IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HOSPIRA, INC., Plaintiff; v. AMNEAL PHARMACEUTICALS, LLC, Defendant.	Civil Action No. 15-cv-697-RGA

MEMORANDUM OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

Plaintiff brought this patent infringement action against Amneal Pharmaceuticals, LLC in 2015. (D.I. 1). At issue in this case are ready-to-use formulations of the compound dexmedetomidine. Dexmedetomidine itself is claimed in U.S. Patent No. 4,910,214 ("the '214 patent"), which is not at issue in this case. The '214 patent issued on March 20, 1990 and expired on July 15, 2013. (Trial Transcript ("Tr.") 1081:9-12, 1082:10-15; '214 patent; D.I. 96-1 at 37).[1] Dexmedetomidine, which is the d-enantiomer of racemic 4-[1-(2,3-dimethylphenyl)ethyl]-lH-imidazole, is a sedative and is the active ingredient in Hospira's Precedex products. ('106 patent at 1:26-28, 1:34-37; Tr. 5:6-9). Amneal filed Abbreviated New Drug Application ("ANDA") No. 207551, seeking to engage in the commercial manufacture, use, and sale of generic versions of Hospira's 4μg/mL dexmedetomidine products ("Precedex premix") in 50 mL and 100 mL glass vials. (D.I. 96-1 at 3-4; PTX-63 at p. 6).

Since its FDA approval in 1999, Hospira's original Precedex product (100 μg/mL dexmedetomidine hydrochloride), also known as Precedex concentrate, has been sold in a 2 mL glass vial. (Tr. 6:11-15; D.I. 96-1 at 2). Before Precedex concentrate is administered to a patient, it must be diluted to an appropriate concentration per the instructions on the Precedex concentrate label. (Tr. 6:17-20). The delay in drug administration to patients and increased risks of dosing error and contamination associated with this dilution step led Hospira to develop ready-to-use formulations of Precedex. (*Id.* at 7:7-10). In 2013, Hospira received FDA approval for 50 mL and 100 mL glass bottles containing a ready-to-use 4 μg/mL formulation of dexmedetomidine hydrochloride. (D.I. 96-1 at 2). FDA approval of the same formulation in a 20 mL glass vial followed in 2014. (*Id.* at 3).

[1] The trial transcript is available on the docket at D.I. 114-117. It is consecutively paginated.

The Court held a bench trial from August 21-24, 2017. Plaintiff asserts that Defendant's ANDA submission constitutes infringement of claims 3 and 4 of U.S. Patent No. 8,242,158 ("the '158 patent"), claim 4 of U.S. Patent No. 8,338,470 ("the'470 patent"), claim 5 of U.S. Patent No. 8,455,527 ("the'527 patent"), and claim 6 of U.S. Patent No. 8,648,106 ("the '106 patent"). (Tr. 3:15-20; D.I. 101 at 3). The asserted patents are part of the same patent family and share a common specification. (D.I. 96 at 4).

Independent claim 1 and dependent claims 2-4 of the '158 patent read as follows:

> **1.** A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL disposed within a sealed glass container.
>
> **2.** The ready to use liquid pharmaceutical composition of claim 1, further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.
>
> **3.** The ready to use liquid pharmaceutical composition of claim 2, wherein the sodium chloride is present at a concentration of about 0.9 weight percent.
>
> **4.** The ready to use liquid pharmaceutical composition of claim 1, wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.

('158 patent at claims 1-4).

Independent claim 1 and dependent claim 4 of the '470 patent read as follows:

> **1.** A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container.
>
> **4.** The ready to use liquid pharmaceutical composition of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 μg/mL.

('470 patent at claims 1, 4).

Independent claim 1 and dependent claim 5 of the '527 patent read as follows:

> **1.** A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient disposed within a sealed glass container.
>
> **5.** The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 μg/mL.

('527 patent at claims 1, 5).

Independent claim 1 and dependent claim 6 of the '106 patent read as follows:

> **1.** A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof disposed within a sealed glass container, wherein the liquid pharmaceutical composition when stored in the glass container for at least five months exhibits no more than about 2% decrease in the concentration of dexmedetomidine.
>
> **6.** The ready to use liquid pharmaceutical composition of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 μg/mL.

('106 patent at claims 1, 6).

I. LEGAL STANDARDS

A. Claim Construction

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324) (alteration in original). When construing patent claims, a court considers the literal language of the claim, the patent

specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [This is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312-13. "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317-19. Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

B. Obviousness

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1369 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-63 (Fed. Cir. 2000); *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Secondary considerations of nonobviousness are important because they "serve as insurance against the insidious attraction of the siren hindsight . . . ." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101-02 (Fed. Cir. 2015). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple, Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016)

(en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc. v. Aptoex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). That burden stays always with the patent challenger. *Id.* at 1359-60.

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Id.* at 1361. That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success . . . is measured as of the date of the invention[] . . . ." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

C. Anticipation

"To show that a patent claim is invalid as anticipated, the accused infringer must show by clear and convincing evidence that a single prior art reference discloses each and every element of a claimed invention." *Silicon Graphics, Inc. v. ATI Techs., Inc.*, 607 F.3d 784, 796 (Fed. Cir. 2010). "[E]very element of the claimed invention [must be] described, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009). As with infringement, the court construes the claims and compares them against the prior art. *See Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1337 (Fed. Cir. 2010).

D. Indefiniteness

A patent must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). To determine indefiniteness, courts examine "the patent record—the claims, specification, and prosecution history—to ascertain if they convey to one of skill in the art with reasonable certainty the scope of the invention claimed." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). "[I]f necessary, a court may consult extrinsic evidence to understand the meaning of a term in the relevant art." *Transcend Med., Inc. v. Glaukos Corp.*, 2015 WL 5546988 at *5 (D. Del. Sept. 18, 2015) (citation omitted).

E. 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). A two-step analysis is employed in making an infringement determination. *See Markman*, 52 F.3d at 976. First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). "Literal infringement of a claim exists when every limitation recited in the claim is found in the accused device." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1477 (Fed. Cir. 1998). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

For jurisdictional purposes, 35 U.S.C. § 271(e)(2)(A) defines filing an ANDA application for a drug covered by a patent as an act of infringement. 35 U.S.C. § 271(e)(2)(A); *see also Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) ("[Section] 271(e)(2) provided patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity."). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). Therefore, "when a drug manufacturer seeks FDA approval to market a generic compound within the scope of a valid patent, it is an infringement as a matter of law." *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1280 (Fed. Cir. 2013). When an ANDA is silent with respect to at least one claim limitation of the patents at issue, however, *Sunovion* does not apply, and "the relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1382, 1388 (Fed. Cir. 2014) (citation omitted).

II. DISPUTED CLAIM CONSTRUCTIONS

The parties dispute the constructions for "ready to use" and "sealed glass container," each of which appear in all of the asserted claims. Although the parties stipulated that Defendant's proposed ANDA products meet the "ready to use" limitation for purposes of infringement, they dispute the plain meaning of the term for purposes of assessing invalidity. (Tr. 4:10-15). There was no stipulation with respect to the "sealed glass container" limitation for purposes of assessing infringement. (*Id.* at 3:22-4:8).

At trial, Plaintiff argued for a construction defining the plain meaning of "ready to use" as "formulated to be suitable for administration to a patient upon manufacture without dilution or reconstitution." (*Id.* at 262:9-263:1). Defendant asserts that the plain meaning of "ready to use" is "requiring no further dilution or reconstitution before administration to a patient." (*Id.* at 581:12-19). The common specification of the asserted patents reveals that the patentees acted as their own lexicographers with respect to this term. In a section titled "Definitions," the specification states that "ready to use" formulations "refer to premixed compositions that are suitable for administration to a patient without dilution." (*See, e.g.*, '106 patent at 3:66-4:2). Therefore, I conclude that the construction of "ready to use" is "suitable for administration to a patient without dilution."

During trial, I proposed several constructions for "sealed glass container." (Tr. 1176:2-21). Among those constructions was "a container that is closed tightly to maintain sterility." (Tr.1176:12-20). The parties appear to have agreed to this construction. (D.I. 100 at 34-35 ("Amneal submits that either of the Court's two proposed definitions of 'sealed' would be proper, so long as a further tamper-[evident limitation] is not added."); D.I. 101 at 5 n.3 ("So long as this construction includes the limitation of 'glass,' Hospira agrees that this proposed meaning is supported by the record because a sealed container in this context maintains sterility."); *see also* '106 patent at 9:9-15 (disclosing a sealed glass container packaging embodiment that "can maintain the sterility of, or prevent the contamination of, a premixed dexmedetomidine composition")). Accordingly, I will construe "sealed glass container" as "a glass container that is closed tightly to maintain sterility."

III. VALIDITY OF THE '158, '470, '527, AND '106 PATENTS

The '158, '470, and '106 patents each describe ready-to-use pharmaceutical compositions of dexmedetomidine or a pharmaceutically acceptable salt thereof for parenteral administration, disposed within a sealed glass container. The asserted claims of these patents claim or encompass dexmedetomidine concentrations of 4 μg/mL. Certain asserted claims contain additional limitations, such as the presence of sodium chloride at a concentration of about 0.9 weight percent in the dexmedetomidine formulation ('158 patent at claim 3), certain volumes of the dexmedetomidine formulation (*id.* at claim 4), and formulations losing no more than about 2% dexmedetomidine concentration at 5 months ('106 patent at claim 6). Asserted claim 5 of the '527 patent claims a method of providing sedation to a patient via parenteral administration using a 4 μg/mL dexmedetomidine formulation disposed within a sealed glass container. ('527 patent at claim 5).

Defendant argues that all the asserted claims are invalid as obvious, and further asserts that claim 3 of the '158 patent, claim 4 of the '470 patent, and claim 5 of the '527 patent are invalid as anticipated. (D.I. 100 at 8, 36). Additionally, Defendant contends that claim 6 of the '106 patent is indefinite under 35 U.S.C. § 112. (*Id.* at 26).

A. Findings of Fact

1. For the product claims, the person of ordinary skill in the art ("POSA") holds an advanced degree, such as a Ph.D., M.D., or Pharm.D., in chemistry, pharmacology, or pharmaceutical development.

2. For the method of treatment claim, the POSA would have some formal education in science, chemistry, pharmacology or pharmaceutical development, and would have several years of experience administering pharmaceuticals to patients, including clinical experience in anesthesia or sedation and familiarity with parenteral injections. The POSA's practical experience may vary depending on the POSA's level of formal education.

3. The priority date for the asserted patents is January 4, 2012. (D.I. 96-1 at 5).

4. Each of the asserted patents is assigned to Hospira. (D.I. 96-1 at 2).

5. The Precedex Concentrate product, the 2010 Precedex concentrate label, Cain, and Trissel are prior art to the asserted patents. (D.I. 96-1 at 5-8).

6. Evidence supporting commercial success of Plaintiff's Precedex Premix product is weak due to the '214 blocking patent covering the dexmedetomidine compound and due to Plaintiff's business practices in marketing its Precedex Premix product.

7. Each of claims 3 and 4 of the '158 patent, claim 4 of the '470 patent, and claim 5 of the '527 patent is obvious over the 2010 Precedex concentrate label and the Precedex concentrate product, in view of the pharmaceutical packaging knowledge in the art.

