

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEALS BOARD

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AMNEAL PHARMACEUTICALS LLC  
Petitioner

v.

HOSPIRA, INC  
Patent Owner

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*Inter Partes* Review No. IPR2016-01578  
Patent 8,338,470

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**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,338,470**

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Patent Trial and Appeal Board  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

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## LIST OF EXHIBITS

<b>Exhibit No.</b>	<b>Description</b>
1001	U.S. Patent No. 8,338,470
1002	Declaration of Dr. James Cain
1003	Declaration of Dr. Alpaslan Yaman
1004	U.S. Patent No. 4,544,664
1005	U.S. Patent No. 4,910,214
1006	U.S. Patent No. 6,716,867
1007	2010 Precedex™ Label
1008	U.S. Application No. 13/343,672
1009	“Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection”
1010 – 1012	INTENTIONALLY LEFT BLANK
1013	FDA Memorandum by Cynthia G. McCormick, M.D., dated November 30, 1999 (“the McCormick FDA Memorandum”)
1014	INTENTIONALLY LEFT BLANK
1015	Giorgi et al., International Journal for Quality in Health Care, Vol. 22, No. 3, 170-178 (2010)
1016	Eichhorn, The Official Journal of the Anesthesia Patient Safety Foundation, Spring 2010
1017	Palmgren, European Journal of Pharmaceutics and Biopharmaceutics, June 29, 2006.
1018	Lavoisier Documents; Lavoisier Sodium Chloride Product Sheet, June 2009

- 1019 FDA Memorandum by Bob A. Rappaport, M.D., dated November 5, 1999 (“the Rappaport FDA Memorandum”)
- 1020 Gerlach et al., A new dosing protocol reduces dexmedetomidine-associated hypotension in critically ill surgical patients, *Journal of Critical Care*, Vol. 24, No. 4, 568-574 (2009)
- 1021 Dyck et al., *Anesthesiology* 78:813-820 (1993)
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- 1024 Venn et al. *Anaesthesia* 54:1136-1142 (1999)
- 1025 *Packaging Drugs and Pharmaceuticals*, Wilmer A. Jenkins and Kenton R. Osborn, p. 259, 1993
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- 1027 “Sterile Pharmaceutical Packaging: Compatibility and Stability” Y. John Wang and Yie W. Chien, p. 16, 1984.
- 1028 Paula Youngberg Webb, et al. “The Keys to RTU Parenterals,” *Pharmaceutical Formulation & Quality*, Vol. 11, No. 5, p. 40, September 2009
- 1029 “Parenteral Preparations”, Ch. 84, p. 1469, Remington’s *Pharmaceutical Sciences* 16th Edition (1980).
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- 1035 Cain, *TraumaCare*, July 2007, p. 5
- 1036 US Food and Drug Administration Approved Drug Products with Therapeutic Equivalence Evaluations (“Orange Book”) - Precedex™ Listing
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- 1038 Anderson et al., *Am. J. Health Syst. Pharm.* 69:595-7 (2012)
- 1039 G. DiSilvio, M. Jacoby, D. Weiner, A. Broussard, P. Callahan, and J. Cain, “Intranasal Dexmedetomidine & Midazolam: A Novel Sedation Technique for Infant PFT,” *Society for Pediatric Anesthesia*, Phoenix, Arizona (March 2015)
- 1040 Neu et al., *Crit. Care Med.* 10:610-12 (1982)
- 1041 Potts et al., *Pediatrics* 113:59-62 (2004)
- 1042 Merry et al., *Pediatric Anesthesia* 21:743-753 (2011)
- 1043 Rodriguez-Gonzalez et al., *J. Am. Med. Info. Assoc.* 1:72-78 (2012)
- 1044 “Injectable medicines,” WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, <http://whocc.goeg.at/Glossary/PreferredTerms>
- 1045 Chrysostomou et al., *Pediatric Crit. Care Med.* 10:654-60 (2009)
- 1046 INTENTIONALLY LEFT BLANK
- 1047 U.S. Patent No. 8,242,158 to Priyanka Roychowdhury & Robert A. Cedergren, issued August 14, 2012
- 1048 U.S. Application No. 13/541,524
- 1049 Office Action Response, mailed Sept. 17, 2012, U.S. Application No. 13/541,524

1050 – 1055            INTENTIONALLY LEFT BLANK

1056      Notice of Allowance, mailed Oct. 22, 2012, U.S. Application No.  
            13/541,524

1057      Declaration of Huailiang Wu, U.S. Application No. 13/541,524

1058      Office Action, issued Aug. 17, 2012, U.S. Application No. 13/541,524

## **I. INTRODUCTION**

Anneal Pharmaceuticals LLC (“Petitioner”) submits this Petition for *Inter Partes* Review seeking cancellation of claims 1-7 of U.S. Patent No. 8,338,470 (Ex. 1001; “the ’470 patent”) as unpatentable under 35 U.S.C. §103(a) in view of the prior art.

The claims of the ’470 patent do not represent patentable subject matter and are merely an obvious combination of well-established prior art and common practices in the drug formulation and clinical arts. For the reasons explained below, Petitioner is at least reasonably likely to prevail on the asserted Grounds 1, 2 and/or 3, with respect to the challenged claims. Accordingly, Petitioner respectfully requests that this Board institute IPR and cancel each of challenged claims 1-7 of the ’470 patent.

## **II. GROUNDS FOR STANDING**

In accordance with 37 C.F.R. § 42.104(a), Petitioner certifies that the ’470 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR of any of the challenged claims.

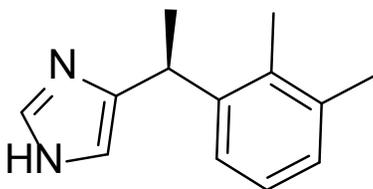
## **III. STATEMENT OF THE PRECISE RELIEF REQUESTED**

The Office should institute IPR under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-42.80 and 42.100-42.123, and cancel claims 1-7 of the ’470 patent as unpatentable under 35 U.S.C. § 103, as set forth herein.

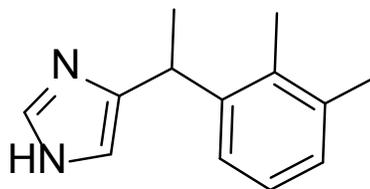
## IV. BACKGROUND

### A. History of Dexmedetomidine

The medical field has recognized dexmedetomidine as a general sedation/analgesic agent since 1988. Ex. 1005, U.S. Patent No. 4,910,214, “the ‘214 patent,” col. 3, ll. 55-59; Ex. 1002, ¶12. Dexmedetomidine ((S)-4-[1-(2,3-dimethylphenyl)-ethyl]-*1H*-imidazole), which is the S-enantiomer of medetomidine (4-[1-(2,3-dimethylphenyl)ethyl]-*1H*-imidazole), has the following structure:



**Dexmedetomidine**



**medetomidine**

Ex. 1002, ¶¶12-13.

Medetomidine, a racemic mixture, was first disclosed in the prior art in 1985 (Ex. 1004, U.S. Pat. No. 4,544,664, col. 19, l. 47 – col. 20, l. 38) and separated into two enantiomers, one of which was dexmedetomidine, in 1988. Ex. 1005, col. 1, ll. 8-43; Ex. 1002, ¶14. Administration of dexmedetomidine to a patient parenterally, including by intravenous bolus or infusion, intramuscular injection, intranasal and buccal, as well as oral routes was also disclosed in the prior art. Ex. 1002, ¶18. *See* Ex. 1004; Ex. 1005; Ex. 1021; Ex. 1022; Ex. 1023.

Additionally, as early as in 1999, the prior art disclosed methods of sedating a patient by administering dexmedetomidine, or a pharmaceutically acceptable salt thereof, to the patient. Ex. 1024; Ex. 1006; Ex. 1002, ¶¶15-16.

In the prior art, dexmedetomidine was provided as a concentrate to be diluted prior to administration to a patient. *See, e.g.*, Ex. 1007, Sec. 2.4; Ex. 1002, ¶19. Dexmedetomidine formulations for sedation were commercially available in the U.S. as early as December 23, 1999, as Precedex<sup>TM</sup> injection for intravenous infusion following dilution (or alternatively “Precedex<sup>TM</sup> Concentrate”). *See, e.g.*, Ex. 1007; Ex. 1002, ¶19.

## **B. Formulation of Parenteral Drugs**

Parenteral pharmaceutical formulations include a variety of active ingredients, which may be incorporated into liquids. Ex. 1028. A given formulation may require certain formulation or physiochemical parameters such as tonicity, particular storage material, and/or active ingredient stability, of which one with ordinary skill in the field of parenteral drug formulation would routinely select, test for and analyze. *Id.*

### **1. Storage material studies**

A pharmaceutical producer has a responsibility to make certain that a selected storage container does not interact physically or chemically with the pharmaceutical solution placed in it. Ex. 1025. For this reason, pharmaceutical

producers routinely perform studies to evaluate interactions with materials involved in parenteral administration to determine, for example, the appropriate storage materials for any particular formulation. Ex. 1026. Typical formulation studies include storing, in various glass and plastic containers, prepared admixtures at a desired concentration of the active pharmaceutical ingredient. *Id.* at 162. Samples are periodically withdrawn from the containers as a function of time and evaluated for potency, pH, color and particulate matter. *Id.* The container in which essentially no potency change is observed, from the initial potency that is measured, is then recommended for clinical use. *Id.*

In some studies, plastic containers have been shown to absorb or adsorb active drug ingredients into or onto the plastic material, causing reduced potency and efficacy of the formulation. Ex. 1027. For example, medetomidine, from which dexemedetomidine is the optically active stereoisomer, is known to display deleterious interactions with polyvinylchloride. Ex. 1017. For at least this reason, glass has been traditionally considered “the container material of choice for most sterile pharmaceutical products.” Ex. 1027 at 3. Glass containers are generally classified according to their degree of chemical resistance by the United States Pharmacopeia. *Id.* at 7.

