NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HOSPIRA, INC., et al., Plaintiffs, v. SANDOZ INC., et al., Defendants.	CIVIL ACTION NO. 09-4591 (MLC) **AMENDED MEMORANDUM OPINION**

COOPER, District Judge

Plaintiffs, Hospira, Inc. ("Hospira") and Orion Corporation ("Orion"), brought this action against Defendants Sandoz Inc., and Sandoz Canada Inc. (collectively, "Sandoz"), which are generic drug manufacturers.[1] Plaintiffs allege infringement of United States Patent No. 4,910,214 ("'214 Patent") and United States Patent No. 6,716,867 ("'867 Patent"). The '214 Patent and '867 Patent are directed to the composition and use of dexmedetomidine hydrochloride, which Hospira markets under the tradename Precedex. Plaintiffs' action is based upon Defendants' submission of Abbreviated New Drug Application ("ANDA") No. 91-465 to the United States Food and Drug Administration ("FDA") seeking approval to

[1] The claims asserted against Defendant Sandoz International GmbH were dismissed by stipulation on December 12, 2011. (Dkt. entry no. 338.)

engage in the commercial manufacture, use, or sale in the United States of a generic version of Precedex ("ANDA product").

Defendants filed counterclaims asserting that the '214 Patent is invalid as anticipated under 35 U.S.C. § 102; invalid as obvious under 35 U.S.C. § 103; and unenforceable due to inequitable conduct. Defendants also claim that the '867 Patent is invalid as anticipated under 35 U.S.C. § 102; invalid as obvious under 35 U.S.C. § 103; and unenforceable due to inequitable conduct. The parties stipulated that the ANDA product would infringe the claims of the '214 Patent and '867 Patent, should the claims be found valid and enforceable. (Dkt. entry nos. 349, 349-1, Final Pre-Trial Order, Exs. A & B.)

The Court conducted a trial from February 27, 2012, through March 7, 2012. The parties submitted proposed findings of fact and conclusions of law on April 2, 2012, and the Court heard closing arguments on April 5, 2012. This Memorandum Opinion constitutes the Court's findings of fact and conclusions of law on the issues of invalidity and unenforceability pursuant to Federal Rule of Civil Procedure 52(a). For the reasons set forth herein, the Court finds that the '214 Patent is valid, enforceable, and infringed by Defendants. The Court further finds the '867 Patent is not anticipated, not unenforceable due to inequitable conduct, but is obvious pursuant to 35 U.S.C. § 103 and therefore invalid.

BACKGROUND

I. The '214 Patent

The '214 Patent is directed toward an "optical isomer of an imidazole derivative medetomidine as an alpha-2-receptor agonist." (See generally '214 Patent.) The '214 Patent issued on March 20, 1990, and has a foreign priority date of July 16, 1987. (Dkt. entry no. 369, Pls. Post-Trial Br. ("Pls. Br.") at 2.)[2] Orion is the owner and assignee of this patent. (Id.) Drs. Arto Karjalainen, Raimo Virtanen, and Eino Savolainen are listed as the inventors. (Dkt. entry no. 367, Defs. Post-Trial Br. ("Defs. Br.") at 6.)

Defendants contend that each claim of the '214 Patent is anticipated and/or obvious. Claim 1 covers the d-enantiomer of medetomidine ("dexmedetomidine") or a non-toxic, pharmaceutically acceptable salt of the d-enantiomer. ('214 Patent, 6:15-16.) Claim 2 teaches "[a] pharmaceutical composition suitable for use in a method of sedation/analgesia or treatment of anxiety or hypertension comprising[:]

> [1] the d-enantiomer of medetomidine or a non-toxic pharmaceutically acceptable acid addition salt thereof

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[2] The Court will cite the parties' post-trial briefs with the understanding that those briefs contain the relevant citations to the record and that such citations are incorporated herein for purposes of this Memorandum Opinion. The Court will supplement citation to the briefs with citations to the record and exhibits when necessary.

> [2] in an amount sufficient to produce the desired effect in association with a pharmaceutical carrier.

(Id. at 6:17-23.)

The remaining '214 Patent claims are dependent claims. Claim 3 narrows the method of use of the enantiomer of claim 1 to treating sedation/analgesia and anxiety or hypertension. (Id. at 6:24-27.) Similarly, claim 4 narrows the method of use of the compound of claim 2 to treating sedation/analgesia and anxiety or hypertension. (Id. at 6:28-31.)

II. The '867 Patent

The '867 Patent is directed toward the use of dexmedetomidine for sedation in the intensive care unit ("ICU"). The '867 Patent issued on April 6, 2004, and has a priority date of April 1, 1998. (Pls. Br. at 2.) Hospira and Orion co-own the '867 Patent. (Id. at 2.) The inventors of the '867 Patent are Drs. Riku Aantaa, Romeo Bachand, and Esa Heinonen. (Defs. Br. at 8.)

Defendants assert that all claims of the '867 Patent are anticipated and/or rendered obvious by prior art. Claim 1 teaches:

> A method of sedating a patient in an intensive care unit, which comprises[:]
>
> [1] administering to the patient an effective amount of dexmedetomidine or a pharmaceutically acceptable salt thereof,
>
> [2] wherein the patient remains arousable and orientated.

('867 Patent, 14:12-16.) Claim 2 depends on claim 1, adding the

limitation that dexmedetomidine or the pharmaceutically acceptable salt of dexmedetomidine is "the sole active ingredient." (Id. at 14:19-20.)

Claim 3 is similar to claim 1 and covers:

> A method of sedating a patient in an intensive care unit, comprising[:]
>
> [1] administering a pharmaceutical composition to the patient,
>
> [2] wherein the pharmaceutical composition comprises an active agent and an inactive agent,
>
> [3] wherein the active agent consists of dexmedetomidine or a pharmaceutically acceptable salt thereof, and
>
> [4] wherein the patient remains arousable and orientated.

(Id. at 14:20-26.)

The remaining '867 Patent claims are dependent claims. Claim 4 depends on claim 1, narrowing this method to achieving "a plasma concentration of 0.1-2 ng/ml." (Id. at 14:27-30.) Claim 5 further limits claim 4 to intravenous administration. (Id. at 14:31-33.) Claim 6 narrows the method of claim 5 by requiring administration to be via a loading dose and a maintenance dose. (Id. at 14:37-36.) Claim 7 requires that the patient of the method in claim 6 be a human. (Id. at 14:38-39.)

Dependent claims 8 through 12 teach specific loading and maintenance doses. Claim 8, dependent on claim 7, claims a loading dose of 0.2-2 µg/kg, and claim 9 requires that this

loading dose be administered in about 10 minutes. (Id. at 14:39-42.) Claim 10, also dependent on claim 7, requires a maintenance dose of 0.1-2.0 µg/kg/h. (Id. at 14:43-45.) Claims 11 and 12 further narrow the maintenance dose to 0.2-0.7 µg/kg/h and 0.4-0.7 µg/kg/h, respectively. (Id. at 14:45-48.)

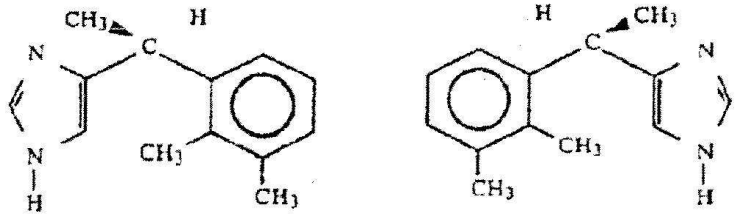
III. Precedex

Precedex is an intravenous sedative approved by the FDA in December 1999 for initially intubated and mechanically ventilated patients in an intensive care setting for a period not to exceed 24 hours. (Defs. Br. at 5.) Precedex was approved for a second indication in October 2008: sedation of non-intubated patients before and/or during surgical and other procedures. (Id.)

The active pharmaceutical ingredient in Precedex is dexmedetomidine, which is a selective α2-adrenergic receptor agonist. (Id.)[3] An agonist works by binding to a receptor and stimulating or activating the receptor to produce an effect in the body. (Defs. Br. at 39.) How tightly or strongly an agonist binds to a receptor, or if it even binds at all, depends on the agonist's shape (i.e., how its atoms are arranged in space). (Pls. Br. at 29.) Thus, the physical shape of an agonist can determine the agonist's affinity and activity at the receptor. (Id.)

[3] The Court will use the terms "α2-adrenergic receptor," "α2-adrenoreceptor," and "α2-adrenoceptor" interchangeably.

Dexmedetomidine is also an enantiomer. An enantiomer is one of a pair of stereoisomers, which are molecules that have the same chemical formula. (See Pls. Br. at 23.) But each stereoisomer's atoms are arranged differently in space. (See id.) Specifically, enantiomers are non-superimposable mirror images of each other due to a central carbon that is asymmetric or "chiral." (See id.) Below, dexmedetomidine and its mirror image enantiomer are reproduced from the '214 Patent:



Dexmedetomidine Levo-medetomidine

('214 Patent, 1:28-43.)

As enantiomer pairs, also known as "chiral compounds," have the same chemical formula, scientists distinguish them by the way each enantiomer rotates light. (Id.) The enantiomer that rotates light to the left is called the levo, lev-, l- or (-)- enantiomer. (Id.) The other enantiomer rotates light to the right and is called the dextro, dex-, d- or (+)- enantiomer. (Id.) When a scientist creates a chiral molecule in the laboratory, he or she forms both enantiomers simultaneously. (Defs. Trial Ex. 206 at 905 (hereinafter "D-").) This mixture is called a racemate or

racemic mixture and consists of equal amounts of two enantiomers. (See Defs. Br. at 56-57.)

Receptors can distinguish between the enantiomers of a racemate because each enantiomer has a different shape. (Defs. Br. at 32.) A receptor will often prefer one enantiomer's shape to the other. As a result, one of the enantiomers generally produces the characteristic physiological effect of the racemate while the other enantiomer produces less of an effect, no effect, or an entirely different effect. (Id.) When a receptor prefers one enantiomer over another (i.e., one enantiomer shows a higher affinity for or activity at the receptor), the receptor is considered "stereoselective." (See Pls. Br. at 26.)

The racemic mixture medetomidine (50% dexmedetomidine and 50% levo-medetomidine) is an α2-adrenoceptor agonist with sedative properties. Medetomidine was studied by scientists at Farmos Group (the predecessor to Orion) in the late 1970s and early 1980s. (Id. at 7.) The scientists at Farmos wanted to investigate medetomidine's enantiomers but first needed to resolve or separate the two enantiomers. (Id.) They were successful in this task and found that dexmedetomidine is responsible for all of the activity at the α2-adrenoceptor. (Id.) In particular, dexmedetomidine has sedative, analgesic, anxiolytic, and anti-hypertensive effects. (Id.) On the other hand, the l-enantiomer

has little to no activity at the α2-adrenoceptor. (Id.) Put another way, the α2-adrenoreceptor is strongly stereoselective for medetomidine because one enantiomer of medetomidine, dexmedetomidine, has most or all of the activity at the α2-adrenoceptor. Orion filed a patent application claiming dexmedetomidine, which issued as the '214 Patent. (Id. at 8.)

Farmos and Orion studied the therapeutic use of dexmedetomidine in the late 1980s. (Id. at 8.) Farmos first studied it as a pre-surgery medication agent in healthy volunteers but later abandoned this use. (Pls. Br. at 8.) In 1994, Orion and Abbott Laboratories (Hospira's processor) started a clinical development program and conducted clinical trials from 1995 to 1997 to study dexmedetomidine as a hemodynamic stabilizer. (Id.) But that clinical use also turned out to be unsuccessful. (Id.)

Orion and Abbott began clinical trials studying the use of dexmedetomidine for ICU sedation in the fall of 1997. (Id. at 9.) Based on the results of these clinical trials, Abbott filed a New Drug Application ("NDA") with the FDA to manufacture and market dexmedetomidine hydrochloride for ICU sedation. (Id.) The FDA approved dexmedetomidine hydrochloride, tradename Precedex, in December 1999. (Id. at 3.) In addition to the NDA, Orion and Abbott filed a patent application claiming the use of

dexmedetomidine for ICU sedation, which issued as the '867 Patent. (Id. at 9.)

The FDA-approved Precedex label warns that the drug can cause bradycardia, hypotension, and transient hypertension. (Defs. Br. at 5.) The label further cautions that Precedex can cause patients to be arousable and alert when stimulated. (Id.) Actually, arousability can be an advantage of Precedex because it can facilitate taking a patient off a mechanical ventilator, reduce a patient's time on a ventilator, and allow patients to participate in their own care by notifying their physicians of discomfort or potential medical problems. (Pls. Br. at 11.)

Precedex sales did not immediately meet Hospira's expectations. (Pls. Br. at 10.) Today, however, approximately 1,100 hospitals per month purchase Precedex, with over 60% of the money spent on ICU sedatives being used to buy Precedex. (Id.) Precedex has generated just under $600 million in sales (id.), and captured an estimated 3.53% of the ICU sedatives market. (Defs. Br. at 126.)

