EXHIBIT 1

FDA DECISION LETTER (AUG. 18, 2014)
DOCKET NO. FDA-2014-N-0087

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Docket No. FDA-2014-N-0087

SENT VIA EMAIL

Dear Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant:

On January 15, 2014, the U.S. Food and Drug Administration (FDA or the agency) established a public docket to solicit comment on certain legal and regulatory issues that pertain to Precedex (dexmedetomidine hydrochloride injection, 100 mcg (base)/mL packaged in 200 mcg (base)/2 mL single-dose vials). As described in detail below, FDA also sent a letter describing the issue to Hospira, Inc. (Hospira), the holder of New Drug Application (NDA) No. 21-038 for Precedex and to all applicants that submitted Abbreviated New Drug Applications (ANDAs) to FDA referencing Precedex. The letter also was posted on the website for FDA's public dockets at http://www.regulations.gov.

Today's letter reflects FDA's determinations with respect to permissibility of labeling carve outs for ANDAs referencing Precedex. For the reasons set forth below, FDA concludes that regardless of whether the original use code or the revised use code applies, the agency can approve an ANDA that submits a "section viii" statement and omits labeling that discloses the protected use (as identified by Hospira). FDA further concludes that such omissions do not render the drug less safe or effective for the remaining non-protected conditions of use.

I. FACTUAL BACKGROUND

In the letters sent to NDA holder Hospira and ANDA applicants and posted to the docket, FDA noted the following:

Precedex is approved for the following indications:

1. Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours.

2. Sedation of non-intubated patients prior to and/or during surgical and other procedures.

Hospira has, over time, listed several patents covering the Precedex product referenced above. Only a method-of-use patent remains: U.S. Patent No. 6,716,867 (the '867 patent), which expires (including a pediatric exclusivity period) on October 1, 2019.[1]

[1] U.S. Patent No. 4,910,214 expired on July 15, 2013, and an associated pediatric exclusivity period expired on January 15, 2014.

Hospira originally listed the '867 patent in May 2004 with the following use code (U-572): "Intensive care unit sedation." In November 2008, Hospira listed U.S. Patent No. 5,344,840 (the '840 patent) with the following use code (U-912) in the Orange Book: "Sedation of non-intubated patients prior to and/or during surgical and other procedures." That patent expired on September 6, 2011. On January 6, 2014, Hospira sought to amend the '867 patent use code to "intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures." FDA, in accordance with the ministerial manner in which it implements patent use code information, changed the use code on January 8, 2014.

FDA sought comments on the following issues:

1. Does the breadth of the new use code description for the '867 patent foreclose ANDA applicants from gaining approval for any of the approved indications (or for any subset of those indications) before the '867 patent expires? For example, would it be permissible as a scientific, regulatory, and legal matter for an ANDA applicant to submit a statement under 21 U.S.C. §355(j)(2)(A)(viii) and a corresponding carve out that results in an approval for a subset of the second approved indication, *i.e.*, an approval explicitly limited to procedures outside of an intensive care setting? In this context, is it acceptable to add new words to the approved indication to limit the indication to exclude only that portion of the indication that is covered by the use code (i.e., to exclude sedation of non-intubated patients in the ICU setting only)? If you believe a carve out of this type is permissible, if you wish, you may submit a side by side of the indication section of the labeling for dexmedetomidine hydrochloride injection showing the carve out that you believe would be acceptable.

2. Whether the fact that Hospira changed the use code information outside of the 30-day window after the patent issued means that the use code change is late listed as to any ANDAs pending with a section viii statement at the time the use code was changed. *See* 21 C.F.R. § 314.53(c), (d). If so, would any ANDA with an existing section viii statement be entitled to retain that statement (and corresponding carve out) under 21 C.F.R. § 314.94(a)(12)(vi), notwithstanding the change in use code?

3. What relevance, if any, to a determination of whether the use code change was timely submitted is the fact that Hospira previously listed the '840 patent with very similar use code information to that now listed for the '867 patent, and did not change the use code for the '867 patent until after the '840 patent expired?[2]

FDA requested a response by close of business on January 24, 2014. Commenters submitting in the initial comment period had an opportunity to respond to comments from other commenters by close of business January 31, 2014. The agency received 22 comments, which can be accessed at http://www.regulations.gov.

[2] Dear Applicant Letter from FDA Center for Drug Evaluation and Research to Hospira Inc. re. Dexmedetomidine Hydrochloride Injection NDA ANDA , Docket No. FDA-2014-N-0087 (Jan. 15, 2014).

II. LEGAL AND REGULATORY BACKGROUND

A. The Statutory and Regulatory Framework for Patent Protection for NDAs and for Labeling Differences for ANDAs

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought.[3] Under the statute, an NDA applicant also must submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product in the NDA. Specifically, section 505(b)(1) of the FD&C Act requires an NDA applicant to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[4] FDA is required to publish this patent information[5] and does so in the publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book.

The statute also provides that if a relevant patent is issued after NDA approval, the NDA sponsor must file the required patent information with FDA not later than 30 days after the date the patent is issued.[6] FDA's regulations further require that an applicant seeking approval of certain supplements, including a supplement for a new indication, submit with its supplement the patent information required for NDA approvals for a patent that claims the drug, drug product, or method of use.[7]

A drug product with an effective approval under section 505(c) or 505(j) of the FD&C Act is known as a "listed drug."[8] Under the *Drug Price Competition and Patent Term Restoration Act of 1984* (Public Law 98-417) (the Hatch-Waxman Amendments), an applicant may submit an ANDA under section 505(j) of the FD&C Act for approval of a generic version of a listed drug previously approved under section 505(c).[9] The ANDA approval process shortens the time and

[3] Section 505(b)(1) of the FD&C Act.

[4] Sections 505(b)(1) of the FD&C Act (emphasis added). See also 21 CFR 314.53(c)(2)(ii).

[5] Section 505(b)(1), (c)(2) and (j)(7) of the FD&C Act.

[6] Section 505(c)(2) of the FD&C Act; 21 CFR 314.53.

[7] 21 CFR 314.53(d)(2).

[8] Under 21 CFR 314.3(b), "[l]isted drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each drug approved under 505(c). 21 CFR 314.53(e).

[9] *Drug Price Competition and Patent Term Restoration Act of 1984,* Pub. L. No. 98-417, 98 Stat. 1585.

effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling), and that its product is bioequivalent to the listed drug.

The ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, any patent protection for the listed drug that the ANDA references and whether the ANDA applicant challenges those patents.[10] In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) that such patent information has not been filed (a paragraph I certification),
(II) that such patent has expired (a paragraph II certification),
(III) the date on which such patent will expire (a paragraph III certification), or
(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[11]

The purpose of this requirement is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible."[12]

If an applicant files a paragraph I or II certification, the patent in question (there is none in the case of a paragraph I certification) will not be a barrier to ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking final approval of its ANDA. If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA or is unenforceable, the applicant must submit a paragraph IV certification to FDA. An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its patent certification, including a description of the legal and factual basis for the ANDA holder's assertion that the patent is invalid or not infringed.[13]

[10] See section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the FD&C Act.

[11] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[12] *Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003).

[13] Section 505(j)(2)(B) of the FD&C Act.

If a patent is listed at the time an ANDA is submitted and, in response to a paragraph IV certification, the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order.[14] When the 30-month period has expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval. FDA plays a ministerial role in patent listing and any method-of-use descriptions submitted by the NDA sponsor, meaning FDA does not review the patent to confirm or deny the appropriateness of the listing or the accuracy of the descriptions.[15]

The four patent certifications described above are not the only way in which an ANDA applicant may address all relevant patents. When a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use covered by the listed patent need not file a paragraph III or IV certification for that patent. Instead, the applicant may submit a "section viii statement" acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval. Specifically, section 505(j)(2)(A)(viii) of the FD&C Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use."[16]

Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use.[17] If an ANDA applicant files a section viii statement (and makes the requisite labeling carve out), the patent claiming the protected method of use will not serve as a barrier to ANDA approval, nor will any 180-day exclusivity for which another ANDA applicant may be eligible with respect to that patent serve as such a barrier to approval of the section viii applicant's product.[18] Under the FD&C Act, an ANDA applicant must submit either a patent

[14] Section 505(j)(5)(B)(iii) of the FD&C Act.

[15] See, *e.g., Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1349 (Fed. Cir. 2003); *aaiPharma v. Thompson*, 296 F.3d 227, 242-43 (4th Cir. 2002).

[16] When a patent is submitted that claims both the drug product and a method of using the drug, and if a sponsor does not seek approval for the method of use claimed by the patent but seeks approval of the drug product for a different use before the patent expires, FDA allows a *split* certification to that patent. This permits a paragraph IV certification to the drug product claim and a section viii statement to the method-of-use claim (and an accompanying labeling carveout). See, e.g., Letter fr. J. Woodcock to R. Wilk-Orescan and J. Hurst re. Docket Nos. FDA-2008-P-0343 and -0411 (Dec.4, 2008) (Repaglinide Citizen Petition Response), at 18. The current circumstances do not involve a split certification.

[17] 21 CFR 314.92(a)(1) and 314.94(a)(12)(iii).

[18] See also H.R. REP. NO. 857 (Part I), 98th Cong., 2d sess. 21.

> ...The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for

certification or a section viii statement for each listed patent. FDA implementing regulations describe when a section viii statement is required:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[19]

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[20]

The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts. Thus, in *Purepac Pharmaceutical Company v. Thompson*, the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent."[21] Similarly, in *Torpharm*, the D.C. District Court stated that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval."[22] These courts have upheld the Agency's

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> hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

[19] 21 CFR 314.94(a)(12)(iii). FDA regulations implementing this statutory provision use the term "indications" to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent. 21 CFR 314.94(a)(l2)(iii). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule*, 59 FR 50338, 50347 (Oct. 3, 1994)). FDA has consistently allowed use codes and labeling carve outs that correspond to methods of use other than indications (e.g., dosing schedules). Moreover, when the ANDA labeling proposes not to include the indication or other method of use, only the section viii statement is appropriate. The preamble to the final rule emphasizes that such an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement where the patent claims only a single method of use. Id. The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (*Abbreviated New Drug Application Regulations; Proposed Rule,* 54 FR 28872, 28886 (July 10, 1989)).

[20] See also *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final Rule* (68 FR 36676 (June 18, 2003) (Patent Submission and Listing Rule). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent." Id. at 36682. We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent." Id.

[21] *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004).

[22] *Torpharm Inc. v. Thompson*, 260 F. Supp. 2d at 73.

interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent, and under those circumstances, that patent will not be a barrier to ANDA approval.

B. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress's intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. In 21 CFR 314.92(a)(l), FDA explicitly states that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of ... an existing patent may be omitted."[23]

The FD&C Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug... except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new drug and the listed drug are produced or distributed by different manufacturers."[24] Similarly, 21 CFR 314.94(a)(8)(iv) requires that:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

This subparagraph also sets forth examples of permissible differences in labeling that may result because the generic drug product and RLD are produced or distributed by different manufacturers. These differences include "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C Act]." FDA's regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are

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[23] To note, an ANDA applicant may not carve out a condition of use for a product that is not protected by patent or exclusivity.

[24] Section 505(j)(2)(A)(v) of the FD&C Act. See also Section 505(j)(4)(G) of the FD&C Act (providing that FDA must approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers").

protected by patent" the agency must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."

Case law affirms an ANDA applicant's ability to carve out protected labeling in a manner consistent with the "same labeling" requirement. For example, in *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer. Thus, under the statute, regulations, and applicable case law, the carve out of patent and exclusivity-protected labeling is generally permitted as a permissible difference due to difference in manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

III. DISCUSSION

As indicated above, FDA received numerous comments from the NDA holder and ANDA applicants and other interested parties to the public docket. The comments generally fell within one of two categories: those asserting that FDA should not approve an ANDA for dexmedetomidine hydrochloride injection that contains a section viii statement to the '867 patent and carves out labeling associated with the patent because the use code precludes any such approvals; and those that assert that any protected information in the use code does not foreclose approval of an ANDA under the applicable statute, regulations, and the agency's past practice. FDA has carefully reviewed these comments in considering the issues, but will not separately address each comment. Rather, the agency will address the various positions asserted where appropriate to explain FDA's conclusions on this issue.

A. FDA's Authority to Determine Permissible Labeling Carve Out

As a threshold matter, Hospira asserts that FDA's ministerial role in patent listing and use code matters requires FDA to accept Hospira's view of its use code, as well as Hospira's view that no ANDAs are approvable.[25] While Hospira is correct that, as described above, FDA takes a ministerial role in listing patent information and we do not independently evaluate the information provided in the use code in relation to the patent, we nevertheless regularly evaluate what portions of labeling appropriately correspond to the use code provided and whether ANDAs may be approvable with labeling that carves out protected information that corresponds to the use code provided. Such determinations fall squarely within the ambit of FDA's scientific expertise.

[25] Letter to FDA fr. R. Bedward, Hospira, Inc. re Docket No. FDA 2014-N-0087 (Jan. 24, 2014) (Hospira Jan. 24 Letter), at 3, 8-9.

In particular, we evaluate, in light of the patented method of use as described by the NDA sponsor, whether an ANDA can be approved by omitting protected information and what information must be omitted, as well as whether the product with the protected information omitted will be rendered less safe or effective for its remaining non-protected conditions of use without that information.[26] In accordance with our statutory and regulatory authority and past practice, we have determined that in this instance, we can approve an ANDA that omits the information Hospira has identified as protected by the use code because we have concluded that such omissions do not render the drug less safe or effective for the remaining non-protected conditions of use. As described below, this is true regardless of whether the carve out is done with reference to the original use code or the revised use code that Hospira submitted to the agency on January 6, 2014.[27] Because we are not independently assessing the scope of the patent but instead are relying on the information that Hospira has provided, our decision-making process is consistent with our ministerial role in patent listing matters.

B. ANDA Sponsors May Carve Out the Use Protected by the '867 Patent

As described above, Hospira originally listed the '867 patent in May 2004 with the use code (U-572): "Intensive care unit sedation." In November 2008, Hospira listed the '840 patent with the following use code (U-912) in the Orange Book: "Sedation of non-intubated patients prior to and/or during surgical and other procedures." On January 6, 2014, without making any other changes to its approved drug product or approved labeling, Hospira sought to amend the '867 use code to "intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures." Consistent with its ministerial role, FDA changed the use code on January 8, 2014.

Hospira asserts that both its original and its revised use code overlap not only with the first indication for Precedex but also with the second indication for that drug because there is a subset of non-intubated patients that may receive Precedex for procedural sedation (the second indication) in the ICU setting. Hospira argues that because its use code(s) for the '867 patent fully cover the first indication and may overlap with the second indication, an applicant with a section viii statement to the '867 patent must carve out both the first and the second indications in their entirety, thereby precluding approval of any ANDAs with carved out labeling.[28] In support of this position, Hospira cites the Supreme Court's decision in *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1677 (2012), in which the Court summarized its understanding of FDA's practice: "the FDA will not approve an ANDA if the generic's proposed carve out label overlaps at all with the brand's use code" (citing the Patent Submission and Listing Rule, 68 Fed. Reg. at 36682-83).

[26] See, e.g., Repaglinide CP response, at 9-14.; Letter to Macdonald, Apotex Corp. fr. J. Woodcock, FDA re. Docket Nos. 01P-0495/CP1, 02P-191/CP1, & 02P-0252/CP1, at 7-11 (June 11, 2001) (Tramadol CP Response).

[27] Because the outcome is the same regardless of whether the original or revised use code is used, FDA is not addressing separately whether the revised use code is late-listed and the consequences, if any, of the timing of its submission.

[28] Hospira Jan. 24 Letter, at 5, 7-9.

We reject Hospira's argument. Both the original and the revised use codes are limited to "intensive care unit sedation." Although the revised use code includes additional language specifying some of the types of patients that Hospira claims are encompassed within the "intensive care unit sedation" use, i.e., non-intubated ICU patients prior to and/or during surgical and other procedures, it does not broaden the claimed method of use beyond "intensive care unit sedation." Hospira itself recognized this, having noted that the use code overlaps with the second procedural sedation indication but only "to the extent such sedation occurred in an ICU."[29] Nor does the clarified use code and its explicit inclusion of a subset of patients that may undergo procedural sedation somehow expand the patented use to encompass and prevent approval for all patients who seek to use the drug for the separately delineated procedural sedation indication. As described below, FDA previously has determined that it can approve ANDAs for broad, general indications that may partially overlap with a protected method of use, so long as any express references to the protected use are omitted from the labeling. The procedural indication and related information in the labeling do not impermissibly disclose the use of Precedex for procedures in the ICU (i.e., for the use covered by the use code). ANDAs therefore may be approved for the second indication, consistent with how FDA has implemented use codes and allowed carve outs in other circumstances.[30]

FDA previously took a similar approach for repaglinide. In 2008, Novo Nordisk's (Novo's) repaglinide product (first approved in 1997) was approved for a single indication, "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."[31] Previously, it had been approved for three distinct uses: 1) as a monotherapy treatment; 2) for use in combination with metformin; and 3) for use in combination with thiazolidinediones (TZDs).[32] In 2004, Novo submitted U.S. Patent No. 6,677,358 (the '358 patent) that was identified with the following use code: "Use of repaglinide in combination with metformin to lower blood glucose." FDA later requested that Novo consolidate the three separate indications into a single, more general indication (i.e., as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus). Novo petitioned FDA to refrain from approving any ANDA for a repaglinide product, asserting that there was no longer a separate indication for metformin combination therapy that could be carved out, and that FDA's only option was to omit the entire indication (which partially overlapped with the protected use) or to require ANDA applicants to change from section viii statements to paragraph IV certifications (and omit nothing at all).[33]

[29] Id. at 3. Hospira also stated that "unlike here," the use code in *Caraco* had been significantly broadened. Id.

[30] We also note that Hospira previously listed the '840 patent as covering the general procedural indication, and that it only changed its use code for the '867 patent after the '840 patent expired. Thus, Hospira appears to be attempting to resurrect patent coverage to which it is no longer entitled by arguing that the '867 patent precludes approval of an ANDA for dexmedetomidine for procedural sedation to the same extent the '840 patent did – that is, in its entirety.

[31] Repaglinide CP Response, at 2.

[32] Id.

[33] Id. at 9.

FDA rejected this argument, noting that "[s]ection 505(j)(2)(a)(viii) of the Act refers to 'a use' for which the applicant is seeking approval."[34] FDA determined that it could approve an ANDA with all explicit references to use of repaglinide in combination with metformin carved out from the labeling; the ANDAs would be approved for the entire indication (as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus) with the combination metformin information removed from the ANDA labeling in sections where such combination use was mentioned expressly.[35] FDA made this decision even though the scope of the broad indication partially overlapped in substance with the method of use described by the use code at that time (use of repaglinide in combination with metformin). This "overlap" was not explicit in the indication section of the labeling, which was silent as to the specific method of use protected by the patent. Because the patented use described in the use code was not expressly disclosed in the labeling as carved out, FDA determined that ANDAs carving out the protected information were approvable.[36]

Later, Novo submitted and FDA published a broader use code for the '358 patent. In its new use code, Novo certified that the '358 patent claimed use of repaglinide "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus" to mirror the approved indication without any reference to the more specific use in combination with metformin. In light of the explicit and complete overlap of the new use code and the only approved indication for repaglinide, FDA determined that it could no longer approve any ANDAs with carved out labeling because ANDAs could not carve out the only approved indication that was claimed to be protected by the '358 patent (as described in the use code). Caraco Pharms. Labs. Ltd. (Caraco) filed a counterclaim in a related patent infringement action, seeking a determination that Novo's new use code was overly broad, and Novo challenged Caraco's ability to raise such a counterclaim. In *Caraco*, ultimately the United States Supreme Court held that Caraco could challenge the breadth of that use code by filing a counterclaim in patent infringement litigation.[37]

Hospira argues that the Supreme Court's dicta about the effect of a use code on an ANDA applicant's ability to obtain approval with carved out labeling controls here. Hospira asserts that if there is even partial overlap between an approved indication and a submitted use code, that approved indication must be carved out in its entirety in order for an ANDA with a section viii statement to obtain approval. However, the Supreme Court was opining in *Caraco* in light of the unique facts at issue in that case, where the use code and the approved indication were exact duplicates of one another (but the patent arguably claimed less than the entire indication stated in the use code). In that case, if references to the use described in the use code were carved out, there would be no indication left to reference. The factual situation

[34] Id.

[35] Id. at 13 ("[T]he INDICATIONS AND USAGE section for the generic repaglinide labeling will be identical to Prandin. Only the references to metformin combination therapy in other sections of the drug labeling will be carved out from the generic product's labeling.").