## 2. Tonicity

For solutions intended for parenteral administration, it is well known in the art that patient discomfort (and even injury) is often minimized by adjusting the pharmaceutical solution to include a buffer system that has approximate isotonicity with body fluid. *See* Ex. 1029. When introduced into a patient, an isotonic solution has an osmotic pressure equal to that of the patient's cells. *Id.* Consequently, the intracellular volume of cells in the patient stays constant because the osmotic pressure on the cell membrane due to the parenteral solution is equalized. *Id.* It is well known that a buffer system of 0.9% sodium chloride at 37°C mimics the approximate isotonicity of body fluid. *Id.* Introduction of isotonic fluids can reduce the risk of hemolysis in patient cells as compared to solutions with different tonicity. Ex. 1030 at 395. Furthermore, it is known in the art that human red cells are least fragile in isotonic NaCl solutions. *Id.* For at least these reasons, 0.9% sodium chloride solutions are typically chosen for parenteral administration. Ex. 1029 at p. 1469.

### **C. “Ready to Use” Formulations**

It is well known in the art that some drug products intended for parenteral administration may be premixed in an intravenous diluent and stored in a container until time of administration to a patient. Ex. 1028 at p. 40. Commercially available in 50 mL to 1000 mL glass or plastic containers, such products are referred to as

ready-to-use (RTU) intravenous products or “premix” drug solutions. *Id.* There are many other examples of active pharmaceutical ingredients available in RTU form, such as nitroglycerine (*Id.*), propofol microemulsions (Ex. 1032), and esmolol hydrochloride (Ex. 1033).

Historically, RTU medications were proposed as a way to standardize drug preparation and improve medication safety. Ex. 1020; *see also* Ex. 1015 (advocating that the most effective way to reduce microbial contamination and dilution error is use of ready to use solution) and Ex. 1034 (citing substantial cost savings in using RTU pharmaceutical products compared to conventional admixtures).

#### **D. The '470 Patent**

The specification of the '470 patent discloses premixed, or ready-to-use pharmaceutical compositions of dexmedetomidine for parenteral administration. Ex. 1001, col. 1, ll. 61-66. The specification identifies, as suitable containers for these formulations of the drug, glass vials, ampoules, syringes, and plastic flexible containers, such as polyvinyl chloride (PVC), VisIV™, polypropylene, and CR3 containers. *Id.* at col. 9, ll. 17-23. The specification also provides numerous suitable concentrations for the premixed concentrations, including the claimed concentration of 4 µg/mL. *Id.* at col. 7, l. 64 – col. 8, l. 16.

## **E. Prosecution History of the '470 Patent**

The application that issued as the '470 patent was filed on July 3, 2012, as U.S. Application No. 13/541,524. Ex. 1048, (“the '524 application”). The '524 application was a continuation of U.S. Application No. 13/343,672 (Ex. 1008), now U.S. Patent No. 8,242,158 (Ex. 1047; “the '158 patent”). Concurrently with the filing of the '524 application, the applicants submitted a Petition to Make Special under Accelerated Examination Program under 37 C.F.R. § 1.102, as set forth in M.P.E.P. § 708.02. With the Petition, the applicants submitted Accelerated Examination Support Document in which applicants argued that the claims are novel and inventive over numerous prior art references, including “Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection” (“the Precedex Draft Label,” Ex 1009).

On August 17, 2012, the Examiner issued an Office Action rejecting the claims as obvious over numerous references including Precedex™ Package Insert (“the Precedex Label,” Ex. 1007) in combination with several other references. Ex. 1058, pp. 3, 6, 8. The Office Action asserted that the Precedex Label provides dexmedetomidine HCl solution formulated as a liquid for intravenous infusion (i.e., parenteral administration). *Id.* The dexmedetomidine solution is provided by the label at a concentration of 100 µg/mL, and the Precedex Label instructs that this solution must be diluted to 4 µg/mL concentration prior to use. *Id.* at p. 9. The

Examiner recognized that the diluted dexmedetomidine is not provided in a sealed glass container but provided that “the use of such containers for parenteral pharmaceuticals is common and well known” as evidenced by other drugs that are provided in sealed glass containers. *Id.* at pp. 9-10. The Examiner also rejected all of the claims for nonstatutory obviousness-type double patenting over all claims of the '158 patent. *Id.* at pp. 11-12.

The applicants responded on September 17, 2012 traversing all rejections without amending the claims. Ex. 1049, p. 2. The applicants argued that the Precedex Label fails to suggest or describe a premixture composition comprising about 0.005 to about 50 µg/mL of dexmedetomidine disposed within a sealed glass container that is ready to use without dilution. *Id.* at p. 5. Specifically, the applicants argued that “upon withdrawing the claimed composition from a sealed glass container, an artisan of ordinary skill can administer the composition directly to a subject” whereas the Precedex Label composition would “not suitable for administering to a patient upon withdrawing the composition from a sealed container.” *Id.* at p. 6.

Citing Examples 1 and 3 in the specification, applicants further argued that a ready-to-use premixture composition in a sealed glass container is more stable over a prolonged period compared to, for example, the premixture composition stored in a plastic container. *Id.* at p. 6. Applicants did not rebut the Examiner’s

obviousness determination by showing that one of skill in the art would not have had a reasonable expectation of success of storing the diluted formulation for extended periods of time (i.e., longer than 24 hours) in glass. Ex. 1049, p. 8. Instead, applicants submitted a Declaration of Huailiang Wu (“The Wu Declaration,” Ex. 1057) to further support the stability of the glass-stored composition compared to PVC-stored composition. *Id.*, pp. 6, 8. Applicants argued that the Wu Declaration demonstrated that “storing a ready to use dexmedetomidine composition at concentrations of 1, 10, 15 and 50 µg/mL in glass containers surprisingly increased the stability of the dexmedetomidine compositions compared to storage in plastic PVC bags.” *Id.* at pp. 8-9.

Applicants also relied upon an FDA Memorandum by Cynthia G. McCormick, M.D., dated November 30, 1999 (“the FDA Memorandum”) to support their argument that a diluted 4 µg/mL dexmedetomidine composition was expected to be stable for only 24 hours. Ex. 1049, p. 8 citing to Ex. 1013, p. 8. The Examiner took applicants’ arguments at face value and allowed the claims on December 22, 2012 following the applicants’ filing of a terminal disclaimer on September 17, 2012. Ex. 1056.

## **V. STATEMENT OF THE REASONS FOR THE RELIEF REQUESTED**

### **A. Claims for Which Review is Requested**

Under 35 U.S.C. § 311, Petitioner respectfully requests review and cancellation of claims 1-7 of the '470 patent.

### **B. Statutory Grounds of Challenge**

Petitioner requests that claims 1-7 of the '470 patent be cancelled under 35 U.S.C. § 103(a). This petition offers claim construction, reasons for unpatentability, and specific evidence supporting this request.

### **C. Level of Ordinary Skill in the Art**

The person of ordinary skill in the art (“POSA”) would have held an advanced degree, such as a Ph.D or M.D., in the field of drug development and formulation, or in the alternative would have significant clinical experience in anesthesia or sedation with familiarity using parental injection as of January 4, 2012. Ex. 1002, ¶23. The amount of experience in the field would depend upon the level of formal education and particular experience with pharmaceutical formulations. *Id.*

### **D. Claim Construction**

For purposes of an *inter partes* review, a claim should be given its broadest reasonable interpretation in light of the specification of the patent in which it appears. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee*, 136 S.Ct.

2131 (2016). Accordingly, claims as construed before the Board may not necessarily be the same as a federal court would construe them using an “ordinary and customary meaning” standard under *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005).<sup>1</sup> Nevertheless, the Board’s construction “cannot be divorced from the specification and the record evidence, and must be consistent with the one that those skilled in the art would reach.” *Microsoft Corp. v. Proxycorr, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (internal citations and quotations omitted).

The claim terms are construed from the point of view of a person of ordinary skill in the art at the time of invention, as identified above.

1. Ready to Use

Each claim of the ’470 patent recites a “ready-to-use” liquid composition of dexmedetomidine. “Ready-to-use” is a well-known term of art in the medical and pharmaceutical industry. Ex. 1002, ¶30; Ex. 1003, ¶¶47-49. One of skill in the art would understand the term “ready-to-use” to mean “requiring no further dilution or reconstitution before transfer to an administration device.” Ex. 1002, ¶31; Ex. 1003, ¶48; Ex. 1044. The ’470 patent specification states that:

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<sup>1</sup> Thus, this claim construction analysis should not be viewed as a concession as to the proper scope of any claim term in litigation.

[i]n certain embodiments, the compositions of the present invention can be formulated as ‘ready to use’ compositions *which refer to premixed compositions that are suitable for administration to a patient without dilution.* For example, in certain embodiments, the compositions of the present invention are ‘ready to use’ upon removing the compositions from a sealed container or vessel.”<sup>2</sup>

Ex. 1001 at col. 3, ll. 56-63 (*emphasis added*). These two definitions provide the same result: under the broadest reasonable interpretation standard, the term “ready-

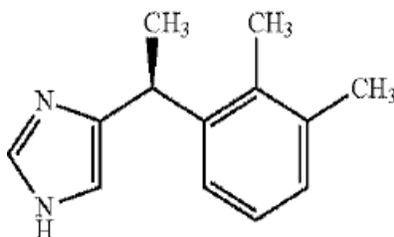
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<sup>2</sup> The specification defines “premixture” as “a pharmaceutical formulation that does not require reconstitution or dilution prior to administration to a patient. For example, in contrast to non-premixed formulations of dexmedetomidine, the premixed compositions provided herein are suitable for administration to a patient without dilution by, for example, a clinician, hospital personnel, caretaker, patient or any other individual.” Ex. 1001 at col. 3, ll. 48-55. In addition, applicants agreed to an Examiner’s Amendment that removed the limitation “wherein the composition is disposed... as a ready to use premixture” and amended the preamble to “A ready to use liquid pharmaceutical composition...” (Ex. 1056, Examiner’s Amendment, p. 2), thereby acknowledging that “ready to use” is equivalent to “ready to use premixture”.

to-use” should be construed as requiring no further dilution or reconstitution before administration to a patient. Ex. 1002, ¶31.

## 2. Dexmedetomidine

Each claim of the '470 patent likewise requires “dexmedetomidine.” Under the broadest reasonable interpretation, one of skill in the art would understand the term “dexmedetomidine” to mean “substantially pure, optically active dextrorotary stereoisomer of medetomidine, as the free base or pharmaceutically acceptable salt.” Ex. 1001, col. 3, ll. 24-27; Ex. 1002, ¶33. The specification defines “dexmedetomidine” as “(S)-4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole,” and provides the following chemical formula:



Ex. 1001, col. 3, ll. 21-45; Ex. 1002, ¶¶32-33.

