

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. IPR2016-01579  
Patent 8,455,527

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**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,455,527**

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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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1001	U.S. Patent No. 8,455,527 to Priyanka Roychowdhury & Robert A. Cedergren, issued June 4, 2013.
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. 13/541,524
1009	“Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection”
1010 – 1011	INTENTIONALLY LEFT BLANK
1012	Office Action Response, mailed Mar. 13, 2012, U.S. Application No. 13/343,672
1013	FDA Memorandum by Cynthia G. McCormick, M.D., dated November 30, 1999 (“the McCormick FDA Memorandum”)
1014	INTENTIONALLY LEFT BLANK
1015	Giorgi, I., 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 Product Sheet, Sodium Chloride, June 2009 (“the Lavoisier Documents”)
- 1019 FDA Memorandum by Bob A. Rappaport, M.D., dated November 5, 1999 (“the Rappaport FDA Memorandum”)
- 1020 Gerlach, A., 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)
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- 1026 “Pharmaceutical dosage forms, parenteral medications” edited by Kenneth E. Avis, et al. 2nd Edition, p. 161, 1992
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- 1030 Ponder, The Tonicity-Volume Relations for Systems Containing Human Red Cells and the Chlorides of Monovalent Cations, The Journal of General Physiology, 398 (1949)
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- 1034 Linden, P., et al., Ready-to-use injection preparations versus conventional reconstituted admixtures: economic evaluation in a real-life setting, *PharmacoEconomics*, Vol. 20, No. 8, 529-536 (2002)
- 1035 Cain, *TraumaCare*, July 2007, p. 5
- 1036 US Food and Drug Administration Approved Drug Products with Therapeutic Equivalence Evaluations (“Orange Book”) – Precedex Listing
- 1037 Hospira June 2015 Form 10-Q (Note 24)
- 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,  
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- 1045 – 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. 13/343,672
- 1049 Office Action Response, mailed Sept. 17, 2012, U.S. Application No. 13/541,524

- 1050 INTENTIONALLY LEFT BLANK
- 1051 U.S. Application No. 13/678,260
- 1052 INTENTIONALLY LEFT BLANK
- 1053 U.S. Patent No. 8,338,470 to Priyanka Roychowdhury & Robert A. Cedergren, issued December 25, 2012
- 1054 U.S. Application No. 13/678,148
- 1055 Notice of Allowance, Jan. 11, 2013, U.S. Application No. 13/678,148
- 1056 Notice of Allowance, Oct. 22, 2012, U.S. Application No. 13/541,524
- 1057 Declaration of Huailiang Wu submitted with Office Action Response, mailed Sep. 17, 2012, U.S. Application No. 13/541,524
- 1058 – 1060 INTENTIONALLY LEFT BLANK
- 1061 "Tobias, ""Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology,"" *Pediatr Crit Care Med* 8:2 (2007)"
- 1062 Martin E, Ramsay G, Mantz J, Sum-Ping STJ. The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. *J Intensive Care Med.* 2003, 18:29-41.
- 1063 Precedex 2009 Dosing Guidelines

## **I. INTRODUCTION**

Amneal Pharmaceuticals LLC (“Petitioner”) submits this Petition for *Inter Partes* Review seeking cancellation of claims 1-11 and 13 of U.S. Patent No. 8,455,527 (Ex. 1001; “the ’527 patent”) as unpatentable under 35 U.S.C. §103(a) in view of the prior art.

The claims of the ’527 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 1-11 and 13 of the ’527 patent.

## **II. GROUNDS FOR STANDING**

In accordance with 37 C.F.R. § 42.104(a), Petitioner certifies that the ’527 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR of any of the challenged claims.

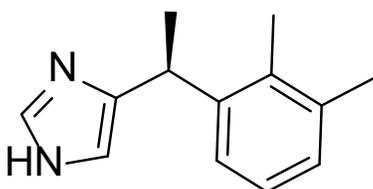
## **III. STATEMENT OF THE PRECISE RELIEF REQUESTED**

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 1-11 and 13 of the ’527 patent as unpatentable under 35 U.S.C. § 103, as set forth herein.

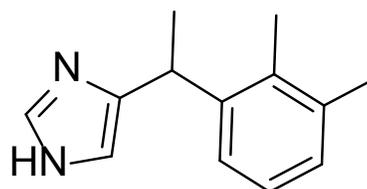
## IV. BACKGROUND

### A. History of Dexmedetomidine

The medical field has recognized dexmedetomidine as a general sedation/analgescic agent since 1988. Ex. 1005, 4,910,214, “the ‘214 patent,” col. 3, ll. 55-59. 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**

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. Administration of dexmedetomidine to a patient parenterally, including 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, U.S. Pat. No. 6,716,867.

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. 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.

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

Parenteral pharmaceutical formulations include a variety of active ingredients, which may be incorporated into liquids. Ex. 1028, pp. 2-4. 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, p. 259. 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, p. 161. 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. 1028. For example, medetomidine, from which dexemedetomidine is the optically active stereoisomer, is known to display deleterious interactions with polyvinylchloride. Ex. 1017, Palmgren. For at least this reason, glass has been traditionally considered “the container material of choice for most sterile pharmaceutical products.” Ex. 1028 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, p. 1469. 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. 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 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 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 '527 Patent**

The specification of the '527 patent relates to compositions and methods comprising premixed dexmedetomidine pharmaceutical compositions useful for sedation. Ex. 1001, col. 2, ll. 3 – 9, col. 10, ll. 1 – 25. The specification discloses various glass (vials, ampoules, syringes), and plastic (polyvinyl chloride (PVC), VisIV™, CR3, and polypropylene) containers. *Id.*, col. 9, ll. 21–29. The specification discloses concentration ranges for the premixed compositions, including between about 0.005 to about 50 µg/mL. *Id.*, col. 7, l. 44 – col. 8, l. 19.

## **E. Prosecution History of the '527 Patent**

The application that issued as the '527 patent was filed on November 15, 2012 as U.S. Application No. 13/678,148 (Ex. 1054, "the '148 application"). The '148 application was a continuation of U.S. Application No. 13/541,524 (Ex. 1048, "the '524 application"), which was filed on July 3, 2012, and issued as U.S. Patent No. 8,338,470 (Ex. 1053; "the '470 patent"). The '524 application, in turn, was a continuation of the U.S. Application No. 13/343,672 (Ex. 1008), now U.S. Patent No. 8,242,158 (Ex. 1047; "the '158 patent").