DISCUSSION

I. Applicable Legal Standards

A. Presumption of Validity and Burden of Proof

A patent is presumed to be valid, and each claim is presumed valid independent of the validity of other claims. 35 U.S.C. § 282. An accused infringer seeking to overcome the presumption of

validity bears the burden of showing by clear and convincing evidence that the patent is invalid. Microsoft Corp. v. i4i Ltd. P'ship, 131 S.Ct. 2238, 2242 (2011). This standard requires that the factfinder have "an abiding conviction that the truth of its factual contentions are 'highly probable.'" Colorado v. New Mexico, 467 U.S. 310, 316 (1984) (citation omitted).

B. Anticipation

Under 35 U.S.C. § 102, a claim is invalid as anticipated if "each and every limitation" of the claim is "found either expressly or inherently disclosed in a single prior art reference." PIN/NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235, 1243 (Fed.Cir. 2002) (citation omitted). The single prior art reference must enable a person of ordinary skill in the art to practice the claimed invention. See Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1345 (Fed.Cir. 2008). In other words, the reference must contain sufficient detail such that a person of ordinary skill could practice what is described without undue experimentation. See Elan Pharms., Inc. v. Mayo Found., 346 F.3d 1051, 1054-1055 (Fed.Cir. 2003).

Even if the prior art reference does not expressly disclose every claim limitation, it is still anticipatory provided that a person of ordinary skill in the art would understand that every claim limitation is disclosed. Arthrocare Corp. v. Smith &

Nephew, Inc., 406 F.3d 1365, 1373-74 (Fed.Cir. 2005). But such "anticipation by inherent disclosure" is proper only if the reference necessarily discloses all claim limitations. Transclean Corp. v. Bridgewood Servs., 290 F.3d 1364, 1373 (Fed.Cir. 2002). Anticipation cannot be found based upon the mere probability or possibility that a claim limitation is disclosed by the prior art reference. Trintec Indus. Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed.Cir. 2002).

C. Obviousness

> A patent may not be obtained . . . 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(a); see Graham v. John Deere Co., 383 U.S. 1, 13-14 (1966). The ultimate determination of obviousness under § 103 is a question of law, but it is based on underlying questions of fact. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 427 (2007); Dennison Mfg. Co. v. Panduit Corp., 475 U.S. 809, 811 (1986).

Graham requires a court to determine: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) any objective evidence of nonobviousness, such as skepticism of those in the art, long-felt industry need,

commercial success, and copying. See Agrizap, Inc. v. Woodstream Corp., 520 F.3d 1337, 1344 (Fed.Cir. 2008).

A party seeking to invalidate a patent for obviousness must demonstrate that a person of ordinary skill in the art would have been motivated to combine the teachings of the prior art references to achieve the claimed invention and that the person of ordinary skill in the art would have a reasonable expectation of success in doing so. Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 944 (Fed.Cir. 2009).

D. Inequitable Conduct

Persons involved in the preparation and prosecution of a patent application "have a duty to prosecute patent applications in the U.S. Patent and Trademark Office (PTO) with candor, good faith, and honesty." Advanced Magnetic Closures, Inc. v. Rome Fastener Corp., 607 F.3d 817, 829 (Fed.Cir. 2010). The duty of candor rests on "(1) each named inventor, (2) each attorney or agent that prepares or prosecutes the application, and (3) every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor or assignee." Avid Identification Sys., Inc. v. Crystal Import Corp., 603 F.3d 967, 973 (Fed.Cir. 2010) (citing 37 C.F.R. § 1.56(c)). A breach of the duty of candor constitutes inequitable conduct and renders the patent unenforceable.

Bristol-Meyers Squibb v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1233 (Fed.Cir. 2003); Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed.Cir. 1995).

To succeed on a claim of inequitable conduct, an accused infringer must present evidence that a person having a duty of candor "(1) misrepresented or omitted material information, and (2) did so with specific intent to deceive the PTO." Am. Calcar, Inc. v. Am. Honda Motor Co., Inc., 651 F.3d 1318, 1334 (Fed.Cir. 2011). These two requirements are separate. Courts no longer apply a "sliding-scale, where a weak showing of intent may be found sufficient based upon a strong showing of materiality, and vice versa." Therasense, Inc. v. Becton, Dickinson & Co., 649 F.3d 1276, 1290 (Fed.Cir. 2011).

When assessing the materiality of a reference, "the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference." Id. at 1291. A party must demonstrate this but-for materiality by a preponderance of the evidence, giving claims their "broadest reasonable construction." Id. at 1291-92.

To satisfy the intent prong, an accused infringer must prove, by clear and convincing evidence, that the patent applicant acted with specific intent to deceive the PTO. See id. at 1290. Where non-disclosure of a reference is at issue, the

evidence presented must show that the patentee knew of the reference and its materiality, but instead chose to deliberately withhold it. See id. While a court "may infer intent from indirect and circumstantial evidence[,] . . . the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" Id. (quoting Star Sci., Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1366 (Fed.Cir. 2008)).

II. Validity of the '214 Patent

A. Anticipation

Defendants assert that the claims of the '214 Patent are invalid as anticipated. Claim 1 of the '214 Patent covers the d-isomer of medetomidine. All other claims of the '214 Patent have, as an element, the d-enantiomer of medetomidine. The parties have agreed that the "d-enantiomer of medetomidine" is defined as the "substantially pure, optically active dextrorotary stereoisomer of medetomidine." (Defs. Br. at 10.)

Defendants argue that a thesis by Dr. Juha-Matti Savola titled "Cardiovascular and Sedative Effects of Novel Detomidine-Like Arylalkyl Imidazoles and Related Derivatives" ("Savola thesis") anticipates every claim of the '214 Patent. (Id. at 60.) The Savola thesis was presented publicly on October 17, 1986 and copyrighted in 1986. (Id.) It is therefore prior art under 35 U.S.C. § 102(a).

This thesis describes Dr. Savola's study of the sedative and cardiovascular effects of detomidine and related imidazoline compounds including medetomidine. (Id. at 25.) The reference specifically refers to medetomidine as being a racemic mixture, citing its chemical name "(±)-4-(α,2,2-trimethylbenzyl)imidazole." (Id.) Defendants' expert Dr. Paul A. Insel testified that a person of ordinary skill in the art would understand that medetomidine was used as a racemate in Dr. Savola's experiments because the "(±)" symbolizes a racemate. (Id.)

The Savola thesis also discloses that medetomidine is a selective α2-adrenoceptor agonist that would be interesting to study further. (Id.) In fact, the reference states that, as other imidazoline compounds have demonstrated stereoselectivity at the α2-adrenoceptor, the (+) and (-) enantiomers of medetomidine are "also to be studied." (Id. at 25-26.) Dr. Insel concluded that it was likely that medetomidine's enantiomers had already been isolated and studied at the time Dr. Savola presented his thesis in 1986. (Id. at 26.) Dr. Insel testified that, "seeing the other evidence that was presented, that [Dr. Savola's] coworkers separated the two forms by late 1985, makes me wonder if that experiment hadn't already been conducted." (Id.) Defendants conclude, therefore, that the Savola thesis discloses that dexmedetomidine had been isolated. (Id.)

The Court rejects Defendants' argument. Dr. Savola's statement that the medetomidine enantiomers are "also to be studied" is insufficient to prove that the Savola thesis discloses that medetomidine's resolution had actually taken place. In fact, the Court reads the phrase to suggest the opposite is true since "to be studied" suggests a future event.[4] Indeed, Dr. Insel conceded that the Savola thesis does not describe any separation of medetomidine nor does it disclose a method for doing so. (Pls. Br. at 12.)

Even if the resolution of medetomidine into its d- and l-enantiomers had taken place by the time the Savola thesis was presented, the Court still cannot find that the Savola thesis anticipates the '214 Patent. The Savola thesis does not disclose the separated enantiomers; it only discloses racemic medetomidine. Yet claim 1 of the '214 Patent covers, and its dependent claims require, the "substantially pure, optically active dextrorotary stereoisomer of medetomidine." While (±)-medetomidine is necessarily 50% dexmedetomidine, it is not "substantially pure" in that form because the dexmedetomidine has not been separated out of medetomidine. See Sanofi-Synthelabo v. Apotex, Inc., 550

[4] The Court is aware that a laboratory report presented at trial shows that resolution of medetomidine took place in 1985. (See Defs. Br. at 55-56.) But that is not the relevant inquiry here. Instead, the Court must determine what the Savola thesis discloses, and it does not disclose resolution of medetomidine.

F.3d 1075, 1084 (Fed.Cir. 2008) ("[K]knowledge of the existence of enantiomers is not a description of a specific enantiomer 'substantially separated' from the other.").

Because the Savola thesis fails to teach the "substantially pure" limitation, it cannot anticipate any claim of the '214 Patent. Therefore, the Court holds that the '214 Patent is not invalid as anticipated under 35 U.S.C. § 102.

B. Obviousness

Defendants argue that the '214 Patent is invalid as obvious pursuant to 35 U.S.C. § 103. Specifically, Defendants assert that a person of ordinary skill would have been motivated to isolate and test the enantiomers of medetomidine; that it would be likely that one of those enantiomers would have all or most of the activity at the α2-adrenoceptor; and that a person of ordinary skill would have a reasonable likelihood of success in isolating dexmedetomidine. (Defs. Br. at 16.)

1. Graham Framework

To determine whether the claims of the '214 Patent are obvious, the Court must make the following factual findings: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, such as unexpected results, skepticism of those

in the art, long-felt industry need, commercial success, and copying. Ruiz v. A.B. Chance Co., 234 F.3d 654, 663, 664-67 (Fed.Cir. 2000).

a. Level of Ordinary Skill in the Art

The Court evaluates obviousness from the perspective of a person of ordinary skill in the art of the patent. Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed.Cir. 1985). "A person of ordinary skill is also a person of ordinary creativity, not an automaton." KSR Int'l Co., 550 U.S. at 421.

There is no material disagreement as to the person of ordinary skill in the art of the '214 Patent, which involves two relevant fields. (Pls. Br. at 34.) The first is pharmacology and the study of the optical isomers of imidazoline derivatives. (Id.) In this field, a person of ordinary skill would have a Ph.D, M.D., or some other advanced degree in chemistry, pharmacology, biology, or a related science and familiarly with the principles of stereochemistry. (Id.; Defs. Br. at 16-17.) The second field is medicine, and the person of ordinary skill in this field would have an M.D. with several years of experience administering medication to patients. (Pls. Br. at 34; Defs. Br. at 17.)

b. Scope and Content of the Prior Art

The scope of the prior art includes that which is "reasonably pertinent to the particular problem with which the inventor was involved." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530,

1535 (Fed.Cir. 1983) (citation omitted). The scope and content of the prior art is assessed as of July 16, 1987, the filing date of the '214 Patent. Here, the pertinent prior art covers three areas: (1) references disclosing medetomidine; (2) as cited by the parties, prior art on the stereoselectivity of α2-adrenoceptors for imidazoline compounds; and, (3) as cited by the parties, references teaching resolution of racemic mixtures.

Several references disclose medetomidine. These references are relevant because medetomidine's composition is half dexmedetomidine and half levo-medetomidine, and therefore, a person of ordinary skill would look to medetomidine to learn what characteristics dexmedetomidine could be expected to have. U.S. Patent No. 4,544,664 ("'664 Patent") claims a number of imidazole derivatives including medetomidine. (Defs. Br. at 23.) The Savola thesis, as previously described, teaches that medetomidine is racemic and explains that it is a selective α2-adrenoceptor agonist. (Id. at 25-26.) Dr. Savola also characterized medetomidine as a potential pharmacological intervention in 1986 ("Savola 1986"). (Id. at 21.) To make medetomidine, Dr. Savola took detomidine and added a methyl group to its bridge carbon, transforming non-chiral detomidine into chiral medetomidine. (Id.) Adding the methyl group to detomidine results in an increase in activity at the α2-adrenoceptor. (Id.)

Consistent with activity at the α2-adrenoceptor, Dr. M. Scheinin et al. in "Dose-Finding and Tolerability Study of Medetomidine in Four Healthy Volunteers" ("Scheinin 1987a") found that medetomidine reduces blood pressure, heart rate, and saliva secretion while revealing dose-dependent sedation or impairment of vigilance. (Id. at 24.)

The prior art also discloses the activity of imidazoline compounds at the α2-adrenoceptor. Since medetomidine is an α2-adrenoceptor agonist with an imidazoline ring, both parties' experts testified that a person of ordinary skill in the art would look to other imidazoline compounds active at the α2-adrenoceptor in predicting the activity of the medetomidine enantiomers. Dr. Insel and Plaintiffs' expert Dr. Brian Kobilka did not agree, however, as to which imidazoline compound was most relevant.

