THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

HOSPIRA, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Nos. 16 C 651, 17 C 7903**
	)	
FRESENIUS KABI USA, LLC,	)	**Judge Rebecca R. Pallmeyer**
	)	
Defendant.	)	

MEMORANDUM OPINION AND ORDER

Plaintiff Hospira, Inc., a Delaware corporation with its primary place of business in Illinois, manufactures pharmaceuticals and medical supplies. One of Hospira's products is a chemical compound known as dexmedetomidine, which Hospira sells to health care providers under the brand name Precedex. Between 2012 and 2014, Hospira obtained four patents covering a new product made from dexmedetomidine: U.S. Patent Nos. 8,242,158 (the "'158 Patent"), 8,338,470 (the "'470 Patent"), 8,455,527 (the "'527 Patent"), and 8,648,106 (the "'106 Patent"). (Complaint in Case No. 16 C 651 [1] ("Pl.'s First Compl."), 3.) The new product, known as Precedex Premix, is a ready-to-use, diluted version of a Hospira product that has been on the market since 1999. That product, known as Precedex Concentrate, is formulated at 100 micrograms per milliliter (µg/mL) and must be diluted with saline to a concentration of 4 µg/mL before being administered to patients. Precedex Premix has the same formulation and the same package configuration as Precedex Concentrate but is pre-diluted with saline to a 4 µg/mL concentration.

Defendant Fresenius Kabi USA, LLC is an American subsidiary of a German pharmaceutical manufacturer which is also registered in Delaware and headquartered in Illinois. In December 2015, Fresenius Kabi notified Hospira that it had filed an abbreviated new drug application ("ANDA") with the FDA, seeking approval to market its own proposed dexmedetomidine products prior to the expiry of Hospira's patents. (Answer to Complaint, Affirmative Defenses, and Counterclaims in Case No. 16 C 651 [10] ("Def.'s First Ans."), ¶ 16.)

Hospira filed suit a month later, alleging patent infringement. (Pl.'s First Compl. 8-10.) In 2017, Hospira obtained a fifth patent covering the same dexmedetomidine product—U.S. Patent No. 9,616,049 (the "'049 Patent")—and filed a second complaint of patent infringement. (Complaint in Case No. 17 C 7903 [1] ("Pl.'s Second Compl."), 3, 5-6.)

Fresenius Kabi initially denied the allegations and counterclaimed for a declaration that the patents are invalid, or, alternatively, that Fresenius Kabi's actions will not infringe. (Def.'s First Ans. 22; Answer to Complaint, Affirmative Defenses, and Counterclaims in Case No. 17 C 7903 [18] ("Def.'s Second Ans."), 7, 14-15.)[1] Following the court's claim construction order in November 2017, the parties jointly agreed to limit the number of patent claims asserted in both actions. (Joint Stipulation in Case No. 16 C 651 [93] ("Joint Stipulation"), 2.) Since then, Hospira has dropped all but claim 6 of the '106 Patent and claim 8 of the '049 Patent. Fresenius Kabi has stipulated that its proposed product would infringe those claims, but maintains its challenges to their validity. (Joint Stipulation 2-3.)

The court held a five-day bench trial on the issue of the validity of these claims on July 16, 2018 through July 20, 2018. Having reviewed the evidence presented at the trial and the parties' briefs, the court concludes that Fresenius Kabi has established by clear and convincing evidence that both claims are invalid as obvious.[2]

BACKGROUND

A. Dexmedetomidine

Dexmedetomidine is a chemical compound known as an alpha$_2$-adrenoceptor agonist. ('106 Patent, JTX 1, col. 1:34-36.) Among other things, dexmedetomidine is effective as a sedative. (*Id.* at col. 1:36-37.) A Finnish corporation, Farmos Yhtyma Oy ("Farmos"), originally

[1] Fresenius Kabi also counterclaimed for a declaration that U.S. Patent No. 9,320,712 is invalid, or, alternatively, that Fresenius Kabi's actions will not infringe. (Def.'s Second Ans. 15-17.)

[2] In light of this conclusion, the court does not reach Fresenius Kabi's alternative argument that claim 6 of the '106 Patent is invalid for lack of enablement.

isolated dexmedetomidine in the 1980s. (Hospira's Post-Trial Responsive Brief [144] ("Hospira Resp."), 4.) In March 1990, Farmos obtained a patent that disclosed and claimed the compound: U.S. Patent No. 4,910,214 (the "'214 Patent"), JTX 134.) The '214 Patent also disclosed and claimed the use of dexmedetomidine as a sedative. (*Id.* at cols. 3-4, col. 6:15-31.) The '214 Patent expired in July 2013. (*See* Certificate Extending Patent Term Under 35 U.S.C. § 156, JTX 134 at 134.5.)

When the '214 Patent issued, the FDA had not yet approved any dexmedetomidine product. (Direct Examination of Dr. James Kipp at 254:7-10.)[3] In 1989, Farmos applied to the FDA for an investigational new drug application ("IND") to begin safety testing for dexmedetomidine formulations in humans. (*See* IND Application, JTX 35.) Farmos proposed and eventually conducted at least two safety studies of dexmedetomidine hydrochloride ("dexmedetomidine HCl") administered intravenously, meaning into a vein or veins. (IND Application at JTX 35.63, 35.69; October 1990 IND Supplement, JTX 38 at 38.3, 38.10; Hospira Resp. 4.) The concentration of dexmedetomidine in the formulation was 20 µg/mL. (IND Application at JTX 35.69; October 1990 IND Supplement at JTX 38.10.) The formulation was stored in flame-sealed glass tubes ("ampoules") made from a kind of glass known in the pharmaceutical industry as Type I glass. (IND Application at JTX 35.271, 273.) The parties agree that the studies revealed adverse safety events and that Farmos abandoned efforts to study the use of 20 µg/mL dexmedetomidine HCl in humans. (Hospira Resp. 5; Fresenius Kabi's Opening Post-Trial Brief [134] ("Fresenius Kabi Br."), 32.)

B. Precedex Concentrate

In 1994, Orion Corporation—which had by then acquired Farmos—licensed to Abbott Laboratories ("Abbott") the exclusive right to make, use, and sell dexmedetomidine for human use in the United States and certain other territories. (1994 Dexmedetomidine License and Supply

[3] Citations to direct and cross examination of witnesses refer to the transcript of the July 2018 bench trial.

Agreement, JTX 110 §§ 1.21, 1.27, 2.1.1; Hospira Resp. 5.) In 1999, Abbott obtained FDA approval for a dexmedetomidine HCl drug formulated at a concentration of 100 µg/mL. (Dexmedetomidine HCl Final Labeling ("Precedex Concentrate Label"), JTX 15 at 15.2.) Abbott marketed the drug under the trade name Precedex, and it is now known as Precedex Concentrate. (*See* Hospira Resp. 7.)

Dexmedetomidine HCl at a concentration of 100 µg/mL is too strong to administer directly to patients. (*See* Precedex Concentrate Label at JTX 15.13; Hospira Resp. 7, 8.) Accordingly, the Precedex Concentrate label directs hospital personnel to dilute the drug to a concentration of 4 µg/mL before intravenously infusing patients with the medication. (*See* Precedex Concentrate Label at JTX 15.13.) The label provides instructions on how to perform the dilution. (*See id.* (directing hospital personnel to add 2 mL of Precedex Concentrate to 48 mL of 0.9 percent sodium chloride solution, which produces a total volume of 50 mL).) The label also provides other important information about the drug, including its contents: 118 µg/mL of dexmedetomidine HCl (equivalent to 100 µg/mL of dexmedetomidine base) and 9 milligrams (mg) of sodium chloride in water. (*Id.* at JTX 15.2; *see also id.* (stating that Precedex Concentrate is "preservative-free," "contains no additives or chemical stabilizers," and has a pH of 4.5 to 7.0).) In addition, the label states that the "partition coefficient" of Precedex Concentrate "in octanol:water at pH 7.4 is 2.89." (*Id.*) Dr. James Kipp, Fresenius Kabi's expert on formulation chemistry, explained that the higher a molecule's partition coefficient, the more lipophilic—meaning likely to interact with plastic—it is. (Direct Examination of Dr. Kipp at 290:22-292:3.) A partition coefficient of 2.89 is high, according to Dr. Kipp. (*Id.* at 292:4-8.) Finally, the Precedex Concentrate label discloses that it is supplied only in 2 mL clear glass vials and 2 mL clear glass ampoules. (Precedex Concentrate Label at JTX 15.14.) It is undisputed that the vials and ampoules are made from Type IA sulfur-treated glass, and that the vials are sealed with coated rubber stoppers. (*See, e.g.*, Fresenius Kabi Br. 1; Direct Examination of Dr. Priyanka Roychowdhury at 153:6-9, 154:14-19; Direct Examination of Dr. Kipp at 310:6-9 (testifying that Precedex Concentrate "includes a sealed glass container as

its final packaging configuration, with a Teflon-coated stopper").)

Abbott transferred its rights in dexmedetomidine to Hospira in 2004 when it spun Hospira off as an independent business. (*See, e.g.*, 2004 Separation and Distribution Agreement, JTX 109 at 109.16-17, 25, 82.)

C. The Patented Invention

1. Development Process

i. Ready-to-Use Product

In 2006, Hospira decided to develop a ready-to-use dexmedetomidine drug—that is, a formulation pre-diluted to the 4 µg/mL concentration used in humans. (Hospira Resp. 8; September 2006 Hospira Precedex Line Extension Proposal ("2006 Premix Proposal"), JTX 72.) The drug, now known as Precedex Premix, is the subject of the patents-in-suit.

In a September 2006 internal document, Hospira observed that hospitals incur "added cost and inconvenience" when their pharmacy departments need to "take the 2 mL vial and convert it to patient ready." (2006 Premix Proposal at JTX 72.2.) Hospira also noted that a ready-to-use product would "have high value to the customer from both a convenience and cost standpoint." (*Id.*)

Dr. Priyanka Roychowdhury, who has a Ph.D. in pharmaceutics, and Dr. Robert Cedergen, who has a Ph.D. in biochemistry, worked on the development of Precedex Premix while they were employed at Hospira. (Direct Examination of Dr. Roychowdhury at 130:18-131:16; Direct Examination of Dr. Cedergen at 197:18-21, 199:1-20.) They are the named co-inventors of the patents-in-suit. (*See* '106 Patent, JTX 1; '049 Patent, JTX 2.) Dr. Roychowdhury testified at trial that from the perspective of a pharmaceutical formulator, a ready-to-use product has obvious advantages; any formulator would be motivated to make a ready-to-use product if there is a patient need for it; and a patient need for it existed before 2012. (Direct Examination of Dr. Roychowdhury at 141:12-15; 143:1-6; 148:23-25.) Drs. Roychowdhury and Cedergen also acknowledged that they did not come up with the idea for Precedex Premix; rather, someone at

Hospira instructed them to make it. (*Id.* at 140:23-141:2; Direct Examination of Dr. Cedergen at 201:13-19.)

According to Drs. Roychowdhury and Cedergen, the Precedex Concentrate label informed their understanding that their goal was to make a 4 µg/mL formulation. (*See* Direct Examination of Dr. Cedergen at 202:2-20; Direct Examination of Dr. Roychowdhury at 134:12-18.) The label, Dr. Roychowdhury testified, also disclosed the appropriate formulation for Precedex Premix. (Direct Examination of Dr. Roychowdhury at 134:19-135:2.) In other words, she agreed, there is "no difference between the formulation of the further diluted Precedex [C]oncentrate versus the Precedex [P]remix product[.]" (*Id.* at 137:20-138:10.) Hospira's corporate representative, Dr. Rao Tata-Venkata, who has a Ph.D. in organic chemistry, likewise testified that when "the concentrated product . . . [is] diluted in the intended diluent, it gives rise to the solution that would ultimately be identical to the already made solution of the premix." (Deposition Designation for Dr. Rao Tata-Venkata ("Tata-Venkata Dep.") at 10:7, 172:17-21.)

ii. Storage Container

Dr. Roychowdhury testified that while she was developing Precedex Premix, she knew that Precedex Concentrate was stored in glass. (Direct Examination of Dr. Roychowdury at 135:18-20.) She also testified that she knew from her experience as a formulator that glass is unlikely to have issues with adsorption (the adhesion of molecules to a surface) or absorption (the entrance of molecules into a material)—both of which affect drug potency. (*Id.* at 150:12-151:8; *see also* Tata-Venkata Dep. at 82:15-83:10 (similar).) Dr. Cedergen similarly agreed that absent evidence to the contrary, glass is assumed to be nonreactive. (Direct Examination of Dr. Cedergen at 205:14-18.) And a Hospira document from 2006 confirms that the company foresaw "[n]o major issues" with storing Precedex Premix in glass. (2006 Premix Proposal at JTX 72.5; *see also* May 2007 Precedex Line Extension Meeting Minutes, DTX 413 (stating that Hospira had conducted tests which showed that "the product appears to be stable in the glass vial").)

According to Dr. Roychowdhury, her team had the capability in 2007 to begin

manufacturing Precedex Premix in glass vials. (Direct Examination of Dr. Roychowdhury at 151:18-152:8.) Hospira, however, instructed her to experiment with plastic containers instead. (*Id.* at 152:9-11.) Dr. Roychowdhury discovered right away that dexmedetomidine interacts with a common plastic called PVC and should not be stored in it. (*Id.* at 149:1-22.) She therefore reverted to glass and tested only one kind: Type IA sulfur-treated glass. (*Id.* at 152:20-153:9.) Dr. Roychowdhury did not know at the time that Precedex Concentrate was stored in that kind of glass; rather, she identified it as the best option based on her "knowledge and experience." (*Id.* at 153:4-9.)