The '148 applicants submitted a Petition to Make Special under the Accelerated Examination Program, and an Accelerated Examination Support Document asserting novelty and non-obviousness over the prior art, including a reference entitled "Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection" ("the Precedex Draft Label", Ex. 1009). After a December 20, 2012, Examiner-Initiated Interview, applicants filed terminal disclaimers over the '158 patent, the '470 patent, and co-pending U.S. Application No. 13/678,260 (Ex. 1051, "the '260 application"). The Examiner allowed the claims on January 11, 2013. Ex. 1055.

## **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 1-11 and 13 of the '527 patent.

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

Petitioner requests cancellation of claims 1-11 and 13 of the '527 patent 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”) held an advanced degree, such as a Ph.D or M.D., in the field of drug development and formulation, or had significant clinical experience in anesthesia or sedation, including parental administration, as of January 4, 2012. Ex. 1002, ¶23.

### **D. Claim Construction**

For purposes of an *inter partes* review, a claim should be given its broadest reasonable interpretation in light of the patent specification 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 construed by the Board may differ in scope from those construed by a federal court 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. Proxyconn, 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 challenged claim of the ’527 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, ¶20; Ex. 1003, ¶23,24,34. 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, ¶¶28-30; Ex. 1003, ¶34; Ex. 1044. The ’527 patent specification states that,

[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

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

compositions of the present invention are ‘ready to use’ upon removing the compositions from a sealed container or vessel.”<sup>2</sup>

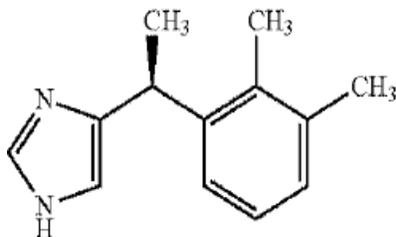
Ex. 1001 at col. 3, ll. 59-65 (*emphasis added*). These two definitions provide the same result: under the broadest reasonable interpretation standard, the term “ready-to-use” should be construed as requiring no further dilution or reconstitution before administration to a patient.

## 2. Dexmedetomidine

Each claim of the ’527 patent likewise requires “dexmedetomidine.” Under the broadest reasonable interpretation, a POSA 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. The specification further defines “dexmedetomidine” as “(S)-4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole,” and provides the following chemical formula:

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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. 52-58.



Ex. 1001, col. 3, ll. 24-50.

## 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.

Ground	35 U.S.C.	Claims	Prior Art References
1	§ 103(a)	1-11, 13	2010 Precedex Label (Ex. 1007) in view of Palmgren (Ex. 1017)
2	§ 103(a)	1-11, 13	US 6,716,867 (Ex. 1006) in view of the 2010 Precedex Label (Ex. 1007) and Palmgren (Ex. 1017)
3	§ 103(a)	1-11, 13	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 where each limitation is found in the prior art, and that the combination of the cited art renders the claims

obvious. Each challenged claim is evaluated based on the scope and contents of the prior art, the differences between the art and the claims, the knowledge of a POSA, and alleged indicia of nonobviousness. *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**

As described in Section IV.E, *supra*, the application that issued as the '527 patent 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 '527 patent is January 4, 2012.

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

The 2010 Precedex Label published in September 2010 and qualifies as prior art against the '527 patent under 35 U.S.C. § 102(b). The 2010 Precedex Label disclosed Precedex (dexmedetomidine hydrochloride) 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) issued on April 6, 2004, and constitutes 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 diluted in 0.9% sodium chloride solution before administration to patients. *Id.* at col. 7, ll. 60-65.

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

Giorgi published in April 2010 and qualifies as prior art against the '527 patent under 35 U.S.C. § 102(b). Giorgi analyzed medication errors in parenteral administration, reporting the frequency and severity of thirty different types errors, and identifying microbial contamination and dilution errors as the most common, and the former most severe, medication errors. 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, published in Spring 2010, qualifies as prior art against the '527 patent under 35 U.S.C. § 102(b), and discusses a Medication Safety Conference of the Anesthesia Patient Safety Foundation. The reference described a “new paradigm” to reduce medication errors 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, published June 29, 2006, qualifies as prior art against the ’527 patent under 35 U.S.C. § 102(b), and disclosed results of experiments on adsorption of drugs (including medetomidine, which inherently includes dexmedetomidine) to 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 ’527 patent under 35 U.S.C. § 102(b), and 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 (20 mL) and glass bottles (50 and 100 mL) were available for use in institutions. *Id.* at p. 2.

**B. Ground 1: Claims 1-11 and 13 of the '527 Patent Are Obvious Over the 2010 Precedex Label in view of Palmgren**

Claims 1-11 and 13 of the '527 patent would have been obvious over the 2010 Precedex Label (Ex. 1007), in view of Palmgren (Ex. 1017). Ex. 1002, ¶¶36,55; Ex. 1003, ¶¶44,62. As described in detail below, a POSA reading those reference would be motivated to combine their teachings to predictably, and with a reasonable expectation of success, achieve a method of administering a solution of Precedex to patients according to the claims 1-11, and 13, of the '527 patent.

**1. Claim 1**

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

a) ***“A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL,”***

The 2010 Precedex Label disclosed a method of providing “sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.” Ex. 1007, Sec 1.1. Precedex® is the trade name for a formulation that includes as an active ingredient “dexmedetomidine hydrochloride”. Ex. 1007, Sec. 11, l. 457.

The 2010 Precedex Label 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. This concentration is encompassed by the *about 0.005 to about 50 µg/mL* concentration range recited in claim 1 of the '527 patent. As noted by Petitioner’s declarant 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, ¶¶49,50,58. The 2010 Precedex Label disclosed that the 4 µg/mL solution of Precedex is ready to use, or “suitable for intravenous infusion following dilution.”

*Id.*

The 2010 Precedex Label also instructs that those solutions are intended for parenteral administration of patients via intravenous infusion. *Id.* ll. 175-184. To the extent that pre-diluted solutions of Precedex® are not explicitly disclosed in the 2010 Precedex Label, it would have been obvious to prepare and administer such solutions at least because Section 2.4 of the 2010 Precedex Label expressly instructs clinicians to do so, and also because it was routine practice in the art for clinicians to administer pre-mixed, parenteral pharmaceutical solutions, including Precedex. Ex. 1002, ¶20.