In the early 1980s, Dr. Robert Ruffolo et al. characterized imidazoline activity at the α1- and α2-adrenoceptors and compared it to the Easson-Stedman Hypothesis ("Ruffolo"). (Id. at 28.)[5] Dr. Ruffolo compared catecholimidazolines to phenethylamines,

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[5] The Easson-Stedman hypothesis theorizes that phenethylamines, such as adrenaline, bind to adrenergic receptors via a three-point attachment. (Pls. Trial Ex. 69 at 471 (hereinafter "P-").) The three-point attachment, according to the hypothesis, is the most favorable stereochemical configuration for interaction with the adrenergic receptors, including the α1- and α2-adrenergic receptors. (Id.) Consequently, the α1- and α2-adrenoceptors demonstrate high stereoselectivity for phenethylamines. (Id.)

which are known to be strongly stereoselective. (Id.) Dr. Ruffolo found that the Easson-Stedman hypothesis does not apply to chiral imidazoline compounds. (Id.) Consequently, the stereochemical demands of the α1- and α2-adrenergic receptors for imidazolines are less than that for phenethylamines. (Id.) Put another way, an imidazoline's enantiomers would not be expected to show a large difference in their affinity and activity at the α1- and α2-adrenoceptor. (Pls. Br. at 26.) In particular, the activity ratio of the phenethylamine enantiomers at the α2-adrenoceptor is about 300-fold whereas the activity ratio of the catecholimidazoline enantiomers is a mere 5.6-fold, with the l-catecholimidazoline being more active. (Id. at 26, 39.)

Other imidazolines studied show similar stereoselectivity at the α2-adrenoceptor. In a 1985 study, B. Wilffert et al. ("Wilffert") investigated the enantiomers of lofexidine, an α2-adrenoceptor agonist in the imidazoline family, and found them to be weakly stereoselective. (Defs. Br. at 29.) The l-enantiomer of lofexidine is about 10-30 times more active than the d-enantiomer at the α2-adrenoreceptor. (Id.)

In 1985, H. Dabiré et al. studied the stereoselectivity of the imidazoline derivative idazoxan ("Dabiré"). (Id.) The study concluded that the α2-adrenoceptor is stereoselective for idazoxan, which is a fused-ring antagonist. (Id. at 29-30.) In

contrast to idazoxan, however, medetomidine, catecholimidazoline, and lofexidine do not contain a fused ring. (Pls. Br. at 27.) Further, idazoxan is an antagonist as opposed to an agonist, which means that idazoxan binds to a receptor and blocks activity rather than stimulating it. (Id. at 25.)

Following up on the Dabiré work, Anthony P. Welbourn et al. characterized the stereoselectivity of idazoxan derivatives in 1986 ("Welbourn"). (Id. at 30.) Welbourn reports a 200-2600 fold difference in activity between the enantiomers of the idazoxan derivatives, with the more active enantiomer varying between the l- and d-enantiomer. (Id.) But Welbourn points out that stereoselectivity for idazoxan antagonists is greater than seen for any imidazoline-containing agonist so far studied. (Pls. Br. at 28.)

The parties cite last to a number of prior art references teaching resolution of racemic mixtures. Enantiomers have identical physical properties; they have the same boiling points, melting points, solubility, and index of refraction. (Id. at 33.) Thus, they cannot be separated and isolated using ordinary physical methods. (Id.)

The parties focused particularly on resolution by a method called fractional crystallization of diastereomeric salts. But there were a number of options in 1987. Dr. Wetzel testified

that six techniques were available: (1) fractional crystallization of diastereomeric salts; (2) separation of diastereomeric covalent derivatives; (3) chiral chromatography; (4) synthesis from optically active starting material; (5) asymmetric synthesis; and (6) kinetic resolution. (Defs. Br. at 47.)

An article by Samuel Wilen on the subject of resolutions in the field of organic chemistry ("Wilen") discloses fractional crystallization and designates it as the most widely used resolution procedure. (Defs. Br. at 34-35.) This technique requires mixing the racemate and a resolving agent (either a chiral acid or base) in a solvent. (Pls. Br. at 33.) For medetomidine, a chiral acid is required because medetomidine is a base. (Id.) A guide called "Enantiomers, Racemates, and Resolutions" by Jean Jacques published in 1981 ("Jacques"), lists 15 to 20 common chiral acids, noting that tartaric acid is commonly used. (Id.; Defs. Br. at 33.) Jacques also lists approximately 50 solvents and solvent mixtures, but advises that it is preferable to work with pure solvents. (Pls. Br. at 33, 45.)

The successful combination of a chiral acid with the racemate in solvent will trigger formation of diastereomeric salts, and then, if all goes well, the crystallization of an isolated enantiomer. (Id. at 33.) But encouraging an enantiomer to crystallize out of solution may require heating, chilling, adding

dust to the solution, or even scratching the glass container holding the solution. (Id.)

The separation references have much to say about the "art" of successfully separating enantiomers. Ernst Eliel wrote in "Stereochemistry of Carbon Compounds," published in 1962, that resolution is a matter of trial and error. (Id. at 31.) A 1984 organic chemistry textbook by Seyhan Eğe cautions that resolutions are not easy and require a great deal of patience and skill, and some good luck. (Id. at 31-32.) On the other hand, Jacques states that "virtually anyone can learn to carry out a purification implicit in a recrystallization. So, too, with resolutions . . . . [T]here need be few—if any—failures in intelligently and systematically executed resolutions." (Defs. Br. at 33.) Indeed, resolution by fractional crystallization is taught to undergraduate students in their basic organic chemistry textbooks. (Id. at 32 (citing "Organic Chemistry" by L.G. Wade, Jr. ("Wade") published in 1987).) So there is considerable disagreement in the field regarding just how difficult resolution of racemates might have been in July of 1987.

c. Differences Between Prior Art and '214 Patent

A claim is obvious "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." 35 U.S.C. § 103. As to the chemical arts, "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed.Cir. 2007).[6]

> [I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with a reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.

Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed.Cir. 2007) ("Aventis").

The Court finds here that the prior art would have motivated a person of ordinary skill to separate medetomidine's enantiomers, but that there was not a reasonable expectation that it could have been done successfully.

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[6] There is no burden-shifting framework in the obviousness analysis. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., Nos. 11-1399, 11-1409, 2012 WL 1320225, at *12 (Fed.Cir. April 16, 2012). The burden of proof remains at all times with the patent-challenger to demonstrate clear and convincing evidence of obviousness. Id. Thus, while several of the cases cited in this Memorandum Opinion may refer to a burden-shifting framework, the Court does not apply one here.

i. Motivation to Separate Medetomidine Enantiomers

Defendants contend that a person of ordinary skill in the art in 1987 would have been motivated to resolve medetomidine, and it would be expected that one of its enantiomers would be more active at the α2-adrenoceptor than the other. The prior art motivates if "the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old". Aventis, 499 F.3d at 1301 (quotations and citations omitted). As stated by the '214 Patent, dexmedetomidine is the d-enantiomer of medetomidine and is suitable for treating sedation, analgesia, anxiety, or hypertension. ('214 Patent, 1:23-26, 2:27-30.)

The '664 Patent claims medetomidine, and the Savola thesis teaches that medetomidine is racemic by using the (±) symbol in front of medetomidine's chemical formula. (Defs. Br. at 36.) Dr. Kobilka explained that a person of ordinary skill would identify from medetomidine's chemical structure that it has a chiral center and it therefore contains equal parts of two enantiomers. (Id. at 36-37.)

The therapeutic properties of medetomidine had also been characterized by 1987. Savola 1986 instructs that medetomidine is a selective α2-adrenoceptor agonist and that it is a potent sedative and lowers blood pressure. (Id. at 37.) Likewise,

Scheinin 1987a teaches that medetomidine has the typical action of an α2-adrenoceptor agonist because it reduces blood pressure, heart rate, and saliva secretion. (Id.) Scheinin 1987a also discloses dose-dependent sedation with medetomidine administration. (Id.) Dr. Kobilka agreed that these effects would be known to a person of ordinary skill in the art in 1987. (Id.) The '214 Patent explains that dexmedetomidine is a selective α2-adrenoceptor agonist and claims dexmedetomidine's anti-hypertensive and sedative-analgesic properties. ('214 Patent, Abstract; Defs. Br. at 6-7.)

Medetomidine contains, in addition to a chiral carbon center, an imidazole ring. (Pls. Br. at 23-24.) Accordingly, a person of ordinary skill would look to other chiral compounds containing imidazole rings to determine the characteristics medetomidine enantiomers are likely to have. See Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed.Cir. 2007) (explaining that the challenger of a patent must demonstrate a motivation to combine the teachings of prior art references). The 1987 prior art relating to imidazoline compounds teaches a person of ordinary skill that the α2-adrenoceptor is stereoselective for imidazoline compounds. (Defs. Br. at 37.) In other words, one of the two enantiomers of a chiral imidazoline compound is more potent than the other. (Id. at 38-39.)

Yet the imidazoline prior art consistently characterizes the chiral imidazolines as weakly stereoselective at the α2-adrenoceptor. (Pls. Br. at 30.) For example, l-catecholimidazoline has a 5- to 9-fold greater activity than d-catecholimidazoline; and l-lofexidine has a 10- to 30-fold greater activity than d-catecholimidazoline. (Id. at 39.) Ruffolo noted that, in comparison, phenethylamine enantiomer activity differences are much higher, ranging from 300- to 1000-fold. (Id. at 26.) While several references teach that idazoxan antagonists show strong stereoselectivity, Welbourn explains that this is inconsistent with the low enantiomer activity differences typical of imidazoline agonists. (Id. at 36-37.)

Even so, given that medetomidine demonstrated therapeutic use and was structurally similar to other stereoselective imidazoline compounds, we find that a person of skill in the art in 1987 would have been motivated to separate, isolate, and study medetomidine's enantiomers. See In re May, 574 F.2d 1082, 1094 (Fed.Cir. 1978) ("basis of the prima facie case of obviousness, at least to a major extent, is based on the presumed expectation that compounds which are similar in structure will have similar properties"). Both parties' experts agreed that a person of ordinary skill in the art would expect that one of medetomidine's enantiomers would be more active than the other. (Defs. Br. at

37-38.) Moreover, a person of ordinary skill would understand that because medetomidine has sedative, analgesic, anxiolytic, and anti-hypertensive effects, the active medetomidine enantiomer would likely have those effects on a greater scale. (Id. at 38.) Indeed, the Savola thesis explicitly provides such a motivation in stating that the medetomidine enantiomers are "to be studied" because of the known differences between imidazoline enantiomers. (Id. at 26.) Consequently, this Court finds that in July 1987, one would be motivated to separate and isolate both medetomidine enantiomers, with the expectation that one of them would be more biologically active.

ii. Reasonable Likelihood of Success

Defendants assert that a person of ordinary skill in the art would have had a reasonable likelihood of success in separating and isolating the enantiomers of medetomidine. (Defs. Br. at 47.) Where there is a motivation to make a claimed compound, a reasonable expectation of success supports the finding of obviousness. See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed.Cir. 2000). Obviousness does not require "absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." In re Merck & Co., 800 F.2d 1091, 1097 (Fed.Cir. 1986) (internal citations omitted).

Several cases address the difficulty associated with separating racemates in the late 1980s, finding that it was not a simple or routine procedure, required undue experimentation, and did not carry a reasonable expectation of success. See Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1077 (Fed.Cir. 2008); Forest Labs, Inc. v. Ivax Pharm. Holdings, Ltd., 501 F.3d 1263, 1267 (Fed.Cir. 2007). But "the determination of obviousness is dependent on the facts of each case", Sanofi, 550 F.3d at 1089, and so this Court cannot rely on what other courts have determined is too difficult or unpredictable.

The '214 Patent discloses that medetomidine can be resolved by fractional crystallization of diastereomeric salts. ('214 Patent, 1:44-56.) The specification teaches that (+)-tartaric acid is an especially useful chiral acid and that methanol, ethanol, or a mixture of methanol and ethanol is a suitable solvent. (Id.)

At least six techniques to resolve racemic mixtures were known in 1987. (Defs. Br. at 47.) Defendants' expert Dr. John M. Wetzel explained that fractional crystallization by diastereomeric salts would have been a likely choice. (Id. at 47-48.) In fact, Dr. Wetzel stated that he supervised undergraduate laboratory courses in 1987 during which students crystallized organic compounds in this manner. (Id. at 48.)