## VI. IDENTIFICATION OF CHALLENGES

Pursuant to 37 C.F.R. § 42.104(b)(4)-(5), the following sections identify the statutory grounds for challenging the validity of the Challenged Claims and provide a detailed analysis of how the claims are unpatentable under the identified statutory grounds. Petitioner respectfully submits that there is a reasonable likelihood that it will prevail on each challenge for the reasons set forth below.

<b>Ground</b>	<b>35 U.S.C.</b>	<b>Claims</b>	<b>Prior Art References</b>
1	§ 103(a)	1-7	2010 Precedex Label (Ex. 1007) in view of Palmgren (Ex. 1017)
2	§ 103(a)	1-7	US 6,716,867 (Ex. 1006) in view of the 2010 Precedex Label (Ex. 1007) and Palmgren (Ex. 1017)
3	§ 103(a)	1-7	2010 Precedex Label (Ex. 1007) in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017) and the Lavoisier Documents (Ex. 1018)

For each asserted ground, Petitioner demonstrates below where each limitation is found in the prior art and that the combination of the cited art renders the claims obvious, by evaluating the scope and content of the prior art, any differences between the art and the challenged claims, the knowledge of a person of ordinary skill in the art, and any available objective indicia of nonobviousness, in accordance with *Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).

**A. Each Cited Reference is Available Prior Art**

The application that issued as the ’470 patent was filed on July 3, 2012 as the ’524 application (Ex. 1048). The ’524 application is a continuation of and

claims priority to the '672 application, issued as the '158 patent, which was filed on January 4, 2012. Accordingly, the earliest possible effective filing date of the '470 patent is January 4, 2012.

1. **2010 Precedex Label (Ex. 1007)**

The 2010 Precedex Label qualifies as prior art against the '470 patent under 35 U.S.C. § 102(b). The 2010 Precedex Label was published September 2010 and disclosed Precedex (dexmedetomidine hydrochloride) injection for intravenous infusion following dilution. Ex. 1007 at 1.

2. **U.S. Patent No. 6,716,867 (Ex. 1006)**

U.S. Patent No. 6,716,867 (“the '867 patent”) (Ex. 1006) was issued on April 6, 2004, and is prior art under 35 U.S.C. § 102(b). The '867 Patent disclosed a method of sedating a patient by administering dexmedetomidine or a pharmaceutically acceptable salt thereof to the patient. Ex. 1006, abstract. The '867 Patent described the use of dexmedetomidine that is diluted in 0.9% sodium chloride solution before administration to patients. *Id.* at col. 7, ll. 60-65.

3. **Giorgi (Ex. 1015)**

Giorgi qualifies as prior art against the '470 patent under 35 U.S.C. § 102(b). Giorgi, published in April 2010, analyzed medication errors in patients receiving injectable drugs. The authors observed patients in the pediatric and neonatal intensive care units, and determined the frequency and severity of thirty different

types of medication errors. The authors determined that microbial contamination and dilution errors were both common, and the former was the most severe medication error. Giorgi further reported aseptic procedures were often violated by staff who were often unaware of the potential harm, and that using ready-to-use injectable drugs, such as vancomycin syringes, offers a safe alternative to reduce both microbiological contamination and dilution errors. Ex. 1015, p. 176.

#### 4. **Eichhorn (Ex. 1016)**

Eichhorn qualifies as prior art against the '470 patent under 35 U.S.C. § 102(b). Eichhorn published in Spring 2010, and discusses a Medication Safety Conference hosted by the Anesthesia Patient Safety Foundation. The reference taught a proposed “new paradigm” to reduce medication errors causing harm to patients in the operating room, based on “Standardization, Technology, Pharmacy/Prefilled/Premixed, and Culture (STPC).” Ex. 1016, pp. 1, 3. It also described a 2008 national consensus conference on the safety of intravenous drug delivery systems, reporting that “there was a clear preference for manufacturer-prepared completely ready-to-use IV medication in all settings...” *Id.* at p. 5.

#### 5. **Palmgren (Ex. 1017)**

Palmgren qualifies as prior art against the '470 patent under 35 U.S.C. § 102(b). Palmgren, published June 29, 2006, disclosed results of experiments on adsorption of drugs (including medetomidine, which inherently includes

dexmedetomidine) to various plastic containers. The authors noted that medetomidine was “known to interact with PVC and polystyrene plastic” and examined medetomidine performance in glass and polypropylene as compared to modified polystyrene. Ex. 1017, p. 370. The authors reported that

“the loss of basic drugs to polystyrene well plates and [modified polystyrene]-tubes in water was a rapid process. All the drug losses were achieved within the first 15 min (Fig. 2). After 4.5 h, the relative amount remaining in [modified polystyrene] tubes in aqueous solution was  $64.7 \pm 6.8\%$ ,  $38.4 \pm 9.1\%$ ,  $31.9 \pm 6.7\%$ , and  $23.5 \pm 6.1\%$  for metoprolol, medetomidine, propranolol, and midazolam, respectively (Table 4) ... As seen in Table 4, the loss of basic drugs to [modified polystyrene]-plastic was much higher than to glass and PP-tubes.”

Ex. 1017, p. 374.

## 6. The Lavoisier Documents (Ex. 1018)

The Lavoisier Documents qualify as prior art against the ‘470 patent under 35 U.S.C. § 102(b). The Lavoisier Documents disclosed that sealed glass containers of 0.9% sodium chloride solution, used for parenteral solutions, were sold in a pharmaceutical form as an injectable solution at least as early as June 2009. Ex. 1018, p. 1. The product sheet (revised June 2009) specified that various volumes of glass ampoules and glass bottles were available in hospital packaging

and approved for institutions. *Id.* at p. 2. The product sheet further specified that hospital-packaged and institution-approved sealed glass ampoules were available at a volume of 20 mL. *Id.* Hospital-packaged and institution-approved sealed glass bottles were available at volumes of, for example, 50 ml and 100 ml. *Id.*

**B. Ground 1: Claims 1-7 of the '470 Patent Are Obvious Over the 2010 Precedex Label in view of Palmgren**

Claims 1-7 of the '470 patent would have been obvious over the 2010 Precedex Label (Ex. 1007), in view of Palmgren (Ex. 1017). Ex. 1002, ¶¶56; Ex. 1003, ¶¶43-70.

**1. Claim 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.*

**a) “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”**

The 2010 Precedex Label identified that Precedex<sup>TM</sup> as the trade name for a formulation of “dexmedetomidine hydrochloride”. Ex. 1007, Sec. 11, l. 457. The

2010 Precedex Label also disclosed that Precedex™ is a parenteral drug product. *Id.*, Sec. 2.4, ll. 175-176, 183-184. The 2010 Precedex Label specified that Precedex comes as a liquid, in a glass vial at a concentration of 200 µg/2 mL (100 µg/mL). *Id.*, Sec. 3, ll. 207-208.

Applicants gained allowance of claim 1 by, *inter alia*, arguing that Precedex™ composition is “not suitable for administering to a patient upon withdrawing the composition from a sealed container” (i.e., “after withdrawing the concentrated 100 µg/mL composition from a sealed container, the composition must be diluted prior to administration to a subject”). Ex. 1049, p. 7. On the contrary, the undiluted Precedex™ solution disclosed in the 2010 Label is ready to use for parenteral administration to patients in some circumstances. Ex. 1002, ¶41. Dr. Cain states that he routinely administers Precedex to patients parenterally, via intramuscular (IM) injection, at the provided, *undiluted* concentration of 100 µg/mL, and directly from the glass vial. Ex. 1002, ¶¶42-44.

The 2010 Precedex Label further directed a POSA to prepare a 4 µg/mL solution of Precedex for parenteral administration via intravenous infusion by diluting 2 mL of Precedex in 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Ex. 1007, Sec. 2.4, ll. 175-184. The directed concentration is encompassed within the *about 0.005 to about 50 µg/mL* concentration range recited in claim 1 of the '470 patent. As noted by Dr. Cain, dilution is routine and necessary in medical

practice in order to tailor the appropriate amount and concentration of drug to be administered under particular sets of circumstances. Ex. 1002, ¶¶49-51; Ex. 1040; Ex. 1041; Ex. 1042; Ex. 1043. The 2010 Precedex Label disclosed that such a 4 µg/mL solution of Precedex is ready to use, or “suitable for intravenous infusion following dilution.” *Id.* In view of the routine nature of medical practice to choose the appropriate amount and concentration of drug to be administered under particular sets of circumstances, it would have been obvious for a POSA to prepare a ready-to-use solution of dexmedetomidine hydrochloride at a concentration of 4 µg/mL, for parenteral administration to a patient via intravenous infusion, because the 1999 and 2010 Precedex Labels directed a POSA to do so. Ex. 1002, ¶¶43, 49; Ex. 1035 (noting that Children’s Hospital of Pittsburgh Pharmacy has been preparing ready-to-use solutions of dexmedetomidine hydrochloride at this concentration since at least 2007).

**b) “disposed within a sealed glass container”**

The 2010 Precedex Label disclosed that Precedex™ is a sterile solution provided “in a glass vial.” Ex. 1007 at Sec. 3, ll. 207-208, and Sec. 16, ll. 698-699. To the extent that the diluted Precedex™ solutions are not ready to use in a sealed glass container, a sealed glass container would have been what a POSA would choose to use for preparing, storing or handling the diluted Precedex™ solutions in

view of the teachings in the art generally and regarding this drug in particular. Ex. 1017; Ex. 1025; Ex. 1027.

The 2010 Precedex label disclosed the use of a glass vial as the only means for storage and handling of Precedex. *Id.* at Sec. 3 and 16. The 2010 Precedex Label disclosed that Precedex has a “potential for absorption” when used with some types of natural rubber. *Id.*, Sec. 206, ll. 203-206. Components having synthetic or coated natural rubber gaskets were therefore recommended for use during administration of Precedex™. *Id.* Indeed, as disclosed in Palmgren (Ex. 1017), it was well known in the art that certain drugs, including medetomidine, a racemic mixture containing two enantiomers (one of which is dexmedetomidine), interact with plastics found in infusion bags (e.g., PVC) and intravenous tubing, which can lead to drug loss and treatment failure. Ex. 1017, p. 370. Additionally, Palmgren noted that medetomidine was “known to interact with PVC and polystyrene plastic,” and examined medetomidine performance in glass and polypropylene as compared to modified polystyrene. *Id.* at p. 370. Palmgren found that the loss of basic drugs, including medetomidine, to polystyrene and polycarbonate was much higher than to glass and polypropylene tubes. *Id.* at p. 374. Palmgren confirmed that the loss of medetomidine was due to adsorption to the container surface, rather than through absorption into the container material or degradation of the drug through a reaction with the container materials. *Id.* at pp.