[36] Id. at 13. See also, e.g., Letter to Docket No. FDA-2010-P-0087, at 9, 10 (July 30, 2010) (Pregabalin CP Response) (relevant inquiry is whether the language of the proposed generic label discloses the protected condition of use).

[37] *Caraco*, 132 S. Ct. at 1688.

here is very different and more analogous to the first set of circumstances FDA considered for repaglinide in the 2008 citizen petition response. Here, Hospira is not asserting (through submission of a use code that precisely duplicates the procedural sedation indication) that its patent covers the entire procedural sedation indication. As the *Caraco* Court observed, "only if the use code provides sufficient space for the generic's proposed label will the FDA approve an ANDA with a section viii statement."[38] Here, sufficient space exists; FDA can approve ANDAs with only the second procedural indication and related information in the labeling without disclosing the protected use.

The Court's description of the changed circumstances after the change in use code for repaglinide is illuminating:

> Because that [new] code indicates that the *'358 patent* protects all three approved methods of using repaglinide to treat diabetes, Caraco's proposed carve out of metformin therapy was no longer sufficient; even with that exclusion, Caraco's label now overlapped with Novo's use code on the other two uses. And Caraco could not carve out those uses as well, *because at that point nothing would be left for it to market.* The FDA has approved repaglinide for only three uses, and Novo's use code encompassed them all.[39]

That is not the case here. Just as FDA concluded that a labeling carve out was proper for repaglinide before Novo broadened its use code to duplicate in its entirety the single approved indication, so, too, here ANDAs for Precedex may carve out the protected information (related to use for ICU sedation), and be approved for procedural sedation despite the fact that use for procedural sedation may at times occur in an intensive care setting. Use in an intensive care setting is not expressly disclosed in any proposed ANDA labeling. Hospira's reliance on a single sentence about a different type of "overlap" at issue in *Caraco* does not control the outcome here.[40]

FDA's decision in this circumstance, i.e., that a labeling carve out is permissible if the proposed ANDA labeling does not disclose the protected use, is consistent with other previous determinations as well. For generic tramadol, for example, FDA allowed ANDAs to carve out a protected titration schedule that was based on a study analyzing the narrow question of the tolerability of the drug in patients who had previously been shown to be tramadol-intolerant and be approved with a broad indication for "management of moderate to moderately severe pain."[41] In that decision, FDA concluded that information specific to the titration schedule

[38] Id. at 1677.

[39] Id. at 1679 (emphasis added). In addition, we note that the Court did not observe or otherwise infer that Caraco's original carve out, which is similar to the proposed carve out here, was improper.

[40] *Caraco*, 132 S.Ct. at 1677 ("the FDA will not approve an ANDA if the generic's proposed carve out label overlaps at all with the brand's use code").

[41] Tramadol CP Response, at 7. In that instance, generic sponsor Teva Pharmaceutical USA had argued that it could be approved for this indication, limited to "acute" pain, much as some of the ANDAs here argue that they can be approved for the procedural indication, limited to use outside an intensive care setting. FDA did not decide this issue, noting instead that the ANDAs could be approved for the entire indication, and that they only needed to excise the particular titration schedule from other portions of the labeling. Id.

could be carved out without rendering the product less safe or effective for the non-protected conditions of use, even though that tramadol-intolerant sub-population may be part of the larger population for which the product is prescribed.[42] In the case at hand, we similarly conclude that ANDAs omitting references to the protected use in an intensive care unit may be approved for the procedural indication. The procedural indication, like the broad indication for "treatment of moderate to moderately severe pain" in the tramadol example, could potentially be practiced in a manner that would implicate a protected use, but approval for the indication is not foreclosed by such a possibility.

Similarly for generic oxandrolone, FDA allowed ANDAs to carve out information on the label related to geriatric use for which the innovator had gained three years of exclusivity. In that case, the agency concluded that generic oxandrolone products would be as safe and effective as the RLD Oxandrin for all of the approved indications if the new geriatric use information were omitted, because the concerns addressed in the new Oxandrin geriatric labeling were adequately addressed by the labeling applicable to all adults, including the geriatric population.[43] The agency did not explicitly limit or disclaim use in geriatric patients for these indications, and allowed the labeling carve out only of information that was explicitly related to geriatric use, not to general information that might pertain to geriatric patients. Here, while it is possible that procedural sedation might be administered in an ICU, an ANDA will be fully labeled for the procedural sedation indication regardless of where the sedation occurs and the omission of information regarding ICU sedation does not render this product any less safe or effective for the remaining non-protected conditions of use.[44]

Finally, we note that FDA's decision to permit generic applicants to obtain approval before expiration of the '867 patent by filing a section viii statement and carving out information explicitly addressing the use of dexmedetomidine for ICU sedation is consistent with the goals of the Hatch-Waxman Amendments. The Amendments provided sponsors of innovator drugs with marketing exclusivity and patent listing protections that protect certain aspects of innovator drugs from generic competition for certain periods of time. As a balance for this increased protection, the Amendments created an abbreviated approval mechanism allowing sponsors of generic drugs to rely on the Agency's finding of safety and effectiveness for innovator drugs in seeking approval of their generic products when intellectual property barriers to approval expire or otherwise are removed.[45]

[42] Id. at 8.

[43] Letter to E. Allera, Buchanan Ingersoll P.C. fr. S. Galson, FDA re. Docket No. 2005P-0383/CP1 & SUP1, at 16 (Dec. 1, 2006) (Oxandrolone CP Response).

[44] See 21 CFR 314.127(a)(7).

[45] See also Letter to E. Lengle, Watson Labs. Inc. fr. J. Woodcock re. Docket No. FDA-2008-P-0069 (July 28, 2009) (Irinotecan CP Response) (concluding that permitting the carve out of protected information related to the use of irinotecan hydrochloride in combination with 5-fluorouracil and leucovorin as first-line therapy when use of irinotecan as second-line monotherapy treatment remained in the label supports the goals of the Hatch-Waxman Amendments).

Sandoz Inc. (Sandoz) asserts that permitting ANDA applicants to carve out the protected information frustrates the goals of the Hatch-Waxman system, because that company filed a paragraph IV certification to the '867 patent rather than a section viii statement, undertook the risk of patent litigation, and maintains that it is entitled to 180 days of exclusivity for its efforts.[46] Sandoz filed paragraph IV certifications to both the '867 and '214 patents, however, and sought approval for both indications earlier than any applicant that filed a section viii statement to the '867 patent and paragraph III certifications to the '214 patent. The company now seeks to benefit from its decision to challenge both patents in a manner not contemplated by the statute. In effect, Sandoz seeks to bar ANDA sponsors from submitting section viii statements when other ANDA sponsors (like Sandoz) have submitted paragraph IV certifications to the same patent and seek approval for both indications. There is no such prohibition in the statute to submitting a section viii statement and carving out an indication (in fact, the statute authorizes this), and FDA declines to infer one here.[47]

C. Omission of the Protected Indication Does not Render Dexmedetomidine Less Safe and Effective for the Remaining, Non-protected Conditions of Use

FDA has determined that permitting ANDA sponsors to omit information from the labeling related to use for ICU sedation does not render the product less safe or effective for the remaining use of sedation of non-intubated patients prior to and/or during surgical and other procedures. The generic labeling will include all of the information necessary to use dexmedetomidine safely and effectively for the procedural sedation indication.[48]

IV. CONCLUSION

Upon the foregoing, FDA concludes that the ANDA sponsors for dexmedetomidine hydrochloride injection can submit a section viii statement and carve out references to ICU sedation under either Hospira's original use code or its amended use code without adding additional language. FDA further concludes that such a carve out would not render the product less safe or effective for the remaining non-protected condition of use (i.e., use for procedural sedation). In light of this conclusion, FDA makes no decision at this time on the

[46] Docket No. FDA-2014-N-0087, Comments of Sandoz Inc., at 6 (Jan. 24, 2014).

[47] We note that 180-day exclusivity would only delay approval of another generic drug application that also contained a paragraph IV certification. It would not block approval of a competing generic drug application in which that applicant sought to enter the market with a labeling carve out.

[48] That studies described in the carved out label may have included ICU patients does not preclude those studies from remaining in the label so long as the study descriptions do not expressly disclose the ICU use. See Letter to R. Trainor, UCB, Inc. fr. J. Woodcock, CDER re. FDA Docket No. 2010-P-0545, at 9-11 (Feb. 24, 2011) (Levocetirizine CP Response) (rejecting argument that a proposed carve-out of Xyzal's allergic rhinitis indications, which the innovator claimed were protected by patent, would require the deletion of all information derived from the study of patients with allergic rhinitis).

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remaining issues identified in our initial letter to the NDA and ANDA sponsors, including: whether an ANDA sponsor could add language to limit the procedural sedation indication; the relevance of Hospira's change of the use code information outside the 30-day window after the patent issued; and the relevance of the use code listed for the expired '840 patent.

Sincerely,

{See appended electronic signature page}

CAPT Jason J.Y. Woo, M.D., M.P.H.
Acting Director, Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

08/18/2014

Associate Director of Review Quality, for
Jason Woo, M.D., M.P.H.

EXHIBIT 2

PATENT PROSECUTION HISTORY EXCERPTS FOR U.S. PATENT NO. 8,242,158 ('158 PATENT)

§ 1

’158 PATENT NON-FINAL REJECTION (FEB. 13, 2012)

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/343,672	01/04/2012	Priyanka Roychowdhury	077350.0344	3876

62965 7590 02/13/2012

BAKER BOTTS L.L.P.
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44th Floor
NEW YORK, NY 10112-4498

EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1629	

NOTIFICATION DATE	DELIVERY MODE
02/13/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DLNYDOCKET@BAKERBOTTS.COM

Office Action Summary for Applications Under Accelerated Examination	**Application No.** 13/343,672	**Applicant(s)** ROYCHOWDHURY ET AL.	
	Examiner Gregg Polansky	**Art Unit** 1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Since this application has been granted special status under the accelerated examination program, NO extensions of time under 37 CFR 1.136(a) will be permitted and a SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE:

ONE MONTH OR THIRTY (30) DAYS, WHICHEVER IS LONGER,
FROM THE MAILING DATE OF THIS COMMUNICATION – if this is a non-final action or a *Quayle* action.
(Examiner: For **FINAL** actions, please use PTOL-326.)

The objective of the accelerated examination program is to complete the examination of an application within twelve months from the filing date of the application. Any reply must be filed electronically via EFS-Web so that the papers will be expeditiously processed and considered. If the reply is not filed electronically via EFS-Web, the final disposition of the application may occur later than twelve months from the filing of the application.

Status

1)☒ Responsive to communication(s) filed on *04 January 2012*.

2)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

- See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/04/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' Information Disclosure Statement filed 1/04/2012 is acknowledged and has been reviewed.

2. Claims 1-4 are pending and presently under consideration.

3. In view of the clear anticipation of the instant claims by the prior art as set forth in the rejection below, a pre-first action interview with Applicant would likely not have resulted in the application being placed in condition for allowance and therefore, the interview was not conducted. However, Applicants' representative, Dennis Bissonnette, was called on 2/02/2012 to inform him of the status of the application and that a First Action was forthcoming.

Claim Rejections - 35 USC § 102/103

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over “"Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection," FDA approved label (dated December 17, 1999, and available online July 26, 2001, pages 1 – 13; cited and provided by Applicants); hereinafter “Draft Labeling”.

Draft Labeling discloses the hydrochloride (HCl) salt of dexmedetomidine (Precedex™) formulated as a liquid for intravenous infusion (i.e., parenteral administration). The formulation comprises dexmedetomidine HCl in a sterile, aqueous, isotonic (i.e., 0.9% sodium chloride) solution. The formulation comprises 118 µg of dexmedetomidine HCl (equivalent to 100 µg of dexmedetomidine base) per milliliter solution. See “DESCRIPTION” at page 1.

The reference teaches that the dexmedetomidine HCl formulation must be diluted in 0.9% sodium chloride solution prior to administration. The reference provides instructions for dilution. The instructions are to “withdraw **2 mL** of PRECEDEX

[dexmedetomidine HCL (100 µg dexmedetomidine base per milliliter) in isotonic saline] and add to 48 mL of **0.9% Sodium Chloride** injection to a total of **50** mL [emphasis added]. Shake gently to mix well." These dilution instructions produce an isotonic solution for parenteral administration of dexmedetomidine HCl, having a concentration of dexmedetomidine base of **4 µg/mL**. See page 12, "Dilution Prior to Administration".

With regard to the instant limitation requiring the composition "disposed within a sealed container", only 2 options are available to the artisan practicing the dilution instructions of the reference: (1) mixing the solution in a sealed container, or (2) mixing the solution in an unsealed container. The artisan would clearly immediately envisage the mixing of the formulation in a sealed container in order to maintain the sterility of the composition for parenteral administration. See *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), where claims to a specific compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound. The broad generic formula seemed to describe an infinite number of compounds but claim 1 was limited to a structure with only one variable substituent R. This substituent was limited to low alkyl radicals. One of ordinary skill in the art would at once envisage the subject matter within claim 1 of the reference.

The above teachings clearly anticipate the instant claims.

Alternatively, the instant claims are prima facie obvious over Draft Labeling, in view of its teaching that Precedex™ must be diluted with 0.9% saline to produce a final

concentration of 4 µg/mL, prior to administration. One of ordinary skill in the art at the time of the invention would have found it obvious to make the dilution in a sealed container (such as a sealed glass vial or an infusion bag) to maintain the sterility of the formulation, which is administered by intravenous infusion.

Conclusion

6. Claims 1-4 are rejected.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/James D Anderson/
Primary Examiner, Art Unit 1629

§ 2

’158 PATENT AMENDMENTS TO THE CLAIMS (MAR. 13, 2012)

AMENDMENTS TO THE CLAIMS

The listing of claims provided below will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) A pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL, wherein the composition is formulated as a liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container as a ready to use premixture.

2. (Original) The pharmaceutical composition of claim 1, further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.

3. (Original) The pharmaceutical composition of claim 2, wherein the sodium chloride is present at a concentration of about 0.9 weight percent.

4. (Original) The pharmaceutical composition of claim 1, wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.

§ 3

’158 PATENT RESPONSE TO OFFICE ACTION (MAR. 13, 2012)

REMARKS

Reconsideration is respectfully requested. Claim 1 is amended to recite sealed glass container and a ready to use premixture. The amendments to claim 1 are fully supported by the claims as originally filed and by the specification, including for example, at page 5, paragraph [0025]; and page 13, paragraph [0060] of the application. Accordingly, Claims 1-4 remain currently pending. The amendments to claim 1 do not constitute new matter.

I. Statement of the Substance of the Interview

In accordance with 37 C.F.R. § 1.2 and M.P.E.P. § 713.04, Applicants respectfully submit this Statement of the Substance of the Interview in reply to the Interview Summary mailed on March 6, 2012, for the above referenced patent application.

Applicants acknowledge with appreciation the courtesy extended by Examiner Gregg Polansky and Primary Examiner James Anderson during the telephone interview on February 28, 2012 with Dennis Bissonnette, Sandra Lee and Jennifer Flory, and for their careful consideration of this application and claims. Applicants have received and reviewed the Interview Summary, and provide the following statements to supplement and clarify the summary provided by the Examiners.

As evident from the Interview Summary, the pending claims were discussed in view of the rejections of record under 35 U.S.C. §§ 102(b) and 103(a). Specifically, the reference "Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection," FDA approved label (dated December 17, 1999, and available online July 26, 2001, pages 1-13) cited in the rejections of record was discussed.

Although no consensus was reached, Applicants noted that the claims are directed to a composition comprising 4 μg/mL dexmedetomidine that is a premixture, which does not require dilution prior to administration to a subject. The claimed composition differs from the formulation described by the cited reference, which requires dilution to a concentration of 4 μg/mL dexmedetomidine prior to administration to a patient. As such, Applicants maintained that unlike the claimed composition, the formulation disclosed by the cited reference is not a ready to use premixture.

II. Rejection Under 35 U.S.C. § 102(b)

Claims 1-4 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by "Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection," FDA approved label (dated December 17, 1999, and available online July 26, 2001, pages 1-13) (hereafter, "the Draft Labeling"). According to the Examiner, the Draft Labeling discloses a composition comprising a hydrochloride (HCl) salt of dexmedetomidine (Precedex) that is formulated as a sterile aqueous liquid (in 0.9% NaCl solution) for intravenous infusion (*i.e.*, parenteral administration) to a patient, wherein the dexmedetomidine HCl is present at a concentration of 118 µg/mL (which corresponds to 100 µg/mL dexmedetomidine). According to the Examiner, the Draft Labeling discloses that prior to administration to a patient, the formulation is diluted with 0.9% NaCl solution to achieve a 4 µg/mL dexmedetomidine formulation in a total volume of 50 mL. The Examiner further alleges that the dilution step would be performed in either a sealed or unsealed container. The Examiner states that in order to maintain the sterility of the composition for parenteral administration, an artisan of ordinary skill would have diluted the composition in a sealed container. Accordingly, the Examiner contends that the diluted composition describes all the elements of the claims.

Applicants respectfully traverse the rejection. Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See M.P.E.P. § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally be present and arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

Independent claim 1 is hereby amended to recite a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 µg/mL, wherein the composition is disposed within a sealed glass container as a ready to use premixture. The claims are not anticipated by the Draft Labeling because the reference does not disclose all the elements of the claims. For example, the Draft Labeling does not disclose a composition comprising about 4 µg/mL dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the composition is disposed within a sealed glass container as a ready to use premixture.

With regard to the claims' recitation that the composition is disposed within a sealed container, the Examiner states that the 100 μg/mL composition of the Draft Labeling could only be diluted in either a sealed or an unsealed container. Applicants note that the Draft Labeling is silent regarding any dilution container. The Examiner relies on *In re Schauman,* 572 F.2d 312, 197 USPQ 5 (CCPA 1978), as supporting the contention that the claim element of a "sealed container" is anticipated by the cited reference because the reference allegedly discloses a genus of container with only a limited number of options (*i.e.*, dilution in a sealed or an unsealed container), wherein the limited number of options are closely related to each other in structure, and possess the same properties of the claim element. However, as noted above, the Draft Labeling does not recite any genus of container into which the concentrated composition is diluted. Accordingly, Applicants note the Examiner's position must be based on a theory of inherent anticipation.

In order for a reference to inherently anticipate a limitation, however, that limitation must necessarily be present in the disclosure. *See, e.g., Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Inherency may not be established by probabilities or possibilities. *See, e.g., In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). For example, a feature is not inherent if it is a mere probability that the limitation would appear in the prior art. *See, e.g., In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). That a limitation may result in a prior art reference from a given set of circumstances is insufficient to prove anticipation. *See, e.g., In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); and M.P.E.P. § 2112.

Applicants respectfully submit that the Office Action fails to make a showing based on the Draft Labeling that meets this standard. As noted above, the claims as amended are directed to a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL, wherein the composition is disposed within a sealed glass container as a ready to use premixture. As discussed above, the Draft Labeling does not disclose a 4 μg/mL ready to use premixture that is disposed within a sealed glass container. Furthermore, a 4 μg/mL ready to use premixture that is disposed within a sealed glass container is not inherent to the Draft Labeling because the reference does not disclose a 4 μg/mL ready to use premixture that is *necessarily* disposed within a sealed glass container. Assuming *arguendo*, with reference to the Examiner's own logic and interpretation of the Draft Labeling, the Examiner

states that "2 options are available to the artisan practicing the dilution instructions of the reference: (1) mixing the solution in a sealed container, or (2) mixing the solution in an unsealed container." (*See* the Office Action, p. 4). Accordingly, any conclusion that the dilution would be disposed within a sealed glass container is based on a mere probability that the skilled artisan would prepare the dilution in a sealed glass container and not in an unsealed container. However, inherency may not be established by probabilities or possibilities, and as such, a conclusion that is based on mere probability is without merit and lacks basis to support a finding of inherent anticipation. *See, e.g., In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

For at least these reasons, Applicants submit that the Draft Labeling does not describe all the elements of the amended claims, and as such, cannot anticipate the claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

III. Rejection Under 35 U.S.C. § 103(a)

As an alternative to the rejection under 35 U.S.C. § 102(b) described above, the Examiner has rejected claims 1-4 under 35 U.S.C. § 103(a) as allegedly obvious over the Draft Labeling. The Examiner relies on the Draft Labeling as described above, and further states that the claims are *prima facie* obvious over the Draft Labeling in view of the reference's disclosure that the 100 μg/mL dexmedetomidine formulation must be diluted with 0.9% saline to produce a 4 μg/mL dexmedetomidine formulation prior to administration to a patient. According to the Examiner, it would have been obvious for one of ordinary skill in the art to dilute the 100 μg/mL dexmedetomidine formulation in a sealed container in order to maintain the sterility of the formulation.