Undergraduate students are usually provided instruction as to the ingredients and steps required to successfully execute a laboratory exercise. On the other hand, a person of ordinary skill in the art who is studying a novel, organic compound must start from scratch. Accordingly, the Court cannot simply retrace the steps taken by the '214 Patent inventors, noting that each step or ingredient required along the way is found in the prior art. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 2012 WL 1320225, at * 8. This would introduce an impermissible hindsight bias. Id.[7]

The Court must start by considering the entirety of the prior art, including fractional crystallization and any other methods available in 1987. Dr. Wetzel explained that the five other techniques available in 1987 would not have been feasible. (Defs. Br. at 47.) He stated that chiral chromatography,

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[7] Defendants point to the 1985 laboratory report showing the resolution of medetomidine in an effort to demonstrate that the patent applicants resolved medetomidine on their first try, and therefore, it must have been a routine application of an obvious technique. (Defs. Br. at 56.) First, there is no conclusive evidence that this report represents the first and only try to resolve medetomidine. Second, the Court must determine whether resolution of medetomidine carried a reasonable likelihood of success as of July 1987 in light of the prior art as a whole. Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc., 520 F.3d 1358, 1364 (Fed.Cir. 2008). Retracing the steps disclosed in the laboratory report, knowing that the end result is successful, improperly relies on hindsight. (Id.)

synthesis from optically active starting materials, asymmetric synthesis, and kinetic resolution were unpromising because of various difficulties in application. (Id.) Separation of diastereomeric covalent derivatives, Dr. Wetzel testified, also was an unlikely option because of the need to choose an appropriate resolving agent and chemical reaction to form and then cleave a covalent bond. (Id.) That experimental process, at its core, seems no different than what would be required to undertake fractional crystallization, but Dr. Wetzel explained that medetomidine's physical features make it an ideal candidate for fractional crystallization. (Id.) The Court notes, however, that Dr. Wetzel could not recall having actually performed a resolution by 1987 and has, to this day, never performed a complete fractional crystallization by diastereomeric salts. (Pls. Br. at 44.) As a result, the Court has concerns with Dr. Wetzel's expert testimony, because it seems to introduce impermissible ex post reasoning. See KSR Int'l Co., 550 U.S. at 421.

Accepting for the sake of argument that Dr. Wetzel's prediction is accurate, a person of ordinary skill trying fractional crystallization would have some direction from the prior art in picking a chiral acid and solvent. Several of the references cited — Wilen, Wade, and Jacques — identify tartaric acid as a widely used chiral acid. (Defs. Br. at 32-35.) Wilen

notes that tartaric acid and its derivatives are used in nearly one-half of resolutions involving a base. (D-207 at 137.)[8] There are also a number of combinations of chiral acids and solvents that have previously succeeded in resolving a racemate. (Defs. Br. at 33-34.) Jacques suggests that tartaric acid should be tried in combination with ethanol, methanol, water, and acetone (in that order). (Id.) The reference cautions, however, that mixing solvents is to be avoided as it is preferable to work with pure solvents. (Id. at 34.) Plaintiffs' expert Dr. Michael Crimmins agreed, testifying that a 3:1 mixture of ethanol to methanol, a mixture that ultimately proved successful in resolving medetomidine, was an unusual combination. (Pls. Br. at 45.)

Even with such guidance, resolutions are nonetheless described by the prior art as difficult procedures. (Pls. Br. at 33.) Dr. Crimmins testified that the process is iterative and that trial and error is normal. (Id.) In the end, the Court is troubled by the various available methods, each of which has numerous steps and ingredients. An "obvious-to-try" standard may be permissible in circumstances where there is a known problem and a "finite number of identified, predictable solutions." KSR Int'l Co., 550 U.S. at 421. But it is less appropriate where, as

[8] Perhaps that is because, as Wade explains, "[a]ny winery can provide large amounts of pure (+)-tartaric acid." (D-208 at 376.)

here, "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell, 853 F.2d 894, 903 (Fed.Cir. 1988). Thus, while "intelligently and systematically designed resolutions" may eventually be successful, that does not mean they necessarily carry a reasonable expectation of success so as to make them obvious to use to isolate dexmedetomidine. In arriving at this conclusion, the Court finds that both experts were credible, but Dr. Crimmins had practical experience with performing resolutions in 1987, whereas Dr. Wetzel did not. Dr. Crimmins, consistent with the Court's own analysis of the prior art, concludes that no separation method was sufficiently reliable or predictable in 1987 so as to offer a reasonable expectation of success in isolating dexmedetomidine.

The Court finds that this factor in the obviousness analysis cuts against a finding of obviousness. While a person of ordinary skill in the art would have been motivated to try to isolate and study the enantiomers of medetomidine, there was no reasonable certainty in 1987 that it could be successfully done. Rather, even with the guidance offered by the prior art, a tedious process of trial and error would be expected.

d. Objective Evidence of Nonobviousness

The objective evidence presented here further demonstrates the nonobviousness of the '214 Patent. Objective evidence of nonobviousness typically includes skepticism of those in the art, long-felt industry need, commercial success, and copying. See Agrizap, Inc., 520 F.3d at 1344. In the context of enantiomers, "evidence that the claimed compound has unexpected properties" is particularly compelling. Aventis, 499 F.3d at 1301. According to Plaintiffs, a person of ordinary skill could deduce two things about dexmedetomidine from the prior art: (1) the l-enantiomer is likely to be the more active enantiomer, and (2) medetomidine's enantiomers would exhibit weak stereoselectivity. (Pls. Br. at 34.) But Plaintiffs point out that neither of those two things proved true for dexmedetomidine.

We find that the first argument is not credible in light of the expert testimony. Medetomidine is most analogous in structure to imidazoline α2-antagonists. (Id. 28-30.) Two in particular, catecholimidazoline and lofexidine, were compared by the parties' experts to medetomidine. In contrast to medetomidine, it was the l-enantiomer of catecholimidazoline and lofexidine that was more active. (Id. at 39.) From that, Plaintiffs argue that a person of ordinary skill in the art would have therefore expected the l-enantiomer of medetomidine to be

the active enantiomer. (Id.) But both experts disagreed. Dr. Insel stated that one would not try to predict the enantiomer that would be more active. (Defs. Br. at 45.) Dr. Kobilka agreed and added that it would be difficult and likely misleading to try to predict the enantiomer that would be the more active one. (Id. at 46.) Moreover, this is not the proper comparison to make. Aventis, 499 F.3d at 1302 (concluding that the defendant must show that a stereoisomer shows unexpected results not over the other stereoisomers, but over the racemic mixture).

The more persuasive evidence is that all of medetomidine's closest structural analogues demonstrate weak stereoselectivity. Therefore, a person of ordinary skill in the art in 1987 would expect that medetomidine's enantiomers would also be weakly stereoselective. At the α2-adrenoceptor, the enantiomers of catecholimidazoline demonstrated a 5- to 9-fold difference in stereoselectivity. (Pls. Br. at 39.) Lofexidine's enantiomers had a 10- to 30-fold difference (Defs. Br. at 29), which Wilffert even described as uncharacteristically high for imidazolines. (D-33 at 30.)

The activity difference for medetomidine's enantiomers was much higher. Tables 1, 3, and 4 of the '214 Patent summarize results from experiments that quantified the d- and l-enantiomers activity. Table 1 shows a 1,995-fold difference in

stereoselectivity at the α2-adrenoceptor. ('214 Patent, 2:50-62.)[9] Tables 3 and 4 studied the sedative/analgesic effects and found a 500- and 1,000-fold difference, respectively. (Id. at 3:23-59.)

Defendants point out that a 5-fold difference means that 80% of the activity resides in the more active enantiomer, and a 10-fold difference means that 90% of the activity resides in the more active enantiomer. (Defs. Br. at 38.) Hence, according to Defendants, this "relatively small difference in activity" means that it would be expected that one enantiomer would be "responsible for all, or substantially all, of the activity" of the racemate. (Id.) But while 80% and 90% seem intrinsically close to 100%, there is nothing to demonstrate their proximity is statistically significant. Therefore, it would be wrong to assume that because 80% or 90% activity is expected, 100% activity would also be expected.

Enantiomer activity must be viewed in light of the activity of the racemate, because as mentioned above, the proper comparison

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[9] Table 2 of the '214 Patent summarizes results from an α2/α1-selectivity in vitro experiment. ('214 Patent, 2:65-3:21.) According to Table 2, dexmedetomidine is three times more active at the α2-adrenoceptor than medetomidine. (Defs. Br. at 143.) But Dr. Insel provided undisputed testimony that the Table 2 data is scientifically impossible because an enantiomer cannot be more than twice as active than its racemate. (Id.) Therefore, the Court will not consider Table 2 in the obviousness discussion and will instead take up the issue of Table 2 in the inequitable conduct discussion.

is between the racemate and the active enantiomer. Aventis, 499 F.3d at 1302. At most, an enantiomer can only be twice as active as its racemate.[10] In other words, there will at most be a 2-fold difference between the racemate and the active enantiomer. But the prior art reveals differences of less than two. For example, the activity of the l-enantiomer of lofexidine was calculated 1.48-, 1.51-, and 1.78-fold greater than its racemate in three different experiments performed by Wilffert. (Pls. Br. at 38.) While 1.78-fold compared to 2-fold may not seem that different at first glance, it nevertheless is biologically significant. (Id.) Indeed, a 1.78-fold difference represents a weak difference (id.), while a 2-fold difference is, by definition, the strongest difference possible. (Defs. Br. at 143-44.) Thus, given the stereoselectivity weakness of other imidazolines and that none of their enantiomers are twice as active as their racemate, one of ordinary skill in the art would not expect dexmedetomidine to be twice as active as medetomidine.

The Court is not persuaded that idazoxan is an appropriate indicator of medetomidine stereoselectivity, despite Defendants'

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[10] By definition, a racemate is 50% d-enantiomer and 50% l-enantiomer. Assume that the d-enantiomer has all of the activity of the racemate and that the l-enantiomer has none. If there are equal amounts of the racemate and the d-enantiomer (e.g., 5 mL of racemate and 5 mL of d-enantiomer), then the d-enantiomer will have twice the effect of medetomidine. (Defs. Br. at 143-44.)

argument to the contrary. Idazoxan does show strong stereoselectivity comparable to medetomidine. Idazoxan, however, is an antagonist whereas medetomidine and the other imidazoline compounds cited in the prior art are agonists. Dr. Insel tried to downplay the antagonist versus agonist distinction, but it is a distinction with a difference. Welbourn states that the stereoselectivity at the α2-adrenoceptor for imidazoline-containing antagonists is much higher than any imidazoline-containing agonist. (Pls. Br. at 28.) Moreover, idazoxan's fused-ring structure makes it less flexible, which may affect its interaction with the α2-adrenoceptor. Dr. Kobilka testified that idazoxan is therefore unhelpful in predicting how medetomidine enantiomers will bind at the α2-adrenoceptor. (Pls. Br. at 37.) The Court finds Dr. Kobilka's conclusion on this point reliable given that it is consistent with Welbourn.

The Court therefore finds that the unexpected result submitted in this case is strong and persuasive evidence of nonobviousness. The Federal Circuit has emphasized this type of evidence in cases involving the obviousness of stereoisomers. In Forest Labs, the patent challenger argued that (+)-citalopram was obvious in light of racemic citalopram because there was a "general expectation in the art that one enantiomer would be more potent than the other provid[ing] reason for a person of ordinary

skill in the art to isolate the enantiomers." Forest Labs, 501 F.3d at 1269. But the Federal Circuit affirmed the district court's determination of nonobviousness, which was based in part on evidence that (+)-citalopram had unexpectedly superior properties. Id. In Sanofi, the unexpected properties of an enantiomer were persuasive enough to overcome a prima facie case of obviousness. Sanofi, 550 F.3d at 1087, 1089. "[T]here was no contrary evidence suggesting, based on the prior art, that the stereoselective properties 'were precisely what one would expect.'" Id. at 1089 (quoting Aventis, 499 F.3d at 1302). The Sanofi court distinguished Aventis, which found that the prior art compounds actually predicted the high stereoselectivity of the patented compound. Aventis, 499 F.3d at 1302.

Defendants rely heavily on In re Adamson, 275 F.2d 952 (C.C.P.A. 1960). There, the court held an enantiomer obvious over its racemate because the enantiomer's activity was "particularly expected" based on what was known in the art about enantiomers in general. Id. at 955. The Adamson court was not presented with specific evidence of and did not comment on any unexpected enantiomer activity. Moreover, this Court notes that Adamson did not consider any expert testimony and applied a preponderance of the evidence standard. (Pls. Br. at 20.) Accordingly, it is not helpful in deciding this case.

The Court also finds that Plaintiffs' evidence of commercial success contributes to a finding of nonobviousness. "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." Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1376 (Fed.Cir. 2005). To begin, all sales of Precedex have a nexus to the '214 Patent because the '214 Patent claims dexmedetomidine, the active ingredient in Precedex. (Pls. Br. at 46.)[11]

Plaintiffs' expert Dr. Sumanth Addanki testified that, in 2010, after ten years on the market, he considered Precedex to be a commercial success. (Defs. Br. at 136.) Over 60% of the money spent on ICU sedation in the United States in 2010 was spent on Precedex. But that is largely because Precedex is in competition with generic drugs that are less expensive.[12] Precedex had captured just 3.5% of the unit shares market by 2010. (Defs. Br. at 127.) Units sold, however, is not dispositive on the issue of

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[11] Plaintiffs also assert that the claimed invention of the '867 Patent achieved commercial success. But as will be explained below, there is evidence that some of Precedex's sales do not share a nexus to the '867 Patent. That is not the case with the '214 Patent, and therefore, Plaintiffs' evidence of commercial success here is more indicative of nonobviousness.