374-376. Because dexmedetomidine is the S-enantiomer of the racemic medetomidine, a POSA would have expected that dexmedetomidine would have the same interactions with polystyrene and glass as medetomidine, its racemic mixture. Ex. 1003, ¶54.

Armed with this knowledge, a POSA would have a reasoned basis for using a sealed glass container when formulating dexmedetomidine solutions because both Palmgren and the Precedex 2010 Label disclosed the use and suitability of glass containers to do so, and also because doing so would avoid potentially adverse interactions with other materials. Ex. 1003, ¶¶52-63.

## 2. **Claims 2-4**

Dependent claims 2-4 further recite narrower concentration ranges of the dexmedetomidine or pharmaceutically acceptable salt. Claim 2 recites a concentration of “about 0.05 to about 15 µg/mL.” Claim 3 recites a concentration of “about 0.5 to about 10 µg/mL.” Claim 4 recites a concentration of “about 1 to about 7 µg/mL.”

The Precedex 2010 Label directed a POSA to prepare a 4 mcg/mL [i.e., 4 µg/mL]) solution of Precedex™ for administration to patients. Ex. 1007, Sec. 2.4. The directed concentration is encompassed within the narrowed ranges of concentration recited in claims 2, 3 and 4 of the '470 patent. Because dilution is routine and necessary in medical practice to tailor the appropriate amount and

concentration of drug to be administered under particular sets of circumstances (Ex. 1002, ¶43, 49), it would have been obvious to a POSA to prepare a ready-to-use solution of dexmedetomidine hydrochloride at a concentration of 4 µg/mL, for parenteral administration to a patient via intravenous infusion because the 2010 Precedex Label directed a POSA to do so. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claims 2-4. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

### 3. **Claims 5-6**

Dependent claims 5 and 6 relate to the content of sodium chloride in the composition of claim 1. Claim 5 recites that the composition comprises “sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.” Claim 6 recites that “the sodium chloride is present at a concentration of about 0.9 weight percent.”

The 2010 Precedex Label discloses that “[e]ach mL [of Precedex] contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water.” Ex. 1007, Sec. 11. These instructions expressly define a solution that contains about 0.9 weight percent sodium chloride. The 2010 Precedex Label also discloses that Precedex™ is diluted at an amount of 2 mL per 48 mL of a 0.9% sodium chloride solution. *Id.* at

Sec. 2.4. As discussed in claim 1, the 2010 Precedex Label further discloses that the solution of Precedex™ containing about 0.9% sodium chloride is ready to use for administration to patients. *Id.* Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 5 and claim 6. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

#### 4. **Claim 7**

Dependent claim 7 recites that “the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL, and 100 mL.” As discussed in claim 1 above, the 2010 Precedex Label discloses the formulation of a total volume of 50 mL. Ex. 1007 at Sec. 2.4. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 7. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

#### 5. **Claim Chart**

The correspondence between the elements of claims 1-7 of the ‘470 patents and the disclosures of the art cited in Ground 1 are set forth in the following claim chart. This synopsis supports Petitioner’s argument set forth above that the claims as a whole would have been obvious to a POSA at the earliest priority date of the ‘470 patent in view of the cited art.

Claim Language	The Precedex 2010 Label and Palmgren Disclosures
<b>Claim 1</b>	
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	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4, ll. 175-184; Sec. 3, ll. 207-208; Sec. 11, line 457.
disposed within a sealed glass container.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.6, ll. 203-206; Sec. 3, ll. 207-208; Sec. 16, ll. 698-699.  Palmgren, <u>Ex. 1017</u> , p. 370, ¶¶3-4; p. 374, right col., ¶2; p. 374, Table 4; p. 374-376.
<b>Claim 2</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 µg/mL.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.
<b>Claim 3</b>	
The ready to use liquid pharmaceutical composition of claim 2,	See claims 1 and 2.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 µg/mL.	See claim 2; Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.
<b>Claim 4</b>	

Claim Language	The Precedex 2010 Label and Palmgren Disclosures
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 µg/mL.	See claim 2; Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.
<b>Claim 5</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4; Sec. 11.
<b>Claim 6</b>	
The ready to use liquid pharmaceutical composition of claim 5,	See claim 1.
wherein the sodium chloride is present at a concentration of about 0.9 weight percent.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4; Sec. 11.
<b>Claim 7</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.

Thus, claims 1-7 of the '470 patent would have been obvious over the combination of the 2010 Precedex Label (Ex. 1007) and the Palmgren reference (Ex. 1017).

**C. Ground 2: Claims 1-7 of the '470 Patent Are Obvious Over U.S.**

**6,716,867 in view of the 2010 Precedex Label and Palmgren**

Claims 1-7 of the '470 patent would have been obvious over the '867 patent (Ex. 1006), in view of the 2010 Precedex Label (Ex. 1007) and Palmgren (Ex. 1017). Ex. 1002, ¶56; Ex. 1003, ¶¶74-84.

The relevance of the '867 patent and its applicability to claims 1-7 of the '470 patent under §103(a) is apparent from Patentee's own actions and statements. The Patentee listed the '867 patent in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") as allegedly covering the premix product. Ex. 1036. By listing the '867 patent in the Orange Book, Hospira has conceded that the '867 patent covers the ready-to-use formulation claimed in the '470 patent, which according to the '470 specification is equivalent to a premix drug product. Ex. 1001, col. 3, ll. 48-63.

The Patentee has also made public statements admitting that the '867 patent covers the ready-to-use formulations. In a 2015 quarterly report to the Securities and Exchange Commission, Hospira stated that the current owner of the '867

patent, Eurohealth International Sarl (originally Ben Venue Laboratories, Inc.) had filed an ANDA with the FDA “seeking approval to market a generic version of Hospira's premix version of Precedex.” Ex. 1037. Hospira further stated that it is involved in two lawsuits “based on Eurohealth's ANDAs filed with the FDA for generic versions of Precedex™, *one of which is a premix product.*” *Id.* (emphasis added). The litigations filed by Hospira allege infringement of the '867 patent with respect to the premix product. *See id., Hospira, Inc. et al. v. Ben Venue Laboratories, et al.* No. 14-cv-00487 (D. Del. filed April 18, 2014) and *Hospira Inc. v. Ben Venue Laboratories, Inc.*, No. 14-cv-01008 (D. Del. filed August 1, 2014). Hospira further stated in its complaint that it “seeks a judgment of infringement based on the claims of U.S. Patent No. 6,716,867” as well as injunctive relief. *Id.* By filing this lawsuit for infringement of the premix product, Hospira has admitted that the '867 patent covers the premix product.

In addition to these admissions by Hospira, more detailed specific disclosures within the '867 patent for each claim element are provided below.

1. **Claim 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.*

a) ***“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”***

The '867 patent disclosed “use of dexmedetomidine or a pharmaceutically acceptable salt thereof in intensive care unit (ICU) sedation” and also “use of dexmedetomidine or a pharmaceutical salt thereof in the manufacture of a medicament for intensive care unit sedation.” Ex. 1006, col. 1, ll. 12-14 and 28-31. The '867 patent further disclosed “a method of sedating a patient while in the ICU that comprises administering dexmedetomidine or a pharmaceutically acceptable salt thereof.” *Id.*, col. 3, ll. 38-42. The '867 patent also taught intravenous (a form of parenteral) administration of dexmedetomidine or pharmaceutically acceptable salt thereof. *Id.*, col. 5, l. 7). Both the '867 patent and the 2010 Precedex Label disclosed or otherwise taught parenteral administration of dexmedetomidine via intravenous infusion.

Unlike the 2010 Precedex Label, which disclosed the undiluted dexmedetomidine hydrochloride solution provided in a glass vial at a concentration of 200 µg/2 mL (100 µg/mL), (Ex. 1007, Sec. 3, ll. 207-208), the Examples within the '867 patent disclosed administering dexmedetomidine or its salt in liquid form (“[d]exmedetomidine was used in the form of an HCl salt (100 µg/mL base), in

0.9% sodium chloride solution”) as an intravenous infusion. Ex. 1006, Example 1, col. 5, ll. 53-58.

The dose ranges disclosed within the '867 patent further evidence that the '867 patent disclosed the ready-to-use concentration of 4 µg/mL dexmedetomidine. Specifically, the '867 patent disclosed intravenous administration of a dosage range from “about 0.2-2 µg/kg, preferably about 0.5-2 µg/kg, more preferably 1.0 µg/kg,” for a bolus dose, and from “about 0.1-2.0 µg/kg/h, preferably about 0.2-0.7 µg/kg/h, more preferably about 0.4-0.7 µg/kg/h” for a maintenance dose. Ex. 1003, ¶¶79-80; Ex. 1006, col. 5, ll. 21-28. The 2010 Precedex Label disclosed, after dilution to a ready-to-use concentration of 4 µg/mL, administration of the same loading (i.e., bolus) and maintenance dosing as the “more preferable” dosages disclosed in the '867 patent: “a loading infusion of one mcg/kg over 10 minutes” and “a maintenance infusion of 0.2 to 0.7 mcg/kg/hr.” Ex. 1007, Sec. 2.2, compared to Ex. 1006, col. 5, ll. 21-28.

In view of the direction by the 2010 Precedex Label to a POSA to prepare a concentration of 4 µg/mL dexmedetomidine for parenteral administration via intravenous infusion, and that the diluted solution was ready-to-use, a POSA would have similarly recognized that the disclosed dosage range within the '867 patent is ready to administer to a patient via intravenous infusion without dilution. Ex. 1002, ¶¶49-51, 56. The broadest reasonable interpretation of “ready-to-use”

encompasses such diluted formulations of dexmedetomidine. Ex. 1002, ¶31; Ex. 1003, ¶¶32-35. The '867 patent disclosed diluted formulations of dexmedetomidine. Ex. 1002, ¶17; thus, the '867 patent disclosed “ready-to-use” formulations of dexmedetomidine. Ex. 1002, ¶17. It would have been obvious to a POSA to combine the teachings of the '867 patent and the 2010 Precedex Label to develop a “ready to use” pharmaceutical composition as claimed in claims 1-7.