8. Claim 6 of the '106 patent is not obvious over the 2010 Precedex concentrate label and the Precedex concentrate product, in view of the pharmaceutical packaging knowledge in the art.

9. Trissel does not anticipate any of the asserted claims.

10. Trissel does not render any of the asserted claims obvious in view of the pharmaceutical packaging knowledge in the art.

B. Conclusions of Law

1. Obviousness of the '158, '470, and '527 Patents

Defendant argues that in view of pharmaceutical packaging knowledge in the art, the asserted claims are obvious over the prior art Precedex concentrate product in combination with the 2010 label accompanying it, or obvious over Trissel. (D.I. 100 at 3, 36). Plaintiff responds that the asserted claims are not obvious because the prior art did not disclose a ready-to-use 4 μg/mL dexmedetomidine solution or suggest development of such a solution, the USPTO issued the patents-in-suit over the Precedex concentrate product and the accompanying label, and commercial success of the Precedex premix product supports nonobviousness. (D.I. 106 at 7, 9, 10, 16).

a. Scope and Content of the Prior Art

i. Background

The prior art recognized that it was not unusual for new products "of a similar class or type [to] mimic the packaging used on the first marketed product, even if newer materials and alternative material fabrication, [or] manufacturing . . . offer significant advantages." (DTX-202 at p. 189). As of the priority date, glass had a long history as a successful pharmaceutical packaging material, and was considered "the traditional gold standard for pharmaceutical packaging." (*Id.* at p. 192; Tr. 525:5-526:4). A 2010 literature review recognized glass as "the container material of choice for most small volume injectables." (DTX-219 at p. 12; *see also id.* at p. 7 (recognizing glass as "the most common packaging for liquid and freeze-dried injectables"); DTX-200 at pp. 79-80 (noting in discussion of glass interactions with drug products that "Type I glass will be suitable for all products . . ." and noting the use of treated glass to resolve any product incompatibilities with glass); DTX-553 at p. 809 ("Glass is employed as the container material of choice for most [small-volume injectables]")). A small-volume injectable, or "small volume parenteral, is anything less than a hundred mLs as opposed to [a large-volume parenteral], which is above a hundred mLs." (Tr. 528:1-9).

Glass has several properties that make it desirable for pharmaceutical packaging. Among these are its impermeability and its largely inert chemical nature. (DTX-202 at p. 192). Although glass is not completely inert, its long history and known chemistry allow packaging engineers to alleviate any problems that arise with using glass as a pharmaceutical packaging material for a particular product. (*Id.* at p. 192; DTX-553 at p. 809 (noting that disadvantages of glass "can be minimized by the proper selection of the glass composition")). For example, treated glass may be used to address problems such as adsorption of the active ingredient to the surface of the glass

packaging. (DTX-200 at p. 80).

Glass pharmaceutical packaging does, however, have some chemical and physical drawbacks. (DTX-202 at p. 199). If the glass container is comprised of migratory oxides, such oxides may leach from the glass container into the solution inside it, leading to an increase in the pH of the solution or other unintended chemical reactions. (DTX-553 at p. 809). Some glass compounds are vulnerable to attack by solutions with certain characteristics, and glass flakes may be dislodged into the solution inside the glass container if such an attack occurs. (*Id.*). Glass may shatter if mishandled during shipping or during use in the clinical setting. (Tr. 940:20-941:6). Additionally, glass packaging is more expensive to manufacture and transport than plastic packaging. (DTX-202 at p. 199). The prior art recognized, however, that the use of treated glass could address many of the chemical drawbacks to glass pharmaceutical packaging. (DTX-553 at p. 810; DTX-200 at p. 80).

As of the priority date, clinicians also demonstrated a general preference for ready-to-use pharmaceuticals. (DTX-43 at p. 5 ("At a 2008 national consensus conference on the safety of intravenous drug delivery systems, there was a clear preference for manufacturer-prepared completely ready-to-use IV medication in all settings . . . .")). Ready-to-use pharmaceuticals demonstrated the potential to improve patient safety through eliminating errors associated with dilution from a concentrate form, such as errors in dosing, preparation technique, drug, or base solution. (Tr. 522:15-523:15; DTX-44 at p. 56 ("Premixed formulations may obviate a variety of admixture-related problems, including admixture preparation errors, delays in administration, and interruptions in pharmacy workflow."); DTX-46 at p. 177 (concluding, in neonatal unit university hospital study of relative safety gains for specific tools, that "the involvement of a clinical pharmacist and the introduction of ready-to-use syringes for selected drugs have been shown to be

the most cost-effective tool.")). Additional benefits of ready-to-use formulations include reduced delays in administering medication to patients and minimizing waste and costs. (DTX-44 at p. 56 ("The use of premixed solutions obviates the need for admixture or other manipulations prior to clinical use, thereby . . . improving efficiency and patient safety, facilitating adherence to policies and procedures, and minimizing waste and costs.")).

ii. Precedex Concentrate Product and Package Insert

The prior art Precedex concentrate product is a 100 μg/mL formulation of dexmedetomidine in 0.9% sodium chloride disposed within a 2 mL glass vial. (Tr. 510:20-511:2). The Package Insert is the label that accompanies the Precedex concentrate product. (DTX-23 at p. 5014). It displays a revision date of September 2010, and indicates that Precedex concentrate is approved for intensive care sedation and procedural sedation. (*Id.*). The 2010 label includes instructions to dilute the Precedex concentrate product with 0.9% sodium chloride to achieve 50 mL of a 4 μg/mL dexmedetomidine formulation, to be administered intravenously. (*Id.* at pp. 5014, 5016). Strict aseptic technique is required during dilution, and the label counsels against the use of natural rubber with the product, instead recommending the use of administration components made of synthetic or coated rubber. (*Id.* at pp. 5016-17). No additives or chemical stabilizers are present in Precedex concentrate. (*Id.* at p. 5027). According to the label, each 2 mL glass vial is intended for a single use only, and vials of Precedex concentrate are to be stored at room temperature, "with excursions allowed from 15 to 30°C." (*Id.* at p. 5032).

iii. Trissel

Trissel is a study published in 2002 that sought to determine the "physical compatibility of Precedex with 95 selected other drugs." (DTX-120 at Abstract). Since Precedex is commonly used in intensive care settings, patients receiving Precedex are likely receiving other drugs

simultaneously. (*Id.* at p. 230). To test compatibility, the Trissel authors used a 15 mL borosilicate glass screw-cap culture tube to mix 5 mL of a 4 μg/mL formulation of Precedex (to mimic the Precedex concentration administered to patients) with 5 mL of each of the drugs tested. (*Id.*). To achieve the 4 μg/mL Precedex formulation, the authors diluted the Precedex concentrate product with 0.9% sodium chloride injection to a concentration of 4 μg/mL per the instructions on the label accompanying the Precedex concentrate product. (*Id.*). The authors tested for compatibility at 15 minutes, 1 hour, and 4 hours after sample preparation. (*Id.*). One of the control samples consisted of 4μg/mL Precedex, diluted from the Precedex concentrate product with 0.9% sodium chloride injection. (*Id.*). The Trissel authors concluded that, "Precedex is physically compatible for 4 hours at room temperature with 93 drugs evaluated in this study during simulated Y-site administration." (*Id.* at p. 233).

b. Comparing Prior Art and Claimed Subject Matter

As an initial matter, Plaintiff urges that the asserted claims are nonobvious over the Precedex concentrate product and the 2010 label in part because the patent examiner considered these references during prosecution, and ultimately issued the asserted claims over the references. (D.I. 106 at 7-8). According to Plaintiff, "the examiner explicitly considered and rejected Amneal's arguments that the 2010 package insert disclosed a 'known' ready-to-use solution in a 'known' sealed glass container." (*Id.* at 8). The examiner's findings, however, are not entitled to deference here. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1357 (Fed. Cir. 2013) ("The present case is a district court challenge to an issued patent brought under the Hatch–Waxman Act, not a challenge to a PTO rejection . . . [so t]he initial determinations by the PTO in determining to grant the application are entitled to no deference . . . ."). Nor does the clear and convincing evidence standard to prove invalidity change based on what the examiner considered.

Id. ("[W]e treat the issued patent as having a presumption of validity that must be overcome by clear and convincing evidence. No decision of the Supreme Court or this court has ever suggested that there is an added burden to overcome PTO findings in district court infringement proceedings"); *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("In short, there is no heightened or added burden that applies to invalidity defenses that are based upon references that were before the Patent Office."). The weight of the evidence may change, however, depending on whether it was considered by the examiner during prosecution. *Id.* ("For example, it could be reasonable to give more weight to new arguments or references that were not explicitly considered by the PTO when determining whether a defendant met its burden of providing clear and convincing evidence of invalidity. Conversely, it may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered.").

Plaintiff raises a second threshold issue, asserting that Hospira's internal documents may not be used to prove obviousness. (D.I. 106 at 15-16). These documents are not prior art, Plaintiff contends, because they were not public at the time of invention. (*Id.* at 16). Plaintiff is correct that "[t]he inventor's own path itself never leads to a conclusion of obviousness." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012). Defendant responds that unlike the obviousness theories in the cases Plaintiff has cited, which "merely followed the inventor's chemical modifications," Defendant's obviousness theory is rooted in the prior art. (D.I. 108 at 15). Further, Defendant asserts that Plaintiff's internal documents are probative in assessing the credibility of Plaintiff's witnesses' testimony regarding reasonable expectations of success. (*Id.*). Defendant may rely on Plaintiff's internal documents for the limited purpose of assessing witness credibility. *Merck & Cie v. Watson Labs., Inc.*, 822 F.3d 1347, 1353-54 (Fed. Cir. 2016) (holding

that post hoc "conclusory testimony cannot trump the unambiguous documentary record").

The parties do not dispute that the Precedex concentrate product and its accompanying 2010 label taught many elements of the asserted claims. The 2010 label discloses that Precedex concentrate, once diluted to a concentration of 4 μg/mL, is to be administered intravenously to achieve patient sedation. (DTX-23 at p. 5014; Tr. 511:16-512:5). Additionally, the label directs a POSA to prepare 50mL of a 4 μg/mL dexmedetomidine formulation by diluting the Precedex concentrate product with 0.9% sodium chloride. (DTX-23 at pp. 5014, 5016; Tr. 512:15-513:3). The label further discloses that no additives or chemical stabilizers are present in the Precedex concentrate product. (DTX-23 at p. 5027). Dilution with 0.9% sodium chloride to a concentration of 4 μg/mL would not introduce any such additives or stabilizers, since the Precedex concentrate formulation consists of dexmedetomidine in 0.9% sodium chloride. (Tr. 510:20-511:2).

Therefore, the issue is whether these teachings, combined with what was known in the pharmaceutical packaging art, would have (1) motivated a POSA to develop a ready-to-use 4 μg/mL dexmedetomidine formulation disposed within a sealed glass container, and (2) given a POSA a reasonable expectation of success in doing so. The Precedex concentrate product is disposed within a 2 mL glass vial, which a POSA would know is closed tightly to maintain sterility. (*Id.* at p. 5032). This is supported by the label requirement of "strict aseptic technique" during dilution. (*Id.* at p. 5016). Further, the label advised that the Precedex concentrate diluted to 4 μg/mL be used with synthetic or coated rubber components with (*id.* at p. 5017), such as the coated rubber stoppers that the patentees planned to use for the Precedex premix product ('106 patent at 21:33-48).