Applicants respectfully traverse the rejection. To support an assertion of obviousness, the Examiner must show that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." *See* M.P.E.P § 2143. *See also KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

As described previously, independent claim 1 is amended herein to recite a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a

concentration of about 4 μg/mL, wherein the composition is disposed within a sealed glass container as a ready to use premixture. In contrast to the claims, the Draft Labeling does not suggest or describe that the diluted 4 μg/mL dexmedetomidine composition is disposed within a sealed glass container. Rather, the reference discloses that the dexmedetomidine composition is diluted to 4 μg/mL prior to administration to a subject. (*See*, the Draft Labeling, p. 12). Because the diluted composition is administered to a subject by an intravenous infusion (*see, e.g.,* the Draft Labeling, p. 1), an artisan of ordinary skill would have diluted the dexmedetomidine in a device for infusion, such as a plastic infusion bag or plastic syringe, and not disposed the 4 μg/mL dilution in a sealed glass container. Applicants note that the Examiner has recognized that an infusion bag would be a likely container for diluting the composition in preparation for administration to a subject, as evidenced by the Examiner's statement that the composition could be diluted by "injecting 2 mL of the concentrate into an intravenous bag containing 48 mL isotonic saline." (*See* the Applicant-Initiated Interview Summary dated March 6, 2012, p. 2). The Examiner provides no basis or evidence to suggest that an artisan of ordinary skill would prepare the dilution in a sealed glass container as claimed.

Additionally, Applicants note that a primary difference between the claimed 4 μg/mL premixture composition and the 4 μg/mL diluted composition described by the Draft Labeling, is that the claimed composition is a ready to use premixture that does not require any dilution or reconstitution prior to administration to a subject. (*See* the specification, p. 5, paras. [0024]-[0025]). Accordingly, upon withdrawing the claimed composition from a sealed glass container, an artisan of ordinary skill can administer the composition directly to a subject. In contrast, the composition described by the Draft Labeling is not suitable for administering to a patient upon withdrawing the composition from a sealed container (*i.e.*, a 2 mL vial or ampoule which the concentrated 100 μg/mL formulation is stored in, *see* the Draft Labeling, p. 13). Rather, after withdrawing the concentrated 100 μg/mL composition from a sealed container, the composition must be diluted prior to administration to a subject.

Applicants also submit that the claimed ready to use premixture composition provides for surprising and unexpected advantages over the diluted 4 μg/mL composition described by the Draft Labeling. For example, the claimed ready to use 4 μg/mL premixture composition provides for advantages with regard to the ability to store the composition over prolonged periods of time, while maintaining a stable formulation. Such advantages over the diluted composition of the

Draft Labeling is further evidence of the non-obviousness of the claims over the cited reference. (*See* M.P.E.P. § 716.02(a)). For example, as described by the present application, the claimed pharmaceutical formulation "can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi." (*See* the specification, p. 8, para. [0038]). The ability to store the claimed composition for prolonged periods of time are shown in at least Examples 1 and 3 of the application, which demonstrate that the claimed ready to use 4 μg/mL premixture composition was stable for up to 9 months when stored in a glass container. As described in Example 1, a 4 μg/mL premixture formulation stored in glass vials and ampoules maintained a higher level of potency after a 5 month storage period compared to storage in plastic, CR3 or PVC containers. (*See*, the specification, pp. 18-20, paras. [0086] - [0088]). As described by Table 1, when stored in glass vials or ampoules, the 4 μg/mL premixture maintained over 98% potency after 5 months. However, when stored in plastic or PVC containers, which include plastic syringes and plastic bags, the potency was reduced by as much as 20% after only a two-week storage period. (*See* the specification, pp. 19-20, Table 1). Similarly, Example 3 discloses that the potency of the claimed 4 μg/mL premixture composition maintained relatively unchanged after being stored in glass vials and ampoules at 25°C for 9 months. (*See* the specification, Example 3, pp. 22-23, para. [0095]).

In contrast, the Draft Labeling discloses that the concentrated 100 μg/mL dexmedetomidine composition is suitable for storage, and not the diluted 4 μg/mL composition. (*See* the Draft Labeling, p. 13). Furthermore, as described by the FDA Memorandum by Cynthia G. McCormick, M.D., dated November 30, 1999, in connection with the Medical Reviews of the Precedex (dexmedetomidine hydrochloride injection) Application No. 21-038 submitted to the FDA, and available on the FDA website July 26, 2001 (hereafter, "the Memorandum," Exhibit A, and a copy of which is submitted herewith in an Information Disclosure Statement), the undiluted dexmedetomidine composition is manufactured through an "aseptic fill and terminal sterilization by autoclave," (*see*, the Memorandum, p. 8, third para.), and as such, is suitable for storage. However, once diluted for administration, the diluted composition is stable for only 24 hours. *See* the Memorandum, p. 8, para. 4, stating: "The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours" (emphasis added). Thus, unlike the claimed ready to use 4 μg/mL premixture composition, which can be

stored for prolonged periods of time, the diluted composition described by the Draft Labeling is prepared for use within a 24 hour period, and is not a formulation suitable for prolonged storage.

Accordingly, the memorandum provides further evidence that formulating the claimed 4 μg/mL composition as a ready to use premixture provides for surprising and unexpected advantages over the dilution described by the Draft Labeling. While diluting a 100 μg/mL concentrate to a 4 μg/mL dilution produces a composition that is stable and useable for a 24 hour period after dilution, the claimed 4 μg/mL ready to use premixture can be stored for at least 9 months in a sealed glass container. Such a characteristic is not suggested or disclosed by the cited reference, as evidenced by the Memorandum. Rather, in contrast, an artisan of ordinary skill would understand that a diluted 4 μg/mL composition is only stable and useable for up to 24 hours.

Additionally, in view of the Draft Labeling's disclosure as a whole, an artisan of ordinary skill would understand that the diluted 4 μg/mL formulation is formulated for immediate administration to a subject, and not suitable for prolonged storage. For example, the Draft Labeling discloses that the composition is "preservative-free and contains no additives or chemical stabilizers." (*See* the Draft Labeling, p. 1). Thus, the artisan would have had no expectation that the formulation is suitable for storage. Additionally, the diluted composition is intended for a single use only, and further, such a single use can only be for a period of, at most, 24 hours. (*See* the Draft Labeling, pp. 12 and 13). As such, the artisan would understand that any portion of the diluted composition that is not administered to a subject, or that remains after a 24 hour dosing period, cannot be stored for later use. Finally, contamination with impurities is a greater concern for compositions diluted to a low concentration. "Since the drug is present at such a low concentration 4 μg/mL, even ppb levels of impurities would have a significant contribution toward the impurity limit." (*See* the specification, p. 32, para. [00115]). Accordingly, the skilled artisan would be motivated to immediately use the diluted composition once prepared, and not store the dilution since storage could increase the risk of contamination, *e.g.*, microbe growth resulting from contamination during dilution.

In view of the advantages of the claimed ready to use 4 μg/mL premixture composition over the diluted composition disclosed by the Draft Labeling with regard to storage and stability over prolonged periods of time, and further, in view of the Draft Labeling's failure to provide an artisan of ordinary skill with any suggestion or motivation to dispose the diluted 4 μg/mL

composition in a glass container, Applicants submit that the claims are not obvious over the cited reference, and respectfully request that the rejection be withdrawn.

IV. Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or in a telephone call with the undersigned, the Examiner is invited to call the undersigned at the telephone number indicated below.

Applicants believe that no fee is due in connection with the filing of this paper. However, if any fees are due, or if any overpayment has been made, in connection with the filing of this response, the Commissioner is authorized to charge any such fees or credit any overpayment made, to our Deposit Account No. 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

March 13, 2012
Date

Dennis M. Bissonnette
Patent Office Reg. No. 61,910

Sandra S. Lee
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30 Rockefeller Plaza
44th Floor
New York, NY 10112-4498
212-408-2500

§ 4
’158 PATENT NOTICE OF ALLOWANCE (APR. 18, 2012)

EXAMINER'S AMENDMENT

1. Applicants' Information Disclosure Statement, filed 3/13/2012, is acknowledged and has been reviewed.

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Dennis M. Bissonnette on 3/30/2012.

Claims 1-4 are amended as follows:

1. A ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 µg/mL disposed within a sealed glass container[[,]] ~~wherein the composition is formulated as a liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container as a ready to use premixture~~.

2. The ready to use liquid pharmaceutical composition of claim 1, further comprising sodium chloride at a concentration of between about 0.01 and about 2.0 weight percent.

3. The ready to use liquid pharmaceutical composition of claim 2, wherein the sodium chloride is present at a concentration of about 0.9 weight percent.

4. The ready to use liquid pharmaceutical composition of claim 1, wherein the composition is formulated as a total volume selected from the group consisting of 20 mL, 50 mL and 100 mL.

3. The following is an Examiner's statement of reasons for allowance: Applicants' amendment to Claim 1, requiring the composition to be disposed within a sealed glass container, was effective to overcome the previous rejection under 35 U.S.C 102(b). Applicants argued and pointed to evidence that dexmedetomidine at a concentration of 4 µg/mL was significantly more stable when stored in a sealed glass vial relative to storage in plastic, CR3 or PVC containers. Further, Applicants provided evidence teaching away from storage of dexmedetomidine at a concentration of 4 µg/mL for longer than 24 hours (*see* page number 8 of Applicants' Remarks).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/JAMES D ANDERSON/
Primary Examiner, Art Unit 1629

EXHIBIT 3

PATENT PROSECUTION HISTORY EXCERPTS FOR U.S. PATENT NO. 8,338,470 ('470 PATENT)

§ 1

’470 PATENT NON-FINAL REJECTION (AUG. 17, 2012)

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/541,524	07/03/2012	Priyanka Roychowdhury	077350.0355	8238

62965 7590 08/17/2012

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EXAMINER	
POLANSKY, GREGG	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
08/17/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DLNYDOCKET@BAKERBOTTS.COM

Office Action Summary for Applications Under Accelerated Examination	**Application No.** 13/541,524	**Applicant(s)** ROYCHOWDHURY ET AL.	
	Examiner Gregg Polansky	**Art Unit** 1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Since this application has been granted special status under the accelerated examination program, NO extensions of time under 37 CFR 1.136(a) will be permitted and a SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE:

ONE MONTH OR THIRTY (30) DAYS, WHICHEVER IS LONGER,
FROM THE MAILING DATE OF THIS COMMUNICATION – if this is a non-final action or a *Quayle* action.
(Examiner: For **FINAL** actions, please use PTOL-326.)

The objective of the accelerated examination program is to complete the examination of an application within twelve months from the filing date of the application. Any reply must be filed electronically via EFS-Web so that the papers will be expeditiously processed and considered. If the reply is not filed electronically via EFS-Web, the final disposition of the application may occur later than twelve months from the filing of the application.

Status

1)☒ Responsive to communication(s) filed on *03 July 2012*.

2)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

- See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *7/03/2012 (two)*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' two Information Disclosure Statements filed on 7/03/2012 are acknowledged and have been reviewed.

2. Claims 1-7 are pending and presently under consideration.

3. In view of the rejection of the instant claims over the prior art as set forth in the rejection below, a pre-first action interview with Applicants would likely not have resulted in the application being placed in condition for allowance and therefore, the interview was not conducted. However, Applicants' representative, Dennis Bissonnette, was called on 8/02/2012 to inform him of the status of the application and that a first action on the merits was forthcoming.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyawaki et al. (US 2011/0230534 A1), evidenced by Precedex® Package Insert (Document EN-2680, Hospira, Inc., 9/2010, downloaded on 8/10/2012 from "www.precedex.com/wp-content/uploads/2010/11/Precedex_PI.pdf", pages 1-24), Sunkel et al. (US 6806291 B1), Ibrahim et al. (US 5716988), and Xylocaine® Package Insert (AstraZeneca LP, 2001 and 2007, downloaded on 8/10/2012 from "www.pdr3d.com/print.php?c=4818", pages 1-30).

Miyawaki et al. teach a kit for parenterally administered local anesthesia, including a local anesthetic agent and dexmedetomidine or a salt thereof. The dexmedetomidine concentration disclosed by Miyawaki et al. is between $1x10^{-15}$ M to $1x10^{-6}$ M (i.e., $2x10^{-10}$ µg/ml to 0.2 µg/ml), or more preferably, $1x10^{-10}$ M to $1x10^{-6}$ M (i.e., $2x10^{-5}$ µg/ml to 0.2 µg/ml). See paragraphs [0023] to [0031]. The reference teaches formulating dexmedetomidine hydrochloride with physiological saline (i.e., aqueous 0.9% sodium chloride solution) to prepare solutions having concentrations of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M and $4x10^{-9}$ M (i.e., 0.8 µg/ml, 0.08 µg/ml, 0.008 µg/ml and 0.0008 µg/ml, respectively). See paragraph [0056]. It is noted that the concentrations taught by Miyawaki et al. (e.g., 0.8 µg/ml) is encompassed by the concentration ranges of instant Claims 1-3. Further, 0.8 µg/ml also reads on instant Claim 4 (a concentration of **about 1** to about 7 µg/ml) because 0.8 µg/ml is about 1 µg/ml (see the definition of

"about" at page 7, paragraph [0035] of the instant Specification). The stock dexmedetomidine hydrochloride solution used by Miyawaki et al. to prepare the above solutions was Precedex®, which is provided by the manufacturer in a glass vial. See for evidentiary purposes the Precedex® Package Insert, page 1, bottom of left column.

Although Miyawaki et al. do not teach the use of sealed glass containers (e.g. sealed glass vials or ampules), the use of such containers for parenteral pharmaceuticals is common and well known.

For example, the Xylocaine® Package Insert teaches Xylocaine® (lidocaine HCl) in isotonic solution is provided in glass ampules and single or multiple dose vials, at various concentrations. Further, the ampules and vials are provided comprising various volumes of the parenteral solutions (e.g., 2, 5, 10, 20 and 50 ml). See page 1, the "Description" section, and page 8, the "How Supplied" section. Sunkel et al. disclose pharmaceutical compositions for parenteral administration contained in ampules and multiple dose vials made of glass or plastic. See column 4, lines 14-16 and 29-31. In fact, the compositions of Sunkel et al. may include dexmedetomidine. See column 5, line 5. Ibrahim et al. provide another example of the use of sealed glass vials for parenteral aqueous pharmaceutical solutions. See column 3, lines 45-62, which discloses aqueous solutions of oxaliplatinum contained in 50 ml sealed glass vials.

It would have been obvious to one of ordinary skill in the art to provide the dexmedetomidine in sealed glass containers in the kit taught by Miyawaki et al. because to do so was a common and predictable method of providing parenteral pharmaceutical compositions at the time of the invention. Additionally, further motivation to use sealed

glass containers for the dexmedetomidine solutions taught by Miyawaki et al. comes from the knowledge that the manufacturer of the dexmedetomidine stock solution used by Miyawaki et al. (Precedex®) provides the pharmaceutical in a sealed glass vial (*supra*). Furthermore, only 2 options are available to the artisan practicing the dilution instructions of the reference: (1) mixing the solution in a sealed container, or (2) mixing the solution in an unsealed container. The artisan would clearly immediately envisage the mixing of the formulation in a sealed container in order to maintain the sterility of the composition for parenteral administration. Similarly, there are a limited number of options available to the artisan with regard to the material of the container (e.g., glass, plastic, or PVC). See *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), where claims to a specific compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound. The broad generic formula seemed to describe an infinite number of compounds but claim 1 was limited to a structure with only one variable substituent R. This substituent was limited to low alkyl radicals. One of ordinary skill in the art would at once envisage the subject matter within claim 1 of the reference.

Providing the dexmedetomidine solutions in various volumes (e.g., 20, 50 or 100 ml) would be obvious. The volume of solution provided would depend on the expected administered amount of the composition and other variables specific to the treatment at hand.

Finally, the dexmedetomidine solutions provided in the "kit" of Miyawaki et al. are, by definition, "ready to use."

7. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Venn et al. (British Journal of Anaesthesia, 2002, Vol. 88(5), pages 669-675) , in view of Precedex® Package Insert (Document EN-2680, Hospira, Inc., 9/2010, downloaded on 8/10/2012 from "www.precedex.com/wp-content/uploads/2010/11/Precedex_PI.pdf", pages 1-24), and evidenced by Sunkel et al. (US 6806291 B1), Ibrahim et al. (US 5716988), or Xylocaine® Package Insert (AstraZeneca LP, 2001 and 2007, downloaded on 8/10/2012 from "www.pdr3d.com/print.php?c=4818", pages 1-30).

Venn et al. teach a study of the pharmacokinetics of dexmedetomidine in patients. The intravenous dexmedetomidine solution used in the study was made by diluting dexmedetomidine (supplied in 2 ml ampules) with normal saline to produce a concentration of 8 µg/ml. Precedex® is the source of the 2 ml ampules. See Abstract; page 670, left column 4th full paragraph; and page 674, left column, 6th full sentence.

This concentration of dexmedetomidine is encompassed by the concentration ranges of instant Claims 1-3. Further, 8 µg/ml also reads on instant Claim 4 (a concentration of about 1 to **about 7** µg/ml) because 8 µg/ml is about 7 µg/ml (see the definition of "about" at page 7, paragraph [0035] of the instant Specification).

Although Venn et al. do not teach the use of sealed glass containers (e.g. sealed glass vials or ampules) for the 8 µg/ml dexmedetomidine solution used for intravenous

administration to the patients, the use of such containers for parenteral pharmaceuticals is common and well known.

For example, the Xylocaine® Package Insert teaches Xylocaine® (lidocaine HCl) in isotonic solution is provided in glass ampules and single or multiple dose vials, at various concentrations. Further, the ampules and vials are provided comprising various volumes of the parenteral solutions (e.g., 2, 5, 10, 20 and 50 ml). See page 1, the "Description" section, and page 8, the "How Supplied" section. Sunkel et al. disclose pharmaceutical compositions for parenteral administration contained in ampules and multiple dose vials made of glass or plastic. See column 4, lines 14-16 and 29-31. In fact, the compositions of Sunkel et al. may include dexmedetomidine. See column 5, line 5. Ibrahim et al. provide another example of the use of sealed glass vials for parenteral aqueous pharmaceutical solutions. See column 3, lines 45-62, which discloses aqueous solutions of oxaliplatinum contained in 50 ml sealed glass vials.

It would have been obvious to one of ordinary skill in the art to provide the dexmedetomidine in sealed glass containers prior to administration to patients because to do so was a common and predictable method of providing parenteral pharmaceutical compositions at the time of the invention. Additionally, further motivation to use sealed glass containers for the dexmedetomidine solutions taught by Venn et al. comes from the knowledge that the manufacturer of the dexmedetomidine stock solution used by Venn et al. (Precedex®) provides the pharmaceutical in a sealed glass vial (*supra*). Furthermore, only 2 options are available to the artisan practicing the dilution instructions of the reference: (1) mixing the solution in a sealed container, or (2) mixing

the solution in an unsealed container. The artisan would clearly immediately envisage the mixing of the formulation in a sealed container in order to maintain the sterility of the composition for parenteral administration. Similarly, there are a limited number of options available to the artisan with regard to the material of the container (e.g., glass, plastic, or PVC). See *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), where claims to a specific compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound. The broad generic formula seemed to describe an infinite number of compounds but claim 1 was limited to a structure with only one variable substituent R. This substituent was limited to low alkyl radicals. One of ordinary skill in the art would at once envisage the subject matter within claim 1 of the reference.

Providing the dexmedetomidine solutions in various volumes (e.g., 20, 50 or 100 ml) would be obvious. The volume of solution provided would depend on the expected administered amount of the composition and other variables specific to the treatment at hand.

8. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Precedex® Package Insert (Document EN-2680, Hospira, Inc., 9/2010, downloaded on 8/10/2012 from “www.precedex.com/wp-content/uploads/2010/11/Precedex_PI.pdf”, pages 1-24), and evidenced by Sunkel et al. (US 6806291 B1), Ibrahim et al. (US

5716988), or Xylocaine® Package Insert (AstraZeneca LP, 2001 and 2007, downloaded on 8/10/2012 from "www.pdr3d.com/print.php?c=4818", pages 1-30).