**b) “wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient”**

The broadest reasonable interpretation of “ready to use” encompasses the diluted form of Precedex® taught by the 2010 Precedex Label. The 2010 Precedex Label directs one of skill in the art to prepare a 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 at Sec. 2.4, ll. 175-184. The 2010 Precedex Label further discloses that the 4 mcg/mL solution of Precedex® is ready to use for parenteral administration to patients. Ex. 1007 at Sec. 2.4, ll. 175-176, and Sec. 11, ll. 457-458 (“Precedex (dexmedetomidine hydrochloride) injection is a sterile, nonpyrogenic solution *suitable for intravenous infusion following dilution.*”) (emphasis added).

Based on the specific instructions provided on the 2010 Precedex Label, it would have been obvious for a POSA to parenterally administer a ready to use solution of dexmedetomidine hydrochloride at a concentration of 4 µg/mL (or any other appropriate concentration). Indeed, the 2010 Precedex Label directs a POSA to do precisely that, and Dr. Cain testifies that it was *in fact* routine practice for clinicians to prepare and parenterally administer such ready to use solutions. Ex. 1002, ¶¶20,30,39,41,49-51; 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). Finally, Dr. Cain also attests that, in some circumstances, the *undiluted*, 100 µg/mL form of Precedex is “ready to use” for parenteral administration to patients, and that he routinely administers that concentration via intramuscular (IM) injection, directly from the glass vial. Ex. 1002, ¶¶45-48.

Accordingly, a POSA reading the 2010 Precedex Label, and versed in routine clinical practice, would have found it obvious to employ ready to use solutions of Precedex for parenteral administration according to claim 1 of the ‘527 patent.

**c) “disposed within a sealed glass container.”**

The 2010 Precedex Label disclosed that Precedex® is a ready to use, sterile solution provided “in a glass vial,” and intended for use in a method of parenteral

administration. Ex. 1007 at Sec. 3, ll. 207-208, and Sec. 16, ll. 698-699. The 2010 Precedex Label includes a dilution step prior to administering to patients. To the extent that the undiluted Precedex® solutions described in the label 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 such containers.

The 2010 Precedex Label instructed clinicians to use glass vials to store and handle Precedex® solutions prior to parenteral administration to patients. Ex. 1007, Sec. 3 and 16. No other type of container is indicated or recommended. Furthermore, the 2010 Precedex Label warned 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, 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 at 370. Additionally, Palmgren noted that medetomidine, a racemic mixture containing two enantiomers (one of which is dexmedetomidine) was “known to interact with PVC and polystyrene plastic,” and examined medetomidine performance in glass and polypropylene as compared to modified

polystyrene. *Id.* at 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 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 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, ¶53.

Armed with this knowledge, a POSA would have a reasoned basis for using a sealed glass container when formulating dexmedetomidine solutions used for parenteral administration to patients. Both Palmgren and the 2010 Precedex Label disclosed the use and suitability of glass containers for that purpose, and also taught potentially adverse interactions of dexmedetomidine with other materials. Ex. 1003, ¶¶51-61. Thus, taken together, the 2010 Precedex Label, alone or in combination with Palmgren, would have provided the POSA with a predictable basis for successfully administering parenteral solutions of Precedex from sealed glass containers claimed in the '527 patent.

## 2. Claims 2-5

Dependent claims 2-5 further recite narrower concentration ranges of the dexmedetomidine or pharmaceutically acceptable salt thereof. 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  $\mu\text{g}/\text{mL}$ ,” and claim 5 recites a concentration of “about 4  $\mu\text{g}/\text{mL}$ .”

The Precedex 2010 Label directed a POSA to prepare a 4 mcg/mL [i.e., 4  $\mu\text{g}/\text{mL}$ ] solution of Precedex® for administration to patients, a concentration encompassed by the ranges recited in claims 2 -5 of the '527 patent. Ex. 1007, Sec. 2.4. 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, ¶¶49,50,58), 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, e.g., via intravenous infusion, because the 2010 Precedex Label directed a POSA to do so. Ex. 1007, Sec. 11, ll. 457-458. Accordingly, the 2010 Precedex Label disclosed all of the added features of claims 2-5. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

### 3. **Claims 6 and 7**

Dependent claim 6 recites that “the composition is administered perioperatively.” Dependent claim 7 recites that “the composition is administered before or after surgery.”

In this respect, the 2010 Precedex Label disclosed in Section 1.2 that “Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.” Exhibit 1007, Sec. 1.2 (emphasis added). The POSA would understand that perioperative administration recited in claim 6 comprises administering Precedex® before, during, or after surgery. Ex. 1002, ¶62. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 6 and claim 7. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

### 4. **Claim 8**

Dependent claim 8 recites that “the composition is administered to the patient in an intensive care unit.”

In numerous places, the 2010 Precedex Label disclosed that Precedex® is indicated for treatment “in an intensive care setting.” *See, e.g.*, Ex. 1007, 1.1, ll. 144-149. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 8, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

5. **Claim 9**

Dependent claim 9 depends from claim 1, and recites that “the patient is non-ventilated or intubated.”

The 2010 Precedex Label disclosed that “Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and postextubation.” Ex. 1007, 1.1, ll. 148,149. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 9, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

6. **Claim 10**

Dependent claim 10 recites that “the patient is critically ill.”

The 2010 Precedex Label disclosed that Precedex is used in “an intensive care setting.” Regardless of the meaning of “critically ill”, a person having ordinary skill in the art would understand that it encompasses the type of illness that may be treated in an intensive care setting. Ex. 1002, ¶63. Further, it was known in the art at the time of filing that “[d]exmedetomidine is a sedative with a unique mechanism of action that became available in the United States in 1999 for sedation of critically ill patients.” Ex. 1020 at 2 (emphasis added). Accordingly, the 2010 Precedex Label, by itself or with the knowledge in the art as illustrated in Gerlach, also disclosed all of the added features of claim 10. Thus, the added

limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

**7. Claim 11**

Dependent claim 11 recites that “the composition is administered by intravenous infusion.”

The 2010 Precedex Label disclosed in multiple sections, that “Precedex is indicated for short-term intravenous sedation.” Ex. 1007 at, *e.g.*, Sec. 17. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 11, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

**8. Claim 13**

Dependent claim 13 recites that “the composition is administered as an adjunct to an anesthetic.”

