did not make this statement as a general principle. He made it to distinguish application claims 2 and 6, the only two pending claims with the pH 2.8-3.3 limitation, from the prior art. *See* Appx1066-1067. Each of these claims depended from independent claims that *did recite* a "preservative-free" limitation, along with a pre-release l-epinephrine concentration limitation that the experts agree contemplates low-to-no overage. *See id*.; Appx886; Appx889-890; Appx893-894 (low-overage products are "categorically different" from high-overage products). Thus, Mr. Rubin's statement was "true in the context of preservative-free, low overage formulations" (Appx55)—the *only* context in which the statement was made. That fact completely removes the foundation for the court's inference of deceptive intent—that this is a circumstance "in which Mr. Rubin made

'misleadingly incomplete, if not plainly inaccurate' statements." *See* Appx58 (citing *Apotex, Inc. v. UCB, Inc.*, 763 F.3d 1354, 1362 (Fed. Cir. 2014)).

Because the court had no proper basis to conclude that Mr. Rubin purposefully misrepresented the criticality of the 2.8-3.3 range, and because the court disregarded extensive evidence demonstrating the plausibility for Mr. Rubin's belief in the immateriality of high-overage, sulfite-containing prior art, it committed clear error in finding specific intent to deceive the PTO.

Accordingly, the inequitable conduct decision in this case fails at both the materiality and intent prongs. Since that judgment cannot be sustained on this record under the *Therasense* standard, the unenforceability determination should be reversed outright. *See 1st Media, LLC v. Elec. Arts, Inc.*, 694 F.3d 1367, 1377 (Fed. Cir. 2012); *cf. Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1179 (Fed. Cir. 1991) ("the judgment ... may be reversed, and not just vacated, because on this record, all underlying facts necessary to compel a finding ... have been found, correctly, and a remand on this issue for a new finding and for further analysis would serve no purpose.").

CONCLUSION

Because the district court committed clear error in basing its determination of inequitable conduct on an improper assessment of materiality and disregard of plausible explanations of Mr. Rubin's actions other than intent to deceive, Belcher

respectfully requests that this Court reverse the district court's declaration of inequitable conduct.

Dated: August 13, 2020.

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ADDENDUM

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 compounded 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 Abbojject 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

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

FINAL JUDGMENT

This action, having come to trial before the Court, Honorable Leonard P. Stark, Chief District Judge presiding, the issues having been heard and a decision having been rendered:

IT IS ORDERED AND ADJUDGED this 3rd day of April, 2020, for the reasons set forth in the Court's Opinion and Order dated March 31, 2020 (D.I. 244, 245), that:

1. Judgment shall be and is hereby entered in favor of Defendant Hospira Inc. ("Hospira") and against Plaintiff Belcher Pharmaceuticals, LLC ("Belcher") on Belcher's Count I in its Complaint dated June 16, 2017, for infringement of U.S. Patent No. 9,283,197 ("the '197 patent"). (D.I 1.)

2. Judgment shall be and is hereby entered in favor of Hospira and against Belcher on Hospira's Counterclaim Counts I, II, III, and IV in its First Amended Answer and Counterclaims, dated February 11, 2019, for (1) declaratory judgment of noninfringement of the '197 patent; (2) declaratory judgment of invalidity of the '197 patent; (3) unenforceability of the '197 patent for inequitable conduct; and (4) invalidity of the '197 patent for improper inventorship.

UNITED STATES DISTRICT JUDGE

4/3/2020

US009283197B1

(12) **United States Patent**
Taneja

(10) **Patent No.: US 9,283,197 B1**
(45) **Date of Patent: Mar. 15, 2016**

(54) **MORE POTENT AND LESS TOXIC FORMULATIONS OF EPINEPHRINE AND METHODS OF MEDICAL USE**

(71) Applicant: **Jugal K. Taneja**, Tampa, FL (US)

(72) Inventor: **Jugal K. Taneja**, Tampa, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/460,845**

(22) Filed: **Aug. 15, 2014**

(51) **Int. Cl.**
A61K 31/137 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/137*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/137
See application file for complete search history.

(56) **References Cited**

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* cited by examiner

Primary Examiner — Sreeni Padmanabhan
Assistant Examiner — Jody Karol

(57) **ABSTRACT**

The present invention provides pharmaceutical formulations of levorotatory-epinephrine, l-epinephrine, more potent and less toxic than existing pharmaceutical formulations of epinephrine, along with methods of producing and using these pharmaceutical formulations of l-epinephrine.