The Precedex® Package Insert teaches Precedex® is dexmedetomidine hydrochloride for injection and is provided in a sealed glass vial. The Insert teaches the dexmedetomidine must be diluted prior to use with a 0.9% sodium chloride solution to provide a final concentration of 4 µg/ml, for administration to the patient. See the first page, left, column.

This administered concentration of dexmedetomidine is encompassed by the concentration ranges of instant Claims 1-4.

Although Precedex® Package Insert does not teach the use of sealed glass containers (e.g. sealed glass vials or ampules) for the 4 µg/ml dexmedetomidine solution used for intravenous administration to the patients, the use of such containers for parenteral pharmaceuticals is common and well known.

For example, the Xylocaine® Package Insert teaches Xylocaine® (lidocaine HCl) in isotonic solution is provided in glass ampules and single or multiple dose vials, at various concentrations. Further, the ampules and vials are provided comprising various volumes of the parenteral solutions (e.g., 2, 5, 10, 20 and 50 ml). See page 1, the "Description" section, and page 8, the "How Supplied" section. Sunkel et al. disclose pharmaceutical compositions for parenteral administration contained in ampules and multiple dose vials made of glass or plastic. See column 4, lines 14-16 and 29-31. In fact, the compositions of Sunkel et al. may include dexmedetomidine. See column 5, line 5. Ibrahim et al. provide another example of the use of sealed glass vials for

parenteral aqueous pharmaceutical solutions. See column 3, lines 45-62, which discloses aqueous solutions of oxaliplatinum contained in 50 ml sealed glass vials.

It would have been obvious to one of ordinary skill in the art to provide the dexmedetomidine in sealed glass containers prior to administration to patients because to do so was a common and predictable method of providing parenteral pharmaceutical compositions at the time of the invention. Additionally, further motivation to use sealed glass containers for the dexmedetomidine solutions taught by Venn et al. comes from the knowledge that the manufacturer of the dexmedetomidine stock solution used by Venn et al. (Precedex®) provides the pharmaceutical in a sealed glass vial (*supra*). Furthermore, only 2 options are available to the artisan practicing the dilution instructions of the reference: (1) mixing the solution in a sealed container, or (2) mixing the solution in an unsealed container. The artisan would clearly immediately envisage the mixing of the formulation in a sealed container in order to maintain the sterility of the composition for parenteral administration. Similarly, there are a limited number of options available to the artisan with regard to the material of the container (e.g., glass, plastic, or PVC). See *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), where claims to a specific compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound. The broad generic formula seemed to describe an infinite number of compounds but claim 1 was limited to a structure with only one variable substituent R. This substituent was limited to low alkyl radicals. One

of ordinary skill in the art would at once envisage the subject matter within claim 1 of the reference.

Providing the dexmedetomidine solutions in various volumes (e.g., 20, 50 or 100 ml) would be obvious. The volume of solution provided would depend on the expected administered amount of the composition and other variables specific to the treatment at hand.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 8,242,158. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims only differ in the recited concentrations of dexmedetomidine. The claims of the ‘158 patent are drawn to dexmedetomidine at a concentration of 4 µg/ml. The instant claims recite concentration ranges of dexmedetomidine that encompass 4 µg/ml.

Conclusion

11. Claims 1-7 are rejected.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

§ 2

’470 PATENT RESPONSE TO OFFICE ACTION (SEPT. 17, 2012)

REMARKS

Reconsideration is respectfully requested. Claims 1-7 are currently pending. No amendments have been introduced into the claims. Accordingly, no new matter has been introduced in this response.

I. Rejections Under 35 U.S.C. § 103(a)

A. U.S. Patent Application Publication No. 2011/0230534 as evidenced by a Precedex® Package Insert, U.S. Patent No. 6,806,291, U.S. Patent No. 5,716,988, and a Xylocaine® Package Insert

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent Application Publication No. 2011/0230534 to Miyawaki et al. (hereafter, "Miyawaki") as evidenced by the Precedex® Package Insert, U.S. Patent No. 6,806,291 to Sunkel et al. (hereafter, "Sunkel"), U.S. Patent No. 5,716,988 to Ibrahim et al. (hereafter, "Ibrahim"), and the Xylocaine® Package Insert.

The Examiner contends that Miyawaki discloses a kit for a ready to use parenterally administered local anesthesia, which allegedly includes a local anesthetic agent and dexmedetomidine or a salt thereof. According to the Examiner, the dexmedetomidine can be at a concentration of between $1x10^{-10}$ M and $1x10^{-6}$ M (*i.e.*, $2x10^{-5}$ μg/mL to 0.2 μg/mL), or at specific concentrations such as $4x10^{-6}$ M (*i.e.*, 0.8 μg/mL), wherein the dexmedetomidine is prepared from a Precedex® stock solution of dexmedetomidine hydrochloride that is diluted with 0.9% sodium chloride solution to achieve the desired dexmedetomidine concentrations. The Examiner alleges that the 0.8 μg/mL concentration of dexmedetomidine disclosed by Miyawaki reads on claim 4 because 0.8 μg/mL "is about 1 μg/mL," as recited by claim 4.

The Examiner concedes that Miyawaki does not suggest or describe disposing the parenteral compositions described by the reference within a sealed glass container. However, the Examiner relies on the Precedex® Package Insert, the Xylocaine® Package Insert, Sunkel and Ibrahim as evidence that disposing parenteral compositions in sealed glass containers is common and well known in the art. According to the Examiner, the Precedex® Package Insert describes a 100 μg/mL dexmedetomidine hydrochloride solution disposed within sealed glass vials that is diluted to 4 μg/mL with 0.9% sodium chloride solution for use. The Examiner also purports that the Xylocaine® Package Insert discloses a lidocaine HCl solution provided in glass ampoules and

vials at various concentrations and volumes. Further, the Examiner asserts that Sunkel discloses pharmaceutical compositions for parenteral administration, which may comprise dexmedetomidine, contained in glass ampoules and vials. Lastly, the Examiner alleges that Ibrahim discloses compositions comprising oxaliplatinum contained in 50 mL sealed glass vials.

The Examiner concludes that it would have been obvious to provide the diluted dexmedetomidine composition described by Miyawaki in sealed glass containers since it allegedly was a common and predictable method of providing parenteral pharmaceutical compositions. Furthermore, the Examiner contends that there are a limited number of options available with regard to the material for the container, and as such, the skilled artisan would envisage disposing the dilution in a glass container. Additionally, the Examiner alleges that it would have been obvious to use a sealed glass storage container to preserve the sterility of the dilution.

Applicants respectfully traverse the rejection. To support an assertion of obviousness, the Examiner must show that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." *See* M.P.E.P § 2143. *See also KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 (2007). Applicants submit that the claims are not obvious over the cited references because the combined disclosure of the cited references does not suggest or describe all of the claims elements. Furthermore, practicing the claims results in surprising and unexpected advantages with regard to stability of the claimed composition over the prior art, which is indisputable evidence of the non-obviousness of the claims over the cited references.

Independent claim 1 recites a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container. In contrast to the claims, as conceded by the Examiner, Miyawaki does not suggest or describe that the diluted dexmedetomidine compositions recited by the reference are disposed within a sealed glass container. Rather, Miyawaki discloses a kit for the preparation of a composition for local anesthesia, wherein the composition includes a local anesthetic agent, and an α_2 receptor agonist, such as dexmedetomidine. The kit provides for the combination of components into a single composition in advance of its use for local anesthesia (*see* Miyawaki, page 2, paragraphs [0024] - [0031]; and page 9, paragraph [0095]).

Importantly, contrary to the Examiner's assertions, Applicants submit that none of the Precedex® Package Insert, Sunkel, Ibrahim or the Xylocaine® Package Insert provide an artisan of ordinary skill with guidance, suggestion, or motivation to prepare the diluted dexmedetomidine compositions described by Miyawaki in a sealed glass container.

With regard to the Precedex® Package Insert, the reference does not suggest or describe a composition comprising about 0.005 to about 50 μg/mL dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the composition is disposed within a sealed glass container as a ready to use premixture. In contrast, the Precedex® Package Insert discloses a dexmedetomidine composition that is supplied as a 100 μg/mL concentration that must be diluted to 4 μg/mL prior to administration to a subject. (*See* the Precedex® Package Insert, page 1, col. 1). The reference does not suggest or describe that the dexmedetomidine would have been diluted into a sealed glass container. Rather, because the diluted composition is administered to a subject by an intravenous infusion (*see, e.g.,* the Precedex® Package Insert, page 1, col. 1), an artisan of ordinary skill would have diluted the dexmedetomidine in a device for infusion, such as a plastic infusion bag or plastic syringe, and would not have disposed the 4 μg/mL dilution into a sealed glass container. The Examiner provides no basis or evidence to suggest that an artisan of ordinary skill would have prepared the dilution in a sealed glass container as claimed. Furthermore, Applicants note that in rejecting the claims as allegedly being obvious over the Precedex® Package Insert (*see* the Office Action, item 8, page 9; and section I(C), below), the Examiner concedes that the Precedex® Package Insert does not suggest or describe disposing the diluted 4 μg/mL dexmedetomidine composition in a sealed glass container. Thus, in view of the Precedex® Package Insert, the artisan would not have been motivated to prepare the diluted dexmedetomidine composition described by Miyawaki in a sealed glass container.

Additionally, Applicants note that the Precedex® Package Insert describes dexmedetomidine compositions for intravenous administration to a subject. (*See* the Precedex® Package Insert, page 1, col. 1). In contrast, Miyawaki is directed to compositions for injection that produce a local anesthetic effect. (*See* Miyawaki, page 4, paragraph [0048]). Miyawaki does not suggest or describe that such compositions can be administered via an intravenous infusion. Thus, an artisan of ordinary skill would not have been motivated to combine the features of an intravenous formulation described by the Precedex® Package Insert with a composition formulated for local injection, as described by Miyawaki.

With regard to the references cited by the Examiner, only Miyawaki and the Precedex® Package Insert provide any disclosure related to formulating dexmedetomidine at specific concentrations for use. As evidenced by Miyawaki and the Precedex® Package Insert, dexmedetomidine is presently supplied as a 100 μg/mL concentrated solution, and must be diluted to a lower concentration for use. Applicants note that a primary difference between the claimed ready to use premixture composition and the diluted composition described by the cited references is that the claimed composition is a ready to use premixture that does not require any dilution or reconstitution prior to administration to a subject. (*See* the specification, page 5, paragraphs [0024]-[0025]). Accordingly, upon withdrawing the claimed composition from a sealed glass container, an artisan of ordinary skill can administer the composition directly to a subject. In contrast, the compositions described by the cited references are not suitable for administering to a patient upon withdrawing the composition from a sealed container (*i.e.*, a 2 mL vial or ampoule in which the concentrated 100 μg/mL formulation is stored in, *see* the Precedex® Package Insert, page 1, col. 1). Rather, after withdrawing the concentrated 100 μg/mL composition from a sealed container, the composition must be diluted prior to administration to a subject.

Applicants also submit that the claimed ready to use premixture composition provides for surprising and unexpected advantages over the diluted compositions described by the cited references. For example, the claimed ready to use composition provides for advantages with regard to the ability to store the composition over prolonged periods of time, while maintaining a stable formulation. Such advantages over the diluted compositions of the cited references is further evidence of the non-obviousness of the claims over the cited references. (*See* M.P.E.P. § 716.02(a)). For example, as described by the present application, the claimed pharmaceutical formulation "can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi." (*See* the specification, page 8, paragraph [0038]). The ability to store the claimed composition for prolonged periods of time are shown in at least Examples 1 and 3 of the application, which demonstrate that a ready to use 4 μg/mL premixture composition was stable for up to 9 months when stored in a glass container. As described in Example 1, a 4 μg/mL premixture formulation stored in glass vials and ampoules maintained a higher level of potency after a 5 month storage period compared to storage in plastic, CR3 or PVC containers. (*See*, the specification, pages 18-20, paragraphs [0086] - [0088]). As described by Table 1, when stored in glass vials or ampoules,

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

In contrast, the Precedex® Package Insert discloses that the concentrated 100 μg/mL dexmedetomidine composition is suitable for storage, and not the diluted 4 μg/mL composition. (*See* the Precedex® Package Insert, page 23, section 16). Furthermore, as described by the FDA Memorandum by Cynthia G. McCormick, M.D., dated November 30, 1999, in connection with the Medical Reviews of the Precedex (dexmedetomidine hydrochloride injection) Application No. 21-038 submitted to the FDA, and available on the FDA website July 26, 2001 (hereafter, "the Memorandum," a copy of which was submitted July 3, 2012 in an Information Disclosure Statement Not In Support Of Accelerated Examination Support Document And Petition To Make Special), the undiluted dexmedetomidine composition is manufactured through an "aseptic fill and terminal sterilization by autoclave," (*see*, the Memorandum, page 8, third paragraph), and as such, is suitable for storage. However, once diluted for administration, the diluted composition is stable for only 24 hours. (*See* the Memorandum, page 8, paragraph 4, stating: "The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours" (emphasis added)). Thus, unlike the claimed ready to use premixture composition, which can be stored for prolonged periods of time, the diluted composition described by the cited references is prepared for use within a 24-hour period, and is not a formulation suitable for prolonged storage.

Accordingly, the memorandum provides further evidence that formulating the claimed composition as a ready to use premixture provides for surprising and unexpected advantages over the dilutions described by the cited references. While diluting the 100 μg/mL concentrate produces a composition that is stable and useable for a 24-hour period after dilution, the claimed ready to use premixture can be stored for at least 9 months in a sealed glass container. Such a characteristic is not suggested or disclosed by the cited references, as evidenced by the Memorandum. Rather, in contrast, an artisan of ordinary skill would understand that a diluted dexmedetomidine composition is only stable and useable for up to 24 hours.

Additionally, in view of the Precedex® Package Insert's disclosure as a whole, an artisan of ordinary skill would understand that a diluted dexmedetomidine formulation is formulated for immediate administration to a subject, and not suitable for prolonged storage. For example, the Precedex® Package Insert discloses that the composition is "preservative-free and contains no additives or chemical stabilizers." (*See* the Precedex® Package Insert, page 16, first paragraph). Thus, the artisan would have had no expectation that the diluted formulation is suitable for storage. Additionally, the diluted composition is intended for a single use only, and further, such a single use can only be for a period of, at most, 24 hours. (*See* the Precedex® Package Insert, page 1, col. 1). As such, the artisan would understand that any portion of the diluted composition that is not administered to a subject, or that remains after a 24-hour dosing period, cannot be stored for later use. Finally, contamination with impurities is a greater concern for compositions diluted to a low concentration. "Since the drug is present at such a low concentration . . . even ppb levels of impurities would have a significant contribution toward the impurity limit." (*See* the specification, page 32, paragraph [00115]). Accordingly, the skilled artisan would have been motivated to immediately use the diluted composition once prepared, and not store the dilution since storage could increase the risk of contamination, *e.g.*, microbe growth resulting from contamination during dilution.

Furthermore, as described in the Declaration of Huailiang Wu (hereafter, "the Declaration"), submitted herewith as Attachment A, 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. Specifically, as described by the Declaration, the potency of the 1 μg/mL dexmedetomidine formulation decreased by 1.82% about 12 hours after being disposed in a PVC storage bag (preTS), and by 7.81% (T=0) following autoclave compared to control. After storage for three days in a PVC bag at 25°C and 40°C, the potency of the 1 μg/mL formulation decreased by 8.05% and 8.83%, respectively, compared to control. Similarly, the potency of the 10, 15 and 50 μg/mL formulations stored in PVC bags decreased by 5.84%, 5.54% and 4.32% following autoclave, respectively, compared to control. After storage for three days in PVC bags at 25°C, the potency of the three concentrations decreased by 6.24%, 6.17% and 5.26%, respectively, compared to control. After storage for three days in PVC bags at 40°C, the potency of the three concentrations decreased by 6.28%, 6.62% and 5.36%, respectively, compared to control.

In contrast, when the dexmedetomidine compositions were stored in glass containers, the potency of the dexmedetomidine was maintained. When stored in glass vials, none of the four concentrations of dexmedetomidine experienced any loss in potency after disposing the formulations in glass vials or after autoclaving, compared to control. After storage for 3 days in glass vials at 25°C, the decrease in potency of the 1, 10, 15 and 50 μg/mL dexmedetomidine compositions were 0%, 0%, 0.39% and 0.44%, respectively, compared to control. After storage for 3 days in glass vials at 40°C, the decrease in potency of the 1, 10, 15 and 50 μg/mL dexmedetomidine compositions were 0.42%, 0%, 0.27% and 0.51%, respectively, compared to control.

Thus, as described by the Declaration, storing a ready to use formulation of dexmedetomidine at concentrations recited by the claims in glass containers resulted in an unexpected reduction in potency loss of the dexmedetomidine composition compared to storage in plastic PVC containers. Storing the formulations in PVC containers resulted in a decrease in dexmedetomidine potency after disposition within the containers, after autoclave, and after a three-day storage period at 25°C or 40°C. The maximum detectable loss in potency of the samples stored in PVC containers after the three-day storage period was 8.83%, whereas the glass containers showed a maximum loss of only 0.51%.

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

Thus, maintaining the potency of a ready to use dexmedetomidine composition during autoclave is dependent at least upon the type of container the composition is disposed in. As described by the Declaration, storing the ready to use dexmedetomidine composition in a glass container reduced potency loss compared to plastic PVC containers during autoclave. Additionally, as described by the Declaration, storing the ready to use composition in glass containers inhibited additional potency loss during prolonged storage of the composition. As

described previously, an undiluted dexmedetomidine pharmaceutical composition for parenteral use is manufactured through an "aseptic fill and terminal sterilization by autoclave," (*see*, the Memorandum, page 8, third paragraph). Such a manufacturing process provides a sterile solution that is suitable for storage and safe to dilute for administering to patients. As discussed previously, and described by the Declaration, the ready to use composition recited by the claims is also suitable for storage, and formulated for administration to patients. However, unlike the composition described by the Memorandum, the claimed dexmedetomidine composition does not require dilution prior to administration to a patient. Because the claimed dexmedetomidine composition is formulated as a "ready to use" composition, sterilizing the composition during manufacture through, for example, autoclaving, would be required to produce a composition that is safe for parenteral administration to a patient.

As described by Examples 1 and 2 of the application, and further, as described by the Declaration, ready to use dexmedetomidine compositions at concentrations recited by the claims were more stable over prolonged periods of time when stored in glass containers compared to storage in plastic PVC containers. Such an increase in stability was detectable whether the compositions were autoclaved, for example, as during the manufacture of a dexmedetomidine composition for parenteral use, or not before storage. Such an increase in stability achieved by storing a ready to use dexmedetomidine compositions in a class container is a surprising and unexpected result of practicing the claims, and is evidence of the non-obviousness of the claims over the cited references. (*See* M.P.E.P. § 716.02(a)).

With regard to Sunkel, Applicants note that this reference is directed to pharmaceutical compositions comprising SCP-M series compounds. (*See* Sunkel, col. 2, line 1 to col. 3, line 3). SCP-M series compounds are different compounds that are structurally unrelated to dexmedetomidine, and as such, an obviousness rejection based on a property of the structurally unrelated SCP-M series compounds (*e.g.*, storability in a sealed glass container), would be improper. Generalizing characteristics and properties of a chemical entity to a structurally unrelated chemical entity is not proper, and can not form a basis for an obviousness rejection. This inability to generalize characteristics and properties of different chemical entities is recognized by the USPTO. For example, as described by M.P.E.P. § 2144.09, a rejection based on obviousness is "founded on the expectation that compounds similar in structure will have similar properties." (*See* M.P.E.P. § 2144.09(I)). Because SCP-M series compounds are different

chemical entities from dexmedetomidine, with different chemical structures, it would be improper to base an obviousness rejection on the conclusion that storage conditions applicable to SCP-M series compounds would be suitable for a diluted dexmedetomidine composition. Thus, the reference's disclosure that SCP-M series compounds can be stored in a glass container provides an artisan of ordinary skill with no guidance or suggestion that such storage conditions would have been applicable to a diluted dexmedetomidine composition. Furthermore, as described in greater detail above, dexmedetomidine itself exhibits different properties with regard to stability when formulated as a concentrated stock solution, and after dilution for use. Thus, the disclosure of Sunkel provides an artisan of ordinary skill with no suggestion or motivation to dilute the dexmedetomidine of Miyawaki into a sealed glass container.

Applicants also submit that Sunkel provides no suggestion or disclosure that storage in a glass container provides for any advantages over storage in other containers, such as, for example, a plastic container. In contrast, as described above, the ready to use dexmedetomidine formulations of the present application exhibited surprising and unexpected advantages with regard to stability when stored in a sealed glass container, compared to storage in a plastic container. Such a surprising and unexpected advantage is evidence of the non-obviousness of the claims of the application over the cited references.