Dr. Roychowdhury and her team also determined that Precedex Premix vials, like Precedex Concentrate vials, should be sealed with coated rubber stoppers. (*Id.* at 154:14-19.) Dr. Roychowdhury testified that she reached this conclusion "[a]fter a series of evaluations" that lasted two to three months. (*Id.* at 154:16; Cross Examination of Dr. Roychowdhury at 181:7-11.) But she also testified that at the time, she knew Precedex Concentrate used coated rubber stoppers "to avoid interaction with the drug." (Direct Examination of Dr. Roychowdhury at 135:21-136:1.) A development report she prepared confirms that "it was planned to implement coated stoppers in order to mimic the current product[.]" (Unsigned Hospira Development Report, JTX 62 at 62.12; Direct Examination of Dr. Roychowdhury at 166:15-19.)

iii. Stability Testing

Dr. Cedergen testified that the low concentration of Precedex Premix (4 µg/mL) was the main challenge he and Dr. Roychowdhury faced in developing the product. (Cross Examination of Dr. Cedergen at 233:2-5; *see also id.* at 233:6-9 (stating that at "such a low concentration, any loss in drug would result in a high relative percentage drop in potency"); Cross Examination of Dr. Roychowdhury at 177:22-23, 178:12-13 (testifying that 4 µg/mL is the least concentrated product she has ever worked on and that at 4 µg/mL "the issues of stability are magnified").) In addition, Dr. Tata-Venkata testified that he was not aware of any studies regarding dexmedetomidine at a concentration of less than 100 µg/mL and stored in a glass container before Hospira began its

work on dexmedetomidine. (Tata-Venkata Dep. at 273:4-13.) Notably, however, Fresenius Kabi's formulation chemistry expert Dr. Kipp testified that any concentration in the microgram level is considered low, and Dr. Roychowdhury agreed that a concentration of 100 µg/mL is considered low. (Direct Examination of Dr. Kipp at 286:10-12; Direct Examination of Dr. Roychowdhury at 135:14-17.)

Dr. Roychowdhury and her team studied the stability of 4 µg/mL dexmedetomidine HCl for five months under normal long-term storage conditions and accelerated storage conditions. (Direct Examination of Dr. Roychowdhury at 159:20-24 (discussing Hospira April 2010 Development Report ("April 2010 Dev. Report"), JTX 51 at 51.33).) "Normal long-term storage conditions" refers to storage at room temperature (twenty-five degrees Celsius) and sixty percent relative humidity. (*See* April 2010 Dev. Report at JTX 51.33; Direct Examination of Dr. Kipp at 324:7-9 (stating that "normal storage conditions" refers to storage at room temperature).) "Accelerated storage conditions" here refers to storage at forty degrees Celsius and seventy-five percent relative humidity with inverted vials. (*See* April 2010 Dev. Report at JTX 51.33.) When vials are inverted, the stopper is "in constant contact with the fluid inside the bottle," which is considered a worst-case scenario for maintaining stability. (*See, e.g.*, Cross Examination of Dr. Kipp at 441:18-22.)

Dr. Roychowdhury and her team measured the initial concentration of the formulation and then took only five measurements: one for each month. (April 2010 Dev. Report at JTX 51.33.) Dr. Roychowdhury testified that she observed a loss in concentration of about four percent in the sample stored under accelerated conditions. (Direct Examination of Dr. Roychowdhury at 170:14-25.) In the sample stored under normal conditions, however, the observed drop in concentration was just 2.3 percent. (*Id.* at 159:20-160:14.) Dr. Roychowdhury and her team also conducted stress testing for 4 µg/mL dexmedetomidine HCl. (*Id.* at 163:11-14.) Dr. Roychowdhury agreed that the formulation did not degrade when it was exposed to "extreme acidic and alkaline conditions." (*Id.* at 163:25-164:6.) Only when the team added oxidative reagents such as

hydrogen peroxide to the drug, placed it in an oven heated to fifty degrees Celsius, and left it there for twenty-four hours did they observe "[s]ome minor degradation." (*Id.* at 164:10-24; April 2010 Dev. Report at JTX 51.60.) Interpreting these test results, the team's development report states, "It can be concluded that the degradation of dexmedetomidine HCl is very small even under extreme oxidative conditions." (April 2010 Dev. Report at JTX 51.60.)

Hospira received FDA approval to market Precedex Premix in 2013. (Direct Examination of Fresenius Kabi's Transactions Expert Peter Lankau at 57:4-6.) It sells the product in 20 mL, 50 mL, and 100 mL Type I glass vials sealed with coated rubber stoppers. (Tata-Venkata Dep. at 152:24-153:6; Direct Examination of Dr. Roychowdhury at 153:6-9, 154:14-19.)

2. Patents-in-Suit

Between 2012 and 2017, Hospira obtained five patents covering Precedex Premix, including those asserted in this action: the '106 Patent, which issued on February 11, 2014, and the '049 Patent, which issued on April 11, 2017. ('106 Patent, JTX 1; '049 Patent, JTX 2.) The priority date for both patents is January 4, 2012. ('106 Patent, JTX 1; '049 Patent, JTX 2; Hospira Resp. 4.) Hospira asserts only claim 6 of the '106 Patent and claim 8 of the '049 Patent.

In the '106 and '049 Patents, Hospira summarizes its invention as "premixed pharmaceutical compositions of dexmedetomidine, or a pharmaceutically acceptable salt thereof, that are formulated for administration to a patient, without the need to reconstitute or dilute the composition prior to administration." ('106 Patent, JTX 1, col. 2:7-11; '049 Patent, JTX 2, col. 2:9-13.) The '106 and '049 Patents cover the same basic subject matter—the medication itself—and share a title: "Dexmedetomidine Premix Formulation." ('106 Patent, JTX 1; '049 Patent, JTX 2.) The patents also share a common specification.

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

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

> 6. The ready to use liquid pharmaceutical composition of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 µg/mL.

('106 Patent, JTX 1, col. 26:18-24, 41-43.)

Independent claim 1 and dependent claim 8 of the '049 Patent read as follows:

> 1. A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL disposed within a sealed glass container, wherein the liquid pharmaceutical composition has a pH of about 2 to about 10.
>
> 8. The ready to use liquid pharmaceutical composition of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 µg/mL.

('049 Patent, JTX 2, col. 26:12-18, 42-45.)

After a claim construction hearing in December 2016, this court construed the disputed term "ready to use" to mean "formulated to be suitable for administration to a patient without dilution or reconstitution," and determined that no construction was required for the disputed term "sealed glass container." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, Case No. 16 C 651, 2017 WL 5891058, at *9 (N.D. Ill. Nov. 27, 2017).[4]

D. Prior Art

The parties agree that the prior art includes the '214 Patent, Precedex Concentrate, and the following references.[5] (*See, e.g.*, Fresenius Kabi Br. 40-41; Hospira Resp. 44.)

1. Dexdomitor

Dexdomitor is a ready-to-use, 500 µg/mL dexmedetomidine HCl formulation indicated for commercial veterinary use. (Dexdomitor Label, DTX 288 at 288_0001; Direct Examination of Dr.

[4] This court also construed the disputed term "intensive care unit," which is unique to the '527 Patent and irrelevant for present purposes. *See id.* at *8.

[5] Fresenius Kabi argues, and Hospira disputes, that the Farmos IND is prior art. As the court will discuss, it has determined that Fresenius Kabi has proven the asserted claims are invalid as obvious irrespective of whether the Farmos IND is prior art. The court, therefore, offers no conclusions on this issue.

Kipp at 284:15-286:9.) The European Medicines Evaluation Agency authorized use of the product throughout the European Union in 2002. (Dexdomitor Label at DTX 288_0001; *see also* EUROPEAN MED. AGENCY, EPAR SUMMARY FOR THE PUBLIC, DEXDOMITOR, 3 (2012), https://www.ema.europa.eu/documents/overview/dexdomitor-epar-summary-public_en.pdf.) The Dexdomitor label states that the product is stored in a 10 mL glass vial sealed with a coated rubber stopper. (*Id.* at DTX 288_0002.) It also states that the product has a two-year shelf-life. (*Id.* at DTX 288_0001.) Finally, it states that in stability tests, "[a]ll parameters remained essentially unchanged at all storage conditions and no difference between inverted and upright containers could be noted." (*Id.* at DTX 288_0005.)

2. References Relating to Ready-to-Use Drug Formulations

A November 2011 article by John Fanikos states, among other things, that ready-to-use drug formulations "can reduce the probability of errors related to" drug preparation "while providing timely treatment." (John Fanikos, *Premixed Products Improve Safe Medication Practices: Recent Innovations of Amiodarone IV*, PHARMACY PRAC. NEWS, Nov. 2011 ("Fanikos"), JTX 19 at 19.2.)

Guidelines from the Canadian Society of Hospital Pharmacists, published in March 2008, instruct that "to help reduce the potential for error and the nursing time involved in handling and administering medications[,]" pharmacies should "provide medications in identified dosage units ready for administration, wherever possible and practical[.]" (CANADIAN SOC. OF HOSP. PHARMACISTS, GUIDELINES FOR DRUG-USE CONTROL (2008) ("CSHP Guidelines"), DTX 301 at 301_0001, 0015.)

An article by James G. Cain published in 2007 states that in or around 2007, the pharmacy at Cain's hospital was using "premixed syringes of dexmedetomidine (10 mL with 4 mcg/mL)[.]"[6] (James G. Cain, *Dexmedetomidine and Hextend: Their Role in Trauma Care*, INT'L TRAUMA CARE, 2007 ("Cain"), JTX 16 at 16.2).)

[6] Mcg is another abbreviation for microgram (µg). (*See* Direct Examination of Dr. Kipp at 284:3-10 (discussing Cain).)

3. References Relating to Glass Storage Containers

An article by Gregory A. Sacha published in 2010 states that "[f]or decades, glass sealed ampoules were the most popular primary packaging system for small volume injectable products." (Gregory A. Sacha, et. al., *Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems*, PHARMACEUTICAL DEV. & TECH., 2010 ("Sacha"), JTX 24 at 24.3.) According to Sacha, this was because a drug packaged in a glass ampoule has the potential to interact with only one, as opposed to multiple, packaging materials. (*See id.*) Sacha further states that "glass vial[s]" are now the "most common packaging for liquid and freeze-dried pharmaceuticals." (*Id.*)

A treatise commonly used in the pharmaceutical industry states that "[t]raditionally, glass has been the most widely used container for pharmaceutical products[.]" (REMINGTON: THE SCIENCE OF PRACTICE AND PHARMACY (21st ed. 2006) ("Remington"), JTX 20 at 20.13.) Glass is widely used, Remington explains, "to ensure inertness, visibility, strength, rigidity, moisture protection, ease of re-closure, and economy of packaging." (*Id.*)

E. The "About 2%" Limitation of the '106 Patent

Hospira does not appear to dispute that if one practices the '106 Patent, a 4 µg/mL dexmedetomidine HCl formulation is stable for FDA purposes (though neither party explicitly defined FDA stability parameters). (*See, e.g.*, Direct Examination of Dr. Roychowdhury at 139:24-140:2 (testifying that "premix is now a pharmaceutical product" and "has been proven to be stable throughout manufacturing, throughout storage, up to the expired date at its long-term storage condition").) Hospira's counsel himself acknowledged during his closing argument that "from the standpoint of the FDA, we know what we need to know to be confident that it's stable." (Closing Argument of Mr. Bradford Lyerla at 858:14-16.) A major point of contention between Fresenius Kabi and Hospira, however, is whether 4 µg/mL dexmedetomidine HCl—when stored at room temperature in a Type I glass vial, sealed with a coated rubber stopper—will always "exhibit[] no more than about 2% decrease in the concentration of dexmedetomidine" at five months. ('106 Patent, JTX 1, col. 26:21-24 (the "about 2%" limitation).) Hospira's case for non-obviousness

depends largely on the argument that a 4 µg/mL formulation stored under these conditions will not always meet that limitation. (*See* Hospira Resp. 1, 11-23.)

The '106 Patent itself discloses only one set of five-month stability data for 4 µg/mL dexmedetomidine HCl. (JTX 1, Example 6.) This is the data that Dr. Roychowdhury and her team collected during the stability testing, described above. (*See* April 2010 Dev. Report at JTX 51.33; Direct Examination of Dr. Roychowdhury at 170:25-171:6; Redirect Examination of Dr. Roychowdury at 192:7-22.) The data shows a loss in concentration of about 2.3 percent at five months when the formulation was stored at room temperature in an upright Type I glass vial sealed with a coated rubber stopper. (April 2010 Dev. Report at JTX 51.33.) Dr. Roychowdhury testified that she considers 2.3 percent to be within two percent. (Direct Examination of Dr. Roychowdhury at 162:6-10.) The '106 Patent also discloses the results of an additional stress test conducted for 4 µg/mL dexmedetomidine HCl. (JTX 1, Example 4& tbl. 4.) Among other things, the test shows that the formulation experienced degradation of 12.7 percent after it was mixed with hydrogen peroxide and baked in an oven at sixty degrees Celsius for eight hours. (*Id.*; *see also id.* at col. 17:25-27.)

At trial, Fresenius Kabi and Hospira offered testimony from expert and fact witnesses regarding the "about 2%" limitation. The court summarizes that testimony below.