The parties dispute whether a POSA would have been motivated to develop a ready-to-use 4 μg/mL dexmedetomidine formulation disposed within a sealed glass container. (D.I. 100 at 11,

13; D.I. 106 at 10-12). Defendant maintains the prior art's expressed preference for ready-to-use injectables (*see, e.g.*, DTX-43 at p. 5) and the Cain reference would have provided a POSA ample motivation to modify the Precedex concentrate product to develop a ready-to-use dexmedetomidine formulation. (D.I. 100 at 13). More specifically, Cain's disclosure that a hospital pharmacy was offering dexmedetomidine syringes premixed according to the 2010 label instructions provided evidence of market interest and demand for ready-to-use dexmedetomidine formulations in the clinical setting. (*Id.*; Tr. 520:16-521:6). Plaintiff asserts that because the Cain reference did not explicitly state "that a manufacturer-prepared ready to use 4 μg/mL dexmedetomidine formulation should be developed," the reference is insufficient to indicate market demand for ready-to-use dexmedetomidine formulations. (D.I. 106 at 11). As support for this proposition, Plaintiff identifies one article that calls for a manufacturer to prepare a ready-to-use formulation of a specific drug. (DTX-44 (mentioning amiodarone specifically)). Additionally, Plaintiff discounts as conclusory the testimony of Defendant's expert, Dr. Yaman, about how a POSA would view the Cain disclosure. (D.I. 106 at 11). Plaintiff notes that none of Defendant's other references specifically reference the need for ready-to-use formulations of dexmedetomidine. (*Id.*). At best, Plaintiff contends, the prior art describes a preference "for ready to use products generally, even though the market had not realized its need for a ready to use 4 μg/mL dexmedetomidine solution prior to [Plaintiff's] patented invention." (*Id.*). Plaintiff further argues that a POSA would not have been motivated to use a glass container to store any ready-to-use dexmedetomidine formulation because "glass was not the preferred container closure" due to potential issues such as breakage and adsorption. (*Id.* at 13; Tr. 874:11-15, 940:20-941:6, 944:19-22).

I agree with Defendant that a POSA would have been motivated to develop a ready-to-use dexmedetomidine formulation, and would have combined the Precedex concentrate product with the 2010 label to do so. The 2010 label is a package insert that is included with the Precedex concentrate product with the intent that it be used in combination with the product to ensure its safe and effective use. (DTX-23 at p. 5014). This alone provides sufficient motivation to combine the two. Plaintiff does not dispute that a POSA would have been aware of the general preference for ready-to-use parenteral medications. Although Cain does not explicitly call on manufacturers to bring to market premixed 4 μg/mL dexmedetomidine formulations, it is no great leap to conclude that Cain expressed the market's desire for such formulations. *See KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). Cain's disclosure that a hospital pharmacy was routinely making available to physicians for clinical use premixed 10 mL syringes of 4 μg/mL dexmedetomidine demonstrates that at least one large medical institution (Children's Hospital of Pittsburgh) recognized the value of ready-to-use dexmedetomidine formulations. (DTX-3 at p. 5). Since there was no dexmedetomidine premix product on the market at the time, the hospital took the initiative to make its own premixed 4 μg/mL dexmedetomidine formulation. Contrary to Plaintiff's assertions, this at a minimum demonstrates market interest in 4 μg/mL premixed dexmedetomidine formulations.

The 2010 label's disclosures about Precedex concentrate and its dilution would have provided a POSA with information useful to the development of a premixed 4 μg/mL dexmedetomidine formulation. Regardless of whether the market generally preferred plastic containers to glass containers, the prior art demonstrated that glass was the container of choice for small-volume parenteral pharmaceutical formulations. (*See, e.g.*, DTX-219 at p. 12; DTX-553 at

p. 809). Based on the Precedex concentrate product and the 2010 label, a POSA would have known that Precedex concentrate is stable in a sealed glass container. (Tr. 510:20-511:3; DTX-23 at p. 5027). Having a ready-to-use dexmedetomidine product available in a slightly less desirable container would be preferable to not having the product available at all. The first priority would thus have been to develop the ready-to-use 4 μg/mL dexmedetomidine formulation in whatever container proved workable. The preference for plastic would become relevant only if plastic was found suitable for the ready-to-use formulation. Therefore, I conclude that a POSA would have been motivated to modify the Precedex concentrate product to develop a 4 μg/mL ready-to-use dexmedetomidine formulation disposed within a sealed glass container.

Defendant argues that a POSA would have had a reasonable expectation of success in developing such a formulation because the prior art did not suggest any concerns with storing a low-concentration dexmedetomidine formulation in a sealed glass container. (D.I. 100 at 14). The 100 μg/mL Precedex concentrate product was already a low-concentration dexmedetomidine formulation, and it had proven stable when disposed within a sealed glass container. (*Id.*; Tr. 75:9-11, 140:8-12). As further support, Defendant offers the testimony of one of the inventors that as of December 2006, there was an expectation that they would be successful in finding acceptable packaging for the 4 μg/mL dexmedetomidine formulation by September 2007. (Tr. 839:19-24).

Plaintiff contends that a POSA would not have a reasonable expectation of success in preparing a ready-to-use 4 μg/mL dexmedetomidine formulation in a sealed glass container because neither the Precedex concentrate product nor the 2010 label "disclose[s] any container or seal for the diluted 4 μg/mL dexmedetomidine solution." (D.I. 106 at 12). Although the Precedex concentrate product discloses a dexmedetomidine formulation in a sealed glass container, it does not address a 4 μg/mL dexmedetomidine formulation. (*Id.*). Similarly, although the 2010 label

discloses a 4 μg/mL dexmedetomidine formulation, it does not direct a POSA to store that formulation in a sealed glass container. (*Id.*). Plaintiff faults Defendant for relying on the glass vial used for Precedex concentrate, when, according to Plaintiff, "The issue is whether the 2010 package insert discloses or suggests to a person having ordinary skill in the art, that a 'sealed' or a 'glass container' should be used to store a ready to use 4 μg/mL dexmedetomidine solution." (*Id.*).

I find Plaintiff's arguments unavailing. Plaintiff's argument is essentially that neither the Precedex concentrate product nor the 2010 label discloses all elements of the claimed invention. This is not fatal to the obviousness analysis. For obviousness, a single reference need not disclose every element of the claimed invention. *Pfizer, Inc.*, 480 F.3d at 1361. Defendant may rely on the Precedex concentrate product in combination with the 2010 label to prove obviousness.

Turning to the merits, Plaintiff argues that a POSA would not have a reasonable expectation of success in using a sealed glass container to store the ready-to-use 4 μg/mL dexmedetomidine formulation, because "not every vial will work to store the solution." (D.I. 106 at 12). As evidence, Plaintiff offers the inventors' "concerns about the container material [during] formulation development." (*Id.* at 13). Plaintiff further maintains that Hospira's container closure and stability testing failures during Precedex premix product development demonstrate that glass vials are not interchangeable. (*Id.* at 14). Plaintiff also notes that the prior art did not disclose whether the 4 μg/mL dexmedetomidine formulation diluted from the Precedex concentrate product was stable beyond 24 hours after dilution. (PTX-71 at p. 8 (FDA memorandum recommending approval of the New Drug Application for the Precedex concentrate product stating, "The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours")).[2] According to Plaintiff, since all glass vials are not

[2] Plaintiff also cites PTX-5 at page 304 for this proposition. This citation refers to the PTO's statement of reasons for allowance for claim 1 of the '158 patent. It states that, "Applicants provided evidence teaching away from storage of

interchangeable, and the stability of a 4 μg/mL dexmedetomidine formulation was not known beyond 24 hours, testing would be required "for every potential vial configuration," thus leaving a POSA with no reasonable expectation of success in using a sealed glass container to store the ready-to-use 4 μg/mL dexmedetomidine formulation. (D.I. 106 at 14-15).

Plaintiff's arguments on the merits are not convincing. Aside from its inventors' testimony and the development work that led to the invention, Plaintiff offers no evidence that a POSA would have anticipated problems with using a sealed glass container to store the ready-to-use 4 μg/mL dexmedetomidine formulation. As Plaintiff has noted, its development work was not public, and thus would not have been known to a POSA. (D.I. 106 at 16). Plaintiff presented no evidence that its inventors' concerns about container materials were publicly known. Therefore, neither the inventors' concerns nor failures in testing during development could have informed a POSA's expectation of the feasibility of storing the ready-to-use 4 μg/mL dexmedetomidine formulation in a sealed glass container. Any suggestion by Plaintiff that a POSA would have anticipated problems in finding a suitable glass container is belied by Plaintiff's inventor's testimony that a "glass vial does not have any known issues of adsorption and absorption while a plastic vial does." (Tr. 156:13-21 (explaining why Plaintiff's development work employed glass as a control)). Like the inventors, a POSA would have been familiar with the general knowledge that glass was the

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dexmedetomidine at a concentration of 4 μg/mL for longer than 24 hours (see page number 8 of Applicants' Remarks)." (PTX-5 at p. 304). Page 8 of the Applicants' Remarks cites the FDA memorandum recommending approval of the Precedex concentrate product (PTX-71) for the proposition that "once diluted for administration, the diluted composition is stable for only 24 hours." (PTX-5 at p. 233). The FDA memorandum did not draw conclusions, however, about the stability of the 4 μg/mL dexmedetomidine formulation beyond 24 hours after dilution from the Precedex concentrate product. (PTX-71 at p. 8). In fact, the FDA memorandum contemplated that, "it is projected that this product will be used in ICU for longer than 24 hrs of infusion." (PTX-71 at p. 4). Therefore, the FDA memorandum at most establishes that the stability of the 4 μg/mL solution diluted from the Precedex concentrate product was not known beyond 24 hours after dilution. (*See also* Tr. 75:3-16 ("After ad-mixing to that low concentration, only 24-hour stability was required" for approval)). This does not teach away from storage of 4 μg/mL dexmedetomidine for longer than 24 hours, because the FDA memorandum contemplated use of the 4 μg/mL formulation for infusions longer than 24 hours, and Plaintiff has pointed to no data affirmatively suggesting that the formulation was unstable more than 24 hours after dilution.

preferred packaging for small-volume injectables. (DTX-219 at p. 12). Therefore, I find that Plaintiff has not offered any credible evidence to counter Defendant's evidence that a POSA would have had a reasonable expectation of success in using a sealed glass container to store a ready-to-use 4 μg/mL dexmedetomidine formulation.

Even crediting Plaintiff's assertion that glass vials are not interchangeable (which would increase the number of potential packaging options), the prior art supports a finding that a POSA would have reasonably expected to succeed in using a sealed glass container to store a 4 μg/mL ready-to-use dexmedetomidine formulation. Plaintiff's assertion that the requirement for testing every potential configuration counsels against finding a reasonable expectation of success improperly equates a reasonable expectation with absolute certainty. *See Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success."). That some testing would be required to determine the appropriate packaging material for a 4 μg/mL ready-to-use dexmedetomidine formulation does not undermine a POSA's reasonable expectation of success in finding such packaging, especially since the prior art suggests that a sealed glass container would be suitable.