[12] There are no generic forms of Precedex on the market. Rather, Precedex competes with other ICU sedative drugs propofol, midazolam, and lorazepam, all of which are generic versions.

commercial success. See, e.g., Tec Air, Inc. v. Denso Mfg. Mich., Inc., 192 F.3d 1353, 1360-1361 (Fed.Cir. 1999). The Court finds the almost $600 million in sales, all of which share a nexus to the '214 Patent, sufficient to demonstrate commercial success.

2. Conclusion of Nonobviousness

On the facts here, the Court finds that dexmedetomidine's especially strong affinity for the α2-adrenoceptor would not have been obvious to a person of ordinary skill in the art in July 1987. Rather, one would have predicted a weak stereoselectivity. Such an unexpectedly superior result, the Court's conclusion that separation of medetomidine did not carry a reasonable expectation of success, and the moderate commercial success of Precedex are sufficient to demonstrate nonobviousness. Consequently, the Court holds that Defendants have failed to show clear and convincing evidence that the '214 Patent is invalid as obvious under 35 U.S.C. § 103.

III. Validity of the '867 Patent

A. Anticipation

Defendants assert that claims 1-5 of the '867 Patent are anticipated. The '867 Patent has three limitations at its core: (1) sedating a patient in the ICU; (2) administering to the patient an effective amount of dexmedetomidine or a pharmaceutically acceptable salt thereof; (3) wherein the patient

remains arousable and orientated. A single prior art reference must contain each and every limitation of a claim in order to anticipate. Arthrocare Corp., 406 F.3d at 1373.

Defendants rely on a 1995 publication by Dr. P. Talke et al., titled "Effects of Perioperative Dexmedetomidine Infusion in Patients Undergoing Vascular Surgery" ("Talke"). Talke is prior art under 35 U.S.C. § 102(a) and (b). This reference studied the hemodynamic effects of perioperatively administered dexmedetomidine in a high-risk class of surgical patients. (Defs. Br. at 95.) In addition, Talke discloses observations regarding sedation of the study patients. (Pls. Br. at 13-14.)

The Court first finds that it is beyond reasonable dispute that Talke discloses several limitations found in '867 Patent claims 1-5. First, the surgical patients in Talke were administered dexmedetomidine, a limitation found in each of claims 1-5. (Id. at 12; Defs. Br. at 123.) Talke also discloses administering to patients dexmedetomidine in saline solution, and thus, it teaches the limitation of claim 3: administering a pharmaceutical compound composed of an active and inactive ingredient, where the active ingredient is dexmedetomidine. (Defs. Br. at 124.) The limitations added by dependent claims 2, 4, and 5 are also disclosed in Talke, namely, dexmedetomidine as

the sole active ingredient, achieving a plasma concentration of 0.1-2ng/ml, and intravenous administration, respectively. (Id.)[13]

The issues are therefore narrowed to two: whether Talke discloses a method of sedating ICU patients and whether Talke discloses that those patients remain arousable and orientated.

1. Method of Sedating ICU Patients

Plaintiffs argue that Talke does not describe a method of sedation because the study's purpose was dexmedetomidine use for hemodynamic stability. (Pls. Br. at 13.) That, however, is not relevant to the anticipation analysis; all that matters is whether the reference reads on the claims. See Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 772 (Fed.Cir. 1983) ("The law of anticipation does not require that the reference 'teach' what the subject patent teaches. Assuming that a reference is properly 'prior art,' it is only necessary that the claims under attack, as construed by the court, 'read on' something disclosed

[13] There was testimony at trial that suggested that Talke did not disclose administration of dexmedetomidine in an amount sufficient to achieve a plasma concentration of 0.1-2 ng/ml. (2-29-12 Tr. at 638:6—639:21.) Dr. Aantaa, an inventor of the '867 Patent, testified that the computer-controlled infusion pump used in the Talke study would not provide plasma concentration measurements. (Id.) Rather, the pump was a scientific way to administer dexmedetomidine. (Id.) Considering, however, that the pump was programmed to reach the plasma concentrations claimed in the '867 Patent, the Court concludes that Talke discloses those concentrations. See Verizon Servs. Corp. v. Cox Fibernet Va., Inc., 602 F.3d 1325, 1337 (Fed.Cir. 2010) ("It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under section 102.").

in the reference, i.e., all limitations of the claim are found in the reference, or 'fully met' by it."), overruled in part on other grounds by SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1125 (Fed.Cir. 1985).

The parties stipulated that an "intensive care unit" is "any setting that provides intensive care." (Defs. Br. at 11.) "Intensive care" is care provided to critically ill patients, characterized by a high nurse-to-patient ratio, continuous medical supervision, and continuous monitoring. (Id. at 11; Pls. Br. at 3.) Defendants' expert Dr. Jesse Hall testified that patients were receiving intensive care. (Defs. Br. at 95-96.) His conclusion was based on Talke's description of the various measurements taken: blood oxygen levels, continuous EKG monitoring, and intra-arterial catheterization for measuring blood pressure. (3-7-12 Tr. at 1501:11-23.) Dr. Hall stated that in his own practice, whether a post-operative patient under invasive monitoring is taken to the ICU is based on a number of factors. (Id. at 1435:7-1437:1.) Dr. Hall concluded that, after surgery, a patient in his hospital receives intensive care:

> I think what I said earlier, technically, the patient isn't in the ICU, but I would say until the time they're discharged from the recovery room, they're really an intensive care unit patient. They have invasive monitors in place, a nurse is watching them continuously, doctors are available at beck and call to address things.

(Id. at 1436:5-10.)

While the Court credits Dr. Hall's conclusion as to post-operative patients in his hospital, there is a flaw in his conclusion as applied to the '867 Patent. His testimony is not directed to the relevant time period. Talke only discloses sedation during the first hour before surgery. (Pls. Br. at 13.) In fact, Talke stated that sedation was not observed the day after surgery and the reference is silent as to sedation in the 24 hours after surgery. (Id.) Thus, the critical time frame, and the question posed to the Court for purposes of determining anticipation, is whether Talke patients were receiving intensive care before surgery. Although it is possible, even probable, that the patients were receiving intensive care during that time, the Court finds that Talke does not necessarily disclose that the patients received intensive care. Therefore, the Court concludes that Talke does not disclose, expressly or inherently, a method of sedating ICU patients.

2. ICU Patients Remain Arousable and Orientated

In order to anticipate, Talke must also disclose that the study patients remained "arousable and orientated," which the parties defined as "capable of being awakened and aware of one's environment." (Defs. Br. at 11.) Talke states that, when patients were given dexmedetomidine before surgery, "all patients in the medium- and high-dose groups fell asleep but were easily

arousable." (Pls. Br. at 13.) Defendants conclude that Talke therefore discloses the '867 Patent claim element that patients remain arousable and orientated.

The Court is not clearly convinced that Talke expressly or inherently discloses that patients remained arousable and orientated. The study only makes the observation that, during the 1-hour preoperative period, patients fell asleep but were easily arousable. (Id.)[14] Indeed, Talke is incapable of disclosing lasting arousability, as an hour after receiving dexmedetomidine, patients were placed under anesthesia. (Id. at 14.) For good reason, patients are not capable of being awakened and aware of their environment when given anesthesia to undergo major vascular surgery.

Defendants' anticipation claim, in sum, fails because it relies on "probabilities and possibilities." See In re Robertson,

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[14] Plaintiffs point out that the study patients received 2 mg of lorazepam the night before surgery. (Pls. Br. at 13.) Dr. Aantaa testified that the purpose of giving lorazepam to the study patients was to calm anxiety or sedate them. (Id.) Lorazepam has a half-life of 9 to 16 hours, and so Dr. Aantaa speculated that the Talke patients could have been experiencing a sedative effect from lorazepam the morning of surgery. (Id.) But the Court finds that Talke itself cuts against this argument because it states that dexmedetomidine was given prior to surgery in order to "study the effect of dexmedetomidine in awake and anesthetized patients." (D-243 at 621(emphasis added).) Moreover, neither Dr. Hall nor Plaintiffs' expert Dr. Michael Ramsay were willing to conclude lorazepam had any effect in the patients in the one-hour, pre-operative period. (Defs. Br. at 116-17.)

169 F.3d 743, 745 (Fed.Cir. 1999) (citing Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed.Cir. 1991) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient."). Here, Defendants' evidence proposes that Talke likely discloses continuing arousable sedation, and it likely discloses use in an intensive care setting. This, however, is insufficient to demonstrate clear and convincing evidence that the patent must be invalid as anticipated under 35 U.S.C. § 102.

B. Obviousness

Defendants claim that the subject matter of the '867 Patent — dexmedetomidine for ICU sedation wherein patients remain arousable and orientated — would have been obvious in light of the prior art. In particular, Defendants assert that it would have been obvious to try dexmedetomidine as an intensive care medication with a reasonable expectation that it would have the desired property of arousable and orientated sedation, and, in fact, that dexmedetomidine did have such a result when tested in a clinical setting. (Defs. Br. at 101.)

1. Graham Framework

In analyzing whether the claims of the '867 Patent are obvious, the Court must determine: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; and (3) the differences between the prior art and the claimed

invention. Graham, 383 U.S. at 17. Additionally, the Court must consider objective evidence of nonobviousness such as "commercial success, long felt but unsolved needs, [and] failure of others" that give "light to the circumstances surrounding the origin of the subject matter sought to be patented." Id. at 17-18.

a. Person of Ordinary Skill in the Art

There is no material difference between the parties' definition of a person of ordinary skill level in the art of the '867 Patent. Such a person would have been a physician with training and experience in anesthesia, surgery, and critical care medicine. (Pls. Br. at 56; Defs. Br. at 66.)

b. Scope and Content of the Prior Art

Prior art in the context of an obviousness determination is that which is "from the same field of endeavor, regardless of the problem addressed," or "reasonably pertinent to the particular problem with which the inventor is involved." In re Clay, 966 F.2d 656, 658-59 (Fed.Cir. 1992). The prior art as to the '867 Patent, as of the April 1, 1998 filing date, includes extensive study of the therapeutic use of α2-adrenoceptor agonists, such as clonidine, medetomidine, and, of course, dexmedetomidine.

The first pertinent references are studies of clonidine. There is no serious dispute as to the relevance of clonidine to a person of ordinary skill in the field of the '867 Patent. Dr.

Aantaa called clonidine "the prototype of α2-adrenoceptor agonists" in a review article he co-authored with Dr. M. Scheinin in 1993 on α2-adrenergic agents in anesthesia. (Defs. Br. at 70.) Likewise, Plaintiffs' expert Dr. Ramsay testified that one could make reasonable inferences about dexmedetomidine through study of clonidine. (Id. at 73.)

Long before the '867 Patent was filed, clonidine's properties had been well-characterized. In 1981, Dr. J.L. Reid et al. reviewed the clinical pharmacokinetic and pharmacodynamic properties of clonidine ("Reid"). (Defs. Br. at 83.) The review discloses clonidine's effect on blood pressure and heart rate, also noting that common "dose-limiting side effects" are dry mouth and sedation. (Pls. Br. at 55.) As to sedation, Reid teaches that there is a close relationship between clonidine blood plasma concentration and the intensity of sedation. (D-257 at 298.) The nature of the sedation is described as a "twilight" state in which patients "can relatively easily pass from 'sleep' to wakefulness." (Defs. Br. at 83.) Dr. Ramsay discounted the "twilight" state as something that was not really a defined medical term; he testified that Reid indicated that patients were not awake, alert, and orientated. (Pls. Br. at 55.) Yet it appears to the Court that Dr. Ramsay's testimony ignores Reid's overt explanation that patients could easily pass from sleep to

wakefulness. Indeed, Reid's disclosure agrees with the parties' definition of "arousable and orientated" of "capable of being awakened and aware of one's environment." (Defs. Br. at 11.)

Defendants relied on several other clonidine studies, and although these references measure clonidine's sedative effect, they are limited due in part to study design. For example, Dr. J.M. Bernard et al. studied pain after administration of intravenous clonidine in 1991 ("Bernard"). (Id. at 76.) Patients having undergone spinal fusion surgery were administered intravenous clonidine or a placebo to study whether clonidine could help in pain management. (Id.) But all patients were also given morphine, which has a known sedative effect. (Pls. Br. at 54.) The study recorded no significant change in sedation within or between the clonidine group and placebo group, but noted that all patients were arousable by verbal stimuli. (Defs. Br. at 80.) Bernard explains that "[i]t is likely that we were unable to demonstrate intergroup differences in sedation because we administered a higher dose of morphine in the placebo group than in the clonidine group." (Id.) Bernard ultimately concludes that clonidine delayed onset of pain but that, because it lowers blood pressure, its usefulness may be limited. (Pls. Br. at 54-55.)