The 2010 Precedex Label directed that Precedex® may be “co-administered” with “other concomitant anesthetics.” Ex. 1007, Sec. 2.3.. Accordingly, the 2010 Precedex Label also disclosed all of the added features of claim 13, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label and Palmgren.

## 9. Claim Chart

Claim Language	The Precedex 2010 Label and Palmgren Disclosures
<b>Claim 1</b>	
A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL	2010 Precedex Label, Ex. 1007, Sec 1.1; Sec. 2.4, ll. 175-184; Sec. 3, ll. 207-208; Sec. 11, line 457.
wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient	2010 Precedex Label, Ex. 1007 at Sec. 2.4, ll. 175-184; Sec. 11, ll. 457-458.
disposed within a sealed glass container.	2010 Precedex Label, Ex. 1007, Sec. 2.6, ll. 203-206; Sec. 3, ll. 207-208; Sec. 16, ll. 698-699.  Palmgren, Ex. 1017, p. 370, ¶¶3-4; p. 374, right col., ¶2; p. 374, Table 4; p. 374-376.
<b>Claim 2</b>	
The method of claim 1,	See claim 1.

Claim Language	The Precedex 2010 Label and Palmgren Disclosures
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 µg/mL.	2010 Precedex Label, Ex. 1007, Sec. 2.4; Sec. 11.
<b>Claim 3</b>	
The method of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 µg/mL.	2010 Precedex Label, Ex. 1007, Sec. 11.
<b>Claim 4</b>	
The method 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.	2010 Precedex Label, Ex. 1007, Sec. 11.
<b>Claim 5</b>	
The method of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt	2010 Precedex Label, Ex. 1007, Sec. 11.

<b>Claim Language</b>	<b>The Precedex 2010 Label and Palmgren Disclosures</b>
thereof is at a concentration of about 4 µg/mL.	
<b>Claim 6</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered perioperatively.	2010 Precedex Label, Ex. 1007, Sec. 1.2.
<b>Claim 7</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered before or after surgery.	2010 Precedex Label, Ex. 1007, Sec. 1.2.
<b>Claim 8</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered to the patient in an intensive care unit.	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 144-149.
<b>Claim 9</b>	
The method of claim 1,	See claim 1.
wherein the patient is non-ventilated or intubated.	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148,149.
<b>Claim 10</b>	
The method of claim 1,	See claim 1.
wherein the patient is critically ill.	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148,149.
<b>Claim 11</b>	

Claim Language	The Precedex 2010 Label and Palmgren Disclosures
The method of claim 1,	See claim 1.
wherein the composition is administered by an intravenous infusion.	2010 Precedex Label, Ex. 1007, Sec. 17.
<b>Claim 13</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered as an adjunct to an anesthetic.	2010 Precedex Label, Ex. 1007, Sec. 2.3.

**C. Ground 2: Claims 1-11 and 13 of the '527 Patent Are Obvious Over U.S. Patent No. 6,716,867 in view of the 2010 Precedex Label and Palmgren.**

Claims 1-11, and 13, of the '527 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, ¶¶67,73. A POSA would have had ample reason to combine these references to develop a method of parenteral administration of Precedex® because each is directed to “ready to use” dexmedetomidine compositions for that purpose. Ex. 1002, ¶¶82,87-89,91; Ex. 1003, ¶¶68,71. A POSA would have had a reasonable expectation of success combining each reference because together they yield nothing more than predictable results,

namely, a solution of Precedex® in a glass container, and at a suitable concentration for parenteral administration to patients.

The relevance of the '867 patent and its applicability to claims 1-11, and 13, of the '527 patent under §103(a) is apparent from Patentee's own actions and statements. On its face, the '867 patent states that it provides "a method of sedating a patient while in the ICU that comprises administering dexmedetomidine or a pharmaceutically acceptable salt thereof." *Id.* at col. 3, ll. 38-42. Furthermore, the Patentee listed the '867 patent in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") as allegedly covering the premix, ready to use dexmedetomidine 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, and by extension admits that the '867 patent disclosed methods of administering that solution to patients.

The Patentee has also made public statements admitting that the '867 patent covers the ready-to-use formulations, and by extension admits that it discloses administering such formulations to patients. In a 2015 quarterly report to the Securities and Exchange Commission, Hospira, stated that, Eurohealth International Sarl had filed an ANDA with the FDA "seeking approval to market a generic version of Hospira's premix version of Precedex." Ex. 1037, p. 28 (Note 24). 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 states 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 against another generic company 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 method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL, wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient disposed within a sealed glass container.*

**a) *A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL,***

The '867 patent disclosed “a method of sedating a patient while in the ICU that comprises administering dexmedetomidine or a pharmaceutically acceptable salt thereof.” Ex. 1006, col. 3, ll. 38-42. The '867 patent further 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.” *Id.*, col. 1, ll. 12-14 and 28-31. 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 provide 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. 1002, ¶92; 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 instructions in the 2010 Precedex Label directing a POSA to prepare a concentration of 4 µg/mL dexmedetomidine for parenteral administration via intravenous infusion, a POSA would have similarly recognized that the disclosed dosage range within the '867 patent is ready to administer to a patient via intravenous (parenteral) infusion with or without dilution. Ex. 1002, ¶87-89,91,92. Thus, the '867 patent disclosed methods of administering dexmedetomidine

solutions at the concentrations recited in claim 1 of the '527 patent. Ex. 1002, ¶92. Furthermore, it would have been obvious to a POSA to combine the teachings of the '867 patent and the 2010 Precedex Label to develop the method of parenteral administration dexmedetomidine recited in claim 1 of the '527 patent because they both direct the POSA how to do so.

***b) wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient,***

In view of the specific instruction in the 2010 Precedex Label to prepare a concentration of a ready to use 4 µg/mL dexmedetomidine for parenteral administration via intravenous infusion, 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, ¶87-89,91,92. The broadest reasonable interpretation of “ready-to-use” encompasses diluted formulations of dexmedetomidine. Ex. 1002, ¶30,31; Ex. 1003, ¶35. The '867 patent disclosed diluted formulations of dexmedetomidine. Ex. 1002, ¶87-89; thus, the '867 patent disclosed “ready-to-use” formulations of dexmedetomidine. Ex. 1002, ¶91. It would have been obvious to a POSA to combine the teachings of the '867 patent and the 2010 Precedex Label to develop and administer the “ready to use” pharmaceutical compositions recited in claim 1 of the '527 patent.