Nor would unknown stability of a 4 μg/mL dexmedetomidine formulation beyond 24 hours undermine a POSA's reasonable expectation of success. Although the stability of a 4 μg/mL dexmedetomidine formulation was unknown beyond 24 hours, Plaintiff cites no publicly available data suggesting that such a formulation would be so unstable as to discourage development of a 4 μg/mL dexmedetomidine premix formulation. (PTX-71 at p. 8; *see* D.I. 106 at 14-15). In fact, the prior art suggested glass as a suitable packaging material for parenteral pharmaceutical compositions. (DTX-219 at p. 12; DTX-553 at p. 809).

Plaintiff's expert, Dr. Linhardt, specifically identified adsorption of dexmedetomidine molecules to the surface of the glass container as a concern with using a sealed glass container for 4 μg/mL ready-to-use dexmedetomidine formulations. (D.I. 106 at 13 (citing Tr. 940:18-945:4)).[3] Any dexmedetomidine loss to adsorption could materially impact the concentration of dexmedetomidine in a ready-to-use formulation in light of the low initial concentration of 4 μg/mL. (Tr. 75:17-24). The prior art had recognized and addressed this concern, noting that treated glass could successfully address adsorption and other potential drug interaction issues. (DTX-200 at pp. 79-80 (noting adsorption as a potential "incompatibilit[y] between glass and product," and stating, "If any of these [incompatibilities] are found to occur during product development, then treated glass must be used . . ."); DTX-553 at p. 810 ("Type I glass will be suitable for all products, although sulfur dioxide treatment sometimes is used for even greater resistance to glass leachables.")).

Here, the prior art references uniformly suggest that Type I glass would be suitable for any parenteral pharmaceutical formulation, and further, that treated glass could address the concerns relevant to the dexmedetomidine formulations in this case. (*See, e.g.*, PTX-95 at p. 7; DTX-553 at p. 810). The Precedex concentrate product, disposed within a sealed glass container, further supports an expectation that a sealed glass container would be suitable packaging for a premixed 4 μg/mL dexmedetomidine formulation. Additionally, the 2010 label accompanying the Precedex concentrate product suggested the use of stoppers made of synthetic or coated rubber. (DTX-23 at p. 5017). Plaintiff's own inventor's testimony reveals that, based on the state of the art, POSAs

[3] Plaintiff also cites PTX-95 for this proposition without providing a pincite. PTX-95 is a 23-page excerpt from a technical report on sterile pharmaceutical packaging. The section of the report discussing glass containers identifies many of the same potential issues with glass as Defendant's prior art references, including leachables and attack by solutions inside glass containers. (PTX-95 at pp. 3-4). Like Defendant's prior art references, PTX-95 concludes, "In general, [Type I glass] is suitable for all parenteral drug products although sulfur dioxide treatment is sometimes utilized to increase its chemical resistance still more." (*Id.* at p. 7). Therefore, I find that PTX-95 merely confirms the disclosures in Defendant's prior art references.

such as the inventors did not expect any problems with employing a sealed glass container as the packaging for a premixed 4 μg/mL dexmedetomidine formulation. (Tr. 156:13-157:7). Therefore, I conclude that Defendant has proven by clear and convincing evidence that a POSA would have had a reasonable expectation of success in using a sealed glass container as the packaging for the claimed 4 μg/mL dexmedetomidine formulation.

Defendant also urges that the asserted claims would have been obvious based on Trissel. (D.I. 100 at 36). According to Defendant, the control sample in Trissel would have been "ready to use without further dilution and sufficiently sealed to prevent ingress and egress of materials." (*Id.*). This argument ignores the fact that the samples in Trissel were never intended for administration to patients, and Defendant fails to explain whether the control sample (or any other sample) was prepared in a manner that would comport with the requirements for patient administration. (*See id.*). Defendant's paragraph-long obviousness argument is insufficient to support finding the asserted claims obvious based on Trissel. I therefore conclude that Defendant has failed to prove by clear and convincing evidence that Trissel renders any of the asserted claims obvious.

c. Person of Ordinary Skill

The parties offer similar definitions for the POSA, and both parties' experts testified that adopting the other party's definition of a POSA would not change their opinions. (Tr. 270:21-271:4, 508:7-10). Plaintiff submits that for the product claims, the "POSA would have would have an advanced degree, such as a Ph.D. or Pharm.D. degree in science, chemistry, pharmacology or pharmaceutical development." (*Id.* at 268:9-17). For the method of treatment claim, Plaintiff asserts that the "POSA would be an M.D. with several years of experience administering pharmaceuticals to patients." (*Id.* at 268:17-20). Defendant maintains that for the product claims,

a POSA would have "an advanced degree, such as a Ph.D. or M.D., in the field of drug development and formulation." (*Id.* at 506:23-507:6). For the method of treatment claim, Defendant argues that a POSA would "have clinical experience in anesthesia or sedation" and be familiar "with the use of parenteral injection and would advantageously have familiarity with ready-to-use medications." (*Id.* at 507:7-13). Under Defendant's definition, "The amount of experience in the field would depend upon the level of formal education and particular experience with pharmaceutical formulations." (*Id.* at 507:14-17).

Defendant asserts that since Plaintiff's definition emphasizes formal education to the detriment of experience, it is lacking in the context of "[p]harmaceutics as a field[, which] is an applied field." (*Id.* at 508:1-6). Plaintiff does not specify particular flaws in Defendant's definition, and notes that the parties "agree that a POSA holds an advanced degree in pharmaceutical sciences [and has] knowledge of product formulation." (D.I. 101 at 4 n.2).

I find Defendant's focus on formal education in drug development or formulation unduly narrow with respect to the product claims. Similarly, for the method of treatment claim, I conclude that Plaintiff's limitation of the POSA to someone possessing an M.D is unnecessarily restrictive. Therefore, I conclude that for the product claims, the POSA holds an advanced degree, such as a Ph.D., M.D., or Pharm.D., in chemistry, pharmacology, or pharmaceutical development. For the method of treatment claim, I find that the POSA would have some formal education in science, chemistry, pharmacology or pharmaceutical development, and would have several years of experience administering pharmaceuticals to patients, including clinical experience in anesthesia or sedation and familiarity with parenteral injections. The POSA's practical experience may vary depending on the POSA's level of formal education.

d. Secondary Considerations

Plaintiff asserts that the commercial success of its Precedex premix product supports finding the asserted claims nonobvious. (D.I. 106 at 11). Defendant counters that any inference of commercial success is weak because the '214 compound patent covering dexmedetomidine precluded market entry by others until its expiration on July 15, 2013. (D.I. 100 at 25). Defendant also asserts that Plaintiff failed to prove sufficient nexus between the commercial success and the claimed invention. (*Id.*; Tr. 1080:14-1085:1).

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was nonobvious." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). When "others are legally barred from commercially testing the" ideas of the claimed invention, "[f]inancial success is not significantly probative of that question." *Id.* at 1377. Even when commercial embodiments of the invention enjoy commercial success, the "failure to link that commercial success to the features of [the] invention that were not disclosed in [the prior art] undermines the probative force of the evidence." *Asyst Techs., Inc. v. Emtrack, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Plaintiff argues that its Precedex premix product is a commercial success because, "It sells for a premium price because of the invention in a uniformly generic market." (D.I. 106 at 16). As further evidence of success, Plaintiff offers the fact that its Precedex premix outsells Precedex concentrate at a ratio of $165 million to $5 million, even though Precedex premix sells at a substantial premium over Precedex concentrate. (Tr. 202:12-15, 213:3-10, 218:9-19). Plaintiff

also urges that the required nexus between the new features of the invention and commercial success is met here because the Precedex premix product competes directly with generic dexmedetomidine concentrate products, allowing a direct comparison measuring consumer demand for the new features. (D.I. 106 at 19; Tr. 1047:4-19). With respect to the '214 patent, Plaintiff contends that the facts here are distinguishable from other cases involving blocking patents, such as *Merck* and *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013). (D.I. 106 at 18). Specifically, Plaintiff argues that *Merck* is not relevant because there, "the prior art product never competed against the claimed invention." (*Id.*) According to Plaintiff, *Galderma* "focused on motivation—not blocking patents." (*Id.*).

Defendant submits that Plaintiff has not adequately addressed the '214 blocking patent, because Plaintiff "simply asserts without citing any evidence that the blocking patent did not prevent competition." (D.I. 108 at 16). Additionally, Defendant maintains that the commercial success of Plaintiff's Precedex premix product was driven by Plaintiff's business management efforts, not the new features of the claimed invention. (D.I. 100 at 26; Tr. 1095:10-21). Specifically, Plaintiff launched Precedex premix at ten percent below the price of Precedex concentrate (Tr. 219:1-24) in an effort "to drive conversion of existing sales to the premix formulations and impede generic competition" (*id.* at 1095: 10-21). Defendant thus maintains that the evidence of commercial success is insufficient to support nonobviousness. (D.I. 100 at 25).

Plaintiff's arguments to distinguish *Merck* and *Galderma* are not persuasive. First, whether the invention competed directly with the prior art product may be relevant to the nexus between commercial success and the new features of the invention, but it does not alter the effect of a blocking patent. Plaintiff has thus failed to distinguish *Merck*. Second, that an opinion in a case focuses on a particular issue does not deprive it of precedential value with respect to any other

issues addressed. As was the case in *Galderma*, here a compound patent on the active ingredient in the claimed invention blocked market entry by competitors until after the invention of the product at issue. *Galderma*, 737 F.3d at 735, 740-41.

The '214 patent blocked the market entry of dexmedetomidine products from its issuance on March 20, 1990 until its expiration on July 15, 2013. Since the priority date for the asserted patents is January 4, 2012 (D.I. 96-1 at 5), the '214 patent precluded competitors from entering the market until after Plaintiff had staked its legal claim to ownership of the inventions in the asserted patents, and after the '158, '470, and '527 patents had issued.[4] Therefore, Plaintiff was the only entity that could lawfully have brought a dexmedetomidine premix product to the market prior to July 15, 2013. As was the case in *Merck* and *Galderma*, the evidence of commercial success of the product embodying the invention has little probative value.

Even absent the blocking patent, Plaintiff's business practices in marketing Precedex premix would weaken any inference of commercial success. Plaintiff's internal documents reveal a business strategy to have its sales team "push, push, push premix September to December in anticipation of loss of exclusivity, which refers to generics coming to the market." (Tr. 1096:23-1097:12; DTX-231). By migrating its contracts with medical providers from the Precedex concentrate product to the Precedex premix product, there could be no automatic substitution when generic concentrate products arrived on the market. (Tr. 1097:15-1098:1). Considering the documentary evidence and testimony to the contrary, I cannot credit Plaintiff's conclusory attorney argument that "Hospira's introduction of its new Precedex Premix was designed to highlight the benefits of Premix to the market." (D.I. 106 at 19). Therefore, although the direct competition between the invention and the prior art provides evidence of the required nexus, that evidence is

[4] The '470, '527, and '106 patent applications were all continuations of the application that ultimately issued as the '158 patent.

weakened by the confounding factor of Plaintiff's aggressive business practices that attempted to shift demand to Plaintiff's premix product before generic concentrate product market entry. Since the '214 blocking patent renders weak any evidence of commercial success, and Plaintiff's business practices further weaken evidence of the required nexus, I conclude that considerations of commercial success do not support finding the asserted patents nonobvious.

Considering all of the evidence, I conclude that Defendant has proven by clear and convincing evidence that claims 3 and 4 of the '158 patent, claim 4 of the '470 patent, and claim 5 of the '527 patent are invalid as obvious.