1. Fresenius Kabi's Formulation Chemistry Expert Dr. James Kipp

Dr. Kipp earned bachelor's and master's degrees in chemistry, and a Ph.D. in organic chemistry. (Direct Examination of Dr. Kipp at 244:18-23.) He has thirty-five years of experience in the formulation of pharmaceutical products and testified at trial as an expert on formulation chemistry. (*Id.* at 243:22-244:6.) For purposes of the "about 2%" limitation, Dr. Kipp analyzed several sets of stability data. According to Dr. Kipp, the data shows that none of the tested samples lost more than two percent of their concentration at five months in storage at room temperature.

i. Stability Data for Precedex Premix (4 µg/mL)

Dr. Kipp analyzed stability data for Precedex Premix in 20 mL, 50 mL, and 100 mL glass vials. (Direct Examination of Dr. Kipp at 339:8-340:13.) He did not test samples himself, but rather used the data Hospira submitted in its supplemental New Drug Application ("NDA") for Precedex Premix. (*Id.* at 337:17-24.) Dr. Kipp analyzed three batches of data for each vial size, including upright and inverted vials for each batch. (*Id.* at 340:22-24.) In total, therefore, he analyzed eighteen batch configurations. (*Id.*) Dr. Kipp conducted a simple linear regression of the data for each configuration. (*Id.* at 338:4-6, 339:2-4.) According to Dr. Kipp, a simple linear regression provides "the best approximation for what the actual values are at each point" and is what a person of ordinary skill in the art ("POSA") "would normally do." (*Id.* at 334:3-11.) The regression lines, he testified, showed nothing approaching a loss as great as two percent at five months. (*Id.* at 340:19-341:2.)

ii. Stability Data for IND Batch 027 L1 (20 µg/mL)

Dr. Kipp also analyzed stability data that Farmos included in its original IND submission for 20 µg/mL dexmedetomidine HCl ("IND Batch 027 L1"). (*Id.* at 329:13-20; IND Application at JTX 35.272.) Farmos stored IND Batch 027 L1 in a clear glass ampoule at twenty-five degrees Celsius for twelve months. (IND Application at JTX 35.273.) Farmos reported the original assay percentage, or the percentage of the drug relative to the labeled amount, as ninety-eight. (*Id.* at JTX 35.277; Direct Examination of Dr. Kipp at 330:11-20.) Farmos then took one stability measurement at each of five time-points: two, three, six, nine, and twelve months. (IND Application at JTX 35.277.) It used an assay measurement technique called High Performance Liquid Chromatography (HPLC), for which the relative standard deviation is not more than three percent. (*Id.* at JTX 35.273, 275; Direct Examination of Dr. Kipp at 331:10; Fresenius Kabi Br. 15.) Farmos measured assay percentages between ninety-seven and 100, and two measurements showed percentage increases. (IND Application at JTX 35.277.) Farmos concluded from the data that the formulations "ha[d] not significantly changed during the storage."

(*Id.* at JTX 35.276.)

Dr. Kipp explained that the measured fluctuations in assay percentage reflect what he called "noise," or weighing and measurement errors. (Direct Examination of Dr. Kipp at 330:21-331:2.) So although it is true that an assay percentage cannot actually increase, he opined, "a POSA would look at the data and say that th[e] variability is certainly within 3 percent of the expected noise[.]" (*Id.* at 331:11-20.) Dr. Kipp also opined that the language in the '106 Patent supports this interpretation. Namely, the word "about" modifies the "about 2%" limitation, and the patent specification defines the word "about" as being "within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on . . . limitations of the measurement system." (*Id.* at 332:13-20, 333:2-3 (quoting '106 Patent, JTX 1, col. 5:31-35).)

To account for the assay variability and reach a conclusion regarding the stability of IND Batch NI 027 L1, Dr. Kipp plotted the measured concentration versus time and conducted a simple linear regression. (*Id.* at 334:3-6.) Dr. Kipp testified that the resulting regression line is "completely flat . . . and any deviations from that line would be due to statistical error." (*Id.* at 334:20-25.) He concluded, therefore, that the regression line for IND Batch NI 027 L1 does not show anything close to more than two percent loss at five months. (*Id.* at 335:1-5.) In fact, according to Dr. Kipp, there was "no decrease in drug concentration throughout the whole study." (*Id.* at 336:10-11.)

iii. Whether Concentration Affects Stability

Dr. Kipp also analyzed whether the concentration of dexmedetomidine affects its stability. (*Id.* at 341:11-12.) In his expert report, Dr. Kipp noted that he "compared the mean rates of change in drug concentration for 200, 100, 20, and 4 mcg/mL dexmedetomidine formulation data[.]" (Expert Report of Dr. Kipp ("Kipp Report"), DTX 457, ¶¶ 362-63.) A comparison of this nature, Dr. Kipp explained in his expert report, "allow[s] a POSA to determine the slopes of the lines in order to determine when these concentrations . . . would decrease by 2%." (*Id.* ¶ 363.)

At trial, Dr. Kipp did not describe these calculations in detail. But as the court understands his report, Dr. Kipp applied the mean rate of change for each concentration to stability data from actual batches at that concentration and, using linear regression, "determine[d] how many months would be necessary to show 2% loss of concentration." (*Id.*) For the 4 µg/mL and 20 µg/mL formulations, Dr. Kipp used the same Precedex Premix and Farmos IND data discussed above. (*See id.*) For the 100 µg/mL and 200 µg/mL formulations, Dr. Kipp used data from the Precedex Concentrate NDA. (*See id.*)

Dr. Kipp conducted two analyses for the data: one applying the assumption that dexmedetomidine follows a zero-order loss model and one applying the assumption that it follows a first-order loss model. (*Id.* ¶ 363 & n.2; Redirect Examination of Dr. Kipp at 466:24-467:1.) Under zero-order kinetics, "the rate of reaction is not proportional to the concentration of drug in a solution," so that "at lower concentrations, the percentage of drug loss is greater than it is at higher concentrations." (Cross Examination of Dr. Kipp at 404:4-8; Colloquy Between the Court and Dr. Kipp at 468:12-14.) Under first-order kinetics, "the rate of a reaction is proportional to the concentration of a drug in solution," so that the percentage loss of a drug is the same at high concentrations as at low concentrations. (Cross Examination of Dr. Kipp at 405:5-8; Colloquy Between the Court and Dr. Kipp at 468:17-19.)

Dr. Kipp testified that his calculations for each assumption yielded "very similar" results, including that none of the calculations for any concentration predicted a loss in concentration at five months even close to approaching two percent. (Cross Examination of Dr. Kipp at 411:7-8; Redirect Examination of Dr. Kipp at 450:1-4.) He acknowledged that his calculations showed some variability, and that some calculations appeared to predict increases in concentration. (Redirect Examination of Dr. Kipp at 450:5-12, 451:12-13.) According to Dr. Kipp, because "you obviously can't generate drug from nothing," the calculations showing increases in concentration reflect "that there is no change whatsoever." (*Id.* at 450:13-15.) Overall, he testified, the variability in the data is attributable to "noise." (Cross Examination of Dr. Kipp at 410:8-9.) Dr. Kipp

concluded his calculations showed that "in fact," dexmedetomidine is "a very stable drug." (*Id.*)

In cross examining Dr. Kipp, Hospira's counsel asked a series of questions about the first two calculations Dr. Kipp conducted assuming a zero-order loss model. (Cross Examination of Dr. Kipp at 408:15-409:8.) Those calculations were based on actual samples containing 200 µg/mL and 100 µg/mL dexmedetomidine HCl and predicted that the drug would reach two percent loss at 60.1 and 23.2 months, respectively. (*See id.*) Hospira pointed out that if one were to use 4 µg/mL instead of 200 µg/mL or 100 µg/mL as the concentration (C_o) in the following equation—which describes zero-order kinetics—the time to reach two percent loss would be 1.2 months and .93 months, respectively. (*See id.* at 413:4-16, 414:6-11.)

$$\tau' = \frac{C_0(1-f)}{k'}$$

(*See id.* at 413:4-9, 414:6-11.)[7] In response, Dr. Kipp explained why he believes Hospira's calculation is an improper extrapolation. (*Id.* at 464:21-22.) According to Dr. Kipp, where the actual data shows no change in concentration, as he argues the data shows here, one cannot determine whether the drug follows a zero- or first-order loss model. (*See, e.g.*, *id.* at 465:4-6; Colloquy Between the Court and Dr. Kipp at 468:22-25.) So although one can always fit a regression line to actual data using a zero-order or first-order loss model, one cannot fit the line to other concentrations because "the parameter may change as well." (Cross Examination of Dr. Kipp at 464:19-465:1.) Dr. Kipp testified that "if you look at the data itself and you do the math, you are still seeing . . . no loss at 4 [µg/mL]." (Colloquy Between the Court and Dr. Kipp at 468:2-6.) Although the trial testimony is not entirely clear, the court understands Dr. Kipp to be saying that (1) the rate constant in the equation pictured above is derived from other calculations, which

[7] In this equation, "t'" is the time or shelf-life for a given fractional loss in concentration; "f" is fractional loss; "k'" is a rate constant, and "C_o" is the starting concentration of the drug. (*See id.* at 411:12-20.)

themselves are based on actual data from 100 µg/mL or 200 µg/mL concentrations, or (2) he used a different sequence of concentration-specific calculations, perhaps including the equation pictured above, to predict the time it would take actual samples to reach two percent loss. Either way, Hospira's proposed calculation improperly combines a C_o value of 4 µg/mL with other variables derived from data at other concentrations. This reading is supported by the fact that Dr. Kipp did calculate predictions for 4 µg/mL batches, and those calculations predicted that every batch would take far longer than .93 or 1.2 months to reach two percent loss. (*See id.*)

2. Fresenius Kabi's Witness Shweta Mowli

Ms. Shweta Mowli, who has a bachelor's degree in chemistry and biology and a master's degree in analytical chemistry, works as a project manager for Fresenius Kabi's dexmedetomidine ready-to-use project. (Direct Examination of Ms. Mowli at 717:21-718:3, 719:7-16.) Previously, she worked for eight years as a scientist in Fresenius Kabi's formulation group, including on at least five liquid pharmaceutical drugs. (*Id.* at 719:7-25.) Ms. Mowli testified that Fresenius Kabi measured the stability of its ready-to-use product for the ANDA it submitted to the FDA. (Cross Examination of Ms. Mowli at 735:22-24.) According to Ms. Mowli, the studies show that Fresenius Kabi's ready-to-use product lost less than two percent of its initial concentration after six, twelve, and eighteen months of storage at room temperature. (*Id.* at 735:22-736:7.)

3. Hospira's Statistics Expert Dr. Stephan Ogenstad

Dr. Stephan Ogenstad earned a bachelor's degree in mathematics, statistics, and computer science and a Ph.D. in statistics. (Direct Examination of Dr. Ogenstad at 743:1-2.) He testified at trial as an expert in statistics, biostatistics, and statistical analysis of pharmaceutical data. (*Id.* at 749:2-8.) Dr. Ogenstad analyzed stability data for Precedex Premix (4 µg/mL) and Fresenius Kabi's ready-to-use product (4 µg/mL). He also analyzed data from IND Batch NI 027 L1 (20 µg/mL), as well as another set of data from the Farmos IND that Dr. Kipp did not review: IND Batch OK 29 (20 µg/mL). Finally, he analyzed data for 100 µg/mL and 200 µg/mL formulations of Precedex Concentrate.

i. Precedex Premix and Fresenius Kabi's Ready-to-Use Product (4 µg/mL)

Dr. Ogenstad measured stability data for Precedex Premix and Fresenius Kabi's ready-to-use product packaged in 20 mL, 50 mL, and 100 mL vials. (Direct Examination of Dr. Ogenstad at 775:6-10; *see also* Ogenstad Regression Graphs, PTX 66 at 66.21-27.) Dr. Ogenstad acknowledged that the data for Precedex Premix shows no more than two percent loss at five months, but pointed out that the stability varies among the volumes tested: the data shows "almost no loss at all" for the 100 mL product, about one percent loss at five months for the 50 mL product, and close to two percent loss at five months for the 20 mL product. (Direct Examination of Dr. Ogenstad at 751:11-12, 777:9-14; *see also* Cross Examination of Dr. Ogenstad at 779:2-10.) Dr. Ogenstad also agreed that the data for the Fresenius Kabi batches shows no more than two percent loss at five months. (*See* Cross Examination of Dr. Ogenstad at 779:2-10.)

ii. IND Batch NI 027 L1 (20 µg/mL)

According to Dr. Ogenstad, Dr. Kipp's conclusion regarding the stability of IND Batch NI 027 L1 is unreliable because it is based on only five data points (six including time zero). (*Id.* at 749:23-750:6, 753:21-25.) Furthermore, according to Dr. Ogenstad, the measurements reflect "quite a lot of variability." (*Id.* at 750:6-8.) Dr. Ogenstad testified that under these circumstances, the data "would be very different" if the measurements were taken again. (*Id.* at 753:25-754:5.) He added that because the regression line through the data is positive—which signifies an impossible increase in concentration—a statistician would not conclude that the data shows no loss in concentration, but instead that the data is incomplete or incorrect. (*See id.* at 755:16-25.)

Rather than fit a simple regression line to the data, therefore, Dr. Ogenstad testified that a statistician would interpret the data by producing measures of uncertainty. (*Id.* at 754:8-9.) Dr. Ogenstad explained that he did so by, among other things, generating thirty-six data points to illustrate what the data might show if the stability experiment were repeated. (*Id.* at 756:5-8,

760:6-7.) Dr. Ogenstad generated this simulated data using an algorithm that accounted for the "not more than three percent" standard deviation used for HPLC measurements. (*Id.* at 757:9-759:8; 761:2-5.) In this sense, he testified, the simulated data "follows the actual observations" disclosed in the Farmos IND. (*See id.* at 760:20-22.) Dr. Ogenstad opined that his algorithm generated "an enormous scatter of data points." (*Id.* at 760:6-10.) He analyzed the data using confidence bands, a measure of uncertainty that predicts with ninety-five percent confidence where the true regression line falls within certain boundaries. (*Id.* at 763:7-21.) According to Dr. Ogenstad, the "confidence bands show very clearly that this regression line, instead of being positive, could be extremely negative." (Cross Examination of Dr. Ogenstadat 786:2-4.) Overall, Dr. Ogenstad testified, "It's possibly more than 2 percent degradation." (Direct Examination of Dr. Ogenstad at 750:23-751:1.) On cross examination, however, he acknowledged that the regression line he actually presented to the court shows that there was less than two percent loss in concentration at five months. (Cross Examination of Dr. Ogenstad at 786:6-23.)

iii. IND Batch OK 029 (20 µg/mL)

Dr. Ogenstad applied the same methodology to analyze the data from IND Batch OK 029, another stability study of 20 µg/mL dexmedetomidine HCl stored at room temperature for up to twenty-five months. (*Id.* at 769:14-770:4; IND Batch OK 029 Stability Study, JTX 39 at 39.1.) In Dr. Ogenstad's view, the data showed "a very large amount of variability" and reflected "likely more than 2 percent degradation." (Direct Examination of Dr. Ogenstad at 751:3-5, 771:8-25.) He acknowledged on cross-examination, however, that the authors of the stability study for IND Batch OK 29 had concluded that "[t]he content of the active ingredient has remained unchanged during three months' storage at stress conditions and 25 months at room temperature." (Cross Examination of Dr. Ogenstad at 790:4-10; *see also* IND Batch OK 029 Stability Study at JTX 39.4.) Although Dr. Kipp did not consider IND Batch OK 029 for his expert report, he testified that he reviewed Dr. Ogenstad's analysis and determined that the regression line for the data "does not show . . . any appreciable change in drug concentration versus time over five months." (Direct

Examination of Dr. Kipp at 343:8-18.)

iv. Precedex Concentrate (100 µg/mL and 200 µg/mL)

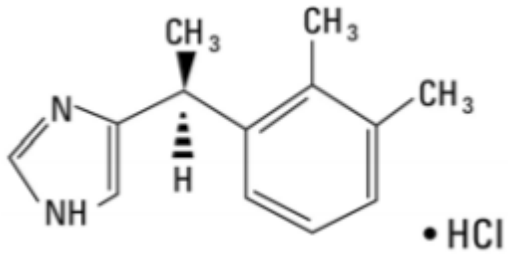
Dr. Ogenstad testified that the stability data he analyzed for Precedex Concentrate (100 µg/mL and 200 µg/mL formulations) shows that the drug experienced no more than two percent loss at five months. (Direct Examination of Dr. Ogenstad at 767:20-768:7; Ogenstad Regression Graphs at PTX 66.18-19; Redirect Examination of Dr. Ogenstad at 792:23-793:25.)