The ready to use dexmedetomidine or pharmaceutically acceptable salt thereof disclosed in the '867 patent is also administered intravenously (a form of parenteral administration). Ex. 1006, col. 5, l. 7. The 2010 Precedex Label discloses that Precedex® is supplied as a liquid, in a glass vial at a concentration of 200 mcg/2 mL (100 mcg/mL). Ex. 1007, Sec. 3, ll. 207-208. The 2010 Precedex Label further discloses that the 0.4% solution of Precedex® is ready to use for administration to patients. *Id.* Sec. 2.4. The 2010 Precedex Label also instructs the parenteral use of Precedex® as a liquid formulation and for sedation – just as disclosed in the '867 patent. For example, Section 11 of the 2010 Precedex Label discloses that “Precedex (dexmedetomidine hydrochloride) injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution.” Ex. 1007, Sec. 11, ll. 457-458. Similarly, Section 1.1 states that “Precedex has been continuously infused” in patients, and Section 2.5 refers to the “Precedex infusion” through “intravenous catheter.” *Id.* Sec. 1.1, ll. 148-149; Sec. 2.5, ll. 184-188.

Accordingly, it would have been obvious to the POSA reading the '867 patent to combine its teachings with those of the 2010 Precedex Label, thereby arriving at a method of parenterally administering a ready to use liquid dexmedetomidine pharmaceutical composition to a patient, according to the express instructions in each reference.

c) *disposed within a sealed glass container.*

The '867 patent does not disclose the container in which dexmedetomidine is provided. However, as exhibited by the 2010 Precedex Label, it was well known in the art that dexmedetomidine was preferably 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 Precedex 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. 1006, Sec. 2.6, ll, 203-206. Components having synthetic or coated natural rubber gaskets were therefore recommended for use during administration. *Id.* As disclosed in Palmgren, it was well known in the art at the time of filing that certain drugs, including medetomidine, interact with plastics found in infusion bags (e.g., PVC) and intravenous tubing, which can lead to drug loss and treatment failure. Ex. 1003, ¶¶52,53,56; Ex. 1017 at 370. Palmgren, noting 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 expect that dexmedetomidine would have the same interactions with various container materials as medetomidine.. Ex. 1003, ¶53.

In view of this prior art, it would have been obvious to a POSA to administer the Precedex® solutions disclosed in the 2010 Precedex Label from a sealed glass container 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 disclosed in the Palmgren reference (Ex. 1017).

## 2. **Claims 2-5**

Dependent claims 2-5 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;” and claim 5 recites a concentration of “about 4 µg/mL.”

The ’867 patent disclosed a range of concentrations of ready-to-use dexmedetomidine, and thus the ranges recited in dependent claims 2-5 of the ’527

patent add nothing to overcome the obviousness of claim 1 over the '867 patent (Ex. 1006), along or in view of the 2010 Precedex Label (Ex. 1007). 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. 1002, ¶92; Ex. 1006, col. 5, ll. 21-28. Similarly, 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.

Thus, administering dexmedetomidine to a patient at the dosing recited in claims 2-5 was recognized in the art, and 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. 1002, ¶91,92. The added limitations for claims 2-5 of the '527 patent do not overcome the obviousness established for claim 1 over the '867 patent and the 2010 Precedex Label in view of the Palmgren reference (Ex. 1017).

### 3. **Claims 6 and 7**

Dependent claims 6 recites that “the composition is administered perioperatively.” Dependent claim 7 recites that “the composition is administered before or after surgery.”

The '867 Patent disclosed the use of dexmedetomidine both before and after surgery. See, e.g., the Examples of the '867 Patent. As Dr. Cain explains, at least Example 7 shows the administration perioperatively, since the patient was returned to surgery following administration of dexmedetomidine. Ex. 2002, ¶97. In addition, the 2010 Precedex Label disclosed that “Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.” Ex. 1007, Sec. 1.2. The POSA would understand that perioperative administration recited in claim 6 comprises administering Precedex before, during, or after surgery. Ex. 1002, ¶62,93.

Accordingly, the '867 patent and the 2010 Precedex Label disclosed the limitations recited in dependent claims 6 and claim 7 of the '527 patent. Therefore, the added limitations do not overcome the obviousness established for claim 1 over the '867 in view of the 2010 Precedex Label.

### 4. **Claim 8**

Dependent claim 8 recites that “the composition is administered to the patient in an intensive care unit.”

The '867 Patent “relates to the use of dexmedetomidine or a pharmaceutically acceptable salt thereof in intensive care unit (ICU) sedation” and also “relates to the 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. Furthermore, in numerous places, the 2010 Precedex Label discloses that Precedex® is indicated for treatment “in an intensive care setting.” *See, e.g.*, Ex. 1007, 1.1, ll. 144-149. Accordingly, the 2010 Precedex Label also disclosed all of the features of claim 8, and the added limitations do not overcome the obviousness established for claim 1 over the '867 patent in view of the 2010 Precedex label.

#### 5. **Claim 9**

Dependent claim 9 recites that “the patient is non-ventilated or intubated.”

The '867 patent disclosed that dexmedetomidine may be used “for non-ventilated, critically ill patients.” Ex. 1006, col. 4, ll. 63-64. The Examples of the '867 patent disclosed patients to whom dexmedetomidine was administered who were mechanically ventilated or intubated. *See, e.g.*, Ex. 1006, Example 1, col. 5, ll. 49-53; Example 2, col. 6, ll. 45-48. In addition, the 2010 Precedex Label disclosed that “Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation.” Ex. 1007, Sec. 1.1, ll. 148, 149.

Accordingly, the '867 patent and 2010 Precedex Label also disclosed all of the features of claim 9, and the added limitations do not overcome the obviousness established for claim 1 over those references.

## 6. **Claim 10**

Dependent claim 10 recites that “the patient is critically ill.”

The '867 Patent disclosed that dexmedetomidine may be used “for non-ventilated, critically ill patients.” Ex. 1006, col. 4, ll. 63-64. In addition, the 2010 Precedex Label discloses that Precedex® is used in “an intensive care setting.” Ex. 1007, Sec.1.1. Regardless of the meaning of “critically ill”, a person having ordinary skill in the art would understand that it encompasses the type of illness that may be treated in an intensive care setting. Ex. 1002, ¶72,95. Further, it was known in the art at the time of filing that “[d]exmedetomidine is a sedative with a unique mechanism of action that became available in the United States in 1999 for sedation of critically ill patients.” Ex. 1020, Gerlach at 2 (emphasis added).