Clonidine was again studied in surgery patients by Dr. M. De Kock et al. in 1993 ("De Kock"). The researchers measured pain,

heart rate, blood pressure, and sedation. (D-262 at 525.) De Kock reports that there was no difference in sedation between patients receiving intravenous clonidine versus those receiving epidural clonidine. (Id. at 528.) But Figure 4 of the paper indicates that most patients were either alert or drowsy but easily arousable to an alert state by verbal command. (Id.) The discussion section does not mention sedation. (Id. at 529-531.)

Plaintiffs place great emphasis on a clonidine reference by H. Böhrer et al. in 1990, which reports on clonidine's use as a sedative adjunct in the ICU ("Böhrer"). (Pls. Br. at 55.) The case report describes a 63-year-old, post-operative patient on controlled ventilation administered clonidine along with other sedatives. While clonidine was very effective for sedation and pain relief, Böhrer warns that the patient had serious circulatory and withdrawal problems associated with the drug's use. (Id.) The Court recognizes that Böhrer teaches away from using intravenous clonidine as a sedative adjunct in the ICU. Plaintiffs argue by extension, that Böhrer teaches away from using dexmedetomidine as an intravenous sedative in intensive care patients. But the Court disagrees because, as detailed below, the prior art actually studying medetomidine and dexmedetomidine, even in sick patients, reports no withdrawal problems at all.

All experts at trial agreed that, as relevant to the '867 Patent, a person of ordinary skill would consider prior art studying medetomidine and dexmedetomidine for therapeutic use. (Defs. Br. at 74-75.) But there was some disagreement as to whether clinical studies using healthy volunteers were relevant. Plaintiffs argue that healthy volunteers are vastly different from ICU patients, and therefore medetomidine and dexmedetomidine administration to healthy volunteers offers no motivation to an ordinary person of skill in the art to try dexmedetomidine sedation in the ICU. (Pls. Br. at 56.) Dr. Aantaa testified that "they are two different worlds" because ICU patients are often receiving other drugs, are in pain, and being invasively treated with catheters or intubation. (Pls. Br. at 56.) But the Court finds that explanation to be conclusory as to the issue of motivation. Of course healthy volunteers and ICU patients are different, but both Dr. Hall and Dr. Ramsay testified that a person of ordinary skill would consider prior art studying healthy volunteers to determine whether dexmedetomidine would be effective in critically ill patients. (Defs. Br. at 74-75.) Dr. Hall also explained that medetomidine and dexmedetomidine's sedative "effects would be as reasonable, or in fact, more reasonable to considering being translated into a clinical circumstance. This is all just sort of routine forward thinking,

in my view, and predictable." (3-7-12 Tr. at 1481:7-11.) Therefore, the Court will consider the clinical studies using healthy volunteers, making sure to give them the weight a person of ordinary skill would give them, that is, with an eye towards potential clinical use.

The sedative effect of medetomidine and dexmedetomidine was studied throughout the 20 years before the '867 Patent was filed. Only one prior art reference discloses therapeutic use of the racemic medetomidine: "Sedative and Cardiovascular Effects of Medetomidine, a Novel Selective α2-Adrenoceptor Agonist, in Healthy Volunteers," by Dr. M. Scheinin et al. in 1987 ("Scheinin 1987b"). (Defs. Br. at 84.) In this study of eight healthy volunteers, Dr. M. Scheinin observed dose-related effects of intravenous medetomidine on blood pressure, heart rate, saliva secretion, and sedation or impairment of vigilance. (D-235 at 443.) As to sedation, Dr. M. Scheinin found that "[d]rug-related subjective sleepiness appeared quite rapidly," and that several subjects "actually fell asleep several times after the highest dose, but could easily be awakened for the measurements." (Id. at 446.) Ultimately, the reference concludes that medetomidine may have therapeutic potential for those with pathological, neuropsychiatric, and cardiovascular conditions associated with increased sympathetic neuronal activity. (Id. at 450.)

Multiple references disclose the clinical study of dexmedetomidine in healthy volunteers. First, Dr. H. Scheinin et al. studied the "Pharmacodynamics and Pharmacokinetics of Intramuscular Dexmedetomidine" in 1992. Dexmedetomidine, administered to six healthy volunteers, caused dose-dependent decreases in blood pressure, heart rate, and plasma norepinephrine. (D-266 at 537.) Dr. H. Scheinin also observed that dexmedetomidine "was clearly sedative" noting that "[m]ost of the subjects actually fell asleep after the highest dose but were easily arousable." (Defs. Br. at 86.) The reference concludes that dexmedetomidine may be suitable for preanesthetic clinical use as an α2-adrenoceptor agonist, with the suggestion that intramuscular administration may be more appropriate than the intravenous route. (Pls. Br. at 52-53.)

Dr. Jon P. Belleville et al. also studied intravenous dexmedetomidine in healthy volunteers in 1992 ("Belleville"). (Defs. Br. at 87.) The study measured sedation, metabolism, and ventilation. (Id.) Minimal ventilatory effects were found, but there was a significant dose-related increase in sedation. (Id. at 88.) The two highest doses of dexmedetomidine resulted in "most subjects [falling] asleep" and "unarousable by normal volume voice commands." (Pls. Br. at 53.) For the two lower doses, the subjects were sedated but nonetheless able to self-report their

sedation and anxiety levels. (Defs. Br. at 88-89.) Dr. Hall explained that the sedative effect of dexmedetomidine reported in Belleville for two of the four doses resulted in the "patient[s] being sedated along a sedation scale, yet being able to participate in the assessment of that sedation, or they're arousable." (Id. at 89.) But Belleville cautions that in older, less healthy patients receiving other drugs, dexmedetomidine may have clinically significant ventilatory effects. (Pls. Br. at 59.)

As early as 1991, Dr. Aantaa, one of the inventors listed on the '867 Patent, reported arousable sedation after studying intravenous dexmedetomidine administration in healthy volunteers ("Aantaa 1991"). (Defs. Br. at 91.) Aantaa 1991 reports that both objective and subjective tests demonstrate that dexmedetomidine has "[d]ose-dependent sedative effects" since "subjective sleepiness" was observed five minutes after administration, peaking at fifteen minutes. (Id. at 92.) "Four of the six volunteers fell asleep several times from 5 min. until 1 hr after the injection of the highest dose of dexmedetomidine, but all remained easily arousable and the tests could be uninterruptedly performed." (Id.) Importantly, during this arousable sedation, patients reported their Visual Analogue Scale ("VAS") pain scores. (Id.) A VAS test requires a patient to pick a value to rate pain using a ruler-like device. (Id. at 69-

70, 97.) Dr. Aantaa testified that people able to respond to a question in a VAS test are arousable and orientated. (2-29-12 Tr. at 553:15-19.)

The concerns raised by Böhrer and Belleville that dexmedetomidine's arousable sedation may not translate to less-healthy, even very sick, patients is addressed by two studies involving surgical patients. In the first, dexmedetomidine was administered to abdominal surgery patients as a two-step intravenous infusion in a study by Dr. M. Aho et al. in 1992 ("Aho"). (Defs. Br. at 99.) The maintenance/loading doses given to four groups were as follows: 120 ng/kg + 6 $ng/kg^{-1}/min^{-1}$; 170 ng/kg + 8.5 $ng/kg^{-1}/min^{-1}$; 220 ng/kg + 11 $ng/kg^{-1}/min^{-1}$; and 270 ng/kg + 13.5 $ng/kg^{-1}/min^{-1}$. (Id. at 100.) Aho explains that, during surgery, dexmedetomidine was well-tolerated with dose-dependent effects on blood pressure, heart rate, norepinephrine concentrations, and sleepiness. (Id. at 99.) Notably, the withdrawal concerns with continuous intravenous clonidine presented in Böhrer are not reported by Aho.

The second study to disclose intravenous dexmedetomidine to surgery patients is Talke. Dr. P. Talke studied the hemodynamic effects of intravenous, perioperatively administered dexmedetomidine in 24 high-risk vascular surgical patients. (Defs. Br. at 95.) In doses of 0.15 ng/ml (low), 0.30ng/ml (medium), or

0.45 ng/ml (high), dexmedetomidine was administered one hour before surgery and continuing until 48 hours after surgery. (Id. at 96.)

The "Methods" section of Talke explains the data collection of blood pressure, heart rate, blood samples, pain, ischemia, and adverse events. (D-243 at 621-24.) Researchers took measurement of blood oxygen levels, used EKG monitoring, and an inserted invasive intra-arterial catheters to measure blood pressure. (Defs. Br. at 96-97.) Pain was measured using the VAS test. (Id. at 97.)

Talke concentrates on the hemodynamic effects of dexmedetomidine, concluding that the drug decreased heart rate and blood pressure. (D-342 at 628.) Talke makes additional observations with respect to sedation in the "Results" section under the sub-heading "Sedation and Analgesia":

> After the 1-h infusion preceding induction of anesthesia, all patients in the medium- and high-dose groups fell asleep but were easily arousable. During the second postoperative day, there was no clinically observable sedation from the study drug. Postoperative VAS pain scores were similar among groups, and postoperative morphine requirements did not differ.

(Id. at 97.)

In the "Discussion" section, Talke explains that "[s]everal studies have reported dose-dependent sedative effects with dexmedetomidine," which is consistent with what occurred during the pre-operative period. (Id.) Sedation was not observed in the day after surgery, but Talke states that "[t]his is consistent

with recent findings of tachyphylaxis to the anesthetic effects of dexmedetomidine in rats." (Id.)[15] Talke does not report any sedation results for the 24 hours after surgery, and the Court infers that this could be because patients were still experiencing some of the effects of anesthesia and such effects would be indistinguishable from dexmedetomidine-induced sedation. Accordingly, the Court makes no finding that Talke specifically teaches sedation after surgery other than that tachyphylaxis is associated with prolonged dexmedetomidine administration.

The Court does find that Talke's disclosure of sedation in the pre-operative period is significant for two reasons. First, the patients are specifically described as sedated but "easily arousable." Dr. Ramsay testified that, if dexmedetomidine is administered such that a patient is arousable, they will also be orientated. (Defs. Br. at 114.) Second, while the Court has determined that Talke does not expressly or inherently disclose that patients in the pre-operative period were necessarily receiving intensive care, it is possible, even likely, that they were. The Talke patients were being extensively monitored and were described as having either a severe medical illness or a

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[15] Tachyphylaxis occurs when the same dose of a medication administered over a period of time begins to lose its effect. (3-7-12 Tr. at 1452:3-17.) The Precedex label states that tachyphylaxis can occur if the drug is administered for a period exceeding 24 hours. (Defs. Br. at 5.)

severe illness that is a constant threat to life as defined by the American Society of Anesthesiology classification system. (Id. at 95-96.) Therefore, even if the care provided to Talke patients did not fit each and every one of the elements of intensive care (critically ill, high nurse-to-patient ratio, continuous medical supervision, and continuous monitoring) so as to trigger anticipation, the Talke patients were, at the least, highly comparable to ICU patients in their condition and treatment.

We can summarize the prior art specific to dexmedetomidine in 1998 as follows. A person of ordinary skill in the art would have recognized that sedation was an expected, dose-dependent side effect of intravenous dexmedetomidine. Moreover, dexmedetomidine induces a sedation from which patients typically are arousable and able to answer questions about their condition and participate in study tests. While the majority of the prior art references studied dexmedetomidine in healthy volunteers, Dr. Aho observed that dexmedetomidine was well-tolerated in patients undergoing surgery, and Dr. Talke observed that the expected sedative effect of dexmedetomidine carried over to patients with severe medical illnesses awaiting vascular surgery.

c. Differences Between Prior Art and '867 Patent

The Court concludes that intravenous dexmedetomidine administration to ICU patients wherein they remain arousable and

orientated would have been obvious to a person of ordinary skill in the art by 1998. Any differences between the method of sedation in the '867 Patent and the prior art are insignificant such that giving those insignificant differences weight would result in an inflexible and rigid application of the obviousness test. See KSR Int'l Co., 550 U.S. at 427 ("Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.").

i. Motivation to Use Dexmedetomidine for Sedation

Early on, the prior art recognized that α2-adrenoceptor agonists caused sedation. Reid described clonidine's sedation as a type of sedation in which patients could pass from sleep to wakefulness. The dexmedetomidine studies demonstrate that, like the α2-adrenoceptor agonist "prototype" clonidine, patients on dexmedetomidine were sedated in a dose-dependent manner while nonetheless being "easily awakened" or "easily arousable" and able to participate in a self-assessment or other study measurements. The sedation described in those references is no different than patients "capable of being awakened and aware of [their] environment" as the parties have defined the term "arousable and orientated" in the '867 Patent. (Defs. Br. at 11.) Thus, the prior art offers strong motivation to use dexmedetomidine for that same purpose.