F. Chemical Structure of Dexmedetomidine

Fresenius Kabi and Hospira also offered expert testimony regarding the chemical structure of dexmedetomidine. The court summarizes that testimony below.

1. Fresenius Kabi's Expert Dr. Kipp

Dr. Kipp characterized dexmedetomidine as a "very small", "inherently very stable" molecule. (Direct Examination of Dr. Kipp at 320:5-6.) The following diagram depicts a dexmedetomidine molecule:



(Fresenius Kabi Br. 5.) The line segments in the diagram represent chemical bonds. (Direct Examination of Dr. Kipp at 320:9-10.) The lines on the outside of the hexagonal ring represent carbon-carbon chemical bonds arranged in what is called an "aromatic ring structure." (*Id.* at 320:11-24.) An aromatic ring structure has "special stability" because it contains six pi electrons. (*Id.* at 320:14-321:1.) Dr. Kipp explained that six pi electrons is a "magic number when it comes to the stabilization of this type of ring, and it's very hard to make modifications to that structure." (*Id.* at 321:2-4.) The structure, therefore, is "chemically fairly inert, and especially under normal storage conditions, you would not expect a lot of chemical change to occur." (*Id.* at 321:4-6.) He

further testified that the pentagonal ring containing N and NH "shows aromatic stabilization for much the same reason." (*Id.* at 322:3-20.)

Dr. Kipp also explained that dexmedetomidine contains no hydrolyzable groups, meaning "organic chemical groups . . . that react more readily with water." (*Id.* at 322:21-323:15.) Due to the molecule's aromatic ring structure, he stated, hydrolysis will not affect it under room-temperature storage conditions. (*Id.* at 343:6-11.) He pointed out that Precedex Concentrate and Dextomidor are formulated with water; if the dexmedetomidine compound had a hydrolyzable group, one would have seen it in the formulations for those products; yet the products had no "reported issues with hydrolysis." (*Id.* at 323:16-24.)

In addition, Dr. Kipp testified about the potential for dexmedetomidine to experience degradation through oxidation, meaning "the removal of electrons by oxygen or another oxidizing species from an organic molecule." (*Id.* at 324:4-5.) The molecule itself does not contain oxidizable groups like catechol or phenol, he noted, and due to the aromatic ring structure, oxidation will not affect the molecule under room-temperature storage conditions. (*Id.* at 324:6-19.) Discussing the carbon-hydrogen bond in the middle of the diagram, Dr. Kipp recognized that hydrogen abstraction might occur, but said this would happen only "oxidatively under . . . very stringent conditions." (*Id.* at 325:2-21.) Similarly, he testified that the CH3 (methyl) components "might be potential sites of oxidation, but in order to get any type of oxidation to occur, you have to really hit on it with a strong oxidizing agent[.]" (*Id.* at 325:25-326:7.)

The '106 Patent shows that oxidation can occur with dexmedetomidine when one adds hydrogen peroxide, which is a strong oxidizing agent, and then places the formulation in an oven at sixty degrees Celsius for eight hours. (*Id.* at 326:18-20, 327:1-6 (discussing '106 Patent, JTX 1, tbl. 4).) Even under these conditions, which Dr. Kipp characterized as "very extremely harsh" and having no connection to real-life conditions, the patent discloses a loss in concentration of only about twelve percent. (*Id.* at 326:18-20, 327:7-11.) Again, Dr. Kipp pointed out, if oxidation were a problem with dexmedetomidine, one would have seen oxidation issues reported for

Precedex Concentrate and Dexdomitor. (*Id.* at 327:12-17.) But in fact, no such issues were reported. (*Id.* at 327:18-20.)

Finally, Dr. Kipp opined that a POSA would have had a very good understanding of organic chemistry; recognized the chemical properties just discussed by looking at the molecule; and concluded that dexmedetomidine would be "rock stable" over "any long period of time." (*See id.* at 319:2-6, 321:16-23, 322:21-323:15, 324:20-325:1.)

2. Hospira's Pharmaceutical Chemistry and Drug Formulation Expert Dr. Robert Linhardt

Dr. Robert Linhardt has a bachelor's degree in chemistry, a master's degree in organic chemistry, and a Ph.D. in organic chemistry. (Direct Examination of Dr. Linhardt at 801:10-12.) He has decades of experience working on stability-related issues in pharmaceutical products, including low-molecular-weight compounds. (*Id.* at 801:25-802:4, 804:11-21.) Dr. Linhardt testified at trial as an expert in pharmaceutical chemistry and drug formulation. (*Id.* at 807:10-14.)

Dr. Linhardt agrees with Dr. Kipp that the aromaticity of the two rings imparts special stability on the molecule. (*Id.* at 818:10-819:15, 824:22-24.) He nevertheless testified that the molecule has "elements of instability in the methyl groups" and in the NH group of the pentagonal ring. (*Id.* at 819:20-820:4, 824:24-825:1.) The methyl and NH groups, Dr. Linhardt testified, are vulnerable to oxidation. (*Id.* at 820:3-4, 823:1-824:18.) Dr. Linhardt stated that although Dr. Kipp acknowledged the possibility of oxidation in the methyl groups under extreme conditions, he failed to discuss the possibility of oxidation in the NH group—where, according to Dr. Linhardt, oxidation is more likely to occur. (*Id.* at 821:4-9.) Dr. Linhardt asserts that instability is "a property of the molecule itself," regardless of concentration, and that the "about 2%" limitation is not inherent to dexmedetomidine. (*Id.* at 813:10-12, 825:14-18; Colloquy Between the Court and Dr. Linhardt at 825:2-6.)

When asked on cross examination whether he could "identify the conditions or time frame

in which any oxidation . . . would occur" by looking at the compound, Dr. Linhardt testified only that "it's likely that that oxidation will occur in the presence of an oxidant, like oxygen, or a proxy oxidant, like hydrogen peroxide[.]" (Cross Examination of Dr. Linhardt at 830:21-831:2.) And although he opined that a POSA would "look at [the] compound and predict that oxidation could occur," he acknowledged that "a POSA would likely test that prediction." (*Id.* at 827:25-828:5.)

LEGAL STANDARDS

Fresenius Kabi argues that claim 6 of the '106 Patent and claim 8 of the '049 Patent are invalid as obvious under 35 U.S.C. § 103(a). (Fresenius Kabi Br. 39.)[8] A patent claim is invalid as obvious under 35 U.S.C. § 103(a) "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) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007). The determination of obviousness is a question of law that turns on underlying factual findings. *See, e.g.*, *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations, such as commercial success, long felt but unsolved needs, and the failure of others." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1369 (Fed. Cir. 2010) (citing *Graham v. John*

[8] Congress amended § 103 when it passed the Leahy-Smith America Invents Act (AIA). Pub. L. No. 112-29, § 3(c), 125 Stat. 284, 287 (2011). The AIA "abolished the first-to-invent interference rule in favor of a first-to-file rule." *Storer v. Clark*, 860 F.3d 1340, 1342 (Fed. Cir. 2017). Among other things, the AIA revised § 103 to provide that obviousness be determined as of "the effective filing date of the claimed invention" rather than "at the time the invention was made." *Compare* § 103 (post-AIA) *with* § 103(a) (pre-AIA). It also revised § 103 to require consideration of "the differences between the claimed invention and the prior art" rather than "the differences between the subject matter sought to be patented and the prior art." *Compare* § 103 (post-AIA) *with* § 103(a) (pre-AIA). Because the priority date of the '106 and '049 Patents is before March 16, 2013, the pre-AIA § 103 applies; but the result here is the same under either version of § 103.

Deere Co., 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)); *see also, e.g.*, *ZUP, LLC*, 896 F.3d at 1371.

As the party contending that the asserted claims are invalid as obvious, Fresenius Kabi "must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (quoting *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)); *see also Microsoft Corp. v. i4i Ltd. P'Ship*, 564 U.S. 91, 95, 131 S. Ct. 2238, 180 L. Ed. 2d 131 (2011) (holding that an invalidity defense must be proved by clear and convincing evidence).

FINDINGS OF FACT

1. A person of ordinary skill in the art ("POSA") is someone who possesses either (1) a Ph.D. in a pharmaceutically related science and two to three years of experience in pharmaceutical formulation, or (2) a master's degree in a pharmaceutically related science and three to four years of experience in pharmaceutical formulation. A POSA would collaborate with other individuals as needed.[9]

2. Drs. Kipp, Linhardt, Roychowdhury, and Cedergen are POSAs, as is Ms. Mowli.

[9] At trial, Hospira and Fresenius Kabi offered competing definitions of a POSA. The parties appear to agree, however, that no outcome of any contested material fact would change depending on which definition the court adopts. (*See, e.g.*, Hospira Resp. 41-42; Direct Examination of Dr. Kipp at 251:5-11 (testifying that his opinions would not change if the court adopted Hospira's definition of a POSA); Direct Examination of Dr. Linhardt at 810:6-10 (accepting and applying Dr. Kipp's definition of a POSA).) The court also notes that Fresenius Kabi's proposed definition states that "[a] POSA would collaborate with other individuals as needed, *including anesthesiologists*," and Hospira's proposed definition states that "[a] POSA would collaborate with other individuals as needed, *including anesthesiologists and biostatisticians*." (Fresenius Kabi Br. 40 (emphasis added); Hospira Resp. 42 (emphasis added).) The court finds that this level of detail is unnecessary and overly restrictive. For example, Dr. Kipp testified that "a POSA would have access to and would collaborate with many other individuals on a research team," without specifying those individuals' areas of expertise. (Direct Examination of Dr. Kipp at 250:18-20.) The court, therefore, has eliminated the italicized language from the definition.

3. The priority date for the '106 and '049 Patents is January 4, 2012.

4. Prior art includes the '214 Patent, Precedex Concentrate, Dexdomitor, Fanikos, the CSHP Guidelines, Cain, Remington, and Sacha because these references were published or otherwise available before January 4, 2012.

5. Precedex Concentrate combined with the knowledge of a POSA, including knowledge that would be informed by Fanikos, the CSHP Guidelines, Cain, Remington, and Sacha, taught a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl.

6. A POSA would have been motivated to combine the disclosures in Precedex Concentrate, Fanikos, the CSHP Guidelines, Cain, Remington, and Sacha to create a ready-to-use 4 µg/mL dexmedetomidine HCl formulation, stored in a Type I glass vial, sealed with a coated rubber stopper.

7. Precedex Concentrate combined with Dexdomitor expressly disclosed a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl.

8. A POSA would have been motivated to combine the disclosures in Precedex Concentrate and Dexdomitor to create a ready-to-use 4 µg/mL dexmedetomidine HCl formulation, stored in a Type I glass vial, sealed with a coated rubber stopper.

9. All stability data in the record for 4 µg/mL dexmedetomidine HCl formulations stored in Type I glass vials, sealed with coated rubber stoppers, and stored at room temperature shows that there was "no more than about 2%" loss in concentration at five months.

10. The "about 2%" limitation of the '106 Patent is inherent in a 4 µg/mL dexmedetomidine HCl formulation, stored in a Type I glass vial sealed with a coated rubber stopper, and stored at room temperature for five months.

11. A POSA would have a considerable understanding of organic chemistry. Based on his or her understanding of the chemical properties of dexmedetomidine, a POSA would have expected it to be stable in room-temperature storage conditions for at least five months.

12. Precedex Concentrate disclosed that the formulation had a pH range of 4.5 to 7.0,

which is within the range of two to ten claimed in claim 8 of the '049 Patent.

13. A POSA would have been motivated to ensure that the pH range of a ready-to-use dexmedetomidine product fell within two and ten.

13. Evidence supporting secondary considerations is weak because the '214 Patent restricted production of any dexmedetomidine drug between March 1990 and July 2013.

DISCUSSION

A. Obviousness of the '106 Patent

Fresenius Kabi argues that claim 6 of the '106 Patent is invalid as obvious. According to Fresenius Kabi, the prior art expressly disclosed the following claim limitations: a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl. (Fresenius Kabi Br. 9.) In its post-trial brief, Hospira does not specifically rebut this contention, but as the court will discuss below, makes several arguments that suggest it has not conceded the point. More central to the parties' dispute is the "about 2%" limitation of the '106 Patent. Fresenius Kabi acknowledges that the prior art did not expressly disclose this limitation. (*See, e.g.*, Cross Examination of Dr. Kipp at 391:9-13 (testifying that "there's nothing that discloses, outside of the patents-in-suit, the . . . 2 percent limitation").) Fresenius Kabi, however, relies on the doctrine of inherency to supply it. (Fresenius Kabi Br. 16-18; *see PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014) (stating that in some circumstances, "inherency may supply a missing claim limitation in an obviousness analysis").) Hospira's key arguments for non-obviousness are that Fresenius Kabi has failed to prove by clear and convincing evidence (1) the inherency of the "about 2%" limitation and (2) that a POSA would have been motivated to combine the prior art teachings with a reasonable expectation of success. (Hospira Resp. 11-23.) The court addresses the parties' arguments in turn.