Accordingly, the '867 patent and 2010 Precedex Label, alone or with the knowledge in the art illustrated in Gerlach, also disclose all of the features of claim 10. Thus, the added limitations do not overcome the obviousness established for claim 1 over the '867 patent in view of the 2010 Precedex label.

## 7. Claim 11

Dependent claim 11 recites that “the composition is administered by intravenous infusion.”

The dexmedetomidine or pharmaceutically acceptable salt thereof disclosed in the '867 patent is administered intravenously. Ex. 1006, *see, e.g.*, col. 5, l. 7. In addition, the 2010 Precedex Label disclosed in multiple sections that “Precedex is indicated for short-term intravenous sedation.” Ex. 1007, *see, e.g.*, Sec. 17. Accordingly, the '867 patent and 2010 Precedex Label disclosed all of the features of claim 11, and the added limitations do not overcome the obviousness established for claim 1 in view of those references.

## 8. Claim 13

Dependent claim 13 recites that “the composition is administered as an adjunct to an anesthetic.”

The '867 patent disclosed the administration of dexmedetomidine as an adjunct to an anesthetic, such as propofol. Ex. 1006, *see, e.g.*, Example 3, case 8, col. 11, ll. 6-10: “[a] dexmedetomidine loading dose (0.4  $\mu\text{g}/\text{kg}/\text{h}$ ) was administered with propofol”. Propofol is identified in the '867 patent as an anesthetic. Ex. 1006, col. 1, ln. 51. As noted in Section 2.3 of the 2010 Precedex 2010 Label, Precedex® may be “co-administered” with “other concomitant anesthetics.” Ex. 1007, Sec. 2.3.

Accordingly, the '867 patent and 2010 Precedex Label disclose all of features of claim 13, and the added limitations do not overcome the obviousness established for claim 1 over the '867 patent and 2010 Precedex Label.

## 9. Claim Chart

Claim Language	U.S. Patent No. 6,716,867, the 2010 Precedex Label, and Palmgren
<b>Claim 1</b>	
A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL	U.S. 6,716,867, Ex. 1006, col. 1, ll. 12-14 and 28-31; col. 3, ll. 38-42; col. 5, ll. 7, 21-28, and 53-58.  2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4;
wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient	U.S. 6,716,867, Ex. 1006, col. 5, line 7.  2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148-149; Sec. 2.5, ll. 184-188; Sec. 3, ll. 207-208; Sec. 11, ll. 457-458.
disposed within a sealed glass	2010 Precedex Label, Ex. 1007, Sec. 2.6, ll. 203-206; Sec. 3, ll. 207-208; Sec. 16, ll. 698-699.

<b>Claim Language</b>	<b>U.S. Patent No. 6,716,867, the 2010 Precedex Label, and Palmgren</b>
container.	Palmgren, Ex. 1017, p. 370, ¶¶3-4; p. 374, right col., ¶2; p. 374, Table 4; p. 374-376.
<b>Claim 2</b>	
The method 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.	U.S. 6,716,867, Ex. 1006, col. 5, ll. 21-28; 2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 3</b>	
The method of claim 1,	See claim 1.
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, Ex. 1006, col. 5, ll. 21-28; 2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 4</b>	
The method 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, Ex. 1006, col. 5, ll. 21-28; 2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 5</b>	

<b>Claim Language</b>	<b>U.S. Patent No. 6,716,867, the 2010 Precedex Label, and Palmgren</b>
The method of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 µg/mL.	U.S. 6,716,867, Ex. 1006, col. 5, ll. 21-28; 2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 6</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered perioperatively.	U.S. 6,716,867, Ex. 1006, Example 3, case 7, col. 10, l. 57. 2010 Precedex Label, Ex. 1007, Sec. 1.2.
<b>Claim 7</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered before or after surgery.	U.S. 6,716,867, Ex. 1006, Example 3, case 7, col. 10, l. 57. 2010 Precedex Label, Ex. 1007, Sec. 1.2.
<b>Claim 8</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered to the patient in an intensive care unit.	U.S. 6,716,867, Ex. 1006, col. 1, ll. 12-14 and 28-31. 2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 144-149.
<b>Claim 9</b>	
The method of claim 1,	See claim 1.
wherein the patient is non-ventilated or intubated.	U.S. 6,716,867, Ex. 1006, col. 4, ll. 63-64; Example 1, col. 5, ll. 49-53; Example 2, col. 6, ll. 45-48.

<b>Claim Language</b>	<b>U.S. Patent No. 6,716,867, the 2010 Precedex Label, and Palmgren</b>
	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148,149.
<b>Claim 10</b>	
The method of claim 1,	See claim 1.
wherein the patient is critically ill.	U.S. 6,716,867, Ex. 1006, col. 4, ll. 63-64. 2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148,149.
<b>Claim 11</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered by an intravenous infusion.	U.S. 6,716,867, Ex. 1006, <i>see, e.g.</i> , col. 5, line 7. 2010 Precedex Label, Ex. 1007, Sec. 17.
<b>Claim 13</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered as an adjunct to an anesthetic.	U.S. 6,716,867, Ex. 1006, <i>see, e.g.</i> , Example 3, case 8, col. 11, ll. 6-10, and col. 1, ln. 51. 2010 Precedex Label, Ex. 1007, Sec. 2.3.

**D. Ground 3: Claims 1-11 and 13 of the '527 Patent Would Have Been Obvious Over the 2010 Precedex Label in view of Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents.**

Claims 1-11 and 13 of the '527 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. 1002, ¶¶99-102). A POSA would have had ample reason to combine these references to

develop a method of parenteral administration of Precedex® because each is directed to preparing “ready to use” dexmedetomidine compositions for that purpose. Ex. 1002, ¶102; Ex. 1003, ¶¶75-80. A POSA would have had a reasonable expectation of success combining each reference because together they yield nothing more than predictable results, namely, a solution of Precedex in a glass container, and at a suitable concentration for parenteral administration to patients. *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, ¶102; Ex. 1003, ¶¶75-80.

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, 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,

¶¶46-48. 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, ¶¶39,49-52; 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).