Plaintiffs cite to inconsequential differences between the sedation observed in the prior art and the sedation claimed in the '867 Patent. For example, Plaintiffs argue Talke does not disclose sedated, arousable, and orientated patients. (Pls. Br. at 57.) But Talke explicitly describes patients as asleep but easily arousable, and Plaintiffs' own expert Dr. Ramsay explained that if patients are arousable, they are also orientated. Thus, Plaintiffs fault Talke essentially because Talke does not use the exact phrase used in the '867 Patent claims. Similarly, Plaintiffs assert that Scheinin 1987b merely disclosed "impaired vigilance." (Id. at 58.) But in elaborating on "impaired vigilance," Dr. M. Scheinin describes "[d]ose-dependent sedative effects" in which the majority of subjects "actually fell asleep several times after the highest dose, but could easily be awakened for the measurements." (Defs. Br. at 85.)

Viewing this prior art as whole, the Court cannot ignore the common sense inferences a person of ordinary skill in the art would make. See KSR Int'l Co., 550 U.S. at 418 ("[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). The Court therefore concludes that a person of ordinary skill in the art in April 1998

would know that dexmedetomidine would cause arousable, orientated sedation and would be motivated to use it for that purpose.

ii. Reasonable Likelihood of Success

Defendants must demonstrate that a person of ordinary skill would have a reasonable likelihood of success in sedating intensive care patients using dexmedetomidine. Plaintiffs point out that no reference discloses ICU patients that are arousable and orientated. (Pls. Br. at 58.) The Court agrees that this is the case and indeed finds that no prior art anticipates this limitation (or any other limitation) of the '867 Patent. The Court, however, sees two problems with Plaintiffs' argument. The first is that it disregards the possibility, even probability, that Talke patients were receiving intensive care in the pre-operative period while they were sedated but easily arousable. SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349, 1359 (Fed.Cir. 2000) (finding patent claim obvious over prior art reference that "leads one to within a hairsbreadth of anticipation"). Second, Plaintiffs' position conflicts with the routine thought process used by a person of ordinary skill in the '867 Patent. Clinical studies using healthy volunteers are performed with the hope that what is true in healthy volunteers will also be true in the relevant patient population. Alone, this hope would be insufficient to demonstrate obviousness. But

Plaintiffs' refusal to grant the person of ordinary skill any ability to draw conclusions concerning ICU patients from studies involving seriously ill surgery patients is unwarranted. See KSR Int'l Co., 550 U.S. at 418 ("[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.").

If the dexmedetomidine studies involving healthy volunteers would not alone demonstrate a reasonable likelihood of success (and the Court believes that they likely would not), Talke and Aho do so demonstrate. Aho teaches that, contrary to problems reported in Böhrer, a continuous intravenous dose of dexmedetomidine is well-tolerated. Moreover, Talke demonstrates that the pharmacodynamic profile characterized in healthy volunteers, including arousable sedation, carries over to severely ill patients. Given the defined need for an animated ICU, not only would a person of ordinary skill in the art be motivated to try dexmedetomidine in ICU patients, Talke and Aho demonstrate that there is a likelihood of success in doing so.

That no prior art discloses clinical trials involving dexmedetomidine sedation in ICU patients is not fatal to Defendants' obviousness claim because "there is no requirement

that a teaching in the prior art be scientifically tested, or even guarantee success, before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success." Duramed Pharms., Inc. v. Watson Labs., Inc., 413 Fed.Appx. 289, 294 (Fed.Cir. 2011). Nor does the fact that Talke set out to study hemodynamic stability detract from its ability to render the '867 Patent obvious as "[a] reference . . . is prior art for all that it discloses." Id.

The Court thus concludes that arousable orientated sedation with dexmedetomidine was predictable as a dose-dependent effect in ICU patients. Sedation had long been known to be an effect of dexmedetomidine as with all α2-adrenoceptor agonists. (See generally '214 Patent.) The '867 Patent prior art further characterized that sedation as dose-dependent and allows those receiving dexmedetomidine to be easily arousable or awakened and thereafter able to interact and participate in tests. Furthermore, the therapeutic advantages of dexmedetomidine were observed not only in healthy patients, but also in "seriously ill" surgery patients. Consequently, there was a reasonable likelihood of success in administering dexmedetomidine to ICU patients wherein they remained arousable and orientated.

2. Objective Evidence of Nonobviousness

Plaintiffs argue that evidence of copying, failure of others, skepticism of others, unexpected results, and commercial success support a finding of nonobvious of the '867 Patent. (Pls. Br. at 60-64.) The Court concludes that none of these objective considerations materially affect the conclusion of obviousness.

Plaintiffs point out that Defendants are copying Precedex as an indication of nonobviousness. In many cases, "[t]he copying of an invention may constitute evidence that the invention is not an obvious one." Vandenberg v. Dairy Equipment Co., 740 F.2d 1560, 1567 (Fed.Cir. 1984). But "evidence of copying is less persuasive as objective evidence of nonobviousness in lawsuits brought by brand name drug companies against generic drug companies." Aventis Pharma S.A. v. Hospira, Inc., 743 F.Supp.2d 305, 349 (D. Del. 2010). That is because the law obligates a generic drug company to copy the brand name drug's active pharmaceutical ingredient and label. See 21 U.S.C. 355(j)(2)(A)(ii) and (iv). Therefore, the copying here is not persuasive evidence of nonobviousness.

Plaintiffs argue that there had been a failure of others to discover the '867 Patent subject matter. The "failure of others to provide a feasible solution to [a] long-standing problem" is probative evidence of nonobviousness. In re Piasecki, 745 F.2d

1468, 1475 (Fed.Cir. 1984). In this case, there had been a need for arousable sedation in the ICU. For example, Plaintiffs cite Dr. Hall's expressed desire for an "animated ICU." (Pls. Br. at 52.) This need was also felt by others who were dissatisfied with the standard of care that left patients paralyzed and unresponsive. (Id. at 50.) The '867 Patent itself explains, "most intensive care doctors in the ICU prefer their patients to be asleep but easily arousable." ('867 Patent, 2:15-20.)

Plaintiffs' evidence of the failure of others in this case were the challenges faced by Orion and Abbott in developing dexmedetomidine as a premedication agent, hemodynamic stabilizer, and anesthesia adjunct. (Pls. Br. at 60.) This argument is peculiar given that, had Orion and Abbott succeeded in developing dexmedetomidine as a premedication agent, hemodynamic stabilizer, or anesthesia adjunct, the unmet need for an animated ICU would still exist. In other words, there are no actual reports of failure to develop an ICU sedative. Second, Plaintiffs' own failures in developing and commercializing dexmedetomidine for other indications are not evidence of the failure of others to develop an ICU sedative. As such, Plaintiffs have submitted no evidence that others tried and failed to develop an ICU sedative.

Skepticism of dexmedetomidine as an ICU sedative, Plaintiffs contend, is also an indication of nonobviousness. Plaintiffs

point out that ICU physicians and staff were hesitant to adopt a treatment protocol that rendered patients sedated, but arousable and orientated. (Pls. Br. at 61.) Indeed, Plaintiffs admit that Precedex sales faltered early on until Hospira educated hospital staff and funded clinical trials resulting in data favorable to Precedex. (Id.) The Court does not find this to be strong evidence of obviousness. The skepticism was not associated with whether arousable, orientated sedation could be achieved before the '867 Patent was filed, but rather with whether it was a desired treatment protocol after dexmedetomidine was available in an FDA-approved form.

Plaintiffs next contend that it was unexpected that Precedex could sedate intensive care patients while leaving them arousable and orientated. The Court finds this to be simply a rehashing of the arguments considered and rejected above. Plaintiffs cite Dr. Aantaa's statement that dexmedetomidine was more promising than he anticipated. (Pls. Br. at 60.) But the question is not whether the inventors believed the invention promising; instead, the inquiry is into whether a person of ordinary skill would find the subject matter obvious. Standard Oil Co., 774 F.2d at 454 ("obviousness is determined entirely with reference to a hypothetical person") (internal quotations omitted). Plaintiffs also argue that it was unexpected that Precedex would be so

effective in weaning patients off a mechanical ventilator. (Pls. Br. at 60.) But the key characteristic of Precedex that makes that possible, absence of ventilatory depression, is not claimed in the '867 Patent. Therefore, the Court concludes that objective evidence of unexpected results does not weigh in favor of nonobviousness.

Plaintiffs also assert that Precedex is a commercial success. See Merck & Co., 395 F.3d at 1376 (stating 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). Evidence of commercial success may be considered only if sales of Precedex have a nexus to the '867 Patent. See Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed.Cir. 2010). Dr. Addanki testified that all sales of Precedex up until October 2008 share a nexus with the '867 Patent because the ICU sedation use was the only approved use of Precedex during that time. (Pls. Br. at 62.) But before the procedural indication was approved in October 2008, Precedex did not meet Hospira's sales expectations. (Defs. Br. at 127-28.)

To differentiate between the two indications after 2008, Dr. Addanki created a regression analysis to estimate the sales of Precedex for ICU sedation, excluding the procedural indication. (Id.) Based on this regression analysis, Dr. Addanki calculated

that from 2000 to 2010, 84% of Precedex sales totaling $390 million were for the ICU sedation indication. (Id.) Dr. Addanki also calculated that Precedex captured 3.5% of the unit shares market in 2010, with over 60% of the money spent on ICU sedation being used to purchase Precedex. (Id.) Ultimately, Dr. Addanki concluded that Precedex achieved commercial success.

Defendants' expert Dr. Ryan Sullivan disagreed with the commercial success analysis used by Dr. Addanki. Dr. Sullivan believed that the regression analysis did not accurately reflect the impact of the new procedural indication and that it did not take into account a shortage of propofol, one of Precedex's competitors. (Defs. Br. at 128-29.) Dr. Sullivan explained that the 2008 "test period," which Dr. Addanki used to verify his model, contained inaccuracies. (Id.) In particular, Dr. Sullivan pointed out that the model was a simple time-trend incapable of taking market events into account. (3-1-12 Tr. at 912:1-18.) But the Court cannot conclude that the regression analysis must therefore be entirely invalid. The Court recognizes that the model is meant as an estimation of ICU sedation sales. Even using Dr. Sullivan's "modified" quadratic version, Precedex sales were still in the millions of dollars.

Defendants also argue that, since there was a shortage of propofol in late 2009 to late 2011, the increase in Precedex

sales during that same time is not properly attributable to the features of the drug covered by the '867 Patent. (Id. at 128.) The Court does not believe that the propofol shortage completely nullifies Precedex's commercial success. Simply because hospitals needed an alternative ICU sedative does not necessarily demonstrate that the purchase of Precedex was completely unrelated to its claimed therapeutic benefits. Moreover, other events likely contributed to an increase in Precedex sales attributable to the ICU sedation indication. For example, the "MENDS" and "SEDCOM" studies provided positive results for Precedex as an ICU sedative. (Pls. Br. at 61.) Yet the shortage does demonstrate that, at least in part, the increase in sales of Precedex cannot be entirely contributed to the '867 Patent.

The Court, in sum, finds that Precedex is a moderate commercial success at present. However, it is not so successful as to contribute to a finding that the '867 Patent is nonobvious. Where, as here, there are several intervening events to which commercial success is attributable, a long delay in achieving commercial success is less probative in the obviousness analysis. See Windsurfing Int'l v. AMF, Inc., 782 F.2d 995, 1000 (Fed.Cir. 1986). While the Court accepts that Precedex is a commercial success today, owing to both indications, both the additional procedural use of Precedex and the propofol shortage detract from

the inferences of nonobviousness appropriately made when a product is commercially successful. Therefore, the Court concludes that Precedex's commercial success does not persuasively demonstrate that the '867 Patent subject matter as a whole was nonobvious.

3. Conclusion of Obviousness

Upon consideration of the Graham factors, the Court concludes that all claims of the '867 Patent would have been obvious to a person of ordinary skill in the art. The prior art taught that dexmedetomidine sedated patients in a dose-dependent manner but that those patients were easily awakened and could participate in study assessments (i.e., they were orientated). Moreover, this effect was seen not only in healthy patients but in sick patients awaiting major vascular surgery. Therefore, a person of ordinary skill in the art would have had a reasonable expectation of success in achieving and maintaining arousable sedation in intensive care patients.

Claims 1, 2, and 3 are obvious because a person of ordinary skill would have been motivated, with a reasonable likelihood of success, to use dexmedetomidine as the active pharmaceutical ingredient in an inactive solution to render intensive care patients sedated but arousable and orientated. Dexmedetomidine was known to provide a dose-dependent sedation from which patients would be easily awakened, and that effect was observed

in both healthy and critically ill patients. Furthermore, when administered, most of the studies choose an intravenous administration as required in claim 5. Indeed, Talke used an intravenous administration to target blood plasma concentrations between 0.15 to 0.45 ng/ml, overlapping with claim 4's plasma concentration range of 0.1 to 2 ng/ml. See In re Peterson, 315 F.3d 1325, 1329 (Fed.Cir. 2003) ("[O]bviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.").