1. Ready-to-Use, Sealed Glass Container with 4 µg/mL Dexmedetomidine HCl

Fresenius Kabi contends that a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl was disclosed in the following combinations of references: (1) Precedex

Concentrate and the knowledge of a POSA, and (2) Precedex Concentrate and Dexdomitor. (Fresenius Kabi Br. 9-10.)[10] Fresenius Kabi also argues that a POSA would have been motivated to combine the disclosed limitations to create a ready-to-use 4 µg/mL dexmedetomidine HCl formulation, stored in a Type I glass vial, sealed with a coated rubber stopper. (*Id.* at 9-14.) For the following reasons, the court agrees.

i. Precedex Concentrate and the Knowledge of a POSA

Precedex Concentrate has been on the market since 1999. Its label discloses the exact contents of its formulation, including that it contains no preservatives, additives, or chemical stabilizers. (*See* Precedex Concentrate Label at JTX 15.2.) A named co-inventor of the '106 Patent, Dr. Roychowdhury, admitted that the label taught her the formulation and that there is "no difference between the formulation of the further diluted Precedex [C]oncentrate versus the Precedex [P]remix product[.]" (Direct Examination of Dr. Roychowdhury at 134:19-135:2, 137:20-138:10.) Hospira's corporate representative, Dr. Tata-Venkata, gave similar testimony. (Tata-Venkata Dep. at 172:17-21.) The Precedex Concentrate label also discloses that the formulation must be diluted to 4 µg/mL before being administered to humans and sets forth the steps to perform the dilution. (*See* Precedex Concentrate Label at JTX 15.13.) Drs. Roychowdhury and Cedergen testified they knew from the label that their goal was to make a 4 µg/mL formulation. (Direct Examination of Dr. Roychowdhury at 134:12-18; Direct Examination of Dr. Cedergen at 202:2-20.) For these reasons, the court concludes that the Precedex Concentrate label disclosed how to make the 4 µg/mL formulation.

The court also concludes that Precedex Concentrate disclosed a glass container as a storage material for dexmedetomidine HCl. The label, for example, expressly states that the product is packaged in glass vials (Precedex Concentrate Label at JTX 15.14), and Dr. Roychowdhury testified that while she was developing Precedex Premix, she knew this was the

[10] Fresenius Kabi also submits that the composition is obvious over Precedex Concentrate and the Farmos IND, but the court has determined that it need not reach that argument.

case. (Direct Examination of Dr. Roychowdhury at 135:18-20.) The evidence also shows that a POSA would have known from his or her experience in the pharmaceutical industry that glass, and specifically Type I glass, was a suitable storage material for the drug. Indeed, Drs. Roychowdhury and Tata-Venkata testified they knew that glass was unlikely to have issues with adsorption or absorption (*id.* at 150:12-151:8; Tata-Venkata Dep. at 82:15-83:10); Dr. Cedergen testified that he assumes glass is non-reactive absent evidence to the contrary (Direct Examination of Dr. Cedergen at 205:14-18); and Dr. Roychowdhury testified that she chose Type I glass as the storage material for Precedex Premix because she knew from experience that it was the best type of glass for the product. (Direct Examination of Dr. Roychowdury at 153:4-9.) The court further finds that in addition to Precedex Concentrate, Remington and Sacha disclosed glass as the most widely used storage material for liquid pharmaceuticals. (Remington at JTX 20.13; Sacha at JTX 24.3.) These references, read with the Precedex Concentrate label, would have taught a POSA that glass was an appropriate storage material for dexmedetomidine HCl.

In addition, the court concludes that Precedex Concentrate disclosed the use of a coated rubber stopper to seal the Type I glass vial. Dr. Roychowdhury, for example, testified that while she was developing Precedex Premix, she knew that Precedex Concentrate used coated rubber stoppers "to avoid interaction with the drug." (Direct Examination of Dr. Roychowdhury at 135:21-136:1.) In fact, a development report she authored states that Hospira "planned to implement coated stoppers in order to mimic the current product[.]" (Unsigned Hospira Development Report at JTX 62.12.) Dr. Kipp, for his part, testified that Precedex Concentrate "include[d] a sealed glass container as its final packaging configuration, with a Teflon-coated stopper." (Direct Examination of Dr. Kipp at 310:6-9.)

The court also has little difficulty in concluding that a POSA would have known from his or her experience in the pharmaceutical industry that a ready-to-use formulation was desirable. Dr. Roychowdury, for example, testified that a formulator knows that ready-to-use formulations have advantages (Direct Examination of Dr. Roychowdhury at 141:12-15), and Dr. Kipp testified that a

ready-to-use product is superior in safety and convenience to a product that requires dilution. (Direct Examination of Dr. Kipp at 271:17-272:4.) Fanikos and the CSHP Guidelines, which discussed advantages and encouraged use of ready-to-use drug formulations, support the conclusion that the idea for a premix product would have been known to a POSA. (Fanikos at JTX 19.2; CSHP Guidelines at DTX 301_0001, 0015.) And if the idea was not known to a POSA, Cain explicitly disclosed it by teaching that a hospital pharmacy was providing syringes containing pre-diluted 4 µg/mL dexmedetomidine HCl. (Cain at JTX 16.2.)

Finally, the court concludes that a POSA would have been motivated to combine his or her knowledge of the industry with the teachings from Precedex Concentrate to create a ready-to-use dexmedetomidine HCl product packaged in a Type I glass container, sealed with a coated rubber stopper. Dr. Roychowdhury, for example, testified that any formulator would be motivated to make a ready-to-use product if there is a patient need for one, and according to both Dr. Roychowdhury and a September 2006 Hospira document, that need was apparent before 2012. (Direct Examination of Dr. Roychowdhury at 143:1-6, 148:23-25; 2006 Premix Proposal at JTX 72.2.) Cain, which demonstrated that there was a market interest in a ready-to-use dexmedetmodine HCl product, would have provided additional motivation in this regard. Next, testimony from Drs. Roychowdhury and Cedergen confirms that a POSA would have obtained the appropriate concentration for a premix product, the ingredients for the formulation, and the dilution instructions from the Precedex Concentrate label. And Dr. Kipp testified that a POSA would have been motivated to use the combination of a sealed glass container with a Teflon-coated stopper. (Direct Examination of Dr. Kipp at 310:6-11.) His testimony is supported by the disclosure in the Precedex Concentrate label that dexmedetomidine HCl has a high partition coefficient—something that would have discouraged a POSA from using a plastic container. (Precedex Concentrate Label at JTX 15.2; Direct Examination of Dr. Kipp at 290:22-292:3.) Dr. Kipp's testimony is likewise supported by evidence that Dr. Roychowdhury and her team "planned to implement coated stoppers in order to mimic the current product[.]" (Unsigned Hospira

Development Report, JTX 62 at 62.12; Direct Examination of Dr. Roychowdhury at 166:15-19.)

ii. Dexdomitor and Precedex Concentrate

Dexdomitor also taught a ready-to-use dexmedetomidine HCl formulation, stored in a glass vial and sealed with a coated rubber stopper. (Dexdomitor Label at DTX 288_0002; Direct Examination of Dr. Kipp at 284:15-286:9.) Although Dexdomitor is a 500 µg/mL formulation, a POSA would have been motivated to combine the disclosures in Dexdomitor with those in the Precedex Concentrate label—including that a 4 µg/mL concentration is safe for humans—to make a ready-to-use 4 µg/mL product, stored in a Type I glass vial and sealed with a coated rubber stopper.

In its post-trial brief, Hospira does not specifically dispute the alleged disclosure of or motivation to combine these teachings to make the above-referenced composition. But it does press two general arguments that suggest it is still challenging both points. First, Hospira states that the Patent and Trademark Office ("PTO") issued the '106 Patent even though it considered Precedex Concentrate "plus the knowledge of a POSA." (Hospira Resp. 2.) Relatedly, Hospira states that in February 2017, the Patent and Trial Appeal Board ("PTAB") declined to institute an *inter partes* review of the '106 Patent. (*Id.* at 4.) These circumstances do not alter the analysis, however. The Federal Circuit has explained that "there is no heightened or added burden that applies to invalidity defenses that are based upon references that were before the Patent Office." *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012); *see also Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1356 (Fed. Cir. 2013) ("[W]e treat the issued patent as having a presumption of validity that must be overcome by clear and convincing evidence. No decision of the Supreme Court or this court has ever suggested that there is an added burden to overcome PTO findings in district court infringement proceedings[.]"). Hospira cannot overcome the overwhelming evidence of the prior art disclosures and the motivation to combine them by hiding behind PTO and PTAB decisions.

Second, Hospira argues that the Precedex Concentrate plus Dexdomitor combination

"makes no sense" because "Dexdomitor is formulated at 500 µg/mL" and "does not teach a POSA that dexmed can be stable when formulated at 4 µg/mL." (Hospira Resp. 2.) But as already discussed, Precedex Concentrate taught a 4 µg/mL dexmedetomidine formulation, and a POSA would have been motivated to combine that teaching with the other limitations that Dexdomitor did disclose. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (stating that for purposes of obviousness, the relevant teachings can be "found in any number of sources"). And the question whether the prior art teaches stability at 4 µg/mL is separate from the question whether it discloses the other claimed limitations.

In sum, Hospira's arguments do not alter the court's conclusion that the prior art disclosed a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl, and that a POSA would have been motivated to combine the teachings to make a composition with Type I glass and a coated rubber stopper.

2. The "About 2%" Limitation

Because the prior art did not explicitly disclose the "about 2%" limitation of claim 6, Fresenius Kabi relies on the doctrine of inherency to supply it. (*See* Fresenius Kabi Br. 16-18.) "[I]nherency may supply a missing claim limitation in an obviousness analysis," but the concept of inherency "must be carefully circumscribed" in this context. *PAR Pharm.*, 773 F.3d at 1194-95; *see also, e.g.*, *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017). In other words, "[a] party must . . . meet a high standard in order to rely on inherency to establish" that a claim limitation exists in the prior art: "the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm.*, 773 F.3d at 1195-96. "Inherency . . . may not be established by probabilities or possibilities." *Id.* at 1195 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *PAR Pharm.*, 773 F.3d at 1195 (quoting *In re Oelrich*, 666 F.2d at 581); *see also, e.g.*, *Millennium Pharm.*, 862 F.3d at 1367. Furthermore, although "[a]ll properties of a composition are inherent

in that composition," "unexpected properties may cause what may appear to be an obvious composition to be nonobvious." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017). "The inherent teaching of a prior art reference is a question of fact" and must be proven by clear and convincing evidence. *PAR Pharm.*, 773 F.3d at 1194, 1196 (internal quotation marks omitted).

As a threshold matter, Hospira contends that Fresenius Kabi has not established inherency because it has failed "to exclude the possibility that the combination could be prepared in a way that would fail the limitation." (Hospira Resp. 12 (citing *Endo Pharm. Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir 2018).) If Hospira is arguing that Fresenius Kabi must prove that every possible embodiment of claim 6 necessarily meets the "about 2%" limitation, that is not the law. Rather, to prove that a claim covering multiple alternative embodiments is invalid, a defendant need only prove that one of the embodiments is invalid. *See, e.g.*, *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) ("It is a 'long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter.'" (quoting *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 n.4 (Fed. Cir. 2008)); *In re Klein*, 987 F.2d 1569, 1570 (Fed. Cir. 1993) (stating that if a "single claim covers plural alternative embodiments . . . § 103 rejection is proper if the prior art demonstrates the obviousness of any one of them"). Fresenius Kabi, therefore, need only prove that the limitation is "necessarily . . . present" in one embodiment. *PAR Pharm.*, 773 F.3d at 1196.

The court in *Endo* did not hold otherwise. There, one of the claim limitations was a pharmaceutical vehicle formulation containing castor oil and benzyl benzoate in a specific ratio. 894 F.3d at 1377. The prior art references (the "Articles") did not disclose the vehicle formulation, but "it was later revealed" that the claimed formulation was the actual formulation that the Articles' authors had used. *Id.* at 1381. Defendant argued that the vehicle formulation was "necessarily present" in the Articles because a POSA would have been able to derive it from the other

information that was disclosed. *Id.* The district court, however, concluded that this was "not enough to establish that the Articles barred the possibility of an alternative vehicle being used in the prior art compositions[.]" *Id.* (internal quotation marks omitted). The district court did not hold that the party challenging a patent must prove inherency for every possible embodiment. Instead, it determined that a POSA would not have had enough information to deduce that the vehicle formulation was necessarily present in Articles. *See id.* at 1381-82. Indeed, in affirming the district court's decision, the Federal Circuit stated that the Articles' "incomplete description" of the formulation "denied skilled artisans from having access to [it], thereby precluding use of the inherency doctrine[.]" *Id.* at 1383.

Here, the "elements explicitly disclosed by the prior art" are a ready-to-use, sealed glass container—made from Type I glass and a coated rubber stopper—with 4 µg/mL dexmedetomidine HCl (hereinafter the "the 4 µg/mL preferred embodiment"). *PAR Pharm.*, 773 F.3d at 1196. There is no dispute that claim 6 covers the 4 µg/mL preferred embodiment. Fresenius Kabi, therefore, need only prove that that embodiment is invalid, *see In re Cuozzo*, 793 F.3d at 1281; *In re Klein*, 987 F.2d at 1570, and thus need only prove inherency for that embodiment.

Alternatively, if Hospira's argument is that inherency can never "be proven by examples alone" (Hospira Resp. 2 (citing *Endo*, 894 F.3d at 1381-82)), the court does not read *Endo* so broadly. The court in *Endo* simply applied the existing law—which allows a finding of inherency where a property "result[s] each and every time a skilled artisan follow[s] the prior art process"—and determined that defendant had not offered "any evidence" to satisfy that standard. 894 F.3d at 1382-83.