With regard to Ibrahim and the Xylocaine® Package Insert, Applicants note that these two references are directed to compositions comprising oxaliplatinum (*see* Ibrahim, col. 3, lines 45-62) and lidocaine HCl (*see* the Xylocaine® Package Insert, page 1, first paragraph), respectively. The references provide no disclosure related to dexmedetomidine or to compositions comprising dexmedetomidine. Each of the oxaliplatinum and lidocaine compounds described by Ibrahim and the Xylocaine® Package Insert are different compounds that are each structurally unrelated to dexmedetomidine. Accordingly, any property of either oxaliplatinum or lidocaine HCl, for example, with regard to storage conditions, can not be generalized to dexmedetomidine. (*See* M.P.E.P. § 2144.09(I)). Additionally, as described above, the inability to generalize properties of one chemical compound to another is further evidenced by dexmedetomidine itself, which exhibits different properties with regard to stability when formulated as a concentrated stock solution, and after dilution for use. Thus, Ibrahim and the Xylocaine® Package Insert's disclosure that oxaliplatinum and lidocaine, respectively, can be stored in a glass container provides an

artisan of ordinary skill with no guidance or suggestion to store a diluted dexmedetomidine composition in a glass container.

Additionally, Applicants note that some of the lidocaine compositions described by the Xylocaine® Package Insert comprise methyl paraben as an antiseptic preservative, sodium metabisulfide as an antioxidant, and citric acid as a stabilizer. (*See* Xylocaine® Package Insert, page 1, Description). In contrast, Miyawaki does not suggest or describe that the diluted dexmedetomidine composition described by the reference includes any preservatives, antioxidants, or stabilizers. Thus, when formulating different chemical entities into pharmaceutical compositions, some chemical entities, such as certain lidocaine compositions described by the Xylocaine® Package Insert, require additional ingredients to successfully formulate the pharmaceutical compositions, while other chemical entities, such as the dexmedetomidine described by Miyawaki, do not. Accordingly, an artisan of ordinary skill would have had no motivation to combine the disclosure of the Xylocaine® Package Insert with Miyawaki since different chemical entities can require different conditions to successfully formulate a pharmaceutical composition.

Furthermore, Applicants note that the Examiner alleges that "there are only a limited number of options available to the artisan with regard to the material of the container" in which the composition described by Miyawaki can be stored in. (*See* the Office Action, page 5). Thus, according to the Examiner, it would have been obvious to the artisan to envisage storing the diluted dexmedetomidine composition described by Miyawaki in a sealed glass container.

Applicants respectfully disagree. In addition to glass, there are numerous materials from which a container for a pharmaceutical composition can be manufactured from. For example, a non-limiting list of examples include but are not limited to polypropylene, polyethylene, cyclo-olefin copolymer, polyolefin, polyester, and polyvinyl chloride -- all of which are materials that can be used for manufacturing containers for pharmaceutical compositions. (*See* the specification, page 13, paragraph [0060], and Examples 1 and 2, pages 18-22; *see, also,* Petersen, "Trends in Pharmaceutical Primary Packaging for Injectables - Solutions for New Challenges," *Drug Development and Delivery*, Issue Date: September 2012, Posted On: 9/5/2012, (hereafter, "Petersen"), submitted herewith in an Information Disclosure Statement Not In Support Of Accelerated Examination Support Document And Petition To Make Special). However, as discussed above, none of the cited references provide any suggestion or guidance to store a diluted

dexmedetomidine composition in a sealed glass container. Accordingly, the Examiner's conclusion that it would have been obvious to store Miyawaki's composition in a sealed glass container is based on the artisan's random selection of a glass storage container for disposing the diluted composition. Such a conclusion is improper in view of at least the surprising and unexpected results achieved by practicing the claims of the present application.

Furthermore, as described by Petersen, when selecting a container to store a pharmaceutical composition, several factors should be considered, for example, "drug product formulation properties, dosage, type of application, and end-user friendliness." (*See* Petersen, page 1). Additionally, containers can be treated with different agents depending on the pharmaceutical composition being stored in the container. For example, surface treatments, such as ammonium sulfate or silica treatment, can be applied to glass containers to minimize sodium ion leaching and a subsequent pH shift, or to prevent interaction of the glass matrix with the drug. (*See* Petersen, page 5, Trend 4: New Materials). However, none of the references cited by the Examiner provide any suggestion or guidance that a glass container would be advantageous for storing the diluted dexmedetomidine composition described by Miyawaki. Additionally, plastic materials "such as cyclic olefins . . . offer far greater design flexibility, facilitate tighter dimensional tolerances, and are more break resistant than glass." (*See* Petersen, page 5, Trend 4: New Materials). Thus, in view of the material options for the storage container, and the advantages provided for by non-glass materials, the selection of a glass container to dispose the dexmedetomidine dilution described by Miyawaki would not have been obvious.

In view of the advantages of the claimed ready to use dexmedetomidine premixture composition over the diluted dexmedetomidine compositions disclosed by the cited references with regard to storage and stability over prolonged periods of time, and further, in view of the cited references' failure to provide an artisan of ordinary skill with any suggestion or motivation to dispose a diluted dexmedetomidine composition at the claimed concentration ranges in a sealed glass container, Applicants submit that the claims are not obvious over the cited reference, and respectfully request that the rejection be withdrawn.

B. Venn in view of the Precedex® Package Insert, and as evidenced by Sunkel, Ibrahim and the Xylocaine® Package Insert

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Venn et al., British Journal of Anaesthesia, 2002, Vol. 88(5), pages 669-675 (hereafter, "Venn") in view of the Precedex® Package Insert, as evidenced by Sunkel, Ibrahim, and the Xylocaine® Package Insert.

The Examiner contends that Venn discloses a study of the pharmacokinetics of dexmedetomidine, wherein the intravenous dexmedetomidine used in the study was prepared by diluting a 100 μg/mL stock solution of dexmedetomidine (*i.e.*, Precedex®) to achieve an 8 μg/mL solution for use. The Examiner alleges that the 8 μg/mL concentration of dexmedetomidine disclosed by Venn reads on claim 4 because 8 μg/mL "is about 7 μg/mL," as recited by claim 4.

The Examiner concedes that Venn does not suggest or describe disposing the parenteral composition described by the reference within a sealed glass container. However, the Examiner relies on the Precedex® Package Insert, as evidenced by the Xylocaine® Package Insert, Sunkel and Ibrahim, for disclosing that disposing parenteral compositions in sealed glass containers is common and well known in the art. According to the Examiner, the Precedex® Package Insert describes a 100 μg/mL dexmedetomidine hydrochloride solution disposed within sealed glass vials that is diluted to 4 μg/mL with 0.9% sodium chloride solution for use. The Examiner also states that the Xylocaine® Package Insert discloses a lidocaine HCl solution provided in glass ampoules and vials at various concentrations and volumes, and that Ibrahim discloses compositions comprising oxaliplatinum contained in 50 mL sealed glass vials. The Examiner further alleges that Sunkel discloses pharmaceutical compositions for parenteral administration, which may comprise dexmedetomidine, contained in glass ampoules and vials. The Examiner concludes that it would have been obvious to provide the diluted dexmedetomidine composition described by Venn in sealed glass containers since it allegedly was a common and predictable method of providing parenteral pharmaceutical compositions. Furthermore, the Examiner contends that there are a limited number of options available with regard to the material for the container, and as such, the skilled artisan would envisage disposing the dilution in a glass container. Additionally, the Examiner alleges that it would have been obvious to use a sealed glass storage container to preserve the sterility of the dilution.

Applicants respectfully traverse the rejection. As described previously, independent claim 1 recites a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container. In contrast to the claims, Venn does not suggest or describe that the diluted dexmedetomidine composition recited by the reference is disposed within a sealed glass container. Rather, Venn discloses diluting a 100 μg/mL stock solution of dexmedetomidine to a concentration of 8 μg/mL for infusion into a patient. (*See* Venn, page 670, col. 1, fourth full paragraph). Furthermore, unlike the ready to use composition recited by the claims, which can be stored for prolonged periods of time, as described previously, Venn describes a diluted dexmedetomidine composition that must be used within a 24 hour period (*see* discussion in Section I(a) regarding the Memorandum), and is not suitable for prolonged storage.

The Examiner relies on the Precedex® Package Insert for the reference's disclosure of a dexmedetomidine pharmaceutical compositions disposed within a sealed glass container. According to the Examiner, as evidenced by Sunkel, Ibrahim and the Xylocaine® Package Insert, storage of pharmaceutical compositions in glass containers is a common and predictable method of providing parenteral pharmaceutical compositions. However, Applicants submit that none of the Precedex® Package Insert, Sunkel, Ibrahim or the Xylocaine® Package Insert provide an artisan of ordinary skill with guidance, suggestion, or motivation to prepare the diluted dexmedetomidine composition described by Venn into a sealed glass container.

With regard to the Precedex® Package Insert, as discussed above, the reference does not suggest or describe a composition comprising about 0.005 to about 50 μg/mL dexmedetomidine, or a pharmaceutically acceptable salt thereof, wherein the composition is disposed within a sealed glass container as a ready to use premixture. In contrast, the Precedex® Package Insert discloses a dexmedetomidine composition that is supplied as a 100 μg/mL concentration that must be diluted to 4 μg/mL prior to administration to a subject, and does not suggest or describe that the dexmedetomidine would have been diluted into a sealed glass container. (*See* the Precedex® Package Insert, page 1, col. 1). Rather, because the diluted composition must be administered to a subject by an intravenous infusion within a 24-hour period, an artisan of ordinary skill would have diluted the dexmedetomidine in a device for infusion, such as a plastic infusion bag or plastic syringe, and would not have disposed the 4 μg/mL dilution in a sealed glass container.

Additionally, the dexmedetomidine compositions described by Venn and the other cited references require dilution from a 100 μg/mL stock prior to use. In contrast, as described above, the ready to use dexmedetomidine premixture recited by the claims does not require dilution prior to use, and preparing the claimed composition in a sealed glass container provides for surprising and unexpected advantages over the diluted compositions described by the cited references with regard to the ability to store the composition over prolonged periods of time. Such advantages over the diluted compositions of the cited references is further evidence of the non-obviousness of the claims over the cited references. (*See* M.P.E.P. § 716.02(a)).

Additionally, as described above, because diluting the dexmedetomidine for use, as described by the cited references, can increase the chance of contamination with impurities, a skilled artisan would have been motivated to immediately use the diluted composition once prepared, and not store the dilution since storage could increase the risk of contamination, *e.g.*, microbe growth resulting from contamination during dilution.

Furthermore, Applicants note that in rejecting the claims as allegedly being obvious over the Precedex® Package Insert (*see* Office Action, item 8, page 9; and section I(C), below), the Examiner concedes that the Precedex® Package Insert does not suggest or describe disposing the diluted 4 μg/mL dexmedetomidine composition in a sealed glass container. Thus, in view of the Precedex® Package Insert, the artisan would not have been motivated to prepare the dexmedetomidine dilution described by Venn in a sealed glass container.

With regard to Sunkel, Ibrahim and the Xylocaine® Package Insert, as described above, these references are directed to pharmaceutical compositions comprising oxaliplatinum, lidocaine-HCl and SCP-M series compounds, respectively, each of which are structurally unrelated to dexmedetomidine. As such, an obviousness rejection based on a property of any one of these structurally unrelated compounds would be improper. Additionally, as discussed above, the Xylocaine® Package Insert describes lidocaine compositions comprising preservatives, antioxidants, and stabilizers. However, in contrast, Venn describes diluting a 100 μg/mL dexmedetomidine composition for use, and does not suggest or describe including preservatives, antioxidants, or stabilizers in the composition. As previously discussed, in view of such differences in formulating different chemical entities into pharmaceutical compositions, an artisan of ordinary skill would not have been motivated to combine the disclosures of Venn and the Xylocaine® Package Insert. Furthermore, as described above, the references provide no

suggestion or disclosure that storage in a glass container provides for any advantages over storage in other containers, such as, for example, a plastic container. Thus, concluding that the skilled artisan would dispose the dexmedetomidine composition of Venn in a glass container is based on a random selection of a glass storage container by the skilled artisan from the numerous available container types. As discussed previously, such a conclusion is improper in view of the surprising and unexpected advantages with regard to stability of the claimed composition, and further in view of the advantages provided for by non-glass storage materials with regard to design flexibility, dimensional tolerances, and break resistance discussed previously.

Accordingly, none of the Precedex® Package Insert, Ibrahim, the Xylocaine® Package Insert, or Sunkel provide an artisan of ordinary skill with any guidance or suggestion to prepare the diluted dexmedetomidine composition described by Venn in a sealed glass container. In view of the foregoing, Applicants submit that the claims are not obvious over the cited references, and respectfully request that the rejection be withdrawn.

C. Precedex® Package Insert as evidenced by Sunkel, Ibrahim and the Xylocaine® Package Insert

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Precedex® Package Insert as evidenced by Sunkel, Ibrahim, and the Xylocaine® Package Insert.

The Examiner contends that the Precedex® Package Insert describes a 100 μg/mL dexmedetomidine hydrochloride solution disposed within sealed glass vials that is diluted to 4 μg/mL with 0.9% sodium chloride solution for use. The Examiner concedes that the Precedex® Package Insert does not suggest or describe disposing the 4 μg/mL dexmedetomidine dilution within a sealed glass container. However, the Examiner relies on the Xylocaine® Package Insert, Sunkel and Ibrahim, as described above, as evidence that disposing parenteral compositions in sealed glass containers is common and well known in the art.

Applicants respectfully traverse the rejection. As described previously, independent claim 1 recites a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container. In contrast, the Precedex® Package Insert discloses a dexmedetomidine composition that is supplied as a 100 μg/mL concentration that must be diluted to 4 μg/mL prior to administration to a subject

within a 24-hour period. (*See* the Precedex® Package Insert, page 1, col. 1). The reference does not suggest or describe that the dexmedetomidine would have been diluted into a sealed glass container, or that the diluted composition would be suitable for storage.

The Examiner relies on Sunkel, Ibrahim and the Xylocaine® Package Insert for the references' disclosure of pharmaceutical compositions disposed within sealed glass containers, which, according to the Examiner, is evidence that storage of such compositions in glass containers is a common and predictable method of providing parenteral pharmaceutical compositions. However, as described previously, Sunkel, Ibrahim and the Xylocaine® Package Insert are each directed to a structurally different compound from dexmedetomidine, and as such, basing an obviousness rejection on a generalization of a property of any of the compounds described by the references is improper. Additionally, some of the lidocaine compositions described by Xylocaine® Package Insert also include preservatives, antioxidants, and stabilizers. These ingredients are not included in the dexmedetomidine composition described by the Precedex® Package Insert. As previously discussed, in view of such differences in formulating different chemical entities into pharmaceutical compositions, an artisan of ordinary skill would not have been motivated to combine the disclosures of the Precedex® Package Insert and the Xylocaine® Package Insert.

Furthermore, as described above, the references provide no suggestion or disclosure that storage in a glass container provides for any advantages over storage in other containers, such as, for example, a plastic container. Thus, disposing the diluted dexmedetomidine composition described by the Precedex® Package Insert in a sealed glass container would be based on a random selection of a glass container for storage. Such a basis is improper in view of the surprising and unexpected advantages with regard to the stability of the claimed ready to use composition, and the advantages provided for by non-glass materials discussed previously. Rather, in contrast to the claims, and as described above, an artisan of ordinary skill would understand that the diluted dexmedetomidine compositions described by the cited references are not suitable for storage. Such an understanding is further evidenced by the Memorandum and the Precedex® Package Insert, which, as previously discussed, disclose that the diluted dexmedetomidine composition is not suitable for storage, and must be used within a 24-hour period.

Thus, Applicants submit that none of Sunkel, Ibrahim or the Xylocaine® Package Insert provide an artisan of ordinary skill with any guidance, suggestion, or motivation to prepare the diluted dexmedetomidine composition described by the Precedex® Package Insert in a sealed glass container. In view of the foregoing, Applicants submit that the claims are not obvious over the cited references, and respectfully request that the rejection be withdrawn.

II. Double Patenting Rejection

Claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 8,242,158. The Examiner contends that although the conflicting claims are not identical, they are not patentably distinct from each other.

Without conceding to the Examiner's contentions, Applicants submit herewith a Terminal Disclaimer over U.S. Patent No. 8,242,158, and respectfully request that the rejection be withdrawn.

III. Formal Request for Interview

Applicants submit that the present application is in condition for allowance at least for the reasons set forth herein. If the present application is not considered to be in condition for allowance by the Examiner, Applicants request an interview with the Examiner to discuss the present application and the prior art of record. Applicants' Attorney can be contacted by telephone at (212) 408-2500 to schedule a mutually convenient date and time and to provide assistance or additional information as required.

IV. Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or in a telephone call with the undersigned, the Examiner is invited to call the undersigned at the telephone number indicated below.

Applicants believe that no fee is due in connection with the filing of this paper. However, if any fees are due, or if any overpayment has been made, in connection with the filing of this response, the Commissioner is authorized to charge any such fees or credit any overpayment made, to our Deposit Account No. 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

September 17, 2012
Date

Dennis M. Bissonnette
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§ 3

’470 PATENT DECLARATION OF HUAILIANG WU, Ph.D. (SEPT. 17, 2012)

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62965 7590 10/22/2012

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NEW YORK, NY 10112-4498

EXAMINER
POLANSKY, GREGG

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 10/22/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/541,524	07/03/2012	Priyanka Roychowdhury	077350.0355	8238

TITLE OF INVENTION: DEXMEDETOMIDINE PREMIX FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/22/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/541,524	07/03/2012	Priyanka Roychowdhury	077350.0355	8238

TITLE OF INVENTION: DEXMEDETOMIDINE PREMIX FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/22/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
POLANSKY, GREGG	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

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❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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EXAMINER	
POLANSKY, GREGG	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 10/22/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/541,524	ROYCHOWDHURY ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants' response to the Office action mailed 8/17/2012*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-7*.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 9/17/2012
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

DETAILED ACTION

Information Disclosure Statement

1. Applicants' Information Disclosure Statements filed on 9/17/2012 and 10/04/2012 are acknowledged and have been reviewed.

Terminal Disclaimer

2. The terminal disclaimer filed on 9/17/2012 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 8,242,158 has been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly, the rejection of record of Claims 1-7 on the ground of nonstatutory obviousness-type double patenting is withdrawn.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: Applicants argue that "practicing the claims results in surprising and unexpected advantages with regard to stability of the claimed composition over the prior art which is indisputable evidence of the non-obviousness of the claims over the cited references." Applicants point to the Specification (page 8, paragraph [0038]) teaching that that the claimed formulation "can be stable under the conditions of manufacture and storage and can be preserved against the

contaminating action of microorganisms such as bacteria and fungi." Applicants assert that Example 1 of the Specification demonstrates that a dexmedetomidine (4 µg/ml) formulation "stored in glass vials and ampoules maintained a higher level of potency after a 5 month storage period compared to storage in plastic, CR3 or PVC containers" (i.e., over 98% potency after 5 months *vs*. as much as a 20% reduction in potency when stored in plastic or PVC containers after a two-week storage period). The Precedex® Package Insert (cited in the art rejections of the previous Office action) discloses that the 100 µg/ml dexmedetomidine concentrate is suitable for storage, but once diluted for use it is not suitable for storage. Furthermore, the Declaration of Huailiang Wu provided by Applicants provides further evidence of the surprising increase in stability of dexmedetomidine compositions (1, 10, 15 and 50 µg/ml) stored in sealed glass containers compared to storage in PVC bags.

Although the prior art (not previously cited) teaches the adsorption to plastic of solutions of certain pharmaceutical agents (resulting in a decreased concentration of the agent), the art does not teach such for dexmedetomidine. For example, see Unger et al., *Biomaterials*, Vol. 22, 2001, pages 2031-2037, attached herewith.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

ATTACHMENT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Roychowdhury *et al.*	Customer No.	:	62965
Appln. No.	:	13/541,524	Confirmation No.	:	8238
Filed	:	July 3, 2012	Art Unit	:	1629
Examiner	:	Polansky, Gregg			
For	:	DEXMEDETOMIDINE PREMIX FORMULATION			

DECLARATION UNDER 37 C.F.R. §1.132

I, Huailiang Wu, Ph.D., hereby declare the following:

1. I am currently employed as a Group Leader, Global Pharma Research & Development, by HOSPIRA, INC., (hereafter "Hospira") having its principal place of business at 275 North Field Drive, Lake Forest, IL 60045. My curriculum vitae is attached as Exhibit A.