**b) “*disposed within a sealed glass container*”**

The '867 patent does not disclose the composition of the container in which the disclosed dexmedetomidine is provided. However, as exhibited by the 2010 Precedex Label, it was well known in the art that dexmedetomidine was provided in a sealed glass container. To the extent that such a disclosure is not explicitly provided in the '867 patent, the 2010 Precedex Label itself disclosed that Precedex™ is provided “in a glass vial.” Ex. 1006, Sec. 3 and 16.

It would have been obvious to one of skill in the art to have prepared, stored, or handled the diluted Precedex™ solutions in sealed glass containers. The only storage and handling container disclosed in the 2010 Precedex Label is the glass vial referred to in Sections 3 and 16. *Id.* The 2010 Precedex Label further disclosed that Precedex has a “potential for absorption” when used with some types of natural rubber. Ex. 2006, Sec. 2.6, ll, 203-206. Components having synthetic or coated natural rubber gaskets were therefore recommended for use

during administration of Precedex™. *Id.* As disclosed in Palmgren, it was well known in the art at the time of filing that certain drugs, including medetomidine, a racemic mixture containing two enantiomers (one of which is dexmedetomidine) interact with plastics found in infusion bags (e.g., PVC) and intravenous tubing, which can lead to drug loss and treatment failure. Ex. 1017 at p. 370. Palmgren noted that medetomidine was “known to interact with PVC and polystyrene plastic,” set out to examine medetomidine performance in glass and polypropylene as compared to modified polystyrene. *Id.* at p. 370. Palmgren found that the loss of basic drugs, including medetomidine, to polystyrene and polycarbonate was much higher than to glass and polypropylene tubes.” *Id.* at p. 374. Because dexmedetomidine is the S-enantiomer of medetomidine, a POSA would have expected that dexmedetomidine would have the same interactions with various container materials as medetomidine. Ex. 1003, ¶54.

In view of this prior art, it would have been obvious to a POSA to prepare, store, and handle the Precedex™ solutions disclosed in the Precedex 2010 Label in a sealed glass container because both Palmgren and the Precedex 2010 Label disclose the use and suitability of glass containers to do so, and also because doing so would avoid potentially adverse interactions with other materials.

## 2. Claims 2-4

Dependent claims 2-4 further recite narrower concentration ranges of the dexmedetomidine or pharmaceutically acceptable salt. Claim 2 recites a concentration “of about 0.05 to about 15  $\mu\text{g}/\text{mL}$ .” Claim 3 recites a concentration “of about 0.5 to about 10  $\mu\text{g}/\text{mL}$ .” Claim 4 recites a concentration “of about 1 to about 7  $\mu\text{g}/\text{mL}$ .”

As noted with respect to claim 1, the '867 patent contained multiple references to the use of dexmedetomidine or its salt in liquid form (“[d]exmedetomidine was used in the form of an HCl salt (100  $\mu\text{g}/\text{mL}$  base), in 0.9% sodium chloride solution”) administered as an intravenous infusion. Ex. 1006, Example 1, col. 5, ll. 53-58.

The dose ranges disclosed within the '867 patent further evidence that the '867 patent disclosed a range of concentrations of ready-to-use dexmedetomidine recited in claims 2-4, including 4  $\mu\text{g}/\text{mL}$ . Specifically, the '867 patent disclosed intravenous administration of a dosage range from “about 0.2-2  $\mu\text{g}/\text{kg}$ , preferably about 0.5-2  $\mu\text{g}/\text{kg}$ , more preferably 1.0  $\mu\text{g}/\text{kg}$ ,” for a bolus dose, and from “about 0.1-2.0  $\mu\text{g}/\text{kg}/\text{h}$ , preferably about 0.2-0.7  $\mu\text{g}/\text{kg}/\text{h}$ , more preferably about 0.4-0.7  $\mu\text{g}/\text{kg}/\text{h}$ ” for a maintenance dose. Ex. 10XX, ¶¶ ; Ex. 1006, col. 5, ll. 21-28. The 2010 Precedex Label disclosed, after dilution to a ready-to-use concentration of 4  $\mu\text{g}/\text{mL}$ , administration of the same loading (i.e., bolus) and maintenance dosing as

the “more preferable” dosages disclosed in the ’867 patent: “a loading infusion of one mcg/kg over 10 minutes” and “a maintenance infusion of 0.2 to 0.7 mcg/kg/hr.” Ex. 1007, Sec. 2.2, compared to Ex. 1006, col. 5, ll. 21-28. To the extent that the admission in the ’867 patent that the dosing of dexmedetomidine was recognized in the art does not itself render obvious the dosages recited in claims 2-4, it would have been obvious to a POSA to use such dosages given the combined teachings of the ’867 patent and the 2010 Precedex Label. Ex. 1003, ¶81.

Accordingly, in addition to the previously stated reasons why it would have been obvious to have combined the knowledge obtained from the ’867 patent and the 2010 Precedex Label so as to arrive at the subject matter of the asserted claims, it would have been further obvious to a POSA that the dexmedetomidine disclosed in the ’867 patent was administered at concentrations within the ranges recited in claims 2-4. It also would have been obvious to a POSA to use the Precedex<sup>TM</sup> compositions disclosed in the 2010 Precedex Label as the dexmedetomidine solutions disclosed in the ’867 patent because both the ’867 Patent and the 2010 Precedex Label disclose the administration of the same dose of dexmedetomidine to the same patient populations using the same methods. Thus, the added limitations do not overcome the obviousness established for claim 1 over the ’867 patent and the 2010 Precedex Label.

### 3. **Claims 5-6**

Dependent claims 5 and 6 relate to the content of sodium chloride in the composition of claim 1. Claim 5 recites that the composition comprises “sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.” Claim 6 recites that “the sodium chloride is present at a concentration of about 0.9 weight percent.” The Examples of the ’867 patent contain multiple references to the use of dexmedetomidine or its salt in in a 0.9% sodium chloride solution. Ex. 1006, Example 1, col. 5, ll. 53-55 (“[d]exmedetomidine was used in the form of an HCl salt (100 µg/mL base), in 0.9% sodium chloride solution”). Thus, the ’867 Patent disclosed the subject matter of claims 5 and 6 with regard to formulations comprising 0.9% sodium chloride solutions.

Accordingly, both the ’867 patent and the 2010 Precedex Label disclosed all of the added features of claim 5 and claim 6. Thus, the added limitations do not overcome the obviousness established for claim 1 over the ’867 patent and the 2010 Precedex Label.

### 4. **Claim 7**

Dependent claim 7 recites that “the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL, and 100 mL.” As discussed in claim 1 above, the ’867 patent did not explicitly disclose the volume of the administered formulation, but the dosage is one that would be recognized by

one of skill in the art. Ex. 1003, ¶¶71-72; Ex. 1006, col. 5, ll. 7-9. Nevertheless, to the extent that the disclosure in the '867 patent that the dosing of dexmedetomidine was recognized in the art does not render obvious the compositions having the total volume recited in claim 4, the added limitations in claim 4 do not overcome the obviousness established for claim 1 over the '867 patent and the 2010 Precedex Label.

As detailed above with regard to claim 1, the '867 patent disclosed diluted, ready-to-use formulations of dexmedetomidine. Ex. 1002, ¶17. The 2010 Precedex Label disclosed the same diluted concentration (4 µg/mL) of dexmedetomidine, and that this diluted concentration was ready-to-use. *See, e.g.*, Ex. 1007, Sec. 2.4, Sec. 11. The 2010 Precedex Label also disclosed the same loading (i.e., bolus) and maintenance dosing as the “more preferable” dosages disclosed in the '867 patent: “a loading infusion of one mcg/kg over 10 minutes” and “a maintenance infusion of 0.2 to 0.7 mcg/kg/hr.” Ex. 1003, ¶¶80-81; Ex. 1007 at Sec 2.2; and Ex. 1006, col. 5, ll. 21-28. In order to administer such dosages, the 2010 Precedex Label disclosed the formulation of a total volume of 50 mL. Ex. 1007, Sec. 2.4.

Because the 2010 Precedex Label and the '867 patent disclose the same concentration of ready-to-use dexmedetomidine, and the same loading and maintenance dosing, a POSA would have understood these two references to also disclose the same total formulation volume recited in claim 4. Ex. 1003, ¶¶82-83.

Thus, the added limitations of this claim do not overcome the obviousness established for claim 1 over the '867 patent and the 2010 Precedex Label.

### 5. Claim Chart

The correspondence between the elements of claims 1-7 of the '470 patents and the disclosures of the art cited in Ground 2 are set forth in the following claim chart. This synopsis supports Petitioner's argument set forth above that the claims as a whole would have been obvious to a POSA at the earliest priority date of the '470 patent in view of the cited art.

Claim Language	U.S. Patent No. 6,716,867 and The Precedex 2010 Label
<b>Claim 1</b>	
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	U.S. 6,716,867, <u>Ex. 1006</u> , col. 1, ll. 12-14 and 28-31; col. 3, ll. 38-42; col. 5, l. 7; col. 5, ll. 21-28.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.2.
disposed within a sealed glass container.	Precedex 2010 Label, <u>Ex. 1007</u> , Sections 3 and 16.  Palmgren, <u>Ex. 1017</u> , p. 370, ¶¶3-4; p. 374, right col., ¶2; p. 374, Table 4; p. 374-376.
<b>Claim 2</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the dexmedetomidine	U.S. 6,716,867, <u>Ex. 1006</u> , col. 5, ll. 21-28; col. 5,

<b>Claim Language</b>	<b>U.S. Patent No. 6,716,867 and The Precedex 2010 Label</b>
or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 µg/mL.	ll. 53-55.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.2.
<b>Claim 3</b>	
The ready to use liquid pharmaceutical composition of claim 2,	See claims 1 and 2.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 µg/mL.	U.S. 6,716,867, <u>Ex. 1006</u> , col. 5, ll. 21-28; col. 5, ll. 53-55.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.2.
<b>Claim 4</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 µg/mL.	U.S. 6,716,867, <u>Ex. 1006</u> , col. 5, ll. 21-28; col. 5, ll. 53-55.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.2.
<b>Claim 5</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.	U.S. 6,716,867, <u>Ex. 1006</u> , col. 5, ll. 53-55.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4; Sec. 11.
<b>Claim 6</b>	
The ready to use liquid pharmaceutical composition of claim 5,	See claim 1.
wherein the sodium chloride is present at a concentration of about 0.9 weight percent.	U.S. 6,716,867, <u>Ex. 1006</u> , col. 5, ll. 53-55.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4; Sec. 11.