Having disposed of Hospira's threshold arguments, the court turns to the question whether Fresenius Kabi has marshaled clear and convincing evidence that the "about 2%" limitation is inherent in the 4 µg/mL preferred embodiment. The court concludes that it has.

First, the court finds that all stability data in the record for the 4 µg/mL preferred embodiment shows that there was "no more than about 2%" loss in the tested samples at five

months. The data includes stability test results disclosed in the patent that show a 2.3 percent loss at five months ('106 Patent, JTX 1, Example 6); eighteen batch configurations of Precedex Premix in upright and inverted storage, which according to Dr. Kipp show no more than two percent loss at five months (Direct Examination of Dr. Kipp at 340:19--341:2); measurements from three batches of Precedex Premix and three batches of Fresenius Kabi's ready-to-use product that Dr. Ogenstad testified show no more than two percent loss at five months (Direct Examination of Dr. Ogenstad at 751:11-12, 777:9-14; Cross Examination of Dr. Ogenstad at 779:2-10; Ogenstad Demonstrative, PDX 57); and testimony by Fresenius Kabi's employee Ms. Mowli that data disclosed in the ANDA for Fresenius Kabi's ready-to-use product shows less than two percent loss at six, twelve, and eighteen months (Direct Examination of Mowli at 735:22-736:7.)

Significantly, this data shows not only that samples from the 4 µg/mL preferred embodiment necessarily lost no more than about two percent of their concentration at five months, but also that many samples lost less than two percent. Dr. Kipp, for example, testified that eighteen Precedex Premix batch configurations showed "not even close to 2 percent loss over five months," and that this was true even of inverted configurations, where the solution was in constant contact with the rubber stopper. (Direct Examination of Dr. Kipp at 338:11-23.) Ms. Mowli, for her part, testified that even at eighteen months, Fresenius Kabi's ready-to-use product lost less than two percent of its concentration. (Direct Examination of Mowli at 736:6-7.) Worth noting, as well, is evidence that the two percent limitation allows leeway for variability: Dr. Roychowdhury considers a 2.3 percent loss to be "within" two percent (Direct Examination of Dr. Roychowdhury at 162:6-10); the claim limitation contains the word "about" and the patent specification defines "about" to mean "within an acceptable error range for the particular value as determined by [a POSA]" ('106 Patent, JTX 1 at col. 5:31-33, 26:23-24); and Drs. Kipp and Ogenstad testified that the error range for HPLC measurements is three percent. (Direct Examination of Dr. Kipp at 331:10; Direct Examination of Dr. Ogenstad at 756:10-24.) This information bolsters the court's conclusion that the data concerning the 4 µg/mL preferred

embodiment shows by clear and convincing evidence that the "about 2%" limitation necessarily results from the combination of the prior art teaching of the embodiment, rather than something that probably or possibly results. *See PAR Pharm.*, 773 F.3d at 1196.

Hospira contends that Fresenius Kabi cannot rely on any of the data for the 4 µg/mL preferred embodiment because it is either Hospira's own development work for the patents-in-suit or is copied from it. (Hospira Resp. 10, 12; *see also id.* at 10 (faulting Dr. Kipp for "conduct[ing] no testing of his own").) In support of this argument, Hospira cites *Millennium Pharmaceuticals*, in which the Federal Circuit reversed a finding of inherency that was based on the inventor's "path," which the court defined as "the method [the patentee] used in finding the invention[.]" 862 F.3d at 1367 (internal quotation marks omitted). The inventor in *Millennium Pharmaceuticals* unexpectedly discovered a new chemical compound (a type of ester) by freeze-drying "bortezomib in the presence of the bulking agent mannitol." *Id.* at 1361-62. The asserted claims of the patents-in-suit included the compound and its method of preparation. *Id.* at 1361. Although no prior art reference "suggested reacting bortezomib with mannitol," the district court concluded that the process was obvious because the prior art did not teach away from it. *Id.* at 1362-63. The district court also concluded that the patentee had conceded that the ester was a natural result of freeze-drying bortezomib with mannitol. *Id.* at 1367. Accordingly, the district court held that "the claims were obvious because they were the inherent result of an . . . obvious process." *Id.* at 1362. The Federal Circuit reversed both findings. Regarding inherency, the Federal Circuit stated that the "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Id.* at 1367 (quoting *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012)).

In this case, unlike in *Millennium Pharmaceuticals*, the limitations alleged to have an inherent property when combined are explicitly disclosed in the prior art, and a POSA would have been motivated to combine them. Analyzing data from this prior art combination in order to

confirm that a property is in fact inherent is not an application of hindsight, even if the data comes from the inventors. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (stating that the asserted claim language "does not impose any additional requirement because the [asserted patent] itself defines mast cell stabilization as a property that is necessarily present"); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (substantial evidence supported finding by the Board of Patent Appeals and Interferences that (1) the patent application's specification "confirm[ed] that the claimed 'food effect' is an inherent property of oxymorphone itself[;]" (2) the "express teachings" in the prior art "render[ed] the claimed controlled release oxymorphone formulation obvious[;]" and (3) "the claimed 'food effect' add[ed] nothing of patentable consequence"); *see also id.* ("[M]erely discovering and claiming a new benefit of an old process cannot render the process again patentable." (internal quotation marks omitted)); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("Even if no prior art of record explicitly discusses the [allegedly inherent limitation], the [applicant's] application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property necessarily present in [the claimed invention]"); *cf. Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316,1328-29 (Fed. Cir. 2001) (stating for purposes of inherent anticipation that "recourse to extrinsic evidence is proper to determine whether a feature, while not explicitly discussed, is necessarily present in a reference" and finding that the patentee's "own documents," as well as testimony from the "principal inventor," confirmed that the claimed limitations were "necessarily met by the disclosure of the [prior art] patent").[11] Fresenius Kabi may properly rely for inherency purposes on stability data that comprises or is derived from Hospira's development work.

[11] Although *Telemac* addressed whether a claim limitation was inherent for purposes of anticipation rather than obviousness, the Federal Circuit stated that "[t]he evidence must make clear that the missing feature is necessarily present, *and* that it would be so recognized by persons of ordinary skill in the relevant art." 247 F.3d at 1328 (emphasis added). This language suggests that the Federal Circuit considered hindsight bias and found it was not a concern when concluding that the patentee's own documents were relevant to the inherency analysis.

Hospira next contends that even if Fresenius Kabi can rely on this data, the data does not prove inherency by clear and convincing evidence. In support of this argument, Hospira submits that Fresenius Kabi ignored that Hospira's development work revealed a 2.3 percent loss in concentration after five months. (*See* Hospira Resp. 10.) As Fresenius Kabi points out, this argument is puzzling because that data supports the only example in the patent of the "about 2%" limitation. (Fresenius Kabi's Reply in Support of its Post-Trial Brief [145] ("Fresenius Kabi Reply"), 2; '106 Patent, JTX 1, Example 6.) And as previously discussed, named co-inventor of the '106 Patent, Dr. Roychowdhury, testified that 2.3 percent is "within" two percent. Hospira's argument that its own development work precludes a finding of inherency is unpersuasive.

In addition, Hospira maintains that "Dr. Kipp's failure to determine" whether dexmedetomidine follows a zero- or first-order model of loss "belies [Fresenius Kabi's] claim that it proved that the 2% limitation is inherent." (Hospira Resp. 8 n.5.) Considering Dr. Kipp's testimony that there was not "enough of a drug loss to be able to discern one model [of loss] from another," the court disagrees. (Cross Examination of Dr. Kipp at 403:1-5.) If anything, the inability to assign a loss model to dexmedetomidine underscores Fresenius Kabi's position that the 4 µg/mL preferred embodiment will necessarily experience no more than two percent loss in concentration at five months.

Finally, Hospira contends that the 20 µg/mL data from IND Batch N027 L1 and IND Batch OK 029 "disprove" inherency. (Hospira Resp. 13-14.) Hospira relies on Dr. Ogenstad's testimony—based on his simulated data and analysis thereof using confidence bands—that the degradation for IND Batch N027 L1 was "possibly more than two percent" and the degradation for IND Batch OK 029 was "likely more than 2 percent[.]" (Direct Examination of Dr. Ogenstad at 750:23-751:1, 771:8-25; *see* Hospira Resp. 10, 13-14.) According to Hospira, Dr. Ogenstad's conclusions are more reliable than Dr. Kipp's because the Remington treatise suggests using a "95% confidence limit" to account for "uncertainty when extrapolating a data set." (Hospira Resp. 13 (quoting Remington at JTX 20.10).) Hospira adds that Dr. Kipp described Remington as the

"bible of formulation science." (Direct Examination of Dr. Kipp at 295:1-2; *see* Hospira Resp. 13.) And Hospira points out that in *Hospira, Inc. v. Amneal Pharm., LLC*—where a federal court in the District of Delaware concluded that a defendant failed to prove inherency of the "about 2%" limitation of the '106 Patent—the court stated that "confidence intervals would be required to establish whether a drug concentration falls outside a specified range at a given time point based on a model relying on experimental data." 285 F. Supp. 3d 776, 800, 811 (D. Del. 2018).

The court does not agree that the 20 µg/mL data from the Farmos IND batches disproves inherency. In making this determination, the court notes Dr. Roychowdhury's testimony that when she conducted the stability test reported in the '106 Patent, she was able to determine from only five data points that "the drop in concentration [was] within 2 percent." (Direct Examination of Dr. Roychowdhury at 162:6-13.) The court also notes her recognition that a decrease in concentration followed by an increase "could be due to an analytical aberration" rather than an actual drop in concentration over time. (Cross Examination of Dr. Roychowdhury at 184:7-17.) Considering that a named co-inventor of the '106 Patent provided this testimony, it was appropriate for Dr. Kipp to conduct a simple linear regression using only the actual data from the Farmos IND batches: five measurements for each. For the same reason, the court credits Dr. Kipp's testimony that a POSA would not conclude the IND data is unreliable or incomplete due to its variability and positively-sloped regression line, but rather that these issues reflect "noise" within the acceptable three percent error range for HPLC measurements. Relatedly, the court finds that Hospira's cited portion of Remington is inapposite because it recommends using confidence intervals when extrapolating future stability data from actual stability data. (*See* Remington at JTX 20.10.) In opining that there was "no decrease in drug concentration throughout the whole study" of IND Batch 027 L1, Dr. Kipp made no attempt to predict future stability data. (Direct Examination of Dr. Kipp at 336:10-11.) And in *Amneal*, where the relevant data was offered for infringement rather than inherency purposes, the court appears to have been particularly concerned that the expert did nothing to account for the potential variability in the data.

See 285 F. Supp. 3d at 811. Here, Dr. Kipp explained why the variability does not change his conclusion, and indeed supports it. (Direct Examination of Dr. Kipp at 330:21-3311:2, 331:11-20, 332:13-20, 333:2-3.) To the extent the court in *Amneal* would require Dr. Kipp to use confidence intervals in his analysis, this court respectfully disagrees.

In this court's view, Dr. Ogenstad's methodology was less reliable than that of Dr. Kipp. Although Dr. Ogenstad appears to have accounted for the actual data and the three percent error range in creating his algorithm, the algorithm ultimately produced simulated, rather than actual, data. Additionally, although Dr. Ogenstad concluded that the resulting data reflected "possible" and "likely" losses of more than two percent, he acknowledged there was uncertainty in the data, and that the actual regression line he presented to the court for IND Batch NI 027 L1 showed that the loss in concentration at two months was less than two percent. (Cross Examination of Dr. Ogenstad at 786:6-23.) The Farmos IND authors' conclusions regarding stability are significant, as well. Specifically, the authors concluded that the content of dexmedetomidine in IND Batch 027 L1 did "not significantly change[] during storage" and that the content of the drug in IND Batch OK 029 "remained unchanged during 3 months' storage at stress conditions and 25 months at room temperature." (IND Application, JTX 35 at 35.276; IND Batch 0K 029 Data, JTX 39 at 39.4; *see also id.* at JTX 39.5 ("The product remains stable for 2 years when stored at room temperature in a clear glass ampoule.").) For these reasons, the court adopts Dr. Kipp's conclusion that the data for IND Batch 027 L1 does not show anything close to more than two percent loss at five months, rather than Dr. Ogenstad's conclusion that the data shows "possibly more than 2 percent degradation." (Direct Examination of Dr. Kipp at 335:1-5; Direct Examination of Dr. Ogenstad at 750:23-751:1.) For the same reasons, the court declines to adopt Dr. Ogenstad's conclusion that the data for IND Batch OK 29 shows "likely more than 2 percent degradation." (Direct Examination of Dr. Ogenstad at 751:3-5, 771:8-25.) Having made these determinations, the court concludes that the stability data for 20 µg/mL formulations does not undermine its finding that the "about 2%" limitation will "necessarily" result from the combination of the other limitations disclosed in the

prior art. *PAR Pharm.*, 773 F.3d at 1196.

The court is aware that in *Amneal*, in which Hospira has asserted claim 6 of the '106 Patent against another defendant, the court determined that the defendant failed to establish inherency of the "about 2%" limitation. *Amneal*, 285 F. Supp. 3d at 800. The *Amneal* court faulted the defendant for "offer[ing] no expert testimony regarding the scientific principles underlying its inherency argument, and rel[ying] on just two examples of stability data covering the claimed 4 µg/mL dexmedetomidine concentration." *Id.* Although "[t]he lack of evidence of degradants or oxidation of dexmedetomidine formulations increase[d] the weight of" the defendant's affirmative examples, the court reasoned, the examples were "insufficiently powered to establish inherency by clear and convincing evidence" due to the "absence of supporting expert testimony." *Id.*

The record before this court is different. As referenced above, Fresenius Kabi has offered far more than two examples of stability data for the 4 µg/mL preferred embodiment, all of which show that the drug lost no more than two percent of its concentration at five months. Additionally, unlike in the defendant in *Amneal*, Fresenius Kabi has offered expert testimony regarding the chemical properties of dexmedetomidine. As the court will discuss below, this testimony supports a conclusion that a POSA would have had a reasonable expectation of success from combining the other limitations disclosed in the prior art.[12]

3. Reasonable expectation of success

Fresenius Kabi argues that a POSA would have had a reasonable expectation of success for developing a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl.