2. HOSPIRA, INC. is the sole Assignee of United States Patent Application Serial No. 13/541,524 (hereafter "the '524 application") pursuant to the Assignment recorded at Reel/Frame: 027480/0592 which was recorded with the United States Patent and Trademark Office (hereafter, "USPTO") on January 4, 2012.

3. I, along with other scientists employed by, and under the direction of, Hospira, designed and conducted assays relating to a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine

or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container. Ready to use parenteral pharmaceutical compositions, such as the claimed dexmedetomidine composition, are manufactured to be sterile so that the compositions are safe to be administered to patients upon removal from their storage container. Sterility can be achieved, for example, by autoclaving the ready to use composition.

4. A first assay (Assay 1) measured the potency of various concentrations of a ready to use dexmedetomidine composition stored in Polyvinyl chloride (PVC) bags and glass vials over a three-day period following autoclave. A second assay (Assay 2) was conducted to measure the potency of various concentrations of a ready to use dexmedetomidine composition without autoclave following storage at ambient temperature over a 24 hour period.

5. As described in greater detail below, Exhibit B (describing the results of Assay 1) demonstrates an unexpected maintenance of potency of 1, 10, 15 and 50 μg/mL dexmedetomidine compositions following autoclave and storage over a three-day period in glass containers compared to storage in PVC plastic containers.

6. Exhibit C (describing the results of Assay 2) demonstrates an unexpected maintenance of potency of 1, 10, 15 and 50 μg/mL dexmedetomidine compositions when stored at ambient temperature over a 24-hour storage period without autoclave in glass containers compared to storage in PVC plastic containers.

7. For Assay 1, ready to use dexmedetomidine solutions were prepared at concentrations of 1 μg/mL, 10 μg/mL, 15 μg/mL and 50 μg/mL by dissolving dexmedetomidine and sodium chloride in water to achieve the target dexmedetomidine concentration and a 0.9% sodium chloride concentration. The solutions were then filtered through a 0.22 μm filter. A sample of the filtered solution was collected and used as the control. The filtered solution was then disposed into 100-mL PVC bags and 50-mL glass vials. The solutions from two PVC bags or two glass vials were tested for dexmedetomidine potency as the "preTS" (pre terminal sterilization) sample about 12 hours after the solutions were disposed into the PVC bags or glass vials. The remaining filled PVC bags and glass vials were autoclaved (terminal sterilization) about 12 hours after the solutions were disposed into the PVC bags or glass vials. The solutions from two PVC bags or two glass vials immediately after autoclave were tested for dexmedetomidine potency as the "T=0" samples. The autoclaved PVC bags and glass vials were stored in stability chambers under conditions of 25°C/60%RH (relative humidity) and 40°C/75%RH for up to two weeks. Samples from the PVC bags and glass vials were tested after storage times of 3 days, 1 week and 2 weeks (for PVC samples only). Testing to determine dexmedetomidine potency in the samples was conducted using HPLC.

8. As shown in Exhibit B, the potency of the 1 μg/mL dexmedetomidine formulation decreased by 1.82% about 12 hours after being disposed in a PVC storage bag

(preTS), and by 7.81% following autoclave (T=0) compared to control. After storage for three days in the PVC bag at 25°C and 40°C, the potency of the 1 µg/mL formulation decreased by 8.05% and 8.83%, respectively, compared to control. Similarly, the potency of the 10, 15 and 50 µg/mL formulations disposed in PVC bags decreased by 5.84%, 5.54% and 4.32% following autoclave, respectively, compared to control. After storage for three days in PVC bags at 25°C, the potency of the three concentrations decreased by 6.24%, 6.17% and 5.26%, respectively, compared to control. After storage for three days in PVC bags at 40°C, the potency of the three concentrations decreased by 6.28%, 6.62% and 5.36%, respectively, compared to control.

9. As described by Exhibit B, in contrast to storing the dexmedetomidine compositions in PVC bags, when the dexmedetomidine compositions were stored in glass vials, the potency of the dexmedetomidine was maintained. When stored in glass vials, none of the four concentrations of dexmedetomidine experienced any loss in potency after disposing the formulations in glass vials or after autoclave, compared to control. After storage for three days in glass vials at 25°C, the decrease in potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions were 0%, 0%, 0.39% and 0.44%, respectively, compared to control. After storage for three days in glass vials at 40°C, the decrease in potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions were 0.42%, 0%, 0.27% and 0.51%, respectively, compared to control.

10. As described by Exhibit B, storing a ready to use formulation of dexmedetomidine at concentrations recited by the claims of the '524 application in glass containers resulted in an unexpected reduction in potency loss of the composition compared to storage in plastic PVC containers. Storing the formulations in PVC containers resulted in a decrease in dexmedetomidine potency after disposition within the containers, after autoclave, and after a three-day storage period at 25°C or 40°C. The maximum detectable loss in potency of the samples stored in PVC containers after the three-day storage period was 8.83%, whereas the glass containers showed a maximum loss of only 0.51%.

11. For Assay 2, dexmedetomidine solutions were prepared as described for Assay 1 at concentrations of 1, 10, 15 and 50 µg/mL. A sample of the filtered solution was collected and used as the control. Prior to storage, the solutions from PVC bags and glass vials were tested for dexmedetomidine potency as the "T=0" sample. PVC bags and glass vials were stored at ambient temperature on a laboratory bench for 24 hours. Samples from the PVC bags and glass vials were tested after storage times of 12 hours and 24 hours. Testing to determine dexmedetomidine potency in the samples was conducted using HPLC.

12. As shown in Exhibit C, when stored in PVC bags, the potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions decreased by 1.48%, 1.22%, 1.06% and 1.78%, respectively, compared to control following the 24-hour storage period. In

contrast, when stored in glass vials, the potency of the 1, 10, 15 and 50 μg/mL dexmedetomidine compositions decreased by only 0%, 0.56%, 0.24% and 0%, respectively, compared to control following the 24-hour storage period.

13. As described above, and as shown in Exhibits B and C, storing a ready to use formulation of dexmedetomidine at concentrations recited by the claims of the '524 application in glass containers resulted in an unexpected reduction in potency loss of the composition compared to storage in plastic PVC containers. Specifically, storing the formulations in PVC containers resulted in a decrease in dexmedetomidine potency after disposition within the containers, after autoclave, and after a three-day storage period at 25°C or 40°C. The maximum detectable loss in potency of the samples stored in PVC containers after the three-day storage period was 8.83%, whereas the glass containers showed a maximum loss of only 0.51%. Similarly, when the dexmedetomidine formulations were stored in glass containers and PVC bags for 24 hours without autoclave, the dexmedetomidine stored in the glass vials maintained greater dexmedetomidine potency than the samples stored in PVC containers. Such a reduction in potency loss of a dexmedetomidine composition after autoclave and storage would not have been expected when stored in a glass container, and as such, is a surprising and unexpected result of practicing the claims of the '524 application.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issuing therefrom.

By: _____ Date: 9/17/12
Huailiang Wu

Title: Group Leader, Global Pharma Research & Development, HOSPIRA, INC.

EXHIBIT A

Huailiang (Leon) Wu, Ph.D.

(224) 212-5262 (O); Email: huailiang.wu@hospira.com

PROFESSIONAL EXPERIENCE

2/11 – Present: Generic, Global Pharma R&D, Hospira, Lake Forest, IL

9/10 – 1/11: Project Manager I (contractor), Global Formulation Sciences, Abbott, Abbott Park, IL

- ✓ Investigation of root cause for unexpected bioperformance of a spray drying dispersion (SDD) tablet product
- ✓ Initiation and evaluation of feasibility of developing a pediatric oral suspension ER
- ✓ Improvement of a SDD tablet product's manufacturability and scale up

5/10 – 9/10: General Manger, Alpharmaca Inc., Shanghai, P.R. China

- ✓ Responsible for setting overall business strategy and managing daily operation for achieving company objectives
- ✓ Applied formulation expertise and innovation to pharmaceutical product design and development without infringing patents of innovators on branded products.
- ✓ Led and oversaw R&D activities with following specific objectives
  - Achieve bioequivalent version of branded products
  - Improve performance and patient compliance for extending lifecycle of branded pharmaceutical products
  - Collaborate with Big Pharma companies in China to co-develop products and to put them through SFDA approval process.

5/10 Principal Scientist and Group leader
10/06 – 5/10: Senior Research Scientist III and Group leader
8/02 – 9/06: Senior Research Scientist I
8/00 - 8/02: Research Scientist
Global Formulation Sciences, GPRD, Abbott Laboratories, North Chicago, IL

- ✓ Lead formulator for formulation design and development of multiple compounds, from early development through various stages of clinical studies (FIM to Phase III).
- ✓ Led independent research activities for bioavailability improvement for insoluble molecules. Supported life cycle management projects and patent filing. Participated in regularly evaluation of external drug delivery technologies.
- ✓ Designed and developed oral formulations, including both immediate and extended release solid dosage form, lipid based systems, solid dispersion formulations and suspension formulation for clinical studies.
  - Developed spray drying dispersion (SDD) tablet formulations at various scales
    - Defined a procedure to effectively screen and optimize SDD formulations
    - Worked with a Third Party Manufacturer to manufacture SDD materials at scale of up to ~4000L/batch
    - Scaled up post-dried SDD tablet formulations at a scale of up to 300kg/batch
  - Defined and developed one lipid formulation for clinical study
  - Developed two controlled release formulations (either matrix tablets or multiparticulate beads)
  - Developed an oral suspension formulation (Phase III)
- ✓ Led, coordinated and managed manufacturing of clinical supplies (tablets or capsules) for many clinical phase studies ranging from Phase I, II to III internally as well as at third party manufacturers (TPM) at scales up to 300kg/batch
- ✓ Authored formulation development and/or CMC section for IND, CTA and IMPD regulatory filings
- ✓ Hands-on experience with manufacture of various oral formulations at lab and pilot plant scales
- ✓ Knowledgeable and experienced in biopharmaceutic and pharmacokinetic evaluations
- ✓ Knowledgeable and skilled in physical pharmacy (mass transport, dissolution, solubility, stability, solid state, etc)

12/99 – 7/00 Postdoctoral Scientist, Exploratory Formulation, Pharmaceutical Development, Pharmacia, MI

- ✓ Developed good understanding of mechanisms by which lipid-based formulations enhance oral absorption/bioavailability
  - Investigated effect of physicochemical properties of formulations on permeability, absorption and bioavailability of insoluble model compounds in animal model.
  - Evaluated effect of bile (salt), surfactants and lipids on bioavailability of the model compounds in animals
  - Hands-on experience with animal studies on oral drug absorption, *in situ* rat intestine perfusion.
  - Experience in analytical chemistry and bioanalysis (HPLC, UV, fluorescence and LC/MS/MS etc)

8/95 – 11/99 Research Assistant, College of Pharmacy, University of Michigan, MI
- ✓ Designed and developed topical delivery systems including microemulsion and liposomal formulations for hydrophilic macromolecules such as protein and DNA
- ✓ Characterized DNA delivery systems and evaluated in *in vivo* animal models

2/94 - 8/95 Visiting Research Investigator II, College of Pharmacy, University of Michigan, MI
Designed and characterized nonionic liposome and emulsion formulations for topical delivery systems

8/87 - 12/93 Assistant Researcher, Nanjing Institute of Materia Medica, Nanjing, China
- ✓ Designed and developed solid and parenteral formulations including analytical method development, pharmacokinetic evaluation and regulatory filing with SFDA
  - Amphotericin B liposomal injectable formulation (Phase II)
  - Famotidine powder/granule for oral suspension (commercial production approved by SFDA)
  - FDC ibubrofen tablet (commercial production approved by SFDA)
  - FeSO4 CR tablets (commercial production approved by SFDA)
  - Developed Yunzhi polysaccharide injection (lyophilized)

9/84 – 7/87 Research Assistant, Pharmaceutical Department, Nanjing Institute of Materia Medica, China
- ✓ Investigated feasibility of increasing efficacy and reducing toxicity of Harringtonine via liposomal iv formulations
  - Isolated and purified the phospholipid from the egg yolk
  - Evaluated impact of formulation factors and preparation methods etc on efficiency of incorporation, stability
  - Develop analytical method
  - Performed PK and in vivo distribution study in rat and rabbit models

2/82 - 8/84 Assistant Engineer/Head of Central Research Lab/Manager
Dongfeng Pharmaceutical Co., Lianyungang, China
- ✓ Developed and manufactured allicin (garlic oil) products
  - Synthesized garlic oil and scaled up
  - Applied microencapsulation techniques to develop allicin (garlic oil) capsule formulation (commercial production approved by SFDA)
  - Developed garlic oil injection (commercial production approved by SFDA)
- ✓ Developed generic products including solid dosage form and parenteral formulations
- ✓ Worked with colleagues from different function areas to solve problems which might happen during production of various products including solid and parenteral formulations

EDUCATION
Ph.D. in Pharmaceutics, College of Pharmacy, University of Michigan, 1999
MS. in Pharmaceutics, China Pharmaceutical University, Nanjing, China, 1987
BS. in Pharmacy, China Pharmaceutical University, Nanjing, China, 1982

PATENT APPLICATIONS
1. Solid Dispersions Containing An Apoptosis-Promoting Agent (Filed application in 6/10)
2. New Pharmaceutical Formulation for ABT-072/ABT-333 (MOI submitted, 2010)
3. Solid Dispersions Containing An Anti-HCV Agent (MOI submitted, 2009)
4. Extended release formulation for ABT-894 (MOI submitted, 2009)
5. Pharmaceutical Formulation for Feno Acid: **Wu, H.**, Lee, D., Ju, T. and Gao, Y. (Filed application in 9/06)
6. 7852US02 (Dissolution criteria for Feno Acid Formulations (NFE)): Ju, T., Davila, C., Engh, E.,Gao, Y., Gustavson, L., Jayaraman, S., LeBlond, D., Lee, D., Zhu, T., **Wu**, H. Filed in 10/06.
7. Pharmaceutical Composition Having Improved Dissolution Profiles For Poorly Soluble Drugs (Provisional application, Case No. 7858.US.L1. Filed 4/05), **Wu, H.**, Lee, D., Zhang, G.
8. Nanoemulsion Formulations (United States Patent Application, 20020155084). Roessler, B., Baker, J., Chandrasekharan, R., Weiner, N. and **Wu, H.**

INVITED SPEECHES
1. *"NCE Based (Oral) Drug Product Development"* The 1st International Innovate and Generic Drug Research &

Development Forum, Canton, China 2010

2. *"Modified Release Formulation Development" College of Pharmacy, University of Michigan, MI, 2009*
3. "Dissolution Enhancement For Formulations Containing Salt of Poorly Soluble Compounds" *AAPS 2005 Annual Meeting, Nashville, TN*
4. "Oral Drug Absorption vs. Formulation Design" *College of Pharmacy, University of Michigan, MI, 2005*
5. "Dissolution Enhancement For Formulations Containing Salt Of Poorly Soluble Compounds" *Pharmaceutical Education Associates Conference: Improving Delivery of Poorly Soluble Compounds: Formulation and Preformulation Approaches, Philadelphia, PA, 2005*
6. "Principle of Oral Controlled-Release Formulation Design" *College of Pharmacy, University of Michigan, MI, 2004*
7. "Topical Delivery Of Hydrophilic Macromolecules With Formulations" AAPS/FIP/SFDA Joint Symposium: Drug Development, Clinical Research and Registration, Nanjing, China, 2004

PUBLICATIONS

1. **Wu, H**.et al. "Topical transfection using plasmid DNA in a water-in-oil nanoemulsion" *Int. J. Pharm*, 221 (2001) 23-34
2. **Wu, H**. et al. "Topical transport of hydrophilic compounds using water-in-oil nanoemulsions" *Int. J. Pharm*, 220 (2001) 63-75
3. Niemiec, S.M., **Wu, H.L**.et al. Effect of polyolprepolymer on the disposition of Retinoic Acid in various strata of hamster ear following topical *in vivo* application of gel formulations: Correlation with disposition in human skin. ***Drug Delivery***, 4, 33-36, 1997
4. Hu, Z., **Wu, H**. et al. Topical delivery of a-interferon from liposomal systems: An *in vivo* study with hairless mouse. *Drug Delivery*, 2, 94-97,1995
5. **Wu, H**. et al. Pharmacokinetics of harringtonine liposomes in rabbits. *Acta Pharmacologica Sinica*, 15, 84-6, 1994
6. **Wu, H**. et al. Distribution of harringtonine in positively and negatively charged liposomes in rat tissues *Acta Pharmacologica Sinica*, 14, 176-8, 1993
7. **Wu, H**. et al. Quantitation of liposomally entrapped and free harringtonine in tissues of rat by HPLC. *Zhongguo Yaoke Daxue Xuebao*, 20, 77-81, 1989
8. Ze, Q. and **Wu, H**. Industrial production of Allicin microcapsule. *J. Chinese Traditional Medicine*, (1): 7-9, 1984.

ABSTRACTS AND PRESENTATIONS

1. **Wu, H**. et al. Formulation Design to Improve Bioavailability and Reduce Biovariability of the Salt of a Poorly Soluble Base Compound, AAPS 2009 Annual Meeting, Los Angeles, CA
2. **Wu, H**. et al. Understanding Dissolution Behavior of the Salt of a Poorly Soluble Acid Compound In Dual Ph Media. *AAPS 2005 Annual Meeting, Nashville, TN*
3. **Wu, H**.et al. Effect of Polymers on Dissolution of the Salt of a Poorly Soluble Acid Compound In Dual Ph Media. *AAPS 2005 Annual Meeting, Nashville, TN*
4. Sever, N., Ibrahim, R., Sharma, S., Schmidt, C., **Wu, H**. Hiestand Indices Predict Tablet Compression Behavior, *AAPS PharmSci, 5(4),2003*
5. Zhang, G., Cao, Y., Gao, Y., Han, J. and **Wu, H**. In Situ Precipitation of Weak Acid In Aqueous Meda: Considerations Beyond Salt Selection, *AAPS PharmSci, 4(4),2002*
6. **Wu, H**. et al. Dissolution Testing Using Multi-Medium In The Development Of Formulations For An Acidic Salt Compound, *AAPS PharmSci, 4(4)2002)*
7. **Wu, H**. et al. Influence of Bile Salt Micelles And Mixed Micelles on the Absorption of PNU-96988 in the Rat Small Intestine, *AAPS Annual Meeting, Indianapolis, 2000*
8. **Wu, H. et al.** Evaluation of Water-in-Oil DNA Microemulsions as Topical Vehicles for Skin Transfection. *AAPS Annual Meeting, New Orleans, LA, 1999.*
9. **Wu, H.** et al Topical Delivery of Expression Plasmid DNA and Transfection *In Vivo* Using A Novel Nonionic Microemulsion System, *American Society of Gene Therapy national meeting, Washington, D.C, 1999*
10. **Wu, H.** et al. A Simple Method to Estimate the Contribution of the Transfollicular Pathway to Transport of Minoxidil into and Across Skin from Various Vehicles. *AAPS Annual Meeting, San Francisco, CA, 1998.*
11. **Wu, H**.et al. Topical Delivery of Tranexamic Acid from Nonionic Liposomal and Emulsion Formulations *Pharm. Res, 14: S-314, 1997*
12. **Wu, H**.et al. Deposition of Taxol from Nonionic Liposomal Systems: An *In Vitro-In Vivo* Study Using Hairless Mouse Skin. *Pharm. Res., 11:S-187, 1994.*
13. Hu, Z., Niemiec, S.M., **Wu, H**. et al. Topical Delivery of Alpha-Interferon from Nonionic Liposomal Formulations *Pharm. Res, 11:S-186,1994*
14. **Wu, H**. et al. Pharmacokinetics of Harringtonine Liposomes in Rabbits. *Chemical Abstracts, 120:24, 1994*

15. **Wu, H**. et al. Distribution of Harringtonine in Positively and Negatively Charged Liposomes in Rat Tissues. *Chemical Abstracts, 118:417, 1993*
16. **Wu, H**. et al. Quantitation of Liposome Encapsulated Harringtonine and Haringtonine in Tissues of Rat by HPLC. *Chemical Abstracts, 112:6,1990.*

PROFESSIONAL ACTIVITIES

A member of 2001 and 2002 AAPS New Investigator Grant in Oral Lipid-based Drug Delivery Systems Selection Committee