7 Claims, No Drawings

MORE POTENT AND LESS TOXIC FORMULATIONS OF EPINEPHRINE AND METHODS OF MEDICAL USE

FIELD OF THE INVENTION

The present invention provides pharmaceutical formulations of levorotatory-epinephrine (l-epinephrine), more potent and less toxic than existing pharmaceutical formulations of epinephrine, along with methods of producing and using these pharmaceutical formulations of l-epinephrine.

BACKGROUND OF THE INVENTION

Epinephrine has a long history of pharmaceutical use that spans many decades since this catecholamine was first chemically synthesized at the turn of the twentieth century. Epinephrine is a sympathomimetic drug that acts on both alpha and beta adrenergic receptors found ubiquitously throughout much of the body. Epinephrine has profound effects on the cardiovascular system. Epinephrine has direct myocardial stimulation that increases the strength of ventricular contraction and cardiac output, positive inotropic action; increases heart rate, positive chronotropic action; and causes vasoconstriction in the veins and many vascular beds, positive vasopressor action. Epinephrine remains the first-line inotrope/vasopressor in many parts of the world and is recognized by the World Health Organization as an essential medicine with many medical uses and forms of administration.

As eye drops, epinephrine provides mydriasis, the dilation of the pupil, during intraocular surgery. As a solution for nebulization, epinephrine provides bronchodilation and relief of bronchospasm to asthmatics and those with chronic obstructive pulmonary disease. As a solution combined with analgesics for injection, including lidocaine for dental applications and bupivacaine for epidural analgesia, epinephrine improves and lengthens pain relief and sensory blockade during surgical procedures. Yet, epinephrine has many life saving uses in emergency room settings. As a solution for intramuscular or subcutaneous injection, epinephrine helps alleviate vasodilation, loss of intravascular fluid volume, hypotension, bronchospasm, and other symptoms associated with anaphylaxis, severe allergic reactions. Injections of epinephrine can also help stop bleeding, such as bleeding associated with peptic ulcers and surgical procedures. As a solution for intravenous injection, epinephrine is used as a critical adjunct in the treatment of cardiac arrest, e.g., to provide return of spontaneous circulation. Lastly, intravenous injection of this vasopressor provides critical care relief of hypotension associated with certain types of shock and fluid refractory shock, including septic shock.

Although epinephrine has many uses, including many life saving uses, existing liquid formulations of epinephrine are associated with reduced potency, less desirable effects, or have the potential to cause harm. Formulations of epinephrine are plagued by two major problems, racemization and oxidation. Racemization is the enantiomeric conversion of l-epinephrine into its less biologically active dextrorotatory isoform, d-epinephrine, which has a significantly low pressor effect; about one-fifteenth that of l-epinephrine. The d-isoform may also affect adrenergic receptor subtypes differently than the l-isoform, resulting in substandard and undesirable effects. Because the United States Pharmacopeia, USP, monograph for epinephrine injection does not include specifications for d-epinephrine content, only total epinephrine content, manufacturers of epinephrine drug products are not required to test the chirality of their formulation and significant racemization occurs, thus leading to a less potent product with less desirable effects. In actuality, the d-epinephrine isoform should be classified as an impurity in an l-epinephrine drug product. It is believed that the epinephrine injection USP monograph does not include specifications for d-epinephrine because preventing its formation through racemization had proven too challenging. Whereas, oxidation of epinephrine can be prevented to a certain extent, including the use of antioxidants. The oxidation of epinephrine's alcohol group forms its less potent ketone form, known as adrenalone, which has little if any beta adrenergic activity. Racemization and oxidation of epinephrine are associated with reduced potency and less desirable effects as the impurities d-epinephrine and adrenalone form at the expense of l-epinephrine.

Drug manufacturers try to deal with the problem of oxidation by adding bisulfite antioxidants and increasing overages, both of which have the potential to cause harm to patients. Preservatives, such as sodium metabisulfite, are added to epinephrine formulations as antioxidants to reduce oxidation and to help keep formulations sterile. Sterilization techniques themselves often result in the loss of total epinephrine, and l-epinephrine, which may be compensated with increased overages. Sodium bisulfite and sodium metabisulfite, bisulfites, can cause mild to severe, life-threatening allergic reactions, including anaphylaxis or asthmatic episodes in susceptible individuals, especially those with sulfite sensitivities. So while epinephrine is indicated for treating anaphylaxis, the presence of sulfites in its formulation puts susceptible patients at great risk of exacerbating their anaphylaxis to the point of death. And for patients who are in other critical situations, such as cardiac arrest or septic shock, such sulfite reactions could greatly worsen the critical condition of these vulnerable patients. Most formulations also use overages of active pharmaceutical ingredient to compensate for degradation of epinephrine content and activity over the course of the product's shelf-life. This results in epinephrine drug products released after manufacturing with a higher than expected activity, which could be hazardous to patients as causing higher infusion and injection doses, thereby increasing side effects such as tachycardia.