Setting aside the "about 2%" limitation, the court finds that a POSA would have had a reasonable expectation of success from combining a 4 µg/mL dexmedetomidine formulation with a Type I glass vial, sealed with a coated rubber stopper. Because the Precedex Concentrate

[12] Because the court has determined that Fresenius Kabi has proved inherency of the "about 2%" limitation by clear and convincing evidence, it does not address Fresenius Kabi's alternative argument that it can invalidate claim 6 by proving "the stability limitation of that claim was *either* inherent or expected." (Fresenius Kabi Br. 2 (emphasis in original).)

label disclosed the ingredients of the formulation and the steps for dilution, a POSA would have been reasonable to expect success in creating the pre-diluted formulation. Testimony from Drs. Roychowdury and Tata-Venkata that Precedex Concentrate diluted to 4 µg/mL is no different from Precedex Premix support this conclusion, as does the fact that Dexdomitor, another ready-to-use product, was on the market before 2012. (Direct Examination of Dr. Roychowdhury at 137:20-138:10; Tata-Venkata Dep. at 172:17-21; Dexdomitor Label at DTX 288_0001.) A POSA would also reasonably have expected Type I glass to be a viable storage container based on his or her knowledge of its inert properties; Remington and Sacha, which taught that glass is the most widely used storage material for liquid pharmaceutical drugs; and Precedex Concentrate and Dexdomitor, which had been on the market for years in glass vials. (Direct Examination of Dr. Cedergen at 205:14-18; Remington at JTX 20.13; Sacha at JTX 24.3; Precedex Concentrate Label at JTX 15.14; Dexdomitor Label at DTX 288_0001, 0002.) Finally, a POSA would have been reasonable in expecting coated rubber stoppers to function as effective sealing mechanisms for glass vials. The market longevity of Precedex Concentrate and Dexdomitor, which used that configuration, support this conclusion. (Dexdomitor Label at DTX 288_0001, 0002; Direct Examination of Dr. Roychowdhury at 154:14-19.)

Whether Fresenius Kabi must also prove that a POSA would have had a reasonable expectation of success concerning the "about 2%" limitation is not entirely clear to the court. *See, e.g.*, *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1335-36 (Fed. Cir. 2018) (discussing, and finding unsupported, patentee's argument that a POSA would not expect a concededly inherent pharmacokinetic profile to result in every patient); *Honeywell*, 865 F.3d at 1355 (stating that the PTAB erred as a matter of law "in dismissing properties of the claimed invention as merely inherent, without further consideration as to unpredictability and unexpectedness"); *compare Millennium Pharm.*, 862 F.3d at 1367 (similar, but seemingly discussing secondary considerations of obviousness); *In re Kao*, 639 F.3d at 1070 (finding that a claimed inherent property "add[ed] nothing of patentable consequence" to a formulation expressly

disclosed in the prior art, without addressing reasonable expectation of success regarding the inherent property). But to the extent such a burden exists, the court concludes Fresenius Kabi has met it.

First, Fresenius Kabi contends that a POSA would have had a reasonable expectation of success based on his or her knowledge of the chemical properties of dexmedetomidine. (Fresenius Kabi Br. 19.) For this argument, Fresenius Kabi relies on the testimony of its formulation chemistry expert Dr. Kipp. According to Dr. Kipp, a POSA would have had a considerable understanding of organic chemistry and would have recognized that dexmedetomidine is "inherently very stable" due to its aromatic ring structure. (Direct Examination of Dr. Kipp at 320:1-321:6, 322:3-10.) A POSA would also have recognized that the compound is stable due to its lack of hydrolyzable and oxidizable groups. (*Id.* at 322:21-323:15, 324:12-19.) A POSA, Dr. Kipp testified, would therefore expect "that there's no way that this thing would react significantly under normal conditions, moderate pH, at room temperature, over . . . any long period of time. It's going to be a rock stable molecule." (*Id.* at 324:20-325:1.)

Hospira disputes Dr. Kipp's conclusion that a POSA would have reasonably expected dexmedetomidine to be extremely stable because according to Hospira's expert Dr. Linhardt, notwithstanding the molecule's aromatic ring structure, it is more vulnerable to oxidation than Dr. Kipp acknowledged. (Direct Examination of Dr. Linhardt at 819:20-820:4, 821:4-9, 823:1-824:18.) The vulnerability is particularly apparent, Dr. Linhardt opined, in the NH group, which Dr. Kipp did not discuss. (*See id.*) Notably, however, Dr. Linhardt did not squarely address whether oxidation can occur under room-temperature storage conditions. Rather, he stated only that "oxidation will occur in the presence of an oxidant, like oxygen, or a proxy oxidant, like hydrogen peroxide[.]" (Cross Examination of Dr. Linhardt at 830:21-831:2.) In addition, other evidence in the record—including the '106 Patent and Hospira's April 2010 Development Report for Precedex Premix—indicates that hydrogen peroxide causes dexmedetomidine to lose more than two percent of its concentration only when the mixture of substances is heated far above room temperature for

several hours. ('106 Patent, JTX 1, Example 4 & tbl. 4; Direct Examination of Dr. Roychowdhury at 164:10-24; *see also* April 2010 Dev. Report at JTX 51.60 (stating that "the degradation of dexmedetomidine HCl is very small even under extreme oxidative conditions").) The court therefore adopts Dr. Kipp's testimony that oxidation affects dexmedetomidine only under "very stringent conditions," and that a POSA "would not [have] expect[ed] a lot of chemical change to occur" in room-temperature storage conditions for five months. (Direct Examination of Dr. Kipp at 321:4-6, 325:2-23; *see Acorda*, 903 F.3d at 1333 ("[T]he expectation of success need only be reasonable, not absolute[.]" (quoting *Pfizer*, 480 F.3d at 1364).)

Hospira presses several other challenges to Dr. Kipp's testimony that a POSA would have reasonably expected dexmedetomidine to be "rock stable." According to Hospira, the 2.3 percent loss at five months that resulted during its own development work shows that dexmedetomidine is not inherently stable, but rather reacts over time. (Hospira Resp. 21.) A POSA, Hospira argues, would have seen this figure and expected to "los[e] significantly more" given his or her lack of "experience with dexmed" in comparison with that of Hospira. (*Id.*) This argument makes no sense, both because the '106 Patent is not prior art, meaning that a POSA would not have reviewed it, and because according to Dr. Roychowdhury herself, a 2.3 percent loss is within two percent. Next, Hospira points to Dr. Ogenstad's testimony that because the stability data for Precedex Premix showed the highest percentage loss in the smallest vial, the molecule must be reactive with glass—the idea being that a greater amount of drug touches glass when the vial is smaller. (*Id.*) This testimony, Hospira argues, "undercuts [Fresenius Kabi's] contention that dexmed is 'rock stable.'" (*Id.*) This argument fails for a similar reason: setting aside whether Dr. Ogenstad is qualified to provide opinions about chemistry and physics, Dr. Ogenstad agreed that even the data for the smallest vial showed no more than two percent loss at five months. (Cross Examination of Dr. Ogenstad at 751:11-12, 777:13-14.) Finally, Hospira quotes a statement from Remington that "all drug substances have the potential to degrade;" contends that Remington does not make "an exception for molecules with" aromatic ring structures; and concludes that a

POSA reviewing Remington would have "assume[d] that dexmed . . . had the potential to degrade." (Hospira Resp. 21.) This argument is without merit, as it depends on an assumption that a POSA would have relied on a discussion about degradation generally rather than his or her understanding of dexmedetomidine's chemical structure specifically. Overall, the court finds that a POSA's knowledge of dexmedetomidine's chemical structure would have supported a reasonable expectation that it would lose very little concentration at five months.

In maintaining that a POSA would have had a reasonable expectation of success for the "about 2%" limitation, Fresenius Kabi next contends a POSA would have expected a reduction in concentration to "help stability—not hurt it." (Fresenius Kabi Br. 19.) With this, the court disagrees. This theory was not a focus at trial and there is not enough evidence in the record for the court to assess it. Much more compelling is Fresenius Kabi's related argument that a POSA would not expect a reduction in concentration to affect stability at all. For this point, Fresenius Kabi cites Dr. Linhardt's concession that the instability he attributes to the dexmedetomidine molecule "is true regardless of the concentration." (*See* Colloquy Between the Court and Dr. Linhardt at 825:2-6; Fresenius Kabi Br. 19 (citing same).) Fresenius Kabi also cites a document in which Hospira stated in 2006 that it foresaw "[n]o major issues" with storing a 4 µg/mL product in glass. (Fresenius Kabi Br. 20 (citing 2006 Premix Proposal at JTX 72.5).) This evidence supports a finding that a POSA would reasonably have expected a 4 µg/mL formulation to lose very little concentration in room-temperature storage conditions at five months.

Last, Fresenius Kabi argues that a POSA would reasonably have expected a 4 µg/mL formulation to meet the "about 2%" limitation due to the information disclosed in the Dexdomitor and Precedex Concentrate labels. Fresenius Kabi points out that both products are considered low in concentration and that neither contains chemical stabilizers. (Fresenius Kabi Br. 20 (citing Direct Examination of Dr. Roychowdhury at 135:14-17 (testifying that a 100 µg/mL product is low in concentration); Cross Examination of Ms. Mowli at 735:15-17 (same); Direct Examination of Dr. Kipp at 286:10-12 (testifying that concentrations in the microgram level are low)); Fresenius

Kabi Br. 21 (citing Precedex Concentrate Label at JTX 15.2; Dexdomitor Label at DTX 288_0001).) Fresenius Kabi also points out that both products have two-year shelf lives. (Fresenius Kabi Br. at 20-21.)[13] Finally, Fresenius Kabi highlights Dr. Kipp's testimony that the "about 2%" limitation is "[n]ot at all" an extreme standard. (Direct Examination of Dr. Kipp at 316:18-20.) Dr. Kipp explained that "if one were to consider a 10 percent loss over a customary shelf-life of two years, then five months would correspond nearly exactly to about 2 percent," and testified that an assumption of this nature is "standard in [his] field." (*Id.* at 316:21-25.) Considering this information, Fresenius Kabi argues, a POSA would reasonably have expected a 4 µg/mL formulation to meet the stability limitation.

The court agrees. In industry guidance for stability testing, the FDA defines "significant change for a drug product" in a twelve-month study to include "[a] 5 percent change in assay from its initial value[.]" (U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (2003), 11, https://www.fda.gov/downloads/drugs/guidances/ucm073369.pdf.) Similarly, an academic article published in 2011 states that a typical shelf life for a pharmaceutical product is one to two years and defines shelf life as "the time a product, stored under certain conditions, is expected to remain stable or retain, in most cases, at least 90% of its potency." (Brian Du et al., *Evaluation of Physical and Chemical Changes in Pharmaceuticals Flown on Space Missions*, 13 AM. ASS'N PHARMACEUTICAL SCIENTISTS J. 299, 299 (2011).) Although the parties have not themselves put this evidence in the record, and although Hospira disputes the inherency of the "about 2%" limitation, the parties do not appear to dispute the notion that two percent degradation after five

[13] The court notes that Fresenius Kabi's citations do not directly support this proposition. But the Dexdomitor Label expressly discloses a two-year shelf life (*see* DTX 288_0001, 0005); the cited supplement to the Farmos IND proposes a two-month shelf life for 100 µg/mL dexmedetomidine HCl (*see* March 1992 IND Supplement, PTX 62 at 62.35); and testimony by both Dr. Roychowdhury and Dr. Kipp indicates that a two-year shelf life is an industry standard. (*See* Direct Examination of Dr. Roychowdhury at 162:14-163:4, Direct Examination of Dr. Kipp at 316:18-23.) Finally, Hospira does not appear to dispute that both products have two-year shelf lives. (*See* Hospira Br. 17.)

months, and ten percent degradation after two years, are considered acceptable stability results. Because Precedex Concentrate and Dexdomitor are considered low in concentration, have two-year shelf lives, and do not contain chemical stabilizers, a POSA would have expected a 4 µg/mL formulation to have a two-year shelf life. And although Hospira argues that Fresenius Kabi has "established no correlation between meeting the 2% limitation and having a . . . 10% loss over two years" (Hospira Br. 17), Dr. Kipp credibly explained that a POSA would expect a ten percent loss over two years to correspond with a two percent loss at five months. (Direct Examination of Dr. Kipp at 316:18-25.)

Hospira contends that this conclusion is unsupported because "the trial record establishes that a 4 µg/mL formulation . . . is materially different from a 100 µg/mL" formulation for purposes of stability. (Hospira Resp. 16.) The court disagrees. Hospira supports its argument with Dr. Roychowdhury's testimony that stability issues are "magnified" at 4 µg/mL and Dr. Kipp's testimony that under a zero-order loss model, the percentage of drug loss is greater at lower concentrations than at high concentrations. (*See* Hospira Resp. at 16-17.) But as already discussed, even Dr. Ogenstad agreed that the stability data for 4 µg/mL, 100 µg/mL, and 200 µg/mL formulations all showed a loss of less than two percent at five months. (Direct Examination of Dr. Ogenstad at 767:20-768:7; Cross Examination of Dr. Ogenstad at 779:2-10; Redirect Examination of Dr. Ogenstad at 792:23-793:25; Ogenstad Regression Graphs at PTX 66.18-19.) He also conceded that the regression line he presented to the court for the 20 µg/mL IND Batch NI 027 L1 showed the same result. (Cross Examination of Dr. Ogenstad at 786:6-23.) And the court does not agree with Hospira that the data from the Precedex Concentrate NDA regarding 100 µg/mL and 200 µg/mL concentrations would have exhibited a loss of two percent in "just one month" if the samples had been formulated at 4 µg/mL. (*See* Hospira Resp. 10.) Rather, the court is persuaded by Dr. Kipp's response to this argument: because the stability data in the record shows so little loss in concentration, one can fit a regression line to the actual data but cannot extrapolate the line to other concentrations. (Cross-Examination of Dr. Kipp at 464:19-

465:1; Colloquy Between the Court and Dr. Kipp at 468:2-6, 22-25.) For these reasons, the court concludes that a POSA reviewing the Dexdomitor and Precedex Concentrate labels would have had a reasonable expectation that a 4 µg/mL formulation would experience very little loss in concentration at five months, and would therefore meet the "about 2%" limitation.