Claim Language	U.S. Patent No. 6,716,867 and The Precedex 2010 Label
<b>Claim 7</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.	U.S. 6,716,867, <u>Ex. 1006</u> , col. 5, ll. 7-9; col. 5, ll. 21-28.  Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.2; Sec. 2.4.

Thus, claims 1-7 of the '470 patent would have been obvious over the combination of the '867 patent (Ex. 1006), the 2010 Precedex Label (Ex. 1007) and the Palmgren reference (Ex. 1017).

**D. Ground 3: Claims 1-7 of the '470 Patent Are Obvious Over the 2010 Precedex Label in view of Giorgi, Eichhorn, Palmgren and the Lavoisier Documents**

Claims 1-7 of the '470 patent would have been obvious over the 2010 Precedex Label (Ex. 1007), in view of the knowledge of one of skill in the art at the time of filing, as evidenced by Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017) and the Lavoisier Documents (Ex. 1018) (Ex. 1003, ¶¶85-91). A POSA would have had ample motivation to combine each reference because each of these references is directed to standardizing preparations of diluted “ready

to use” dexmedetomidine for parenteral administration. Ex. 1002, ¶56; Ex. 1003, ¶¶90-91. A POSA would have had a reasonable expectation of success of combining each reference because the combination of these references yields nothing more than predictable results. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) (“any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed”). Ex. 1002, ¶56; Ex. 1003, ¶91.

Petitioner incorporates herein the disclosure and teachings of the prior art references, the 2010 Precedex Label (Ex. 1007), and Palmgren (Ex. 1017), cited with respect to Ground 1. Briefly, as previously discussed above, the 2010 Precedex Label disclosed a liquid formulation of dexmedetomidine hydrochloride stored in a glass vial at a concentration of 200 µg/2 mL (100 µg/mL), which is intended for parenteral administration via intravenous infusion. Ex. 1007, Sec. 2.4, ll. 175-184, Sec. 11, l. 457, and Sec. 3, ll. 207-208. The undiluted Precedex solution disclosed in the 2010 Label is ready to use for parenteral administration to patients in some circumstances as described by Dr. Cain, who has provided patient therapy using undiluted concentrations of 100 µg/mL, directly from the glass vial. Ex. 1002, ¶¶41-44. The 2010 Precedex Label also disclosed preparation of a 4 µg/mL solution of Precedex for parenteral administration by diluting 2 mL of

Precedex in 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Ex. 1007, Sec. 2.4, ll. 175-184.

It would have been obvious for a POSA to prepare a ready-to-use solution of dexmedetomidine hydrochloride at a concentration of 4 µg/mL, for parenteral administration to a patient via intravenous infusion, at least because the routine nature of medical practice to choose the appropriate amount and concentration of drug to be administered under particular sets of circumstances. Ex. 1002, ¶¶43, 49; Ex. 1035 p. 5 (noting that Children’s Hospital of Pittsburgh Pharmacy has been preparing ready-to-use solutions of dexmedetomidine hydrochloride at this concentration since at least 2007).

Notwithstanding the above, to the extent that the diluted Precedex™ solutions are not “ready to use” in a sealed glass container, it would have been obvious to a POSA to have prepared, stored, or handled the diluted Precedex™ solutions in sealed glass containers for at least two reasons. First, the 2010 Precedex Label disclosed that Precedex has a “potential for absorption” when used with some types of natural rubber. Ex. 1007, Sec. 206, ll. 203-206. Second, Palmgren (Ex. 1017), disclosed that it was well known in the art that medetomidine, a racemic mixture containing dexmedetomidine, interacts with plastics found in infusion bags (e.g., PVC) and intravenous tubing, which can lead to drug loss and treatment failure. Ex. 1017, p. 370. Accordingly, a POSA would

have a reasoned basis for using a sealed glass container when formulating dexmedetomidine solutions because both Palmgren and the Precedex 2010 Label disclosed the use and suitability of glass containers to do so, and also because doing so would avoid potentially adverse interactions with other materials. Ex. 1003, ¶¶52-63.

1. **Claim 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.*

**a) “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”**

Applicants gained allowance of claim 1 by, *inter alia*, arguing that Precedex<sup>TM</sup> composition is “not suitable for administering to a patient upon withdrawing the composition from a sealed container” (i.e., “after withdrawing the concentrated 100 µg/mL composition from a sealed container, the composition must be diluted prior to administration to a subject.”). Ex. 1049, p. 7. But in the field of clinical medicine, dilution of pharmaceutical formulations was routine and

necessary to achieve the appropriate amount and concentration of drug to be administered under particular sets of circumstances. Ex. 1002, ¶¶49-51; Ex. 1040; Ex. 1041; Ex. 1042; Ex. 1043. In addition, the 2010 Precedex Label explicitly instructed the POSA to prepare a ready-to-use solution of Precedex at a concentration of 4 µg/mL. Ex. 1007, Sec. 2.4, ll. 175-184. It would have been obvious for a POSA to prepare a solution of dexmedetomidine hydrochloride at a concentration of 4 µg/mL for parenteral administration to a patient via intravenous infusion in view of these instructions as understood by a POSA well versed in routine medical practice.

**b) “disposed within a sealed glass container”**

The 2010 Precedex Label taught the use of a glass vial alone to store and handle Precedex (Ex. 1007, Sec. 3 and 16), and further taught that Precedex should be maintained in glass because the drug could be absorbed into rubber. *Id.*, Sec. 2.6. Palmgren disclosed that it was well-known that medetomidine, a racemic mixture containing the enantiomer dexmedetomidine, interacts with plastics found in infusion bags and intravenous tubing, which can lead to drug loss and treatment failure. Ex. 1017, p. 370. Moreover, Palmgren disclosed the results of studies that confirmed loss of medetomidine was much higher in polystyrene and polycarbonate than in glass and polypropylene *Id.*, p. 374-376; *See* Sec. VI.B.1.b, above.

This Ground 3 adds the prior art references Giorgi, Eichhorn, and the Levoisier Documents to Petitioner's *prima facie* obviousness determination, evidencing that one of skill in the art would have been motivated to prepare ready to use or premixed, diluted solutions of Precedex at the 4 µg/mL concentration as instructed in the 2010 Precedex Label. These references establish that, at the time of filing, those of skill in the art recognized the need for and indeed had been advocating for additional standardization of drug preparation methods. A POSA would have been motivated to prepare a ready to use liquid pharmaceutical composition as disclosed in claims 1-7, in view of this prior art.

Giorgi disclosed that both microbial contamination and dilution errors were common treatment failures, with microbial contamination the most critical reason for treatment failure associated with injectable medications. Ex. 1015, p. 176. Giorgi further reported that aseptic procedures were often violated by staff unaware of the potential harm. *Id.*, p. 176. The 2010 Precedex Label expressly cautioned that microbial contamination must be avoided during handling, stating: “[s]trict aseptic technique must always be maintained during handling of Precedex.” Ex. 1007, Sec 2.4. Giorgi taught that use of ready-to-use injectable drugs, such as vancomycin syringes, offered a safe alternative to reduce instances of both microbial contamination and dilution errors. Ex. 1015, p. 176.

Eichhorn reported that a January 26, 2010 consensus conference by the Anesthesia Patient Safety Foundation “to develop new strategies for ‘predictable prompt improvement’ of medication safety in the operating room,” recommended that “[r]outine provider-prepared medications should be discontinued whenever possible. ... [and s]tandardized pre-prepared medication kits by case type should be used whenever possible.” Ex. 1016, p. 1. Eichhorn also referred to “a 2008 national consensus conference on the safety of intravenous drug delivery systems, [where] there was a clear preference for manufacturer-prepared completely ready-to-use IV medication in all settings.” *Id.*, p. 5.

The Lavoisier Documents show that 0.9% sodium chloride solutions were routinely available in sealed glass containers in 2009 for use as an injectable solution, and detailed the availability of hospital-packaged, institution approved sealed glass ampoules and bottles at several volumes, including 20 mL ampoules and bottles at a volume of 50 ml in 125 ml, and 100 ml in 125 ml. Ex. 1018, pp. 1-2. Likewise, the use of 0.9% sodium chloride was routinely used in the industry, as this concentration results in an isotonic solution, which is desired for the formulation of parenteral drugs. Ex. 1003, ¶90. A POSA preparing the diluted Precedex<sup>TM</sup> solutions following the instructions in Section 2.4 of the 2010 Precedex Label would have been directed to add 2 mL of the concentrated Precedex<sup>TM</sup> to 48 mL of a 0.9% sodium chloride solution, which itself was already

in a sealed glass container. Ex. 1003, ¶90. As a result, a POSA, following the directions found in both the Precedex 2010 Label would prepare a 4 µg/mL solution of Precedex<sup>TM</sup> in a sealed glass container. Ex. 1003, ¶91.

There was ample motivation for a POSA to provide pre-formulated diluted solutions of Precedex<sup>TM</sup> as disclosed in the 2010 Precedex Label in a sealed glass container in view of this prior art. Palmgren disclosed the advantages of resistance to drug loss by using sealed glass containers (Ex. 1017, pp. 374-376); Eichhorn disclosed reduction of the risk of adverse drug events and human error, as well as the advantages of drug standardization and adherence to industry standards using sealed glass containers (Ex. 1016, pp. 1, 5); Giorgi disclosed the benefits of avoiding microbial contamination by using pre-prepared medications packaged in sterile, sealed glass containers (Ex. 1015, abstract); and the Lavoisier Documents disclosed the availability and routine use of already-available glass bottles for this purpose (Ex. 1018, pp. 1-2). These references illustrate that the use of sealed glass containers for diluting drug products such as dexmedetomidine was known in the art and provided a ready solution for an appropriately diluted dexmedetomidine solution as recited in the claims of the '470 patent. A POSA also would have had a reasonable expectation of success of combining each reference because the combination of these references yields nothing more than predictable results. *KSR Int'l*, 550 U.S. at 420.