Claim 4 and claims 8 through 12 limit the administration of dexmedetomidine to certain loading and maintenance doses. Aho discloses maintenance/loading doses given to four groups as follows: 120 ng/kg + 6 ng/kg^{-1}/min^{-1}; 170 ng/kg + 8.5 ng/kg^{-1}/min^{-1}; 220 ng/kg + 11 ng/kg^{-1}/min^{-1}; and 270 ng/kg + 13.5 ng/kg^{-1}/min^{-1}. (Defs. Br. at 100.) Converted into the '867 Patent units of measurement, Aho discloses 1.2 µg/kg + 0.36 µg/kg/hr, 1.7 µg/kg + 0.51 µg/kg/hr, 2.2 µg/kg + 0.66 µg/kg/hr, and 2.7 µg/kg + 0.81 µg/kg/hr. (Id.) Thus, claim 8's loading dose range of 0.2-2.0 µg/kg overlaps with the loading doses disclosed in Aho; and the maintenance dose ranges disclosed in claims 10, 11, and 12 (collectively 0.1 to 0.7 µg/kg/hr) substantially overlap with the Aho maintenance doses. Aho also discloses the loading dose being successfully administered over 10 minutes in two of its patient

groups, thereby disclosing the limitation in claim 9. Moreover, Dr. Hall explained that the values in claims 8 through 10, in view of Aho and Talke, are the types of ranges that can be optimized with routine experimentation. (Defs. Br. at 113.) "[I]t is not inventive to discover the optimum or workable ranges by routine experimentation." In re Geisler, 116 F.3d 1465, 1470 (Fed.Cir. 1997).

To summarize, the Court finds clear and convincing evidence that a person of ordinary skill in 1998 would have thought the '867 Patent subject matter as a whole obvious in light of the prior art. This is a conclusion the Court does not make lightly considering the high burden of proof Defendants are required to meet. However, to find the '867 Patent nonobvious, the Court would need to deviate from the expansive and flexible § 103 analysis required by the United States Supreme Court. KSR Int'l Co., 550 U.S. at 415. After careful consideration of the expert testimony and after its own thorough review of the prior art, the Court is convinced that both the motivation and reasonable expectation for success were present in April 1998 to practice the claimed subject matter. Moreover, an analysis of the objective criteria of obviousness presented here satisfies the Court that impermissible hindsight was not used. Accordingly,

the Court holds the '867 Patent claims invalid as obvious under 35 U.S.C. § 103.

IV. Enforceability of the '214 Patent

Defendants contend that Dr. Virtanen committed inequitable conduct before the PTO by submitting the erroneous data in Table 2 of the '214 Patent and failing to correct it. Defendants must demonstrate both that Dr. Virtanen specifically intended to deceive the PTO and that the correct data is material.

A. Materiality

"When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." Am. Calcar, 651 F.3d at 1334. Here, the patent applicants relied on the Table 2 data to overcome a rejection to the '214 Patent claims. In a September 1989 response to a first office action, the applicants specifically pointed out, based on the data contained in Table 2, that it was surprising that the d-enantiomer of medetomidine is three times more active at the α2-adrenoceptor than medetomidine. (Defs. Br. at 7.) In response to the applicant's argument, the PTO examiner issued a notice of allowance and the '214 Patent issued. (Id. at 7-8.)

It is undisputed that the Table 2 data was not only incorrect, but scientifically impossible. Further, it appears

that the PTO examiner relied on the Table 2 data and the applicant's argument based on that data to find the '214 Patent claims allowable. Defendants assert that, had the applicants submitted a corrected version of the experiment conducted in Table 2, the examiner would not have issued the patent. The correct data, generated by Dr. Savola, was put in an internal Farmos report in 1988 (the "Savola data"). (Id. at 57.) The Savola data demonstrated that dexmedetomidine was twice as active as medetomidine at the α2-adrenoceptor rather than three times as active. (Id.)

Thus, had the examiner been presented with the Savola data in place of the Table 2 data, it is likely that the '214 Patent claims again would have been rejected. As explained above, the Court finds even the results represented by the Savola data to be unexpected (i.e., it was unexpected that dexmedetomidine would be twice as active as medetomidine). But "even if a district court does not invalidate a claim based on a deliberately withheld reference, the reference may be material if it would have blocked patent issuance under the PTO's different evidentiary standards." Therasense, 649 F.3d at 1292 (Fed.Cir. 2011). Here, the Court finds this to be the case. The prosecution history of the '214 Patent demonstrates that the examiner found the claims to be patentable based on the data summarized in Table 2, and if aware

of the Savola data, it is more likely than not that the examiner would have rejected the claims. Accordingly, the Court finds the Defendants have satisfied the materiality standard.

B. Intent

The Therasense decision emphasized that "gross negligence or negligence under a 'should have known' standard does not satisfy this intent requirement." Id. Rather, there must be "knowledge and deliberate action" on the part of Dr. Virtanen. The Court, however, cannot conclusively determine from the evidence presented that Dr. Virtanen appreciated the materiality of Table 2 and therefore deliberately deceived the PTO by failing to submit it.

Defendants argue that Dr. Virtanen would have been aware of the problems with Table 2 in light of the new data reported by Dr. Savola. Plaintiffs counter that Dr. Virtanen was not doing the types of experiments generating the data summarized in Table 2 because his academic background was in animal physiology and biology. (Pls. Br. at 67; 4-5-12 Tr. at 2062:9-20.) But the Court notes that the experiment underlying Table 2 required rat membranes, and "was studied essentially as described by Virtanen and Nyman". ('214 Patent, 2:65-67, 3:2-3.) Therefore, it is unlikely that Dr. Virtanen was totally ignorant of the type of work that went into creating Table 2.

Dr. Savola, who was also a Farmos employee, conducted the same receptor binding experiments underlying Table 2 and put the

results in a September 1988 report. (Defs. Br. at 145.) But there is no evidence to suggest that Dr. Virtanen saw the new data at that time. (Pls. Br. at 66.) As Plaintiffs point out, Dr. Savola was actually in California when his report issued; Dr. Virtanen was in Finland. (Id.) Defendants simply assume that because Dr. Virtanen was in some supervisory capacity that he would have been aware of the data. But such an assumption is insufficient to demonstrate clear and convincing evidence of intent that Dr. Virtanen therefore deliberately withheld the data. Nor will the Court attribute specific intent to Dr. Virtanen simply by virtue of his signature on a 100-page report that contained the Savola data on page 61. (Pls. Br. at 66-67.) Gross negligence in failing to submit data is not adequate.

Dr. Virtanen could not recall whether he or anyone else submitted the Savola data to the Orion Patent Department. (Defs. Br. at 147-48.) Dr. Virtanen's lack of memory is frustrating, but it cannot be used to demonstrate specific intent to deceive. That is a jump in reasoning the Court is unwilling to and cannot make. See Therasense, 649 F.3d at 1291 ("The absence of a good faith explanation for withholding a material reference does not, by itself, prove intent to deceive."). Consequently, the Court holds that Defendants have failed to carry their burden in demonstrating a specific intent to deceive the PTO. Therefore,

we conclude that the ’214 Patent is not unenforceable due to inequitable conduct.

V. Enforceability of the ’867 Patent

Defendants’ final claim is that the ’867 Patent is unenforceable due to inequitable conduct. Specifically, Defendants cite Dr. Aantaa’s failure to disclose the Talke reference to the PTO during prosecution of the ’867 Patent. To succeed on this inequitable conduct claim, Defendants must prove that (1) the Talke reference is material, and (2) Dr. Aantaa acted with specific intent to deceive the PTO.

A. Materiality

Where a claim is “invalidated in district court based on the deliberately withheld reference, then that reference is necessarily material.” Therasense, 649 F.3d at 1292 (Fed.Cir. 2011). The Court finds that the Talke reference was material. Talke was indispensable to the Court’s obviousness analysis as it demonstrated a likelihood of success in practicing the ’867 Patent claims.

The Court further finds that the PTO would not have allowed the ’867 Patent claims had it been aware of Talke. The “arousable and orientated” nature of dexmedetomidine sedation was critical to its allowance by the PTO. (Defs. Br. at 150.) The patent applicants initially claimed only a method of sedation comprising

dexmedetomidine administration. (Id. at 9.) After a final rejection, Plaintiffs argued to the examiner in an interview that "dexmedetomidine allows for sedation wherein the patient remains arousable and orientated, unlike the previously held view that one could achieve either appropriate sedation or arousability." (Id.) The Plaintiffs then filed a request for continued examination and amended the '867 Patent claims to include an "arousable and orientated" limitation, and the claims were thereafter allowed. (Id. at 10.) As detailed in the Court's obviousness analysis, however, Talke discloses that patients on dexmedetomidine could be sedated yet at the same time be easily arousable and consequently orientated. (Id.) Therefore, the Court finds the Talke reference meets the but-for materiality standard.

B. Intent

To prevail on the claim of inequitable conduct, Defendants also must prove by clear and convincing evidence that Dr. Aantaa "knew of the reference, knew that it was material, and made a deliberate decision to withhold it." Therasense, 649 F.3d at 1290. If a court is to infer intent from circumstantial evidence, intent must be "the single most reasonable inference able to be drawn from the evidence." Id. (quoting Star Sci., 537 F.3d at 1366).

Dr. Aantaa knew of the Talke reference. In his testimony, he described the study protocol, purpose, and results. (Defs.

Br. at 151.) He described it as a feasibility study designed to assess whether dexmedetomidine could decrease hemodynamic instability and myocardial ischemia. (Id.) When pressed, Dr. Aantaa recalled that study patients were "perioperatively tired." (Id. at 151-52.) He also described the results as "exciting" and testified that he likely acquired a copy of the publication of the study results (i.e., the Talke reference). (Id.)

Dr. Aantaa also made a deliberate decision to withhold the Talke reference from the PTO, yet the Court cannot conclude that he did so knowing it was material to the '867 Patent. He expressly stated that Talke "was not given as a reference to the Patent Office". (Id. at 156.) His explanation, however, is significant. Dr. Aantaa stated that Talke was not given to the PTO because he believed it was irrelevant to the '867 Patent. The Court finds Dr. Aantaa's explanation credible. Throughout his testimony, Dr. Aantaa repeatedly refers to and describes Talke as a study that focused on hemodynamic outcomes rather than sedation. (See e.g., 2-29-12 Tr. at 488:23-491:7 601:16-603:14.) The Court concludes, therefore, that Dr. Aantaa had a genuine belief that Talke did not need to be disclosed to the PTO. While it is certainly one inference that could be made, specific intent to deceive is not the single most reasonable inference to be drawn from Dr. Aantaa's actions. Defendants have failed to prove intent

by clear and convincing evidence, and thus the Court holds that the '867 Patent is not unenforceable due to inequitable conduct.

VI. Remedies

Plaintiffs seek a permanent injunction to enjoin Defendants and their officers, agents, attorneys, and employees and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, or offer for sale within the United States, and/or importation into the United States of generic dexmedetomidine hydrochloride as described in ANDA No. 91-465. (Dkt. entry no. 349-7; Final Pre-Trial Order, Exhibit H at 9.) "[A] plaintiff seeking a permanent injunction must . . . demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." See eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388, 391, 126 (2006).

A permanent injunction is appropriate here. The Court found the '214 Patent to be valid, enforceable, and infringed. This is an irreparable injury for which monetary damages are inadequate compensation. See Ortho-McNeil Pharm., Inc. v. Mylan Labs. Inc., No. 04-1689, 2007 WL 869545, at *1 (D.N.J. Mar. 20, 2007), aff'd,

520 F.3d 1358 (Fed. Cir. 2008). Additionally, the balance of hardships weigh in favor of Plaintiffs and the public interest would not be disserved by a permanent injunction because of a strong interest in protecting valid patent rights. Therefore, having considered these factors, and in exercise of equitable discretion, the Court concludes Plaintiffs are entitled to a permanent injunction, as to the '214 Patent.

Plaintiffs also seek an order decreeing that the effective date of any approval of ANDA No. 91-465 be no earlier than the expiration of the date of the last of the patents-in-suit to expire, including any applicable extensions. While the Court finds only the '214 Patent valid and enforceable, such an order is appropriate and will be entered pursuant to 35 U.S.C. § 271(e)(4)(A) ("For an act of infringement . . . the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed.").

CONCLUSION

For the foregoing reasons, the Court holds the '214 Patent is not invalid as anticipated pursuant to 35 U.S.C. § 102; not invalid as obvious under 35 U.S.C. § 103; and not unenforceable due to inequitable conduct. The Court holds that the '867 Patent

is not unenforceable for inequitable conduct; not invalid as anticipated pursuant to 35 U.S.C. § 102; but is invalid as obvious under 35 U.S.C. § 103. The Court will enter judgment in favor of Plaintiffs on their claims of infringement of the claims of the '214 Patent. Further, the Court will permanently enjoin Defendants from the commercial manufacture, use, sale or offer for sale in the United States or importation into the United States of their generic dexmedetomidine hydrochloride product until such time as the '214 Patent expires, and will set the effective date for Defendants' ANDA No. 91-465 until such time, including any applicable extensions. The Court will issue an appropriate order and judgment.

s/Mary L. Cooper
MARY L. COOPER
United States District Judge

Dated: May 4, 2012