Hospira submits several other challenges to Fresenius Kabi's argument that a POSA would have had a reasonable expectation of success for meeting the "about 2%" limitation. Hospira, for example, argues that Fresenius Kabi ignores evidence from Remington about difficulties with stability in "incredibly low concentration[s]." (Hospira Resp. 18.) A statement in Remington that "the percentage of decomposition is greater in more dilute solutions," Hospira contends, would have caused a POSA to expect zero-order kinetics when considering the prospect of making a 4 µg/mL formulation. (*Id.* (quoting Remington at JTX 20.9).) Taking this argument further, Hospira contends that a POSA would not have had a reasonable expectation of success for stability at that concentration because Remington states that "[i]ncreasing the concentration of active ingredient that is hydrolyzing by zero-order kinetics will slow the percentage decomposition." (*Id.* (quoting Remington at JTX 20.9).)

Hospira's argument is flawed because the statements quoted from Remington refer to drugs that are "prone to hydrolysis" and follow a zero-order loss model. (Remington at JTX 20.8-9.) Dr. Kipp testified that a POSA would know from the chemical structure of dexmedetomidine that it is not prone to hydrolysis in room-temperature storage, and Dr. Linhardt did not rebut that testimony. (*See* Direct Examination of Dr. Kipp at 323:3-24.) Dr. Kipp also testified that it would have been routine for a POSA to conduct stability tests. (Cross Examination of Dr. Kipp at 358:11-18; *see also* Cross Examination of Dr. Linhardt at 827:25-828:5 (testifying that a POSA would likely test predictions regarding oxidation in dexmedetomidine).) The court agrees that a POSA would have studied the chemical structure of the molecule and conducted stability tests rather than assume based only on Remington that dexmedetomidine follows a zero-order loss model. And because the stability data in the record shows very little loss across several concentrations,

the court finds that a POSA would have reached the same conclusion as Dr. Kipp: the data shows that dexmedetomidine is so stable that its model of loss cannot be determined. The court's conclusion in this regard also disposes of Hospira's argument that because there was no publicly available information before 2012 regarding stability of a 4 µg/mL dexmedetomidine formulation, a POSA could not have had a reasonable expectation that it would experience minimal losses in concentration at that formulation. (*See* Hospira Resp. 9 (citing Direct Examination of Dr. Roychowdhury at 139:8-13 (testifying that her development team had no data regarding whether a 4 µg/mL concentration would be stable for more than 24 hours once in use); Cross Examination of Dr. Kipp at 382:4-8, 391:9-14 (testifying there was no publicly available data regarding stability at a 4 µg/mL concentration and that the prior art did not disclose the "about 2%" limitation); Tata-Venkata Dep. at 219:22-220:5, 272:22-273:13 (testifying there was no publicly available data regarding stability at a 4 µg/mL concentration).)

Next, Hospira argues that a POSA would not have reasonably expected to meet that "about 2%" limitation because in an internal document, Fresenius Kabi mentioned delays associated with working "at a concentration 25 fold lower than the concentrate." (Hospira Resp. 19 (quoting August 2013 New Project Approval Form, JTX 26 at 26.8).) The cited document, however, does not indicate whether the delays related to stability. (August 2013 New Project Approval Form at JTX 26.8.) Hospira also points to another internal document wherein a Fresenius Kabi employee acknowledged that at a 4 µg/mL concentration, "any tiny variation has a huge effect on the overall assay[.]" (September 2015 Meeting Minutes, PTX 15 at 15.2; Hospira Resp. 19 (quoting same).) The project manager for Fresenius Kabi's product, however, indicated that this concern was no different than for a 100 µg/mL product. Specifically, she testified that Fresenius Kabi took the same precautions in manufacturing the 4 µg/mL and 100 µg/mL products. (Direct Examination of Ms. Mowli at 726:5-18.) In addition, Hospira points to a third internal document wherein Fresenius Kabi discussed the potential risk posed by leachable and extractable materials at a 4 µg/mL concentration. (Hospira Resp. 19 (citing June 2014 Stage

Gate Meeting Presentation ("June 2014 Presentation"), PTX 18 at 18.24).) The cited portion of the document, however, does not make comparisons to other concentrations, does not discuss any stability data, and states that it was "[a]cceptable to move forward" with the risk. (June 2014 Presentation at JTX 18.24.) The court finds that none of these documents suggest a POSA would not have expected a 4 µg/mL formulation to meet the "about 2%" limitation.

Hospira also argues that because it began introducing nitrogen throughout the solution preparation and filling process for Precedex Premix—a process called nitrogen sparging—"to minimize oxidation," a POSA could not reasonably have expected a 4 µg/mL formulation to meet the limitation. (Hospira Resp. 19-20; *see* April 2010 Dev. Report at JTX 51.43.) But Hospira's own development report shows that it decided to introduce nitrogen sparging only after an equipment failure caused oxidation, and continued doing so only as an extra precaution. (April 2010 Dev. Report at JTX 51.43.) Additionally, according to Dr. Kipp, a POSA would have known from the chemical structure of dexmedetomidine that oxidation does not affect it in room-temperature storage conditions. The court, therefore, finds that Hospira's decision to introduce nitrogen sparging does not suggest that a POSA would have lacked a reasonable expectation of success for meeting the "about 2%" limitation.

Finally, Hospira argues that "a POSA might reasonably conclude that there were problems with manufacturing and storing concentrations lower than 100 µg/mL" because neither Orion nor Abbott manufactured a ready-to-use product. (Hospira Resp. 20.) But a POSA would likely not have known about Orion's development work because the Farmos IND was confidential. (*See id.* at 42.) And there is no reason to believe a POSA would have assumed that the entities had failed, rather than chosen not to, manufacture a ready-to-use product. Hospira's argument is unconvincing.

For the foregoing reasons, the court concludes there is clear and convincing evidence that a POSA would have had a reasonable expectation of success in meeting the "about 2%" limitation based on the chemical properties of dexmedetomidine; evidence tending to show that

dexmedetomidine's concentration does not affect its stability; and the disclosures in the Precedex Concentrate and Dexdomitor labels.

4. Secondary Considerations

Hospira presented no evidence of secondary considerations at trial. In its post-trial briefing, however, Hospira alludes to secondary considerations by emphasizing that before Drs. Roychowdhury and Cedergen developed Precedex Premix, "no one had demonstrated that a ready-to-use 4 µg/mL formulation of dexmedetomidine . . . could be disposed in a sealed glass container such that it would lose 'not more than about 2%' of its potency in a five month period." (Hospira Resp. 1.) The court interprets this statement as an argument that the failure of others to do the same warrants a finding of non-obviousness.

"Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012). "While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure." *Id.* (quoting *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)). "This is particularly true when the evidence indicates that others found development of the claimed invention difficult and failed to achieve any success." *In re Clyclobenzaprine*, 676 F.3d at 1081. "In such circumstances, 'evidence of failed attempts by others could be determinative on the issue of obviousness.'" *Id.* (quoting *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000)).

Although Hospira has offered some evidence that Fresenius Kabi expected challenges in developing a ready-to-use product (*see* August 2013 New Project Approval Form at JTX 26.8; September 2015 Meeting Minutes at PTX 15.2; June 2014 Presentation at PTX 18.24), it has presented no evidence of any "failed attempts." *In re Clyclobenzaprine*, 676 F.3d at 1081. Moreover, as noted, the '214 Patent barred Hospira's competitors from entering the market from

its issuance in March 1990 until its expiration in July 2013. (*See* '214 Patent, JTX 134; Certificate Extending Patent Term Under 35 U.S.C. § 156 at JTX 134.5.) Based on the limited record of secondary considerations before the court, the failure of others to outpace Hospira in creating a ready-to-use product is more likely attributable to a legal inability to do so than an actual inability to do so. *See Acorda*, 903 F.3d at 1339 (stating that whether a blocking patent diminishes "the significance of evidence that nobody but the blocking patent's owners or licensees arrived at" the invention "covered by the later patent" is a "fact-specific inquiry" (quoting *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 731 (Fed. Cir. 2017)).) Accordingly, in this case the failure of others does not support a finding of non-obviousness.

The court acknowledges there is also some evidence in the record tending to show a long-felt need for a ready-to-use product. For example, the Precedex Concentrate label instructed healthcare providers that they must dilute the formulation to 4 µg/mL before administering it to patients, and the prior art taught that ready-to-use formulations are advantageous. (Precedex Concentrate Label at JTX 15.13; Fanikos at JTX 19.2; CSHP Guidelines at DTX 301_0015; Cain at JTX 16.2.) "[A]lthough long-felt need is closely related to failure of others, these considerations are distinct[.]" *Millennium Pharm.*, 862 F.3d at 1369 n.5. Here, however, the '214 Patent is a common thread running through both considerations. And as the court has already stated, Hospira has presented no affirmative evidence or arguments regarding secondary considerations. Under these circumstances, given the existence of the '214 Patent, evidence of long-felt need does not support a finding of non-obviousness.

Finally, the court notes there is clear and convincing evidence of expected, rather than unexpected, results. Namely, Dr. Kipp testified that a POSA would have expected the combination of 4 µg/mL dexmedetomidine HCl, packaged in a Type I glass container with a coated rubber stopper, to be successful. (*See, e.g.*, Direct Examination of Dr. Kipp at 301:19-302:4.) As previously discussed, the prior art, including Precedex Concentrate, Dexdomitor, Remington, Sacha, and Cain support this testimony. Dr. Kipp further testified that a POSA would have

expected dexmedetomidine to be stable based on his or her understanding of its chemical properties. (*Id.* at 319:2-6, 321:16-23, 322:21-323:15, 324:20-325:1.) The court, therefore, concludes that unexpected results do not support a finding of non-obviousness. *Cf. Millennium Pharm.*, 862 F.3d at 1367 (rejecting argument that an unexpected result was "inevitable" and thus "inherent," because "obviousness is measured objectively in light of the prior art, as viewed by a person of ordinary skill in the field of the invention," and "[n]o expert testified that they foresaw, or expected, or would have intended" the process that created the claimed result, or the result's "long-sought properties and advantages").

The court concludes Fresenius Kabi has proven by clear and convincing evidence that claim 6 of the '106 Patent is invalid as obvious. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations . . . . To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." (citation omitted).)

B. Obviousness of the '049 Patent

In its post-trial briefing, Hospira has not challenged Fresenius Kabi's contention that claim 8 of the '049 Patent is invalid as obvious, so the court addresses the matter only briefly.

Like claim 6 of the '106 Patent, claim 8 of the '049 Patent covers a ready-to-use, sealed glass container with 4 µg/mL dexmedetomidine HCl. The court has already concluded for purposes of claim 6 of the '106 Patent that the prior art discloses each of these limitations; a POSA would have been motivated to combine the disclosures; and a POSA would have had a reasonable expectation of success in doing so. That conclusion applies equally to claim 8 of the '049 Patent.

Claim 8 of the '049 Patent also covers the same composition having "a pH of about 2 to about 10." (JTX 2, col. 26:16-17.) The court agrees with Fresenius Kabi that the prior art disclosed the claimed pH range. Specifically, the Precedex Concentrate label states that the

formulation has a "pH of 4.5 to 7.0," which is within the range of two to ten. (Precedex Concentrate Label at JTX 15.2; *see Santarus*, 694 F.3d at 1353 (finding that prior art disclosed claim limitation regarding ratio of buffering agent to proton pump inhibitor where it taught a ratio within the claimed range).) In addition, Dr. Kipp testified that nothing besides "using dexmedetomidine in normal saline" is required to achieve the pH range disclosed in the Precedex Concentrate label. (Direct Examination of Dr. Kipp at 271:3-11.) Hospira has not offered a rebuttal to that testimony, and the court finds that the Precedex Concentrate label supports it by disclosing that the formulation has no preservatives, additives, or chemical stabilizers. (Precedex Concentrate Label at JTX 15.2.)

The court further finds that a POSA would have been motivated to ensure that the pH of a ready-to-use product fell within the range of two to ten because Dr. Roychowdury agreed that "it wouldn't make sense to formulate anything with a pH of greater than 10 or less than 2." (Direct Examination of Dr. Roychowdhury at 157:13-15.) Dr. Kipp similarly testified that a pH range of two to ten is extremely broad, and that anything outside of it "would be clinically unacceptable" for a pharmaceutical injectable. (Direct Examination of Dr. Kipp at 306:4-10.) Relatedly, because the Precedex Concentrate label discloses both a pH range of 4.5 to seven and the lack of preservatives, additives, or chemical stabilizers, a POSA viewing the label would have had a reasonable expectation of success in creating a 4 µg/mL formulation with a pH range of two to ten.

The court's analysis of secondary considerations for claim 6 of the '106 Patent likewise applies to claim 8 of the '049 Patent. The court adds that, for the reasons just discussed, a 4 µg/mL formulation having a pH range of two to ten would be an expected, rather than an unexpected, result. *Cf. Millennium Pharm.*, 862 F.3d at 1367.

Fresenius Kabi has proven by clear and convincing evidence that claim 8 of the '106 Patent is invalid as obvious.

CONCLUSION

For the foregoing reasons, the court concludes Fresenius Kabi has proven by clear and convincing evidence that claim 6 of the '106 Patent and claim 8 of the '049 Patent are invalid as obvious. Fresenius Kabi and Hospira's pending motions [Case No. 16 C 651, dkt. nos. 102, 105, 124, 165, 170] [Case No. 17 C 7903, dkt. nos. 42, 45, 63, 99, 104] are terminated.

ENTER:

Date: December 17, 2018

REBECCA R. PALLMEYER
United States District Judge