## 2. Claims 2-4

Dependent claims 2-4 further recite narrower concentration ranges of the dexmedetomidine or pharmaceutically acceptable salt. Claim 2 recites a concentration “of about 0.05 to about 15  $\mu\text{g}/\text{mL}$ ,” claim 3 recites a concentration “of about 0.5 to about 10  $\mu\text{g}/\text{mL}$ ,” and claim 4 recites “a concentration of about 1 to about 7  $\mu\text{g}/\text{mL}$ .”

The Precedex 2010 Label directed a POSA to prepare a 4 mcg/mL [i.e., 4  $\mu\text{g}/\text{mL}$ ] solution of Precedex<sup>TM</sup> for administration to patients. Ex. 1007, Sec. 2.4. The directed concentration is encompassed within the narrowed ranges of concentration recited in claims 2, 3 and 4 of the '470 patent. Because dilution is routine and necessary in medical practice to tailor the appropriate amount and concentration of drug to be administered under particular sets of circumstances (Ex. 1002, ¶¶43, 49), it would have been obvious to a POSA to prepare a ready-to-use solution of dexmedetomidine hydrochloride at a concentration of 4  $\mu\text{g}/\text{mL}$ , for parenteral administration to a patient via intravenous infusion because the 2010 Precedex Label directed a POSA to do so. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claims 2-4. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

### 3. Claims 5 and 6

Dependent claims 5 and 6 relate to the content of sodium chloride in the composition of claim 1. Claim 5 recites that the composition comprises “sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.” Claim 6 recites that “the sodium chloride is present at a concentration of about 0.9 weight percent.”

The 2010 Precedex Label discloses that “[e]ach mL [of Precedex] contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water.” Ex. 1007, Sec. 11. These instructions expressly define a solution that contains about 0.9 weight percent sodium chloride. The 2010 Precedex Label also disclosed that Precedex<sup>TM</sup> is diluted at an amount of 2 mL per 48 mL of a 0.9% sodium chloride solution. *Id.* at Sec. 2.4. As discussed in claim 1, the 2010 Precedex Label further disclosed that the solution of Precedex<sup>TM</sup> containing about 0.9% sodium chloride is ready to use for administration to patients. *Id.* Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 5 and claim 6. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

4. **Claim 7**

Dependent claim 7 recites that “the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL, and 100 mL.” As discussed in claim 1 above, the 2010 Precedex Label disclosed formulation of a total volume of 50 mL. Ex. 1007, Sec. 2.4. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 7. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

5. **Claim Chart**

The correspondence between the elements of claims 1-7 of the ‘470 patents and the disclosures of the art cited in Ground 3 are set forth in the following claim chart. This synopsis supports Petitioner’s argument set forth above that the claims as a whole would have been obvious to a POSA at the earliest priority date of the ‘470 patent in view of the cited art.

<b>Claim Language</b>	<b>The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents</b>
<b>Claim 1</b>	
A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4, ll. 175-184; Sec. 3, ll. 207-208; Sec. 11, line 457.

Claim Language	The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents
of about 0.005 to about 50 µg/mL	
disposed within a sealed glass container.	<p>Precedex 2010 Label, <u>Ex. 1007</u>, Sec. 3 and 16.</p> <p>Giorgi, <u>Ex. 1015</u>, p. 170, Abstract.</p> <p>Eichhorn, <u>Ex. 1016</u>, p. 1; p. 5.</p> <p>Lavoisier Documents, <u>Ex. 1018</u>, pp. 1-2.</p> <p>Palmgren, <u>Ex. 1017</u>, p. 370; 374-376.</p>
<b>Claim 2</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 µg/mL.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.
<b>Claim 3</b>	
The ready to use liquid pharmaceutical composition of claim 2,	See claims 1 and 2.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 µg/mL.	See claim 2; Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.
<b>Claim 4</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 µg/mL.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4.

<b>Claim Language</b>	<b>The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents</b>
<b>Claim 5</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4; Sec. 11.
<b>Claim 6</b>	
The ready to use liquid pharmaceutical composition of claim 5,	See claim 1.
wherein the sodium chloride is present at a concentration of about 0.9 weight percent.	See claim 5; Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.4; Sec. 11.
<b>Claim 7</b>	
The ready to use liquid pharmaceutical composition of claim 1,	See claim 1.
wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.	Precedex 2010 Label, <u>Ex. 1007</u> , Sec. 2.2; Sec. 2.4.

Thus, claims 1-7 of the '470 patent would have been obvious over the 2010 Precedex Label (Ex. 1007), in view of the knowledge of one of skill in the art at the time of filing, as evidenced by Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017) and the Lavoisier Documents (Ex. 1018).

**E. Any Secondary Considerations are Insufficient to Overcome the *Prima Facie* Case**

During prosecution of the '524 application, applicants successfully argued that secondary considerations overcame the Examiner's *prima facie* obviousness rejection over several prior art references, including the 2010 Precedex Label. Ex. 1056. But none of the secondary considerations submitted during prosecution are sufficient to overcome the *prima facie* obviousness determination asserted for the first time here, over the 2010 Precedex Label in view of Palmgren.

Applicants argued “that the claimed ready to use premixture composition provides for surprising and unexpected advantages over the diluted 4 µg/mL composition described by the cited references.” Ex, 1049, p. 6. Applicants supported their assertions with the disclosure presented in Examples 1 and 3:

The ability to store the claimed composition for prolonged periods of time are shown in at least Examples 1 and 3 of the application, which demonstrate that the claimed ready to use 4 µg/mL premixture composition was stable for up to 9 months when stored in a glass container. As described in Example 1, a 4 µg/mL premixture formulation stored in glass vials and ampoules maintained a higher level of potency after a 5 month storage period compared to storage in plastic, CR3 or PVC containers. (See, the specification, pp. 18-20,

paras. [0086] - [0088]). As described by Table 1, when stored in glass vials or ampoules, the 4 µg/mL premixture maintained over 98% potency after 5 months. However, when stored in plastic or PVC containers, which include plastic syringes and plastic bags, the potency was reduced by as much as 20% after only a two-week storage period. (See the specification, pp. 19-20, Table 1). Similarly, Example 3 discloses that the potency of the claimed 4 µg/mL premixture composition maintained relatively unchanged after being stored in glass vials and ampoules at 25°C for 9 months. (See the specification, Example 3, pp. 22-23, para. [0095]).

Ex. 1049, pp. 6-7; Ex. 1001, col. 13, l. 17 – col. 14, l. 59, col. 15, l. 23 – col. 16, l. 35.

Cumulative to the evidence provided by Examples 1 and 3, Applicants also submitted a Declaration of Huailiang Wu pursuant to 37 C.F.R. § 1.132 (“the Wu Declaration”) to show that “storing a ready to use dexmedetomidine composition at concentrations of 1, 10, 15 and 50 µg/mL in glass containers surprisingly increased the stability of the dexmedetomidine compositions compared to storage in plastic PVC bags.” Ex. 1049, p. 8 citing to Ex. 1057. These arguments were submitted to support Applicants’ assertion that the results were surprising and unexpected and

this secondary consideration rebutted the Examiner's asserted *prima facie* obviousness determination. Ex. 1049, p. 8.

Contrary to Applicants' statements during prosecution, these results would have been entirely expected and fail to provide any "surprising" advantages that were not already known in the prior art. Ex. 1003, ¶¶52-62. The 2010 Precedex Label taught that Precedex (i.e., dexmedetomidine HCl) has a "potential for absorption" when used with some types of natural rubber and recommended using components having synthetic or coated natural rubber gaskets. Ex. 1007, Sec. 2.6, ll. 203-206. More importantly, Palmgren taught that medetomidine in particular was "known to interact with PVC and polystyrene plastic," and disclosed that medetomidine performed advantageously in glass and polypropylene as compared to modified polystyrene. Ex. 1017, p. 370. Palmgren found that, in unbuffered water solutions, the loss of medetomidine (and other basic drugs) in polystyrene and polycarbonate containers was much higher than the loss of medetomidine in glass containers and polypropylene tubes. *Id.*, p. 374. Ex. 1003, ¶54. Because dexmedetomidine is simply the S-enantiomer of the racemic medetomidine, these two molecules are otherwise identical (Ex. 1003, ¶54) and their interaction with containers made from plastics or rubber would be expected to be similarly identical. Ex. 1003, ¶54. A POSA would have expected that dexmedetomidine would have the same interactions with various container materials as

medetomidine under conditions disclosed in Examples 1 and 3 and by the Wu Declaration. Ex. 1003, ¶¶54, 62.

The evidence proffered by applicants during prosecution simply confirms Palmgren’s teachings that medetomidine should be confined to glass containers because it interacts deleteriously with PVC and polystyrene containers. Ex. 1003, ¶¶54, 62. A POSA would have *expected* a ready-to-use dexmedetomidine solution as disclosed in Examples 1 and 3 stored in a glass container to be more stable than the same composition stored in plastic, for example, a PVC container. Ex. 1003, ¶¶62. There was nothing unexpected or surprising to the POSA about the evidence presented in Examples 1 and 3, and this evidence is not sufficient to negate a conclusion of obviousness over the 2010 Precedex Label in view of Palmgren.

Applicants also argued that “contamination with impurities is a greater concern for compositions diluted to a low concentration.” Ex. 1049, p. 8. “Since the drug is present at such a low concentration ... even ppb levels of impurities would have a significant contribution toward the impurity limit.” *Id.* citing Ex. 1001, col. 22, ll. 40-44. Applicants stated that “the artisan would have had no expectation that the diluted formulation [having concentration of 4 µg/mL as provided by the 2010 Precedex Label] is suitable for storage” “since storage could increase the risk of contamination, *e.g.*, microbe growth resulting from contamination during dilution.” Ex. 1049, p. 8. The Wu Declaration, however,

presented data to support that maintaining the potency is more dependent on a type of container than on the concentration of dexmedetomidine. For example, when Dr. Wu stored the compositions having different concentrations *without sterilization* and at ambient temperature, he found that the compositions stored in glass containers were more stable over a 24-hour storage period than the compositions stored in PVC containers. In fact, the 1 µg/mL dexmedetomidine composition had the same stability as the 50 µg/mL dexmedetomidine composition in glass and better stability in PVC:

when the dexmedetomidine compositions [ ] were stored at ambient temperature in glass containers or PVC containers without autoclaving, the compositions stored in glass containers were more stable over a 24-hour storage period. For example, when stored for 24 hours in PVC containers, the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions experienced a decrease in potency of 1.48%, 1.22%, 1.06% and 1.78%, respectively, compared to control. In contrast, when stored for 24 hours in glass containers, the potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions only decreased by 0%, 0.56%, 0.24% and 0%, respectively, compared to control.