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, ¶¶53-57.

1. **Claim 1**

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

This Ground 3 adds the prior art references Giorgi, Eichhorn, and the Levoisier Documents to Petitioner's *prima facie* obviousness determination. Individually, and in combination, these additional references establish that one of skill in the art would have been motivated to administer ready to use, or premixed, diluted solutions of Precedex at the 4 mcg/mL concentration from glass containers as instructed in the 2010 Precedex Label. Ex. 1002, ¶¶99-102; Ex. 1003, ¶¶75-80.

These references establish that, at the time of filing, those of skill in the art recognized, and indeed had been advocating for, additional standardization of drug administration methods. Ex. 1002, ¶102; Ex. 1003, ¶¶76-79. Thus, a POSA would have been motivated to parenterally administer a ready to use, liquid pharmaceutical composition as disclosed in claims 1-11, and 13, 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.* at 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. 1003, ¶77; 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 (parenteral) 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. 1002, ¶39,40; Ex. 1003, ¶79. A POSA preparing and administering the diluted Precedex® 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® to 48 mL of a 0.9% sodium chloride solution, which itself was already in a sealed glass container. Ex. 1003, ¶47,51,52, 79. As a result, a POSA, following the directions found in the 2010 Precedex

Label would administer a ready to use 4 µg/mL solution of Precedex® from a sealed glass container. Ex. 1003, ¶¶76-79.

Accordingly, a POSA reading these references would find ample motivation to use pre-formulated, diluted solutions of Precedex® in a sealed glass container for parenteral administration to patients, as disclosed in the 2010 Precedex Label. Palmgren disclosed the advantages of resistance to drug loss by using sealed glass containers (Ex. 1017, pp. 374-376); Giorgi disclosed the benefits of avoiding microbial contamination by using pre-prepared medications packaged in sterile, sealed glass containers (Ex. 1015, abstract); 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); and the Lavoisier Documents disclosed the availability and routine use of already-available glass bottles for this purpose (Ex. 1018, pp. 1-2). Ex. 1003, ¶¶76-79.. These references illustrate that parenteral administration of drug products such as dexmedetomidine was known in the art and provided a ready solution for administering appropriately diluted dexmedetomidine solution as recited in the claims of the '527 patent. A POSA also would have had a reasonable expectation of success 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 2-5

Dependent claims 2-5 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  $\mu\text{g}/\text{mL}$ ,” and claim 5 recites a concentration of “about 4  $\mu\text{g}/\text{mL}$ .”

As noted with respect to claim 1 in the preceding sections, the 2010 Precedex Label disclosed “a required concentration (4 mcg/mL [i.e., 4  $\mu\text{g}/\text{mL}$ ])” of Precedex® in 0.9% sodium chloride that is ready to use for administration to patients. Ex. 1007, Sec. 2.4. This concentration is encompassed by each of the concentration ranges recited in claims 205 of the ’527 patent. As noted by Petitioner’s declarant 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, ¶¶20,30,39,41,49-51; Ex. 1035. The 2010 Precedex Label disclosed that the 4  $\mu\text{g}/\text{mL}$  solution of Precedex is ready to use, or “suitable for intravenous infusion following dilution.” *Id.* Moreover, the Label instructs that those solutions are intended for parenteral administration of patients via intravenous infusion. *Id.* ll. 175-184. To the extent that pre-diluted solutions of Precedex® are not explicitly disclosed in the 2010 Precedex Label, it would have been obvious to prepare and administer such

solutions at least because Section 2.4 of the 2010 Precedex Label expressly instructs clinicians to do so, and also because it was routine practice in the art for clinicians to administer pre-mixed, parenteral pharmaceutical solutions at a concentration necessary to treat a given patient. Ex. 1002, ¶¶49-51. Accordingly, the 2010 Precedex Label also disclosed all of the features of claims 2-5, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018).

### 3. **Claims 6 and 7**

Dependent claim 6 recites that “the composition is administered perioperatively.” Dependent claim 7 recites that “the composition is administered before or after surgery.”

In this respect, the 2010 Precedex Label disclosed that “Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.” Ex. 1007, Sec. 1.2. The POSA would understand that perioperative administration recited in claim 6 comprises administering Precedex before, during, or after surgery. Ex. 1002, ¶¶62,93. Accordingly, the 2010 Precedex Label also disclosed all of the features of claim 6 and claim 7. Thus, the added limitations do not overcome the obviousness established for claim 1 over the

Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018).

4. **Claim 8**

Dependent claim 8 recites that “the composition is administered to the patient in an intensive care unit.”

In numerous places, the 2010 Precedex Label disclosed that Precedex® is indicated for treatment “in an intensive care setting.” *See, e.g.*, Ex. 1007, 1.1, ll. 144-149. Accordingly, the 2010 Precedex Label also disclosed all of the features of claim 8, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018).

5. **Claim 9**

Dependent claim 9 recites that “the patient is non-ventilated or intubated.”

The 2010 Precedex Label disclosed that “Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and postextubation.” Ex. 1007, 1.1, ll. 148,149. Accordingly, the 2010 Precedex Label also disclosed all of the features of claim 9, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018)..

## 6. Claim 10

Dependent claim 10 recites that “the patient is critically ill.”

The 2010 Precedex Label disclosed that Precedex® is used in “an intensive care setting.” Ex. 1007, Sec.1.1. Regardless of the meaning of “critically ill,” a person having ordinary skill in the art would understand that it encompasses the type of illness that may be treated in an intensive care setting. Ex. 1002, ¶72,95. Further, it was known in the art at the time of filing that “[d]exmedetomidine is a sedative with a unique mechanism of action that became available in the United States in 1999 for sedation of critically ill patients.” Ex. 1020, Gerlach at 2 (emphasis added). Accordingly, the 2010 Precedex Label, by itself or in combination with Gerlach, also disclosed all of the features of claim 10. Thus, the added limitations do not overcome the obviousness established for claim 1 over the Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018).

## 7. Claim 11

Dependent claim 11 recites that “the composition is administered by intravenous infusion.”

The 2010 Precedex Label disclosed that “Precedex is indicated for short-term intravenous sedation.” Ex. 1007, Sec. 17. Accordingly, the 2010 Precedex Label also disclosed all of the features of claim 11, and the added limitations do

not overcome the obviousness established for claim 1 over the Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018).

**8. Claim 13**

Dependent claim 13 recites that “the composition is administered as an adjunct to an anesthetic.”