In addition to the degradants d-epinephrine and adrenalone, which have been mentioned to have little pharmacological activity compared with l-epinephrine, lesser other degradants include adrenochrome and adrenolotin. A potentially toxic impurity, epinephrine sulfonate, forms by sulfonation reaction in epinephrine drug products containing sulfites.

Due to the deficiencies in existing pharmaceutical formulations of l-epinephrine, the identity, strength, quality, purity, and/or potency of the drug product cannot be adequately assured, or neither can its safety. There exists a great need for a liquid formulation of l-epinephrine that is both preservative-free and sulfite-free, with minimal overage, if any, and with minimal levels of degradants, including d-epinephrine, while maintaining a sterility guarantee. The present invention fulfills this great medical need by teaching improved l-epinephrine formulations, providing new methods of their preparation, and providing methods of safer medicinal use to achieve an improved standard of patient care.

DETAILED DESCRIPTION OF THE INVENTION

Past solutions of epinephrine have included a microbial preservative in order to assure the sterility of the drug product, even if the drug product was a single-use vial used immediately after opening. Sulfites were able to counter the oxidative behavior of epinephrine by reacting with residual oxygen in its container instead of reacting with epinephrine, and thus,

sequestered the free oxygen. When dissolution of the epinephrine was carried out by means of addition of diluted hydrochloric acid, HCl, some excess of acid could maintain a low pH near 2.2 and slow the degradation of epinephrine, also by forming inactive sulphonic acid.

Improved methods of preparation of sulfite-free pharmaceutical formulations of epinephrine included the compounding of the drug substance, followed by initial filtration, filling and sterilization. In order to produce and assure a sterile pharmaceutical solution of epinephrine as a drug product for injectable use, and without including preservatives such as metabisulfites, terminal heat sterilization following filling and/or final filtration under aseptic conditions during filling must be employed.

The compounding step utilized an active l-epinephrine pharmaceutical ingredient base, such as l-epinephrine hydrochloride, USP. This compounding step was performed to place the solid/powder active pharmaceutical ingredient into aqueous solution. Water for injection was the solvent. Mixing alone will not bring l-epinephrine into aqueous solution adequately. The pH of the solution must be lowered in order for the l-epinephrine base to dissolve properly. The pH can be lowered with an acid, such as an organic acid, and preferably 1 Normal (1N) hydrochloric acid that serves as a dissolution agent and a pH adjuster. Since the final solution will be injected into patients, the tonicity of the solution must be increased with a tonicity agent. Although various tonicity agents can be employed, the present methods preferably employ the use of sodium chloride as a tonicity agent. The batch formula per mL was 1.1 mg epinephrine base as the drug substance, 8.6 mg sodium chloride as the tonicity agent, 7.26 g hydrochloric acid (1N) as the dissolution agent, additional hydrochloric acid (1N) as a pH adjuster to lower pH to 2.2 to 2.6, and 987.04 mg water for injection as a solvent. Ideally, the compounding step and subsequent filtration step were conducted under inert nitrogen atmosphere to help prevent exposure of epinephrine and its solution to oxygen. It can be seen from this batch formula that a high 10% overage of epinephrine base was used to compensate for degradation over time, when the desired final concentration is 1 mg/mL epinephrine.

The compounded solution of l-epinephrine was then filtered, such as by a 0.22 micrometer filter and transferred to a sterilized, preferably glass, vessel. Filtration of the compounded solution removed any particulates, whether bacterial or undissolved ingredients.

The filtered solution of epinephrine was then filled into sterilized or sterile containers using sterilized filling equipment. Sterile containers included, but were not limited to, glass ampules, glass vials with caps, glass bottles with caps, and syringes to make prefilled syringes or autoinjectors. To help protect the epinephrine solution against oxidation since no metabisulfites were used in the formulation, the filling step was performed under an inert atmosphere of nitrogen that is essentially devoid of oxygen to reduce the residual oxygen content in the empty space of the filled container. This filling step could be performed under aseptic conditions along with additional filtration, such as by a 0.22 micrometer filter integrated with the filling equipment. Alternatively, or additionally, filled containers could be sterilized by heat, such as by using an autoclave or by steam sterilization. Terminal sterilization at a temperature above the boiling point of water, such terminal sterilization at 121° C., with overkill conditions assured sterility guarantee of the final drug product. For example, a F_0 of 10 minutes by means of a steered sterilization cycle was initially chosen to reduce the thermal stress on the epinephrine solution. Because thermal stress was not found to degrade epinephrine, over-kill conditions of sterilization could be used. Degradation of epinephrine was found mainly attributed to exposure to oxygen, which was directly related to nitrogen purge accuracy during the production and filling phases, instead of thermal treatment.