*Id.*, p. 9; Ex. 1057, ¶ 12, Exhibit C. Similarly, under autoclave conditions, the dexmedetomidine compositions maintained their potency when stored in glass

vials irrespective of their concentration. For example, under autoclave conditions, the 1 µg/mL dexmedetomidine composition had better stability than the 50 µg/mL dexmedetomidine composition in glass:

After storage for three days in glass vials at 25°C, the decrease in potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions were 0%, 0%, 0.39% and 0.44%, respectively, compared to control. After storage for three days in glass vials at 40°C, the decrease in potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions were 0.42%, 0%, 0.27% and 0.51%, respectively, compared to control.

Ex. 1057, ¶ 9, Exhibit B. These data further support that maintaining potency is highly dependent on the type of container as provided by the prior art. Ex. 1003, ¶ 62.

Applicants further relied on the McCormick FDA Memorandum to support their contentions regarding the unexpected properties of the claimed 4 µg/mL composition in glass. Specifically, applicants argued that the McCormick FDA Memorandum established that the diluted 4 µg/mL dexmedetomidine composition was known in the art to be stable for only 24 hours. These contentions were used to support their argument that the claimed ready-to-use 4 µg/mL dexmedetomidine premixture compositions were non-obvious because they “can be stored for

prolonged periods of time.” Ex. 1049, pp. 8-9 citing to Ex. 1013, p. 8. Applicants specifically relied on the following statement from the Memorandum:

The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours.

Ex. 1013, p. 8. But other than this broad generalization, the McCormick FDA Memorandum did not provide anything a POSA could rely upon to evaluate applicants’ contentions, in particular the conditions for dilution or storage of the diluted 4 µg/mL dexmedetomidine composition. Not only did applicant’s reliance on this single statement not fully support their position, there was inconsistent evidence from the FDA itself. In an earlier FDA Memorandum by Bob A. Rappaport, M.D., dated November 5, 1999 (“the Rappaport FDA Memorandum”), the FDA found that:

[p]rior to recommending administration of dexmedetomidine *for greater than 24 hours*, the sponsor should also undertake appropriate studies to assure persistent effectiveness and that there are no new safety concerns that arise when the drug is administered as a long-term continuous infusion.

Ex. 1019, p. 29. Even in the McCormick FDA Memorandum itself, relied upon by applicants, the FDA stated:

[t]here is adequate evidence to support the efficacy of dexmedetomidine to approve it for ICU sedation by continuous infusion for 24 hours. It is anticipated that there will be increasing demand for more prolonged use of this product once it is approved. In addition to collecting additional safety data on prolonged use, there should be a better characterization of the activity, toxicity and fate of the metabolites.

Ex. 1013, p. 9. These statements establish that *no studies* had been performed to determine whether diluted dexmedetomidine at a concentration of 4 µg/mL in 0.9% sodium chloride loses any or a significant amount of potency when stored for over a 24-hour period. As identified in the McCormick FDA Memorandum, this is likely because at the time, dexmedetomidine was only approved for ICU sedation by continuous intravenous infusion for *up to 24 hours*. Ex. 1002, ¶53.

The fact that the prior art did not disclose studies where dexmedetomidine diluted to a concentration of 4 µg/mL in 0.9% sodium chloride had not been tested after storage for longer than 24 hours does not support applicants' argument that their results were unexpected. As disclosed in the specification of the '470 patent, applicants used the *diluted* form of dexmedetomidine (4 µg/mL) stored in a glass container on a lab bench, as a *control* to determine loss of potency of the same diluted concentration (4 µg/mL) stored in PVC container over a 7 day period. Ex.

1001, Example 2, col. 14, l. 67 – col. 15, l. 18. Applicants themselves thus considered storage of diluted dexmedetomidine in a glass container sufficiently stable to act as a control. Ex. 1003, ¶62. There is evidence that a POSA would have expected dexmedetomidine to be stable, even in a diluted form, when stored in a glass container. Ex. 1003, ¶62. The prior art recognized glass, an inert substance, to be the “gold standard” for drug packaging in the pharmaceutical industry. Ex. 1003, ¶60. Applicants’ results are consistent with the industry standards and what a POSA would have expected when placing a premixed dexmedetomidine solution in a glass container. Ex. 1003, ¶62. These results could not be considered surprising in view of this prior art. Ex. 1003, ¶62.

The secondary considerations asserted by applicants during prosecution of the ’524 application are not sufficient to rebut the obviousness of claims 1-7 of the ‘470 patent over the 2010 Precedex Label in view of Palmgren. Based on the prior art as understood by a POSA, a ready-to-use dexmedetomidine solution having a concentration of about 4 µm/mL stored in a glass container would have been expected to be more stable than the same composition stored in PVC container. Ex. 1003, ¶62. Applicants failed to offer any evidence to support assertions that diluted dexmedetomidine solution (for example, at 4 µM/mL concentration) would not have been expected by a POSA to be stable *after* 24 hours, or provided any direct

comparison between the diluted and ready-to-use premixed compositions. Ex. 1003, ¶62.

## VII. CONCLUSION

Petitioner respectfully submits that this Petition shows a reasonable likelihood that Petitioner will prevail with respect to at least one of the claims of the '470 patent for which Petitioner seeks review. Accordingly, Petitioner requests that the USPTO grant this Petition, initiate *inter partes* review of Claims 1-7 of the '470 patent, and cancel these claims as unpatentable.

## VIII. MANDATORY NOTICES

**Real Party-In-Interest (37 C.F.R. § 42.8(b)(1)):** Petitioner identifies Amneal Pharmaceuticals LLC as the real party-in-interest. Amneal Pharmaceuticals LLC is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at 400 Crossing Boulevard, 3<sup>rd</sup> Floor, Bridgewater, New Jersey 08807.

**Related Matters (37 C.F.R. § 42.8(b)(2)):**

*Hospira Inc. v. Amneal Pharmaceuticals LLC*, 1:15-cv-00697-RGA (D.Del.). The Complaint alleging infringement of the '470 patent against Amneal was filed and served on August 11, 2015, and is currently pending.

Petitioner is also filing concurrently petitions for IPR of U.S. Patent Nos. 8,242,158, 8,455,527, and 8,648,106. Petitioner contacted counsel for

Hospira/Pfizer, who consented to electronic service. Service is being performed contemporaneously with the filing of this petition.

**Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):**

Petitioner identifies the following counsel (a power of attorney accompanies this Petition):

**Lead Counsel**

Paul S. Tully, Ph.D.  
McDonnell Boehnen Hulbert &  
Berghoff LLP  
300 South Wacker Drive  
Chicago, Illinois 60606

Phone: (312) 913-0001  
Fax: (312) 913-0002  
Email: tully@mbhb.com  
USPTO Reg. No. 44,377

**Back-up Counsel**

Kevin E. Noonan, Ph.D.  
McDonnell Boehnen Hulbert &  
Berghoff LLP  
300 South Wacker Drive  
Chicago, Illinois 60606

Phone: (312) 913-0001  
Fax: (312) 913-0002  
Email: noonan@mbhb.com  
USPTO Reg. No. 35,303

Andrea Orth  
McDonnell Boehnen Hulbert &  
Berghoff LLP  
300 South Wacker Drive  
Chicago, Illinois 60606

Phone: (312) 913-0001  
Fax: (312) 913-0002  
Email: orth@mbhb.com  
USPTO Reg. No. 68,000

**Notice of Service Information (37 C.F.R. § 42.8(b)(4)):** Please direct all correspondence to lead and back-up counsel at the above address. Petitioner consents to electronic service at counsels' email addresses provided above.

Pursuant to 37 C.F.R. § 42.103, the U.S. Patent and Trademark Office is authorized to charge Deposit Account No. 13-2490 the review fee set forth in 37 C.F.R. § 42.15(a)(1) and the institution fee set forth in 37 C.F.R. § 42.15(a)(1). Further, Petitioner authorizes a debit from Deposit Account No. 13-2490 for any additional fees regarding this Petition.

Respectfully submitted,  
/Paul S. Tully/  
Paul S. Tully, Ph.D  
tully@mbhb.com  
USPTO Reg. No. 44,377

Paul S. Tully, Ph.D.  
Email: tully@mbhb.com  
USPTO Reg. No. 44,377

Kevin E. Noonan, Ph.D.  
Email: noonan@mbhb.com  
USPTO Reg. No. 35,303

Andrea Orth  
Email: orth@mbhb.com  
USPTO Reg. No. 68,000

**McDonnell Boehnen Hulbert & Berghoff LLP**  
300 South Wacker Drive  
Chicago, Illinois 60606  
Phone: (312) 913-0001  
Fax: (312) 913-0002

*Attorneys for Petitioner, Amneal Pharmaceuticals LLC*

## CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. § 42.105, I hereby certify that on August 10, 2016, a true copy of the accompanying PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,338,470 (“the ’470 patent”), including all exhibits, was served via electronic mail (e-mail) to Sara Horton at shorton@jenner.com under 37 C.F.R. §§ 42.6(e)(1) and 42.105(b), as agreed upon by the parties.

Respectfully submitted,  
/Aaron V. Gin/  
Aaron V. Gin, Ph.D.  
gin@mbhb.com  
USPTO Reg. No. 69,068

Paul S. Tully, Ph.D.  
Email: tully@mbhb.com  
USPTO Reg. No. 44,377

Kevin E. Noonan, Ph.D.  
Email: noonan@mbhb.com  
USPTO Reg. No. 35,303

Andrea Orth  
Email: orth@mbhb.com  
USPTO Reg. No. 68,000

**McDonnell Boehnen Hulbert & Berghoff LLP**  
300 South Wacker Drive  
Chicago, Illinois 60606  
Phone: (312) 913-0001  
Fax: (312) 913-0002  
*Attorneys for Petitioner, Amneal Pharmaceuticals LLC*