The 2010 Precedex Label disclosed that Precedex® may be “co-administered” with “other concomitant anesthetics.” Accordingly, the 2010 Precedex Label also disclosed all of the features of claim 13, and the added limitations do not overcome the obviousness established for claim 1 over the Precedex label in view of Giorgi (Ex. 1015), Eichhorn (Ex. 1016), Palmgren (Ex. 1017), and the Lavoisier Documents (Ex. 1018).

**9. Claim Chart**

<b>Claim Language</b>	<b>The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents</b>
<b>Claim 1</b>	
A method of providing sedation to a patient in need thereof, the method comprising administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a	2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4;

<b>Claim Language</b>	<b>The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents</b>
concentration of about 0.005 to about 50 µg/MI	
wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148-149; Sec. 2.5, ll. 184-188; Sec. 3, ll. 207-208; Sec. 11, ll. 457-458.
disposed within a sealed glass container.	2010 Precedex Label, Ex. 1007, Sec. 2.6, ll. 203-206; Sec. 3, ll. 207-208; Sec. 16, ll. 698-699.  Palmgren, Ex. 1017, p. 370; 374-376.  Giorgi, Ex. 1015, p. 176.  Eichhorn, Ex. 1016, p. 1; p. 5.  Lavoisier Documents, Ex. 1018, pp. 1-2.
<b>Claim 2</b>	
The method 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.	2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 3</b>	
The method of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 µg/mL.	2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 4</b>	
The method of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a	2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.

<b>Claim Language</b>	<b>The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents</b>
concentration of about 1 to about 7 µg/mL.	
<b>Claim 5</b>	
The method of claim 1,	See claim 1.
wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 µg/mL.	2010 Precedex Label, Ex. 1007, Sec. 2.2; Sec. 2.4; Sec. 11.
<b>Claim 6</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered perioperatively.	2010 Precedex Label, Ex. 1007, Sec. 1.2.
<b>Claim 7</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered before or after surgery.	2010 Precedex Label, Ex. 1007, Sec. 1.2.
<b>Claim 8</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered to the patient in an intensive care unit.	2010 Precedex Label, Ex. 1007, <i>e.g.</i> , Sec. 1.1, ll. 144-149; Sec. 5.1; Sec. 5.5; Sec 6.1.
<b>Claim 9</b>	
The method of claim 1,	See claim 1.
wherein the patient is non-ventilated or intubated.	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148,149.
<b>Claim 10</b>	
The method of claim 1,	See claim 1.
wherein the patient is critically ill.	2010 Precedex Label, Ex. 1007, Sec. 1.1, ll. 148,149.
<b>Claim 11</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered by an intravenous infusion.	2010 Precedex Label, Ex. 1007, Sec. 17.

Claim Language	The Precedex 2010 Label, Giorgi, Eichhorn, Palmgren, and the Lavoisier Documents
<b>Claim 13</b>	
The method of claim 1,	See claim 1.
wherein the composition is administered as an adjunct to an anesthetic.	2010 Precedex Label, Ex. 1007, Sec. 2.3.

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

In determining patentability of the '527 claims, the Examiner considered the arguments and secondary considerations submitted in the related '524 application, Ex. 1056, p. 2. The Examiner cited to Example 1 and a Declaration of Huailiang Wu pursuant to 37 C.F.R. § 1.132 (“the Wu Declaration”) in his reasons for allowance *Id.*

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 citing

increased stability in glass. Ex. 1049, p. 6-7; Ex. 1001, col. 13, l. 21 – col. 14, l. 59, col. 15, l. 25 – col. 16, l. 23.

Applicants also submitted cumulative evidence in 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. 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. 7-10.

These results would have been entirely expected and fail to provide any “surprising” advantages not already known in the prior art. Ex. 1003, ¶61. 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 at Sec. 2.6, ll. 203-206. Palmgren taught that medetomidine 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, ¶¶53,56. A POSA would expect 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, because dexmedetomidine is simply the S-enantiomer of the racemic medetomidine. Ex. 1003, ¶¶53, 61

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, ¶¶51,53. 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, for example, in a PVC container. Ex. 1003, ¶¶51- 61. 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. Applicants state 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. *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. 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, ¶¶51- 61.

In the reasons for Allowance, the Examiner emphasized that Precedex® concentrate disclosed in the Precedex Label “once diluted for use it is not suitable for storage.” Ex. 1056, p. 2 (emphasis in original). While the examiner did not provide basis for this statement, such conclusion also appears to be based on

applicants assertions during the prosecution of the '524 application. During the prosecution of the '524 application, applicants 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. 1012, pp. 8-9. 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*.

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 '158 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, ¶61. There is evidence that a POSA would have expected dexmedetomidine to be stable, even in a diluted form, when stored in a glass container. *Id.* The prior art recognized glass, an inert substance, to be the “gold standard” for drug packaging in the pharmaceutical industry. Ex. 1003, ¶59. 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, ¶¶51- 61. These results could not be considered surprising in view of this prior art.

More importantly, the McCormick FDA Memorandum also provides that Precedex® concentrate disclosed in the Precedex Label is stable for up to 2-years under the International Council for Harmonisation (ICH) guidelines accepted by the FDA:

The drug product is prepared using standard methods, has undergone stability testing (undiluted) *under ICH storage conditions generating data to support a 2-year shelf life*, and has been shown to be stable in light.

Sterility of the drug product is achieved through aseptic fill and terminal sterilization by autoclave. The process and data have been reviewed by microbiology and found to be acceptable.

Ex. 1013, p. 8.

The secondary considerations asserted by applicants during prosecution of the '524 application, and relied on by the Examiner during the prosecution of the '527 patent, are not sufficient to rebut the obviousness of claims 1-11 and 13 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 µg/mL stored in a glass container would have been expected to be more stable than the same composition stored in PVC container. Ex. 1003, ¶¶51- 61. Applicants failed to offer any evidence to support assertions that diluted dexmedetomidine solution (for example, at 4 µg/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.

## 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 '527 patent for which Petitioner seeks review. Accordingly, Petitioner requests that the USPTO grant this Petition, initiate *inter partes* review of Claims 1-11 and 13 of the '527 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 '527 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. 8,338,470, 8,242,158, and 8,648,106.

**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):

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**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,  
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## 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. 8,455,527 (“the ’527 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,  
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