2. Obviousness of the '106 Patent

Defendant argues that claim 6 of the '106 patent is obvious because the "no more than about 2% decrease" in dexmedetomidine concentration limitation is inherent in a 4 μg/mL dexmedetomidine formulation in normal saline disposed within a sealed glass container. (D.I. 100 at 15). Plaintiff counters that Defendant's evidence is insufficient to prove inherency. (D.I. 106 at 19).

Inherency must be proven by clear and convincing evidence. *Par Pharm.*, 773 F.3d at 1196. To rely on inherency in an obviousness analysis, a party must meet a high standard—"the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Id.* at 1195-96. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient to render the result inherent." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (citations omitted).

Defendant argues that "the 'no more than about 2% decrease' limitation is simply an inherent characteristic of the obvious 4 μg/mL dex formulation disposed in a sealed glass container" for two reasons. (D.I. 100 at 15). First, Defendant offers examples of dexmedetomidine

formulations in 0.9% sodium chloride disposed within a sealed glass container, each of which exhibit no more than about 2% decrease in dexmedetomidine concentration at five months under long-term conditions. (*Id.* at 16). Second, Defendant contends that Plaintiff's response to Interrogatory No. 15 is an admission that the claimed stability is an inherent property of a 4 μg/mL dexmedetomidine formulation in 0.9% sodium chloride. (*Id.* at 15).

Plaintiff responds that Defendant has failed to prove inherency for three reasons. First, Defendant's examples are insufficient without corroborating expert testimony to explain the scientific principles supporting the inference of inherency. (D.I. 106 at 20). Second, Defendant's examples are not probative evidence of inherency because they impermissibly rely on the Plaintiff's inventors' development work that resulted in the claimed invention. (*Id.* at 24). Third, Plaintiff's response to Interrogatory No. 15 is not an admission of inherency. (*Id.* at 25). I address each of Defendant's arguments in turn.

a. Defendant's Examples

Defendant offers several examples that it asserts demonstrate that the claimed stability is an inherent property of dexmedetomidine formulations disposed in a sealed glass container. First, Plaintiff stipulated that all of the product volumes (i.e. 20 mL, 50 mL, 100 mL) of its Precedex premix product meet the "not more than about 2%." limitation. (Tr. 5:6-9). Relying on Plaintiff's internal testing documents, Defendant's expert Dr. Yaman testified that the 20 mL Precedex premix product, packaged in Type I glass with a coated synthetic stopper, meets that limitation. (Tr. 546:2-547:10; DTX-113 at p. 2764-65). Second, Defendant offers Plaintiff's internal testing documents demonstrating that the 50 mL and 100 mL Precedex premix product volumes meet the limitation. (Tr. 547:17-549:5; DTX-113 at pp. 2798, 2817). Third, according to Defendant, the 1989 investigational new drug submission to the FDA covering dexmedetomidine demonstrates

that dexmedetomidine is inherently stable in a sealed glass container. (D.I. 100 at 21). That FDA submission showed that a 20 μg/mL dexmedetomidine formulation in a 5 mL sealed glass ampoule met the claimed "no more than about 2%" limitation at 6 months of storage under long-term conditions. (Tr. 550:3-551:17; DTX-199 at p. 348). Fourth, according to Defendant, the investigational new drug application similarly demonstrates that 100 μg/mL formulations of dexmedetomidine were stable at room temperature for periods up to 60 months. (Tr. 551:8-24; DTX-114 at pp. 30-31). Characterizing its evidence as "unrebutted experimental evidence," Defendant claims that examples alone are sufficient under the law to prove inherency. (D.I. 100 at 17, 22 (citing *3form, Inc. v. Lumicor, Inc.*, 678 F. App'x 1002, 1010 (Fed. Cir. 2017); *Par Pharm., Inc. v. TWi Pharm., Inc.*, 120 F. Supp. 3d 468, 475 (D. Md. 2015), *aff'd*, 624 F. App'x 756 (Fed. Cir. 2015))). Defendant also argues that the lack of evidence of degradants or oxidation of dexmedetomidine formulations stored in sealed glass containers at room temperature further support the inherency of the claimed stability. (D.I. 100 at 20).

Plaintiff responds that examples alone cannot prove inherency, because at a minimum, Defendant must "offer competent expert testimony explaining the scientific principles supporting the inference it urged the court to draw that [Defendant's] examples demonstrated inherency." (D.I. 106 at 20). According to Plaintiff, Defendant has failed to offer any such testimony, because Defendant's expert, Dr. Yaman, is not a chemist and thus cannot explain any chemistry principles that may underlie Defendant's inherency argument. (*Id.*). For example, Dr. Yaman "offered no explanation of the chemical characteristics of dexmedetomidine that 'necessarily' cause it to meet the 'not more than about a 2% loss' at five months at a concentration of 4 μg/mL in a sealed glass container." (*Id.* at 22). Although Dr. Yaman testified that "the drug product itself [] has no apparent mechanisms of degradation," he also stated, "I would hypothesize that it's going to be

stable, but then I would go and do my experimentation to prove my hypothesis one way or the other." (Tr. 661:16-662:8). Dr. Yaman further conceded that a POSA could not infer the one-year stability of a 4 μg/mL dexmedetomidine formulation in 0.9% sodium chloride from the 2010 label for the 100 μg/mL Precedex concentrate product. (*Id.* at 666:14-21).

Additionally, Plaintiff argues that Defendant's examples represent the development work of the inventors, and thus cannot be used to prove inherency. (D.I. 106 at 20). According to Plaintiff, accepting these examples as competent evidence of inherency would allow hindsight to taint the subsequent analysis. (*Id.* at 24). Finally, Plaintiff submits that due to the high number of potential glass container-stopper combinations that could meet the "sealed glass container limitation" of claim 6 of the '106 patent, the claimed stability cannot be an inherent property, because a 4 μg/mL dexmedetomidine formulation may not be stable in all of them. (*Id.* at 22). As support, Plaintiff cites its inventor's testimony that leachables and extractables from a stopper "in some cases could have some interaction with the drug substance," necessitating compatibility testing for each glass-stopper combination. (Tr. 122:20-123:22).

I find that Defendant has failed to prove inherency by clear and convincing evidence. Although Plaintiff stipulated that its 20 mL, 50 mL, and 100 mL Precedex premix products meet the claimed stability limitation, only two of Defendant's experimental examples deal with the claimed 4 μg/mL dexmedetomidine formulation. These two examples rely on the same data that underlies Plaintiff's stipulation—Plaintiff's internal testing documents related to the development of Plaintiff's Precedex premix products. Even taking Defendant's examples as unrebutted and assuming Defendant may rely on the inventors' development work, in the cases Defendant relies on for the proposition that examples alone are sufficient proof of inherency, the evidentiary records also contain expert testimony "confirming the scientific principles underlying" the inherent

property. *Par Pharm.,* 120 F. Supp. 3d at 475 ("Here, TWi has not only presented several examples of formulations that exhibit the claimed food effect limitations, but also provided expert testimony confirming the scientific principles underlying that result."); *3form, Inc.*, 678 F. App'x at 1009-10 (considering expert testing and testimony in affirming district court holding of inherent anticipation). Here, by contrast, Defendant offers no expert testimony regarding the scientific principles underlying its inherency argument, and relies on just two examples of stability data covering the claimed 4 μg/mL dexmedetomidine concentration. As Plaintiff notes, Defendant's expert conceded that stability data for a 4 μg/mL dexmedetomidine formulation could not be inferred from the Precedex concentrate label, and that he would have had to confirm any stability hypothesis for a 4 μg/mL dexmedetomidine formulation through testing. (Tr. 661:16-662:8, 666:14-21). Rather than supporting Defendant's examples, this testimony weakens Defendant's inherency argument that the claimed stability is the necessary result of a 4 μg/mL dexmedetomidine formulation in 0.9% sodium chloride disposed within a sealed glass container.

The lack of evidence of degradants or oxidation of dexmedetomidine formulations increases the weight of Defendant's affirmative examples of dexmedetomidine's stability at room temperature in a sealed glass container. It does not, however, provide additional affirmative evidence to support Defendant's contention. Despite this additional support for Defendant's examples, given the absence of supporting expert testimony, I find the examples insufficiently powered to establish inherency by clear and convincing evidence.

b. Plaintiff's Interrogatory Response

Defendant also contends that Plaintiff's response to Interrogatory No. 15 constitutes an admission of inherency. (D.I. 100 at 18). Interrogatory No. 15 and its response read as follows:

> **Interrogatory No. 15:** Identify and describe in detail any factual bases and supporting evidence showing that Non-Premixed Precedex concentrate when diluted to 4 μg/mL in 0.9% sodium chloride and stored in a sealed glass container would not exhibit the claimed stability recited in claim 1 of U.S. Patent No. 8.648,106; that is, "when stored in the glass container for at least five months exhibits no more than about 2% decrease in the concentration of dexmedetomidine."
>
> **Answer:** Hospira objects to this Interrogatory as premature because it seeks expert opinion. Hospira also objects to this Interrogatory as vague.
>
> Subject to the foregoing objections, Hospira responds as follows:
>
> The patents-in-suit explain that a solution of 4 μg/mL dexmedetomidine in 0.9% sodium chloride would, in the absence of degradative compounds, exhibit the claimed stability when stored in a sealed glass container. (*See, e.g.*, '106 pat. [a]t 13:63-66.) However, prior to the inventors' work, it was expected that Precedex Concentrate was not stable for more than 24 hours after dilution.

(DTX-191 at p. 8). Defendant further maintains that Plaintiff's expert, Dr. Linhardt, agreed with this response "without any further qualification." (D.I. 100 at 18; Tr. 371:10-373:7, 376:7-13). According to Defendant, "by invoking and citing the patent specification, Hospira conceded that the patents themselves demand this admission." (D.I. 100 at 18). Defendant urges that, like the patentee in *In re Omeprazole Patent Litig.*, 483 F.3d 1364 (Fed. Cir. 2007), Plaintiff has conceded inherency. (D.I. 100 at 19). Since Plaintiff has offered no scientific evidence to rebut inherency at trial and the '106 patent does not suggest anything additional is required to produce the claimed stability, Defendant urges that Plaintiff's interrogatory response is sufficient to prove inherency. (*Id.*).

Plaintiff counters that Defendant seeks to invoke this interrogatory answer to improperly shift the burden of proof to Plaintiff to disprove inherency. (D.I. 106 at 25). Additionally, Plaintiff characterizes its answer as providing "an example of what the inventors had learned about the stability of a 4 μg/mL solution of dexmedetomidine under certain test conditions disclosed in their patents." (*Id.*).

I conclude that Defendant has failed to establish that Plaintiff's response to Interrogatory No. 15 is an admission of inherency. As a threshold matter, Defendant overlooks the mismatch between the interrogatory and Plaintiff's response. Although the interrogatory addresses non-premixed 4 μg/mL formulations of dexmedetomidine formulation, Plaintiff's response refers Defendant to the patent, which claims premixed 4 μg/mL dexmedetomidine formulations. (DTX-191 at p. 8). Plaintiff's answer to this question is thus more accurately characterized as a non-responsive answer than an admission. Additionally, the evidence here does not rise to the same level as the evidence in *Omeprazole*. *Omeprazole* involved several direct admissions by the plaintiff in parallel Korean litigation that the limitation at issue was inherent in a prior art process. *Omeprazole*, 483 F.3d at 1372-73. Here, by contrast, the record does not contain any admissions by Plaintiff that the claimed stability is inherent in a 4 μg/mL dexmedetomidine formulation. Further, unlike the admissions in *Omeprazole*, Plaintiff's interrogatory response cannot be characterized as an admission. Therefore, Defendant has failed to prove that Plaintiff has admitted that the claimed stability is inherent in a 4 μg/mL dexmedetomidine formulation.