The above steps described the overall manufacturing process in making a drug product of preservative-free, sulfite-free solution of epinephrine. Specifically, it was found that this process inclusive of a 10% overage and an in-process pH range of 2.2 to 2.6 produced an epinephrine solution that could support a shelf-life of a 2 mL glass ampule containing 1 mL epinephrine solution for at least 48 months when studied in a climatic chamber at 25° C. for a maximum storage time of 60 months, in a climatic chamber at 30° C. for a maximum storage time of 12 months, and in a climatic chamber at 40° C. for a maximum storage time of 6 months.

However, this drug product produced by this manufacturing process with an in-process pH of approximately 2.5 was found to be inferior, and not only because of its high 10% overage. It was decided to test this epinephrine solution for d-epinephrine content even though there is no such rationale by USP or the industry to do so. When tested for d-epinephrine content by a chiral HPLC analytical method, it was unexpectedly found that approximately 14% of the l-epinephrine had been racemized into d-epinephrine at the product's release. After storage at 25° C. for 6 months, at least 19% of the l-epinephrine was converted to d-epinephrine. The drug product produced in this manner would contain less than 90% l-epinephrine in well under a year, and for all practical purposes, was unsuitable for use.

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. Terminal sterilization of the epinephrine solution only contributed to about 4% racemization, so eliminating heat sterilization and depending solely on aseptic filtration would not solve the racemization problem, nor have as strong of a final sterility guarantee in this antimicrobial-free solution. Lowering the in-process pH was not believed possible due to oxidation issues. The lower the pH was to 2.2, the lower the impact was of potential oxygen residues in the 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.

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.

The new method of preparing a 1 mg/mL solution of l-epinephrine, such as in a glass ampule, has a revised batch formula per mL of: approximately 1.03 mg epinephrine base, as the drug substance, 8.6 mg sodium chloride as the tonicity agent, 7.26 g hydrochloric acid (1N) as the dissolution agent, additional hydrochloric acid (1N) as a pH adjuster to lower pH only to 2.8 to 3.3, and 987.11 mg water for injection as a solvent. The compounding of the drug substance, followed by

initial filtration, filling and sterilization are all conducted under inert nitrogen atmosphere to help prevent exposure of epinephrine and its solution to oxygen.

With less than or no more than a 6% overage, and preferably a 3% overage, a viable shelf-life of at least one year, e.g., at least 15 months, was achieved with the new method with more than 90% l-epinephrine content at the end of the shelf-life. A sealed 2 mL glass ampule served as the container for the 1 mL drug product that was tested. However, the drug product solution of the present invention can be made in larger volumes in other sterile containers, including glass vials and bottles, and syringes and autoinjectors; including autoinjectors conducive with the preservative-free formulation. The new and improved formulation with reduced overage also has less than or no more than 6.5% total impurities, including less than or no more than 6% d-epinephrine and less than or no more than 0.5% adrenalone at release; and less than or no more than 12.5% total impurities, including less than or no more than 12% d-epinephrine and less than or no more than 0.5% adrenalone through a shelf-life of at least 12 months, and preferably through a shelf-life of at least 15 months. If aseptic filtration is used without terminal sterilization, these new methods would allow an l-epinephrine drug product to be prepared without any overage of epinephrine base, so that exactly 1.00 mg of epinephrine base is used per mL in the compounding step.

These inventive methods have discovered and achieved new limits for an injectable liquid pharmaceutical formulation of l-epinephrine sterile solution; less than or no more than about 6% d-epinephrine at release, and less than or no more than about 12% d-epinephrine through a shelf-life of at least 12 months; which has never been accomplished before, even if preservatives/sulfites are optionally included in the formulation as alternate embodiments (e.g., preservatives/sulfites up to about 1 mg per mL, such as sodium metabisulfite). Although these injectable liquid pharmaceutical formulations of l-epinephrine sterile solution introduced by this invention can be produced having any desirable concentration of l-epinephrine, they are preferably compounded in an aqueous solution as approximately 1.0 to 1.06 mg/mL l-epinephrine, and further include a tonicity agent, and include no more than about 6% d-epinephrine and no more than about 0.5% adrenalone at release, 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. Such injectable liquid pharmaceutical formulations of l-epinephrine sterile solution taught by this invention have uncompromised potency of l-epinephrine at release and through their shelf-life.