Therefore, I conclude that Defendant has failed to prove that the "no more than about 2% decrease" limitation in claim 6 of the '106 patent is an inherent property of the 4 μg/mL dexmedetomidine formulation in 0.9% sodium chloride disposed within a sealed glass container. Defendant has thus failed to prove by clear and convincing evidence that claim 6 of the '106 patent is invalid as obvious.

3. Anticipation

Defendant argues that the Trissel reference anticipates the asserted claims because it discloses a control sample, stored in a borosilicate screw-cap glass tube, of 4 μg/mL dexmedetomidine in normal saline that had been prepared according to the product labeling. (D.I.

100 at 36; DTX-120 at p. 230; Tr. 591:2-22, 592:12-22). Trissel also describes that intravenously-administered dexmedetomidine is useful for sedation of patients. (DTX-120 at p. 230; Tr. 590:15-23). In conclusory fashion, Defendant contends that the control sample in Trissel "would be ready to use without further dilution." (D.I. 100 at 36).

Plaintiff counters that Trissel does not anticipate the asserted claims because it does not meet each of the claim limitations. (D.I. 106 at 33-35). According to Plaintiff, the samples in Trissel do not disclose a "liquid pharmaceutical composition for parenteral administration to a subject" because Defendant's expert admitted that the Trissel study did not intend to "use [the samples] in the future on any patient." (Tr. 629:24-630:22). Additionally, since Dr. Yaman admitted that Trissel's 4 μg/mL samples had been diluted from 100 μg/mL Precedex concentrate according to the label's instructions, the Trissel samples do not meet the "ready to use" limitation. (Tr. 629:20-23; *see also* DTX-120 at p. 230 ("For this testing, the Precedex injection was diluted to a concentration of 4 μg/mL in 0.9% sodium chloride injection, USP, (Lot 70-13 5 -JT, Abbott Laboratories), which is recommended in the product labeling.")). Plaintiff also notes that Defendant's argument improperly assumes that the samples in Trissel meet the "no more than about 2%" limitation, when the reference was silent as to stability. (D.I. 106 at 35; Tr. 640:11-15).

Defendant's anticipation argument is less than a page long. (D.I. 100 at 36). Further, Defendant not only fails to respond to Plaintiff's counterarguments regarding anticipation, but also fails to address anticipation at all in its reply brief. I do not believe such limited argument provides a basis for concluding that the Trissel reference meets each of the limitations of the asserted claims, especially in light of Plaintiff's arguments to the contrary. Defendant has therefore failed to prove by clear and convincing evidence that Trissel anticipates any of the asserted claims.

4. Indefiniteness

The essence of Defendant's indefiniteness argument is that because the '106 patent discloses concentration measurements performed under both long-term and accelerated conditions and claim 6 does not explicitly specify which condition to use, a POSA would not know whether the "no more than about 2% decrease" limitation should be measured under long-term or accelerated conditions. (D.I. 108 at 16). Defendant notes that the scientific community recognized and accepted both measures as relevant to drug stability testing. (Tr. 280:10-17, 282:15-20; DTX-207 at p. 8). Additionally, which condition is used may be determinative of infringement. (D.I. 100 at 29-30 (discussing Example 6 of the '106 patent)). Defendant points out that the '106 patent specification discloses stability testing results consistent with the "no more than about 2%" limitation from tests run under both long-term (Examples 3 and 6) and accelerated (Example 1) conditions. (D.I. 108 at 18). According to Defendant, the prosecution history of the '106 patent suggests that the accelerated condition should be used because, "The Examiner identified Example 1 as the basis for allowing the claims." (D.I. 100 at 31). Although Defendant admits that Examples 3 and 6 suggest that long-term conditions should be used, Defendant asserts that the weight of Example 6 in particular is diminished because it "does not say what the actual concentration is at five months." (D.I. 108 at 17-18). Therefore, Defendant urges, "The intrinsic evidence concerning 'no more than about 2% of decrease in the concentration of dexmedetomidine' presents the same kind of inconsistency or contradiction as in *Teva* and *Transcend Medical*," rendering claim 6 of the '106 patent indefinite. (D.I. 100 at 29).

Plaintiff argues that claim 6 of the '106 patent is not indefinite because the '106 patent informs a POSA with reasonable certainty that the relevant storage conditions are long-term storage conditions. (D.I. 106 at 27). According to Plaintiff, because the claim language states that

the dexmedetomidine formulation "is to be administered to a patient, [it] is, by definition, stored at its prescribed storage conditions." (*Id.*). Both parties' experts testified that a POSA would have known that the intended storage condition for dexmedetomidine is room temperature storage, which matches the long-term condition. (Tr. 600:9-19, 968:4-11); *see Teva*, 789 F.3d at 1339 ("Experts may explain terms of art and the state of the art at any given time."). Plaintiff also submits that Example 6 "confirms that the 2% limitation is measured at long-term conditions" because it tested products meeting the "sealed glass container" and "ready to use" limitations under both long-term and accelerated conditions, and only the products tested under long-term conditions met the "no more than about 2%" limitation. (D.I. 106 at 28). According to Plaintiff, Example 1 is not probative because it merely discloses testing different packaging materials—the patent fails to indicate that the products tested in Example 1 meet all of the limitations of claim 6. (*Id.* at 28-29 n.8). Plaintiff further asserts that *Teva* and *Transcend Medical* are distinguishable because the arguments for definiteness in those cases relied on claim term constructions with no support in the intrinsic record. (*Id.* at 31-32). Here, by contrast, Plaintiff maintains that there is ample intrinsic evidence that the relevant storage condition for claim 6 is long-term storage. (*Id.*).

Here, although claim 6 of the '106 patent does not explicitly specify the storage condition under which dexmedetomidine concentration should be measured, the intrinsic evidence demonstrates that the claim is not indefinite. The language of claim 6 indicates that the purpose of the claimed invention is to administer the dexmedetomidine formulation to a patient. ('106 patent at claim 1 ("A ready to use liquid pharmaceutical composition for parenteral administration to a subject . . .")). Additionally, the detailed description of the invention makes clear that the discovery that dexmedetomidine could be stored long-term contributed to generating the invention. (*Id.* at 3:6-10 ("The present invention is based in part on the discovery that dexmedetomidine

prepared in a premixed formulation that does not require reconstitution or dilution prior to administration to a patient, remains stable and active after prolonged storage.")). Examining this intrinsic evidence, even a lay judge can recognize that proper storage of a pharmaceutical is a prerequisite to administering the pharmaceutical intravenously to a patient. *Phillips*, 415 F.3d at 1314 ("In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words.").

The language in the '106 patent would similarly inform a POSA that the storage condition relevant to the asserted claim is proper storage for a dexmedetomidine pharmaceutical formulation. Both parties' experts testified that as of 2012, it was known that the proper storage condition for dexmedetomidine is room temperature storage, or 25°C. (Tr. 600:14-21, 967:2-12, 968:4-20). This aligns with the long-term storage conditions described in Examples 3 and 6 of the '106 patent. ('106 patent at 16:16-20, 22:2-3). Whereas the stability study results for long-term storage in Examples 3 and 6 are consistent with the limitations of claim 6, the accelerated storage results of Example 6 fail to meet the "no more than 2%" limitation of that claim. (*Id.* at 22:3-20). These examples therefore suggest that long-term storage is the relevant condition to use in assessing compliance with the "no more than about 2%" limitation of claim 6.

Defendant's argument that Example 1 suggests accelerated storage conditions as the proper measure ignores the context of Example 1 and cannot overcome the necessary implications of the claim language. As the specification makes clear, Example 1 is directed to selecting a container material for the dexmedetomidine formulation and, after the starting point, took measurements only under accelerated conditions. (*Id.* at 13:22-26, 13:52-66). Example 1 does not mention any sort of seal for the containers discussed, thus failing to account for all limitations relevant to storage

of the claimed pharmaceutical composition. (*See id* at 13:22-14:59). Additionally, although the PTO Examiner's allowance of the claims cites Example 1, it uses Example 1 to provide a direct comparison of dexmedetomidine concentration decreases in glass and plastic containers in the context of a discussion of the advantages of glass over plastic. (PTX-8 at p. 100). Examples 1 and 2 are the only examples in the '106 patent that provide such a direct comparison. (*See* '106 patent). Example 2 describes testing of one type of plastic PVC bag against a glass bottle control under normal storage conditions. ('106 patent at 14:60-15:24). Neither Example 1 nor Example 2 report stability results from tests under accelerated conditions that meet the "no more than about 2% decrease" limitation. (*Id.* at 14:3-19, 15:10-22). Accordingly, they deserve little weight in the indefiniteness analysis.

As Defendant acknowledges, Example 6 suggests that long-term conditions represent the appropriate measure for claim 6 of the '106 patent. (D.I. 108 at 18). Like claim 6, the stability results reported in Example 6 employ glass as the packaging material for the dexmedetomidine formulation.[5] ('106 patent at 21:22-22:24). Example 6 describes the results of testing, under both long-term and accelerated conditions, of different closure systems for glass vials, including sealing tests. (*Id.* at 21:20-64). Example 6 thus addresses all of the relevant storage limitations, and only the long-term data is consistent with the "no more than about 2%" limitation of claim 6. (*Id.* at 21:65-22:24). Although Example 6 does not speak explicitly to the five-month measurement time point, the patent states that, "The total percent drop in potency over three months under long term conditions was 1.1 %. Stability testing at 4 and 5 months for samples stored under accelerated and long term conditions confirmed that potency values had almost leveled off, with small drop in

[5] Example 6 of the '106 patent mentions that, "Plastic vials were also evaluated" under accelerated conditions. ('106 patent at 22:25-31). The only results reported, however, do not provide a direct numerical comparison between plastic and glass packaging—the patent states only that a "[s]imilar trend in potency drop was observed" after 3 months. (*Id.* at 22:32-33).

potency values." (*Id.* at 22:14-20). This suggests that the concentration measured at five months under long-term conditions is consistent with the limitations in claim 6, as the patentee would likely have noted a drop in concentration sufficient to push the dexmedetomidine formulation outside the claimed concentration range. Additionally, it would have taken a drop of nearly 1% to push the concentration of the dexmedetomidine formulation outside the claimed range. In context, it is unlikely that such a decrease would have qualified as a "small drop" as described in the patent. Thus, Example 6 lends further support to the conclusion that the claimed five-month time point in claim 6 is directed to long-term storage conditions.

Defendant's citations to *Teva* and *Transcend Medical* are not persuasive. In *Transcend Medical*, the patent at issue contained two inconsistent definitions for the disputed term, and Defendant's expert offered a third competing definition. 2015 WL 5546988 at *6. That is not the case here. The '106 patent defines accelerated conditions and long-term conditions as different storage conditions that may be used in stability studies. (*See* '106 patent at 22:1-3). No term relevant to claim 6 is inconsistently defined in the patent. Unlike the claim at issue here, the claim at issue in *Teva* merely recited a method of manufacture, offering no limiting purpose for the resulting product. 789 F.3d at 1338. By contrast, the claim at issue here recites that the dexmedetomidine formulation is "for parenteral administration to a subject." ('106 patent at claim 1). A POSA would recognize that this limitation restricts the scope of the claim to formulations that meet industry standards for pharmaceutical injections administered to subjects. Whereas the accelerated condition here is 15°C above the recommended storage for dexmedetomidine, the long-term condition corresponds to dexmedetomidine's normal storage conditions. (Tr. 600:14-21, 967:2-12, 968:4-20). A POSA would know that a pharmaceutical stored for 5 months at 15°C above its recommended or normal storage temperature, and 10°C above the upper limit of its

permitted temperature excursion range, would not likely be deemed suitable for administration to subjects. Therefore, this limitation in claim 6, along with the '106 patent specification, would inform a POSA with reasonable certainty that long-term storage conditions are the relevant storage conditions to measure dexmedetomidine concentration for purposes of claim 6.

Considering all of the evidence, I find that the '106 patent adequately conveys to a POSA that long-term storage is the condition relevant to claim 6. Defendant has failed to provide clear and convincing evidence that claim 6 of the '106 patent is invalid under 35 U.S.C. § 112.

IV. INFRINGEMENT OF THE '158, '470, '527, AND '106 PATENTS

A. Findings of Fact

1. For the product claims, the person of ordinary skill in the art ("POSA") holds an advanced degree, such as a Ph.D., M.D., or Pharm.D., in chemistry, pharmacology, or pharmaceutical development.

2. For the method of treatment claim, the POSA would have some formal education in science, chemistry, pharmacology or pharmaceutical development, and would have several years of experience administering pharmaceuticals to patients, including clinical experience in anesthesia or sedation and familiarity with parenteral injections. The POSA's practical experience may vary depending on the POSA's level of formal education.

3. The parties have stipulated that the proposed ANDA products meet all limitations of the asserted claims except the "sealed glass container" limitation in all asserted claims, and the "no more than about 2% decrease" limitation in claim 6 of the '106 patent. (Tr. 3:22-4:8).

4. Defendant's proposed ANDA products meet the "sealed glass container" limitation of the asserted claims of the '158, '470, '527, and '106 patents. Defendant's proposed ANDA products thus infringe the asserted claims of the '158, '470, and '527 patents.

5. Defendant's ANDA specification seeks approval to market 50mL and 100mL sealed glass containers of 4 μg/mL dexmedetomidine formulations in 0.9% sodium chloride that demonstrate no more than a 10% decrease in dexmedetomidine concentration 5 months from the date of manufacture under normal storage conditions. (JTX-76 at p. 4; Tr. 88:1-6, 278:23-279:16).

6. Defendant's ANDA specification covers products that meet the "no more than about 2% decrease in the concentration of dexmedetomidine" over at least five months limitation in asserted claim 6 of the '106 patent.

B. Conclusions of Law

At trial the parties stipulated that Defendant infringes all limitations of the asserted claims except (1) whether Defendant's ANDA covers products disposed within a "sealed glass container," and (2) whether Defendant's ANDA products, "when stored in the glass container for at least five months[,] exhibit[] no more than about 2% decrease in the concentration of dexmedetomidine," as required by the '106 patent. (D.I. 101 at 3; Tr. 3:22-4:8).

1. "Sealed Glass Container"

Plaintiff argues that Defendant's ANDA documents and the testimony of Plaintiff's technical expert, Dr. Linhardt, establish that Defendant's ANDA products are disposed within a "sealed glass container" under any proposed construction of the term. (D.I. 101 at 4-5). Based on his review of Defendant's ANDA documents, Dr. Linhardt testified that Defendant's ANDA products are disposed in a sealed glass container, closed tightly to "ensure[] the product remains sterile during storage." (Tr. 272:22-273:20, 277:17-21). More specifically, Defendant's ANDA documents establish that the container closure system for its ANDA products comprises a glass vial, a rubber stopper, and a seal. (PTX-64 at p. 5; *see also* Tr. 273:11-20). Additionally, the glass vials containing Defendant's 50 mL and 100 mL ANDA products passed the dye ingress test, which Dr. Linhardt testified is an industry-standard test for seal integrity. (PTX-65 at pp. 2-3, 10-11; Tr. 274:23-276:8; 323:12-14).

Defendant does not argue in post-trial briefing that its ANDA products do not meet the "sealed glass container" limitation. (*See* D.I. 105). Therefore, Defendant has conceded that its proposed ANDA products meet this limitation. I find that Plaintiff has proven by a preponderance of the evidence that Defendant's ANDA products meet the "sealed glass container" limitation.

2. "No More than About 2% Decrease"

Plaintiff asserts that Defendant infringes the "no more than about 2% decrease" limitation of claim 6 of the '106 patent under two separate theories. (D.I. 101 at 6). First, Plaintiff asserts that Defendant infringes the "no more than about 2% decrease" limitation in claim 6 of the '106 patent as a matter of law. (*Id.* at 7). Second, Plaintiff argues that Defendant infringes this limitation as a matter of fact. (*Id.* at 9). Infringement under either theory is sufficient to prove infringement of claim 6 of the '106 patent. *See, e.g.*, *Abbott*, 300 F.3d at 1373 ("[A]n ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry."). I address both theories.

i. Infringement as a Matter of Law

Plaintiff urges that Defendant's ANDA specification establishes that Defendant's proposed ANDA products infringe the "no more than about 2% decrease" limitation as a matter of law under *Sunovion*. (D.I. 101 at 6). Defendant counters that *Sunovion* does not apply in this case because Defendant's ANDA specification does not speak directly to the '106 patent's five month measurement time point for the "no more than about 2% decrease" limitation. (D.I. 105 at 7).

Claim 6 of the '106 patent requires that the claimed dexmedetomidine product, "when stored in the glass container for at least five months exhibits no more than about 2% decrease in the concentration of dexmedetomidine." ('106 patent at claims 1, 6). Defendant's ANDA specification provides that Defendant's proposed ANDA products, as measured by high performance liquid chromatography ("HPLC") assay, will remain within 90-110% of their initial dexmedetomidine concentration claimed on the products' label for the 2-year shelf life also claimed on the label. (JTX-76 at p. 4; Tr. 88:1-6, 278:23-279:16). In other words, Defendant's ANDA specifies that the products will lose no more than 10% dexmedetomidine concentration

over 24 months.

According to Defendant, the 3-5% variability inherent in the HPLC measurement technique specified by its ANDA precludes its ANDA specification from directly addressing the issue of infringement because the possible 3-5% variability in any concentration measurement exceeds the 2% limit of the claimed concentration loss. (D.I. 105 at 9). For example, even at the lower end of HPLC measurement variability, an HPLC-measured concentration loss of 0.1% could represent an actual concentration change anywhere between a 2.9% gain and a 3.1% loss. Plaintiff responds that Defendant's argument fails because the '106 patent accounts for HPLC measurement variability when its specification defines "about" as meaning "within an acceptable error range for the particular value as determined by [a POSA], which will depend in part on . . . the limitations of the measurement system." ('106 patent at 5:31-35; D.I. 109 at 6). On this point I agree with Plaintiff. The '106 patent defines "about" so as to account for measurement variability. Defendant's ANDA specification defines its proposed product concentration using HPLC potency measurements, and the '106 patent explicitly uses HPLC potency measurements in some of its examples. This allows for a direct comparison of the concentration limitations in the '106 patent and Defendant's ANDA specification. The variability inherent in the HPLC measurement technique alone is not sufficient to compel the conclusion that *Sunovion* does not apply.

Plaintiff argues that Defendant's proposed ANDA products infringe as a matter of law because the less than or equal to 10% dexmedetomidine concentration loss in Defendant's ANDA specification directly addresses the claim limitation of "no more than about 2% decrease" in dexmedetomidine concentration after at least 5 months of storage. (D.I. 109 at 5-6). Because the parties agree that dexmedetomidine concentration will not increase over time in a sealed glass container (Tr. 286:21-24, 447:1-9), Plaintiff points out that a requirement for a concentration loss

of 10% or less at 24 months necessarily requires that concentration loss is 10% or less at 5 months. (D.I. 109 at 5). According to Plaintiff, since a concentration loss of no more than 10% includes a concentration loss of no more than about 2%, Defendant's proposed ANDA products infringe under *Sunovion*. (*Id.*). Citing *Ferring*, Defendant submits that *Sunovion* does not apply, because the ANDA product specification does not specify a dexmedetomidine concentration for the claimed five-month measurement time point. (D.I. 105 at 7-8). Plaintiff counters that *Ferring* is inapposite because the ANDA specification there did not speak to all of the limitations in the patent. (D.I. 109 at 5 (citing *Ferring*, 764 F.3d at 1387)).

Ferring and *Sunovion* are instructive. At issue in *Ferring* were patent limitations claiming specific drug dissolution rates measured at selected time points. *Ferring*, 764 F.3d at 1384-85. Two of the asserted patents claimed dissolution of less than about 40% at 15 minutes, less than about 70% at 45 minutes, and not less than about 50% at 90 minutes. *Id.* at 1385. The ANDA at issue specified only at least 80% dissolution at 60 minutes. *Id.* at 1385-86. The Federal Circuit concluded that *Sunovion* did not apply because the "ANDA is silent with respect to the claim limitations of the patents-in-suit, which do not specify the dissolved dissolution rate at 60 minutes." *Id.* at 1387. Nor could the ANDA's specified dissolution be mapped directly to all of the limitations of the asserted claims. The ANDA's specified dissolution of at least 80% at 60 minutes would not compel any conclusions about what the dissolution rates for the ANDA product would be at 15 minutes or 45 minutes. Therefore, the ANDA specification did not directly address infringement because it did not speak to all of the limitations in the asserted claims. *Id.* at 1387. Plaintiff was thus required to prove infringement as a matter of fact. In *Sunovion*, by contrast, the asserted patent claim limited the concentration of a particular isomer to "less than 0.25%," and the amended ANDA specified a product containing "[not more than] 0.6%" concentration of the same

isomer. 731 F.3d at 1274-75. Since the ANDA specification of not more than 0.6% necessarily included products meeting the claim limitation of less than 0.25%, the court held that Defendant had sought "FDA approval to market a generic compound within the scope of a valid patent," and thus infringed as a matter of law. *Id.* at 1280.