The present invention therefore provides improved methods of formulating safer and more reliable pharmaceutical preparations of epinephrine for medicinal use. Unlike other epinephrine formulations, these improved formulations are preservative-free and sulfite-free so that there are no safety issues for anaphylaxis and no toxic epinephrine sulfonate byproducts. These improved epinephrine formulations have no need for high overages, and use minimal overages, if any to assure reliable dosage. The present methods of this invention preferably use l-epinephrine hydrochloride, USP as the active pharmaceutical ingredient base, although other l-epinephrine active ingredients and salts and combinations thereof can be employed, including epinephrine bitartrate. The present methods of this invention preferably use sterile containers including, but not limited to, glass ampules, glass vials with caps, glass bottles with caps, and syringes to make prefilled syringes or autoinjectors. Other inert gases, instead of or in addition to nitrogen, can be used for the manufacturing process. Other concentrations of sulfite-free, l-epinephrine solution greater or lower than approximately 1 mg/mL can also be prepared using these new methods and in-process pH under nitrogen (inert gas) atmosphere, where nitrogen (inert gas) purge accuracy is inversely related to oxygen exposure during the production and filling phases.

The present invention also includes methods of using these more potent and less toxic liquid formulations of l-epinephrine as eye drops to provide mydriasis during intraocular surgery; as a solution for nebulization to provide bronchodilation and relief of bronchospasm to asthmatics and those with chronic obstructive pulmonary disease; as a solution combined with analgesics for injection, including lidocaine for dental applications and tumescent anesthesia and tumescent liposuction; and bupivacaine for epidural analgesia, to improve and lengthen pain relief and sensory blockade during surgical procedures; as a solution for intramuscular or subcutaneous injection to counter symptoms associated with anaphylaxis or to help stop bleeding associated with peptic ulcers and surgical procedures; as a solution for intravenous injection in the treatment of cardiac arrest, to provide return of spontaneous circulation; and as a solution for intravenous injection to relieve hypotension associated with certain types of shock and fluid refractory shock, including septic shock.

Other variations and embodiments of the invention described herein will now be apparent to those of skill in the art without departing from the disclosure of the invention or the coverage of the claims to follow.

What is claimed is:

1. A liquid pharmaceutical formulation of preservative-free and sulfite-free, 1 mg per mL l-epinephrine sterile solution for uses including injection; said liquid pharmaceutical formulation having a pH between 2.8 and 3.3; said 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 having no more than 6.5% total impurities at release, including no more than 6% d-epinephrine and no more than 0.5% adrenalone, and no more than 12.5% total impurities over a shelf-life of at least 12 months, including no more than 12% d-epinephrine and no more than 0.5% adrenalone; said liquid pharmaceutical formulation stored in a container with an inert gas prior to use.

2. The said liquid pharmaceutical formulation of claim **1** compounded in an aqueous solution preferably as 1.03 mg/mL l-epinephrine.

3. The said liquid pharmaceutical formulation of claim **1** further having no more than 12.5% total impurities over a shelf-life of at least 15 months, including no more than 12% d-epinephrine and no more than 0.5% adrenalone.

4. A liquid pharmaceutical formulation of preservative-free and sulfite-free, 1 mg per mL l-epinephrine sterile solution for uses including injection; said liquid pharmaceutical formulation having a pH between 2.8 and 3.3; said liquid pharmaceutical formulation compounded as 1.0 to 1.06 mg/mL l-epinephrine, along with 8.6 mg/mL sodium chloride as the tonicity agent, 7.26 mg/mL of 1 Normal hydrochloric acid as the dissolution agent, 987.11 mg/mL water for injection as a solvent, and with additional hydrochloric acid to adjust pH; said liquid pharmaceutical formulation having less than 6.5% total impurities at release, including less than 6% d-epinephrine and less than 0.5% adrenalone, and less than 12.5% total impurities over a shelf-life of at least 12 months, including less than 12% d-epinephrine and less than 0.5% adrenalone.

5. The said liquid pharmaceutical formulation of claim **4** compounded in an aqueous solution as 1.03 mg/mL l-epinephrine.

6. 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, 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.

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

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

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Case Number: 2020-1799

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