Here, at first glance, the measurement time points specified in Defendant's ANDA and the '106 patent may appear not to read on one another. Claim 6 of the '106 patent specifies a measurement time point of "at least 5 months," and Defendant's ANDA specifies a 24-month measurement time point. ('106 patent at claim 6; JTX-76 at p. 4; Tr. 311:23-312:3, 658:2-11). With the knowledge that dexmedetomidine concentrations cannot increase under the relevant storage conditions, however, it becomes clear that a decrease of not more than 10% over 24 months imposes a limitation not just for 24 months, but for all time points less than 24 months as well. For example, a product would not meet Defendant's ANDA specification if it demonstrated an 11% decrease in dexmedetomidine concentration at 3 months, because that would necessitate an impossible increase in dexmedetomidine concentration between months 3 and 24 to bring the product back within the specified range. This compels the conclusion that Defendant's ANDA necessarily requires a dexmedetomidine concentration decrease of not more than 10% at 5 months, the same time point claimed in the '106 patent. As was the case in *Sunovion*, Defendant's ANDA seeks FDA approval for products that meet the limitations of the asserted claim. The concentration decrease of no more than 10% at 5 months necessarily present in Defendant's ANDA includes the claimed concentration decrease of no more than about 2% at 5 months. Therefore, Plaintiff has proven that Defendant's proposed ANDA products infringe claim 6 of the '106 patent as a matter of law.

ii. Infringement as a Matter of Fact

Even if Defendant's ANDA products do not infringe under *Sunovion*, Plaintiff asserts that the products infringe as a matter of fact. (D.I. 101 at 6). According to Plaintiff, Dr. Linhardt's testimony and his regression analysis of the stability data that Defendant submitted to the FDA prove that Defendant's ANDA products infringe claim 6 of the '106 patent. (*Id.* at 11). Due to flaws in Dr. Linhardt's regression analysis, Defendant maintains that Dr. Linhardt's testimony regarding this limitation is not credible, and Plaintiff has failed to prove that Defendant infringes claim 6 of the '106 patent by a preponderance of the evidence. (D.I. 105 at 11).

As part of the ANDA application process, Defendant submitted stability data for its proposed products to the FDA to demonstrate that the products would remain stable and potent (i.e., maintain their dexmedetomidine concentration) throughout their shelf life. (JTX-56; Tr. 280:10-17). To expedite approval, the FDA allows applicants to correlate results from studies under accelerated conditions using durations less than the shelf life to longer periods under long-term conditions. (Tr. 255:14-256:9). Using the industry-standard Arrhenius equation, which describes the relationship between temperature and reaction rate, data from six months at accelerated conditions would correspond to more than one year at standard storage conditions for the products at issue. (Tr. 100:8-101:14, 298:6-299:11, 702:11-704:1). Defendant submitted data for its 50 mL and 100 mL products, stored in both upright and inverted orientations, under both accelerated (40°C) and long-term (25°C) conditions, for a total of eight data sets. (JTX-56; Tr. 281:4-14, 282:9-20).

Plaintiff urges that under any method of analysis performed by Dr. Linhardt, Defendant's stability data establishes infringement of the "no more than about 2% decrease" at 5 months limitation. (D.I. 101 at 13; Tr. 302:3-7). Dr. Linhardt testified that long-term storage is the

relevant storage condition for the claimed concentration at 5 months (Tr. 255:1-16, 415:17-416:17) because, as the parties agree, long-term upright storage is the relevant condition to assess product stability over its shelf life (*id.* at 416:4-13, 692:1-12). Dr. Linhardt also stated that both adsorption (best represented by a zero-order model) and degradation (best represented by a first-order model) were possible mechanisms of loss for decreased dexmedetomidine concentration. (*Id.* at 294:9-296:20). He thus created zero- and first-order models for each of Defendant's eight data sets to capture all possible mechanisms of concentration loss. (*Id.* at 294:19-295:23). According to Plaintiff, the best fit lines for each of Dr. Linhardt's 16 linear regression models demonstrate infringement, because even the model demonstrating the largest concentration loss (50 mL vial under long-term storage conditions) showed only a 1.8% loss at 5 months. (D.I. 101 at 12; Tr. 288:9-13, 292:23-294:8, 296:24-297:3). Plaintiff further argues that the individual stability data points for inverted 50 mL vials under long-term and accelerated conditions and inverted 100 mL vials under long-term and accelerated conditions support a finding of infringement, because all showed less than 0.5% loss in dexmedetomidine concentration at the relevant time points. (D.I. 101 at 13 (citing JTX-56 at pp. 5, 9, 11, 15)). Finally, Plaintiff offers as evidence of infringement Defendant's statement to the FDA that its proposed products exhibit "no significant change" in dexmedetomidine concentration at 6 months under accelerated conditions or 18 months under long term conditions. (D.I. 101 at 13 (citing JTX-56 at p. 17)).

Defendant identifies what it asserts are several flaws with Dr. Linhardt's model. First, Defendant asserts that Dr. Linhardt's model fails to explain or account for variability among individual data points. (D.I. 105 at 12-13; Tr. 446:13-447:17). Dr. Linhardt testified that the HPLC measurement technique is associated with a 3-5% variability for any given data point, which Defendant asserts swallows the "no more than about 2%" limitation. (Tr. 291:2-5; D.I. 105 at 12-

13). Although Dr. Linhardt testified that measurement variability is typically accounted for with a coefficient of variability, he did not present any evidence that he had employed a coefficient of variability in his model. (Tr. 357:10-358:2, 420:1-421:2). According to Defendant, Dr. Linhardt thus failed to demonstrate that any individual data point or model prediction was more likely than not to represent the true concentration decrease. (D.I. 105 at 13).

Second, Defendant points out that Dr. Linhardt offered no support from any relevant scientific literature for his selection of zero- and first-order models as representative of the rate relationship of adsorption and degradation, nor did he consider the possibility of a mixed-order model for concentration loss. (Tr. 296:11-20 (justifying model selection because chemists "would consider both types of mechanisms possible"), 389:7-16 (acknowledging that he did not cite "any evidence, literature, or data" in support of his model selection), 378:7-21 (acknowledging no citation in opening expert report to support model selection)). According to Defendant, the references Dr. Linhardt offered for the first time in his reply report are insufficient to support his model selection because he admitted he did not use those references in his work and because the references come from journals concerning topics irrelevant to pharmaceutical formulation. (D.I. 105 at 14; Tr. 379:7-11, 380:9-381:5 (admission that Dr. Linhardt does not use JTX-74 in his research), 384:18-385:7 (admission that Dr. Linhardt does not use JTX-73 in his research); JTX-74 (reference appearing in *Water Research*); JTX-73 (reference appearing in *Journal of Hazardous Materials*)). Since Dr. Linhardt's selection of model types is unsubstantiated, Defendant contends that all of the results from the models are speculative and none of the results can prove infringement. (D.I. 105 at 14; Tr. 294:9-17 (admission that the true rate relationship "could be some other loss that we don't really know about"), 437:16-438:5).

Third, Defendant maintains that Dr. Linhardt's calculations cannot be credited because

none of his models provided a prediction that was more likely than not to fall within the claimed "no more than about 2% decrease" limitation. (D.I. 105 at 15). Since Dr. Linhardt's model failed to employ a confidence interval, Defendant submits that it fails to meet the requirements for a valid statistical model. (*Id.* at 15-16). Without a confidence interval, a statistical regression analysis provides no measure of how likely it is that a true value will fall within a given range as predicted by the model. (*Id.*; Tr. 441:9-443:5). As support, Defendants point out that the only drug stability text Dr. Linhardt relied on in his reports confirms that a confidence interval is required to extrapolate stability data from regression analysis. (D.I. 105 at 17-18; Tr. 385:24-386:5; DTX-495 at p. 179 (defining the shelf life of a drug formulation as dictated by "the lower confidence limit of the time at which the drug content diverges from the specification range" in discussion of extrapolating shelf life from experimental data)). Since Dr. Linhardt did not use confidence intervals, and admitted that he provided no opinions on the statistical significance of his data, Defendant asserts that Dr. Linhardt's calculations cannot provide a valid conclusion regarding infringement. (D.I. 105 at 15; Tr. 365:22-366:14, 392:3-7).

Plaintiff urges that the noninfringement testimony of Defendant's expert, Dr. Bloch, should be discounted because he is not a POSA. (D.I. 109 at 7 (citing *Sundance, Inc. v. DeMonte Fabricating, Ltd.*, 550 F.3d 1356, 1362-63 (Fed. Cir. 2008) (holding patent attorney expert witness not trained as a POSA unqualified to testify on issues of infringement or validity))). Additionally, Plaintiff asserts that Dr. Bloch's testimony should be discounted because it is at odds with Defendant's representations to the FDA that there is sufficient data in Defendant's ANDA application to warrant approval. (D.I. 101 at 14). Plaintiff further asserts that Dr. Bloch's testimony is inconsistent with Defendant's position in this litigation that it was not required to produce additional samples of its ANDA product because the ANDA application adequately

described the product. (D.I. 101 at 14).

I find Plaintiff's arguments attacking Dr. Bloch's credibility unconvincing. Dr. Bloch acknowledged that as a biostatistician, he was not a POSA in the field of drug development. (Tr. 447:24). Unlike the patent attorney expert in *Sundance*, Dr. Bloch did not offer opinions based on matters within the expertise of a POSA—he did not assert as a matter of drug formulation that Defendant's proposed ANDA products failed to meet any of the limitations of claim 6 of the '106 patent. (*Id.* at 447:22-448:4). Instead, Dr. Bloch's testimony remained squarely within his realm of expertise. Dr. Bloch opined, as a matter of statistics, on the validity of the conclusions that Dr. Linhardt had drawn from his regression analysis—a statistical analysis. (*Id.* at 287:22-288:20 (Dr. Linhardt acknowledging that regression analysis is a mathematical analysis and that statistics may be involved, but asserting that he would not perform statistical calculations)). I find Dr. Bloch's testimony credible and helpful to assess the appropriate weight to be given to Dr. Linhardt's regression analysis. (*See id* at 450:6-20).

Having concluded that Dr. Bloch's testimony was proper, I turn to the sufficiency of Dr. Linhardt's model. I agree with Defendants that flaws in Dr. Linhardt's model decrease the weight to be afforded to any evidence derived therefrom. Given the 3-5% variability inherent in the HPLC measurement technique and Dr. Linhardt's failure to employ a coefficient of variability or otherwise account for variability in the individual data points, I agree with Defendant that no single data point is probative of infringement. Dr. Linhardt's analysis of individual data points is therefore non-probative. Additionally, I find that Dr. Linhardt's lack of relevant scientific support for his model selection diminishes the weight of any conclusions based on the model. Finally, the statements in the drug stability text relied on by Dr. Linhardt support Dr. Bloch's testimony that confidence intervals would be required to establish whether a drug concentration falls outside a

specified range at a given time point based on a model relying on experimental data. Since Dr. Linhardt provided no confidence intervals, he failed to establish the likelihood that any of his model's predictions for drug concentration represent true values. I therefore cannot say that it is more likely than not that any of Dr. Linhardt's model's predictions for dexmedetomidine concentration represent the true dexmedetomidine concentration values. Plaintiff has therefore failed to prove infringement as a matter of fact.

Considering all of the evidence, I conclude that Plaintiff has proven by a preponderance of the evidence that Defendant infringes claims 3 and 4 of the '158 patent, claim 4 of the'470 patent, and claim 5 of the'527 patent. Plaintiff has proven that Defendant infringes claim 6 of the '106 patent as a matter of law under *Sunovion*.

V. CONCLUSION

Defendant has proven by clear and convincing evidence that the asserted claims of the '158, '470, and '527 patents are invalid. Defendant has failed to prove by clear and convincing evidence, however, that the asserted claim of the '106 patent is invalid. Plaintiff has proven that Defendant infringes the asserted claims of the '158, '470, and '527 patents as a matter of fact, and that Defendant infringes the asserted claim of the '106 patent as a matter of law.

Plaintiff should submit an agreed upon form of final judgment within two weeks.