EXHIBIT B

Exhibit B
Storage in PVC Bags

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0176	100.00	N/A
	1ug/mL-preTS	0.9991	98.18	N/A
	1ug/mL-T=0	0.9381	92.19	100.00
	10ug/mL-control	10.0337	100.00	N/A
	10ug/mL-preTS	9.9222	98.89	N/A
	10ug/mL-T=0	9.4481	94.16	100.00
	15ug/mL-control	15.0155	100.00	N/A
	15ug/mL-preTS	14.9035	99.25	N/A
	15ug/mL-T=0	14.1842	94.46	100.00
	50ug/mL-control	49.8850	100.00	N/A
	50ug/mL-preTS	49.7035	99.64	N/A
	50ug/mL-T=0	47.7288	95.68	100.00
3 days	1ug/mL-40C	0.9277	91.17	98.89
	1ug/mL-25C	0.9356	91.95	99.73
	10ug/mL-40C	9.4037	93.72	99.53
	10ug/mL-25C	9.4078	93.76	99.57
	15ug/mL-40C	14.0222	93.38	98.86
	15ug/mL-25C	14.0887	93.83	99.33
	50ug/mL-40C	47.2099	94.64	98.91
	50ug/mL-25C	47.2603	94.74	99.02
1 wk	1ug/mL-40C	0.9433	92.70	100.55
	1ug/mL-25C	0.9444	92.81	100.67
	10ug/mL-40C	9.4544	94.23	100.07
	10ug/mL-25C	9.5342	95.02	100.91
	15ug/mL-40C	14.2671	95.02	100.58
	15ug/mL-25C	14.2785	95.09	100.66
	50ug/mL-40C	47.9910	96.20	100.55
	50ug/mL-25C	48.1394	96.50	100.86
2 wk	1ug/mL-40C	0.9380	92.18	99.99
	1ug/mL-25C	0.9481	93.17	101.06
	10ug/mL-40C	9.4631	94.31	100.16
	10ug/mL-25C	9.5210	94.89	100.77
	15ug/mL-40C	14.1631	94.32	99.85
	15ug/mL-25C	14.2959	95.21	100.79
	50ug/mL-40C	47.5557	95.33	99.64
	50ug/mL-25C	48.2287	96.68	101.05

Exhibit B
Storage in Glass Vials

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0323	100.00	N/A
	1ug/mL-preTS	1.0392	100.67	N/A
	1ug/mL-T=0	1.0357	100.33	100
	10ug/mL-control	10.1482	101.14	N/A
	10ug/mL-preTS	10.1855	101.51	N/A
	10ug/mL-T=0	10.1771	101.43	100
	15ug/mL-control	15.2373	101.48	N/A
	15ug/mL-preTS	15.2542	101.59	N/A
	15ug/mL-T=0	15.2453	101.53	100
	50ug/mL-control	51.1483	102.53	N/A
	50ug/mL-preTS	51.2673	102.77	N/A
	50ug/mL-T=0	51.3839	103.00	100
3 days	1ug/mL-40C	1.0280	99.58	99.26
	1ug/mL-25C	1.0330	100.07	99.74
	10ug/mL-40C	10.1550	100.07	99.78
	10ug/mL-25C	10.1526	100.04	99.76
	15ug/mL-40C	15.1969	99.73	99.68
	15ug/mL-25C	15.1782	99.61	99.56
	50ug/mL-40C	50.8883	99.49	99.04
	50ug/mL-25C	50.9256	99.56	99.11
1wk	1ug/mL-40C	1.0252	99.31	98.99
	1ug/mL-25C	1.0214	98.94	98.62
	10ug/mL-40C	10.0452	98.98	98.70
	10ug/mL-25C	10.0631	99.16	98.88
	15ug/mL-40C	15.1969	99.73	99.68
	15ug/mL-25C	15.1782	99.61	99.56
	50ug/mL-40C	50.7608	99.24	98.79
	50ug/mL-25C	50.9493	99.61	99.15

Note:
Control: Formulations before filling into PVC bags and glass vials;
PreTS: Formulations filled in PVC bags and glass vials without autoclave;
T0: Formulations filled in PVC bags and glass vials immediately after autoclave
Variability of the analytical method is not greater than 2%

EXHIBIT C

Exhibit C

PVC bags

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0274	100.00	N/A
	1ug/mL-T=0	1.0326	100.51	100.00
	10ug/mL-control	10.2784	100.00	N/A
	10ug/mL-T=0	10.2380	99.61	100.00
	15ug/mL-control	15.1541	100.00	N/A
	15ug/mL-T=0	15.1725	100.12	100.00
	50ug/mL-control	50.7557	100.00	N/A
	50ug/mL-T=0	50.5099	99.52	100.00
12h	1ug/mL	1.0157	98.86	98.36
	10ug/mL	10.1602	98.85	99.24
	15ug/mL	15.0347	99.21	99.09
	50ug/mL	50.0469	98.60	99.08
24h	1ug/mL	1.0122	98.52	98.02
	10ug/mL	10.1532	98.78	99.17
	15ug/mL	14.9934	98.94	98.82
	50ug/mL	49.8515	98.22	98.70

Glass vials

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0274	100.00	N/A
	1ug/mL-T=0	1.0337	100.61	100.00
	10ug/mL-control	10.2784	100.00	N/A
	10ug/mL-T=0	10.2390	99.62	100.00
	15ug/mL-control	15.1541	100.00	N/A
	15ug/mL-T=0	15.1478	99.96	100.00
	50ug/mL-control	50.7557	100.00	N/A
	50ug/mL-T=0	50.5308	99.56	100.00
12h	1ug/mL	1.0405	101.28	100.66
	10ug/mL	10.2327	99.56	99.94
	15ug/mL	15.1351	99.87	99.92
	50ug/mL	50.7833	100.05	100.50
24h	1ug/mL	1.0374	100.97	100.36
	10ug/mL	10.2204	99.44	99.82
	15ug/mL	15.1177	99.76	99.80
	50ug/mL	50.8899	100.26	100.71

Note:
Control: Formulations before filling into PVC bags and glass vials;

§ 4

’470 PATENT NOTICE OF ALLOWANCE (OCT. 22, 2012)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

62965 7590 10/22/2012

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

EXAMINER
POLANSKY, GREGG

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 10/22/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/541,524	07/03/2012	Priyanka Roychowdhury	077350.0355	8238

TITLE OF INVENTION: DEXMEDETOMIDINE PREMIX FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/22/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

62965 7590 10/22/2012
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/541,524	07/03/2012	Priyanka Roychowdhury	077350.0355	8238

TITLE OF INVENTION: DEXMEDETOMIDINE PREMIX FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	01/22/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
POLANSKY, GREGG	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/541,524	07/03/2012	Priyanka Roychowdhury	077350.0355	8238

62965 7590 10/22/2012

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44th Floor
NEW YORK, NY 10112-4498

EXAMINER	
POLANSKY, GREGG	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 10/22/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/541,524	ROYCHOWDHURY ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants' response to the Office action mailed 8/17/2012*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-7*.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 9/17/2012
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

DETAILED ACTION

Information Disclosure Statement

1. Applicants' Information Disclosure Statements filed on 9/17/2012 and 10/04/2012 are acknowledged and have been reviewed.

Terminal Disclaimer

2. The terminal disclaimer filed on 9/17/2012 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 8,242,158 has been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly, the rejection of record of Claims 1-7 on the ground of nonstatutory obviousness-type double patenting is withdrawn.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: Applicants argue that "practicing the claims results in surprising and unexpected advantages with regard to stability of the claimed composition over the prior art which is indisputable evidence of the non-obviousness of the claims over the cited references." Applicants point to the Specification (page 8, paragraph [0038]) teaching that that the claimed formulation "can be stable under the conditions of manufacture and storage and can be preserved against the

contaminating action of microorganisms such as bacteria and fungi." Applicants assert that Example 1 of the Specification demonstrates that a dexmedetomidine (4 µg/ml) formulation "stored in glass vials and ampoules maintained a higher level of potency after a 5 month storage period compared to storage in plastic, CR3 or PVC containers" (i.e., over 98% potency after 5 months *vs*. as much as a 20% reduction in potency when stored in plastic or PVC containers after a two-week storage period). The Precedex® Package Insert (cited in the art rejections of the previous Office action) discloses that the 100 µg/ml dexmedetomidine concentrate is suitable for storage, but once diluted for use it is not suitable for storage. Furthermore, the Declaration of Huailiang Wu provided by Applicants provides further evidence of the surprising increase in stability of dexmedetomidine compositions (1, 10, 15 and 50 µg/ml) stored in sealed glass containers compared to storage in PVC bags.

Although the prior art (not previously cited) teaches the adsorption to plastic of solutions of certain pharmaceutical agents (resulting in a decreased concentration of the agent), the art does not teach such for dexmedetomidine. For example, see Unger et al., *Biomaterials*, Vol. 22, 2001, pages 2031-2037, attached herewith.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

EXHIBIT 4

PATENT PROSECUTION HISTORY EXCERPTS FOR U.S. PATENT NO. 8,455,527 ('527 PATENT)

§ 1

’527 PATENT ACCELERATED EXAMINATION SUPPORT DOCUMENT (NOV. 15, 2012)

PATENT
077350.0359

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Roychowdhury *et al.*		Examiner	To Be Assigned
Application No.:	To Be Assigned	Group Art Unit	To Be Assigned
Filed:	Concurrently Herewith	Confirmation No.	To Be Assigned

For: METHODS OF TREATMENT USING A DEXMEDETOMIDINE PREMIX FORMULATION

ACCELERATED EXAMINATION SUPPORT DOCUMENT

Filed Electronically VIA EFS
Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This accelerated examination support document is provided in support of the petition for accelerated examination filed herewith and the application filed herewith under 35 U.S.C. § 111(a).

Identification of the Limitations of the Claims Disclosed by the Cited References begins on page 2 of this paper.

Detailed Explanation of Patentability begins on Page 44 of this paper.

Statement of Disqualification of Prior Art begins on page 74 of this paper.

Statement of Utility begins on Page 75 of this paper.

Showing of Support of Each Claim Limitation and Statement Regarding Means Plus Function begins on page 76 of this paper.

Conclusion begins on page 82 of this paper.

Identification of the Limitations of the Claims Disclosed by the Cited References:

1. "Dexmedetomidine HCL Draft Labeling: Precedex™ Dexmedetomidine Hydrochloride Injection," FDA approved label, dated December 17, 1999, and available online July 26, 2001, pages 1-13. ("the Precedex™ label").

a. Independent Claim 1

A method of providing sedation to a patient in need thereof, the method comprising

The Precedex™ label discloses a method of providing sedation to a patient in need thereof (p. 1, ¶3; p. 6, ¶4).

Independent claim 1 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 1, which is directed to a 0.005 to about 50 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

administering to the patient an effective amount of a composition, wherein the compostion ccomprises dexmedetomidine or a pharmaceutically acceptable salt thereof

The Precedex™ label discloses administering to a patient an effective amount of a composition, wherein the compostion comprises dexmedetomidine or a pharmaceutically acceptable salt thereof (p. 1, ¶1-¶2; p. 6, ¶4; p. 12, ¶2-¶3; p. 13, ¶5).

Independent claim 1 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 1, which is directed to a 0.005 to about 50 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine

composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

at a concentration of about 0.005 to about 50 μg/mL,

The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein the dexmedetomidine is present at a concentration of about 4 μg/mL (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Independent claim 1 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 1, which is directed to a 0.005 to about 50 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient

The Precedex™ label discloses a liquid pharmaceutical composition for parenteral administration to a patient (p. 1, ¶1-¶2; p. 6, ¶4; p. 12, ¶2-¶3).

Independent claim 1 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 1, which is directed to a 0.005 to about 50 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and

diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

disposed within a sealed glass container.

The Precedex™ label discloses a pharmaceutical composition wherein the composition is disposed within a sealed glass container (p. 13, ¶5-¶6).

Independent claim 1 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 1, which is directed to a 0.005 to about 50 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

b. Dependent Claim 2

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 ug/mL.

The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein the dexmedetomidine is present at a concentration of about 4 μg/mL (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Claim 2 is not anticipated by the Precedex™ label for at least the reason discussed with respect to claim 1. For example, the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 μg/mL disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 2, which is directed to a 0.05 to about 15 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated

as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

c. Dependent Claim 3

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 ug/mL.

The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein the dexmedetomidine is present at a concentration of about 4 μg/mL (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Claim 3 is not anticipated by the Precedex™ label for at least the reason discussed with respect to claim 1. For example, the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 μg/mL disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 3, which is directed to a 0.5 to about 10 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

d. Dependent Claim 4

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 ug/mL.

The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein the dexmedetomidine is present at a concentration of about 4 μg/mL (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Claim 4 is not anticipated by the Precedex™ label for at least the reason discussed with respect to claim 1. For example, the Precedex™ label fails to disclose or suggest a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising

dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 μg/mL disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 4, which is directed to an about 1 to about 7 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

e. Dependent Claim 5

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 ug/mL.

The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein the dexmedetomidine is present at a concentration of about 4 μg/mL (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Dependent claim 5 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 5, which is directed to a 4 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

f. Dependent Claim 6

The method of claim 1, wherein the composition is administered perioperatively

Dependent claim 6 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient perioperatively.

Additionally, dependent claim 6 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 6 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

g. Dependent Claim 7

The method of claim 6, wherein the composition is administered before or after surgery.

Dependent claim 7 is not anticipated by the Precedex™ label because the Precedex™ label fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient before or after surgery.

Additionally, dependent claim 7 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 7 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the

Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

h. Dependent Claim 8

The method of claim 1, wherein the composition is administered to the patient in an intensive care unit.

The Precedex™ label discloses administering a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof to a patient in an intensive care unit (p. 4, ¶4; p. 6, ¶4).

Dependent claim 8 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 8 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

i. Dependent Claim 9

The method of claim 1, wherein the patient is non-ventilated or intubated.

The Precedex™ label discloses administration of a composition comprising dexmedetomidine to a patient that is intubated (p. 4, ¶4).

Dependent claim 9 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 9 which is directed to a dexmedetomidine composition at a

concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

j. Dependent Claim 10

The method of claim 1, wherein the patient is critically ill.

Dependent claim 10 is not anticipated by the Precedex™ label because the Precedex™ label fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is critically ill.

Additionally, dependent claim 10 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 12 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

k. Dependent Claim 11

The method of claim 1, wherein the composition is administered by an intravenous infusion.

The Precedex™ label describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (p. 6, ¶4; p. 7, ¶3-¶5; p. 12, ¶2-¶4).

Dependent claim 11 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is

disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 µg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 11 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 µg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 µg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

l. Dependent Claim 12

The method of claim 1, wherein the composition is administered as an anxiolytic.

The Precedex™ label discloses administration of a composition comprising dexmedetomidine as an anxiolytic (p. 4, ¶3).

Dependent claim 12 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 µg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 12 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 µg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 µg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

m. Dependent Claim 13

The method of claim 1, wherein the composition is administered as an adjunct to an anesthetic.

The Precedex™ label describes administration of a composition comprising dexmedetomidine as an adjunct to an anesthetic. (p. 8, ¶4).

Dependent claim 13 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a

pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 13 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

n. Dependent Claim 14

The method of claim 1, wherein the composition is administered as an analgesic.

The Precedex™ label describes administration of a composition comprising dexmedetomidine as an analgesic. (p. 5, ¶2-¶3, p. 6, ¶2).

Dependent claim 14 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 14 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

o. Dependent Claim 15

The method of claim 1, wherein the composition is administered as an anti-hypertensive agent.

Dependent claim 15 is not anticipated by the Precedex™ label because the Precedex™ label fails to suggest or describe administration of a composition comprising dexmedetomidine as an anti-hypertensive agent.

Additionally, dependent claim 15 is not anticipated by the Precedex™ label because the Precedex™ label fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. The Precedex™ label discloses dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 15 which is directed to a dexmedetomidine composition at a concentration of about 0.005 to about 50 μg/mL disposed within a sealed glass container that is formulated as a ready to use liquid for parenteral administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

2. U.S. Publication No. 20110230534, published September 22, 2011 to Miyawaki et al. ("Miyawaki").

a. Independent Claim 1

A method of providing sedation to a patient in need thereof, the method comprising

Independent claim 1 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe a method of providing sedation to a patient in need thereof.

Additionally, independent claim 1 is not anticipated by Miyawaki because Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof

Miyawaki discloses administering to a patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof (p. 2, ¶25; pp. 2-3, ¶37; p. 3, ¶43; p. 4, ¶56; p. 4, ¶58; p. 5, ¶67-¶68; pp. 7-8, ¶78-81).

Independent claim 1 is not anticipated by Miyawaki because Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

at a concentration of about 0.005 to about 50 μg/mL,

Miyawaki discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively.

Independent claim 1 is not anticipated by Miyawaki because Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient

Miyawaki discloses a liquid pharmaceutical composition for parenteral administration to a patient (p. 2, ¶37; p. 3, ¶41; p. 4, ¶58 p. 5, ¶67-¶68; pp. 7-8, ¶78-81).

Independent claim 1 is not anticipated by Miyawaki because Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

disposed within a sealed glass container.

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95).

Independent claim 1 is not anticipated by Miyawaki because Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

b. Dependent Claim 2

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 ug/mL.

Miyawaki discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between

$1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively.

Dependent claim 2 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

c. Dependent Claim 3

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 ug/mL.

Miyawaki discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively.

Dependent claim 3 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed

within a sealed glass container.

d. Dependent Claim 4

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 ug/mL.

Miyawaki discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively.

Dependent claim 4 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

e. Dependent Claim 5

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 ug/mL.

Miyawaki discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively.

Dependent claim 5 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe a pharmaceutical composition comprising dexmedetomidine at a concentration of about 4 μg/mL.

Additionally, dependent claim 5 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

f. Dependent Claim 6

The method of claim 1, wherein the composition is administered perioperatively.

Miyawaki discloses administering a composition comprising dexmedetomidine to a patient perioperatively (p. 9, ¶92-93).

Dependent claim 6 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

g. Dependent Claim 7

The method of claim 6, wherein the composition is administered before or after surgery.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof to a patient before or after surgery (p. 9, ¶92-93).

Dependent claim 6 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

h. Dependent Claim 8

The method of claim 1, wherein the composition is administered to the patient in an intensive care unit.

Dependent claim 8 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient in an intensive care unit.

Additionally, dependent claim 8 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

i. Dependent Claim 9

The method of claim 1, wherein the patient is non-ventilated or intubated.

Dependent claim 9 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is non-ventilated or intubated.

Additionally, Dependent claim 9 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

j. Dependent Claim 10

The method of claim 1, wherein the patient is critically ill.

Dependent claim 10 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is critically ill.

Additionally, Dependent claim 10 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

k. Dependent Claim 11

The method of claim 1, wherein the composition is administered by an intravenous infusion.

Dependent claim 11 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion.

Additionally, Dependent claim 11 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

l. Dependent Claim 12

The method of claim 1, wherein the composition is administered as an anxiolytic.

Dependent claim 12 is not anticipated by Miyawaki because Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine as an anxiolytic.

Additionally, Dependent claim 12 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

m. Dependent Claim 13

The method of claim 1, wherein the composition is administered as an adjunct to an anesthetic.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof as an adjunct to an anesthetic (p. 2, ¶24-29; pp. 2-3, ¶37; p. 3, ¶43; p. 4, ¶56; p. 4, ¶58; p. 9, ¶ 95).

Dependent claim 13 is not anticipated by Miyawaki because Miyawaki fails to suggest or

disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

n. Dependent Claim 14

The method of claim 1, wherein the composition is administered as an analgesic.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof as an analgesic (p. 2, ¶24-29; pp. 2-3, ¶37; p. 3, ¶43; p. 4, ¶56; p. 4, ¶58; p. 9, ¶ 95).

Dependent claim 14 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

o. Dependent Claim 15

The method of claim 1, wherein the composition is administered as an anti-hypertensive agent.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof as an anti-hypertensive agent (p. 2, ¶32).

Dependent claim 15 is not anticipated by Miyawaki because Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki

discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

3. U.S. Patent No. 5344840, issued September 6, 1994 to Maze *et al.* ("Maze").

a. Independent Claim 1

A method of providing sedation to a patient in need thereof, the method comprising

Maze discloses a method of providing sedation to a patient in need thereof (Claim 3).

Independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof

Maze discloses administering to a patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 1, ll. 12-37; Col. 2, ll. 5-22; Col. 2, ll. 55-61; Col. 4, ll. 9-10).

Independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

at a concentration of about 0.005 to about 50 µg/mL,

Maze discloses administering dexmedetomidine to a subject in an amount of 1, 3 and 10 µg/kg (Col. 2, ll. 54-58), and 1-10 µg/kg (Col. 4, ll. 9-10).

Independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL.

Additionally, independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient

Maze discloses a liquid pharmaceutical composition (Col. 1, ll. 12-20; Col. 2, ll. 5-22 and 55-61; Col. 4, ll. 9-10).

Independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

disposed within a sealed glass container.

Independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is disposed within a sealed glass container.

Additionally, independent claim 1 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

b. Dependent Claim 2

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 ug/mL.

Maze discloses administering dexmedetomidine to a subject in an amount of 1, 3 and 10 μg/kg (Col. 2, ll. 54-58), and 1-10 μg/kg (Col. 4, ll. 9-10).

Dependent claim 2 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.05 to about 15 μg/mL.

Additionally, dependent claim 2 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

c. Dependent Claim 3

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 ug/mL.

Maze discloses administering dexmedetomidine to a subject in an amount of 1, 3 and 10 μg/kg (Col. 2, ll. 54-58), and 1-10 μg/kg (Col. 4, ll. 9-10).

Dependent claim 3 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.5 to about 10 μg/mL.

Additionally, dependent claim 3 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

d. Dependent Claim 4

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 ug/mL.

Maze discloses administering dexmedetomidine to a subject in an amount of 1, 3 and 10 μg/kg (Col. 2, ll. 54-58), and 1-10 μg/kg (Col. 4, ll. 9-10).

Dependent claim 4 is not anticipated by Maze because Maze fails to disclose or suggest a

pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 1 to about 7 μg/mL.

Additionally, dependent claim 4 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

e. Dependent Claim 5

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 ug/mL.

Dependent claim 5 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 4 μg/mL.

Additionally, dependent claim 5 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 4 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

f. Dependent Claim 6

The method of claim 1, wherein the composition is administered perioperatively.

Maze discloses administering a composition comprising dexmedetomidine to a patient perioperatively (Abstract; Col. 2, ll. 11-19; Claim 1).

Dependent claim 6 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

g. Dependent Claim 7

The method of claim 6, wherein the composition is administered before or after surgery.

Maze describes administration of a composition comprising dexmedetomidine to a patient before or after surgery (Col. 4, ll. 11-18).

Dependent claim 7 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

h. Dependent Claim 8

The method of claim 1, wherein the composition is administered to the patient in an intensive care unit.

Dependent claim 8 is not anticipated by Maze because Maze fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient in an intensive care unit..

Additionally, dependent claim 8 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

i. Dependent Claim 9

The method of claim 1, wherein the patient is non-ventilated or intubated.

Maze discloses administration of a composition comprising dexmedetomidine to a patient that is intubated (Col. 2, ll. 23-33).

Dependent claim 9 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

j. Dependent Claim 10

The method of claim 1, wherein the patient is critically ill.

Dependent claim 10 is not anticipated by Maze because Maze fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is critically ill.

Additionally, dependent claim 10 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

k. Dependent Claim 11

The method of claim 1, wherein the composition is administered by an intravenous infusion.

Maze describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (Col. 4, ll. 9-11).

Dependent claim 11 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

l. Dependent Claim 12

The method of claim 1, wherein the composition is administered as an anxiolytic.

Maze discloses administration of a composition comprising dexmedetomidine as an anxiolytic (Col. 1, ll. 38-41; Claim 2).

Dependent claim 12 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

m. Dependent Claim 13

The method of claim 1, wherein the composition is administered as an adjunct to an anesthetic.

Maze describes administration of a composition comprising dexmedetomidine to a patient as an adjunct to an anesthetic (Col. 1, ll. 12-20; Col. 2, ll. 23-26; Claims 2 and 3).

Dependent claim 13 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable

salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

n. Dependent Claim 14

The method of claim 1, wherein the composition is administered as an analgesic.

Maze describes administration of a composition comprising dexmedetomidine to a patient as an analgesic (Claims 2 and 3).

Dependent claim 14 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

o. Dependent Claim 15

The method of claim 1, wherein the composition is administered as an anti-hypertensive agent.

Dependent claim 15 is not anticipated by Maze because Maze fails to disclose or suggest administration of a composition comprising dexmedetomidine as an anti-hypertensive agent.

Additionally, dependent claim 15 is not anticipated by Maze because Maze fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

4. U.S. Patent No. 6716867, issued April 6, 2004 to Aantaa *et al.* ("Aantaa").

a. Independent Claim 1

A method of providing sedation to a patient in need thereof, the method comprising

Aantaa discloses a method of providing sedation to a patient in need thereof (Col. 3, ll. 35-51; Col. 3, ll. 59-67; Col. 4, ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3).

Independent claim 1 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as

a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof

Aantaa discloses administering to a patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 1, ll. 10-31; Col. 3, ll. 24-32; Col. 3, ll. 35-67; Col. 4, ll. 29-43; Col. 5, ll. 5-30; Col. 5, l. 45 – Col. 6, l. 5; Col. 6, ll. 59-64; Col. 14, ll. 33-35).

Independent claim 1 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

at a concentration of about 0.005 to about 50 μg/mL,

Aantaa discloses a composition comprising dexmedetomidine at a concentration of 100 μg/mL (Col. 5, l. 54), and administering a composition comprising dexmedetomidine to a subject at a dosage of about 0.2-2 μg/kg, 0.5-2.0 μg/kg, 1.0 μg/kg, 0.1-2.0 μg/kg/h, 0.2-0.7 μg/kg/h, and about 0.4-0.7 μg/kg/h (Col. 5, ll. 22-30), and 6 μg/kg/h, 0.2 μg/kg/h, and 0.4 μg/kg/h (Col. 5, ll. 59-67).

Independent claim 1 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present 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

Aantaa discloses a liquid pharmaceutical composition (Col. 3, ll. 24-32; Col. 5, ll. 5-30; Col. 5, l. 45 – Col. 6, l. 5; Col. 6, ll. 59-64; Col. 14, ll. 33-35).

Independent claim 1 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and

that is disposed within a sealed glass container.

disposed within a sealed glass container.

Independent claim 1 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is disposed within a sealed glass container.

Additionally, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

b. Dependent Claim 2

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 ug/mL.

Aantaa discloses a composition comprising dexmedetomidine at a concentration of 100 μg/mL (Col. 5, l. 54), and administering a composition comprising dexmedetomidine to a subject at a dosage of about 0.2-2 μg/kg, 0.5-2.0 μg/kg, 1.0 μg/kg, 0.1-2.0 μg/kg/h, 0.2-0.7 μg/kg/h, and about 0.4-0.7 μg/kg/h (Col. 5, ll. 22-30), and 6 μg/kg/h, 0.2 μg/kg/h, and 0.4 μg/kg/h (Col. 5, ll. 59-67).

Dependent claim 2 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.05 to about 15 μg/mL.

Additionally, dependent claim 2 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

c. Dependent Claim 3

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 ug/mL.

Aantaa discloses a composition comprising dexmedetomidine at a concentration of 100 μg/mL (Col. 5, l. 54), and administering a composition comprising dexmedetomidine to a subject at a dosage of about 0.2-2 μg/kg, 0.5-2.0 μg/kg, 1.0 μg/kg, 0.1-2.0 μg/kg/h, 0.2-0.7 μg/kg/h, and about 0.4-0.7 μg/kg/h (Col. 5, ll. 22-30), and 6 μg/kg/h, 0.2 μg/kg/h, and 0.4 μg/kg/h (Col. 5, ll. 59-67).

Dependent claim 3 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.5 to about 10 μg/mL.

Additionally, dependent claim 3 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

d. Dependent Claim 4

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 ug/mL.

Aantaa discloses a composition comprising dexmedetomidine at a concentration of 100 μg/mL (Col. 5, l. 54), and administering a composition comprising dexmedetomidine to a subject at a dosage of about 0.2-2 μg/kg, 0.5-2.0 μg/kg, 1.0 μg/kg, 0.1-2.0 μg/kg/h, 0.2-0.7 μg/kg/h, and about 0.4-0.7 μg/kg/h (Col. 5, ll. 22-30), and 6 μg/kg/h, 0.2 μg/kg/h, and 0.4 μg/kg/h (Col. 5, ll. 59-67).

Dependent claim 4 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 1 to about 7 μg/mL.

Additionally, dependent claim 4 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

e. Dependent Claim 5

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 ug/mL.

Aantaa discloses a composition comprising dexmedetomidine at a concentration of 100 μg/mL (Col. 5, l. 54), and administering a composition comprising dexmedetomidine to a subject at a dosage of about 0.2-2 μg/kg, 0.5-2.0 μg/kg, 1.0 μg/kg, 0.1-2.0 μg/kg/h, 0.2-0.7 μg/kg/h, and about 0.4-0.7 μg/kg/h (Col. 5, ll. 22-30), and 6 μg/kg/h, 0.2 μg/kg/h, and 0.4 μg/kg/h (Col. 5, ll. 59-67).

Dependent claim 5 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 4 μg/mL.

Additionally, dependent claim 5 is not anticipated by Aantaa because Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 4 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

f. Dependent Claim 6

The method of claim 1, wherein the composition is administered perioperatively.

Aantaa discloses administering a composition comprising dexmedetomidine to a patient perioperatively (Col. 5, ll. 46-49; Col. 6, ll. 35-41; Col. 9, ll. 45-65).

Dependent claim 6 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

g. Dependent Claim 7

The method of claim 6, wherein the composition is administered before or after surgery.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient before or after surgery (Col. 5, ll. 46-49; Col. 6, ll. 35-41; Col. 9, ll. 45-65).

Dependent claim 7 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

h. Dependent Claim 8

The method of claim 1, wherein the composition is administered to the patient in an intensive care unit.

Aantaa discloses administration of a composition comprising dexmedetomidine to a patient in an intensive care unit (Col. 3, ll. 35-51; Col. 4, ll. 1-7; Col. 4, ll. 29-48; Col. 5, ll. 46-58; Col. 6, ll. 35-44; Col. 7, ll. 44-56).

Dependent claim 8 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

i. Dependent Claim 9

The method of claim 1, wherein the patient is non-ventilated or intubated.

Aantaa discloses administration of a composition comprising dexmedetomidine to a patient that is non-ventilated or intubated (Col. 4, ll. 49-66; Col. 5, ll. 45-58; Col. 6, ll. 35-55; Col. 8, ll. 2-5).

Dependent claim 9 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

j. Dependent Claim 10

The method of claim 1, wherein the patient is critically ill.

Aantaa discloses administration of a composition comprising dexmedetomidine to a patient that is critically ill (Col. 4, ll. 49-66; Col. 13, ll. 41-42).

Dependent claim 10 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

k. Dependent Claim 11

The method of claim 1, wherein the composition is administered by an intravenous infusion.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (Col. 5, ll. 5-30).

Dependent claim 11 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

l. Dependent Claim 12

The method of claim 1, wherein the composition is administered as an anxiolytic.

Aantaa discloses administration of a composition comprising dexmedetomidine as an anxiolytic (Col. 3, ll. 35-51; Col. 3, ll. 43-51; Col. 3, ll. 59-67; Col. 4, ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3).

Dependent claim 12 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

m. Dependent Claim 13

The method of claim 1, wherein the composition is administered as an adjunct to an anesthetic.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient as an adjunct to an anesthetic (Col. 7, ll. 33-41).

Dependent claim 13 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

n. Dependent Claim 14

The method of claim 1, wherein the composition is administered as an analgesic.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient as an analgesic (Col. 3, ll. 35-51; Col. 3, ll. 43-51; Col. 3, ll. 59-67; Col. 4, ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3).

Dependent claim 16 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

o. Dependent Claim 15

The method of claim 1, wherein the composition is administered as an anti-hypertensive agent.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient as an anti-hypertensive agent (Col. 3, ll. 35-51; Col. 3, ll. 43-51; Col. 3, ll. 59-67; Col. 4, ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3).

Dependent claim 15 is not anticipated by Aantaa for at least the reason discussed with respect to claim 1. For example, Aantaa fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid

pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

5. U.S. Patent No. 4910214, issued March 20, 1990 to Karjalainen *et al.* ("Karjalainen").

a. Independent Claim 1

A method of providing sedation to a patient in need thereof, the method comprising

Karjalainen discloses a method of providing sedation to a patient in need thereof (Col. 3, ll. 21-60; Claims 2-4).

Independent claim 1 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof

Karjalainen discloses administering to a patient an effective amount of a composition, wherein the compositon comprises dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 3, ll. 21-60; Col. 3, l. 61 - Col. 4, 1. 40; Col. 4, ll. 41-63; Col. 4, ll. 30-45; Col. 4, l. 64 - Col. 5, l. 8; Claims 3 and 4).

Independent claim 1 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

at a concentration of about 0.005 to about 50 μg/mL,

Karjalainen discloses administering a composition comprising dexmedetomidine to a subject at a dosage of 0.3, 1, 3, 10, 20, 30 and 100 μg/kg (Col. 3, l. 21 - Col. 4, l. 60).

Independent claim 1 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present 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

Karjalainen discloses a liquid pharmaceutical composition (Col. 4, l. 64 - Col. 5, l. 20).

Independent claim 1 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

disposed within a sealed glass container.

Independent claim 1 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is disposed within a sealed glass container.

Additionally, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

b. Dependent Claim 2

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 ug/mL.

Karjalainen discloses administering a composition comprising dexmedetomidine to a subject at a dosage of 0.3, 1, 3, 10, 20, 30 and 100 μg/kg (Col. 3, l. 21 - Col. 4, l. 60).

Dependent claim 2 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.05 to about 15 μg/mL.

Additionally, dependent claim 2 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 μg/mL that

is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

c. Dependent Claim 3

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 ug/mL.

Karjalainen discloses administering a composition comprising dexmedetomidine to a subject at a dosage of 0.3, 1, 3, 10, 20, 30 and 100 μg/kg (Col. 3, l. 21 - Col. 4, l. 60).

Dependent claim 3 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 0.5 to about 10 μg/mL.

Additionally, dependent claim 3 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

d. Dependent Claim 4

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 ug/mL.

Karjalainen discloses administering a composition comprising dexmedetomidine to a subject at a dosage of 0.3, 1, 3, 10, 20, 30 and 100 μg/kg (Col. 3, l. 21 - Col. 4, l. 60).

Dependent claim 4 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 1 to about 7 μg/mL.

Additionally, dependent claim 4 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

e. Dependent Claim 5

The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 4 ug/mL.

Karjalainen discloses administering a composition comprising dexmedetomidine to a subject at a dosage of 0.3, 1, 3, 10, 20, 30 and 100 μg/kg (Col. 3, l. 21 - Col. 4, l. 60).

Dependent claim 5 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 4 μg/mL.

Additionally, dependent claim 5 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof wherein the dexmedetomidine is present at a concentration of about 4 μg/mL that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container.

f. Dependent Claim 6

The method of claim 1, wherein the composition is administered perioperatively.

Dependent claim 6 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest administering a composition comprising dexmedetomidine to a patient perioperatively.

Additionally, dependent claim 6 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

g. Dependent Claim 7

The method of claim 6, wherein the composition is administered before or after surgery.

Dependent claim 7 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient before or after surgery.

Additionally, dependent claim 7 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a

pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

h. Dependent Claim 8

The method of claim 1, wherein the composition is administered to the patient in an intensive care unit.

Dependent claim 8 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient in an intensive care unit.

Additionally, dependent claim 7 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

i. Dependent Claim 9

The method of claim 1, wherein the patient is non-ventilated or intubated.

Dependent claim 9 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient that is non-ventilated or intubated.

Additionally, dependent claim 9 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

j. Dependent Claim 10

The method of claim 1, wherein the patient is critically ill.

Dependent claim 10 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient that is critically ill.

Additionally, dependent claim 10 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

k. Dependent Claim 11

The method of claim 1, wherein the composition is administered by an intravenous infusion.

Karjalainen describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (Col. 4, ll. 64-67).

Dependent claim 11 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

l. Dependent Claim 12

The method of claim 1, wherein the composition is administered as an anxiolytic.

Karjalainen discloses administration of a composition comprising dexmedetomidine as an anxiolytic (Col. 3, l. 61 - Col. 4, 1. 40; Claims 2-4).

Dependent claim 12 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

m. Dependent Claim 13

The method of claim 1, wherein the composition is administered as an adjunct to an anesthetic.

Dependent claim 13 is not anticipated by Karjalainen because Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient as an adjunct to an anesthetic.

Additionally, dependent claim 13 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

n. Dependent Claim 14

The method of claim 1, wherein the composition is administered as an analgesic.

Karjalainen describes administration of a composition comprising dexmedetomidine as an analgesic (Col. 3, l. 61 - Col. 4, 1. 40; Claims 2-4).

Dependent claim 14 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within a sealed glass container.

o. Dependent Claim 15

The method of claim 1, wherein the composition is administered as an anti-hypertensive agent.

Karjalainen describes administration of a composition comprising dexmedetomidine as an anti-hypertensive agent (Col. 4, ll. 41-63; Claims 2-4).

Dependent claim 15 is not anticipated by Karjalainen for at least the reason discussed with respect to claim 1. For example, Karjalainen fails to disclose or suggest a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL that is formulated as a ready to use liquid pharmaceutical composition for parenteral administration to a subject and that is disposed within

a sealed glass container.

Detailed Explanation of Patentability:

1. **35 U.S.C. § 102**

Applicants respectfully submit that for at least the reasons set forth above in the preceding section, none of the cited references anticipates any of claims 1-15 of the above-captioned patent application under 35 U.S.C. § 102(a)-(g) at least because none of these references discloses each and every limitation of any of claims 1-15. *See* M.P.E.P. 2131.

2. **35 U.S.C. §103(a)**

To reject claims in an application under Section 103, an Examiner must establish a *prima facie* case of obviousness. Using the Supreme Court's guidelines enunciated in *Graham v. John Deere*, 383 U.S. 1, 17 (1966), one determines "obviousness" as follows:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, No. 04-1350 (U.S. April 30, 2007), the Supreme Court reaffirmed the *Graham* test, and indicated that although it should not be rigidly applied, a useful test for determining obviousness is to consider whether there is a teaching, suggestion or motivation in the prior art that would lead one of ordinary skill in the art to combine known elements of the prior art to arrive at the claimed invention.

For the reasons set forth below, Applicants respectfully submit that the Precedex™ label, Miyawaki, Maze, Aantaa and Karjalainen, either alone or in combination, do not render claims 1-15 of the above-captioned patent application obvious under 35 U.S.C. §103.

Independent Claim 1

Independent claim 1 recites a method of providing sedation to a patient by administering to the patient a composition comprising dexmedetomidine wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Specifically, independent claim 1 recites 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.

As set forth in detail above, no single prior art reference discloses a method of providing sedation to a patient in need thereof, the method comprising administering a pharmaceutical composition having each and every feature as claimed. Furthermore, the various references are directed to methods of using compositions comprising dexmedetomidine at different concentrations, none of which are disposed within a sealed glass container as a ready to use formulation for parenteral use at the claimed concentration. There is no suggestion or motivation to combine or incorporate select features of one reference with another to render obvious the claimed methods of using the claimed pharmaceutical composition.

For example, independent claim 1 is directed to 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. In contrast, although the Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL (p. 12, ¶6-¶8; p. 13, ¶5-¶6), wherein the composition is formulated as a liquid for parenteral administration to a subject (p. 1, ¶1-¶2; p. 6, ¶4; p. 12, ¶2-¶3), the reference does not suggest or describe that such a composition is a ready to use composition disposed within a sealed glass container or at the claimed concentration.

Rather, the Precedex™ label discloses a composition comprising dexmedetomidine at a concentration of 100 μg/mL that is disposed within a sealed glass container (p. 1, ¶1-¶2; p. 6, ¶4; p. 13, ¶5-¶6). Unlike the claimed composition that is formulated at a concentration which is ready for administration to a patient upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or

ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6), and as such, does not describe the claims.

Additionally, Applicants submit that the claimed ready to use liquid pharmaceutical composition provides for advantages over the diluted 4 μg/mL composition described by the Precedex™ label. For example, the claimed ready to use liquid pharmaceutical composition provides for advantages with regard to the ability to store the composition over prolonged periods of time, while maintaining a stable formulation. For example, as described by the present application, the claimed pharmaceutical formulation "can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi." (*See* the specification, p. 8, para. [0038]). The ability to store the claimed composition for prolonged periods of time are shown in at least Examples 1 and 3 of the application, which demonstrate that the claimed ready to use liquid pharmaceutical composition was stable for up to 9 months when stored in a glass container. As described in Example 1, a ready to use liquid formulation stored in glass vials and ampoules maintained a higher level of potency after a 5 month storage period compared to storage in plastic, CR3 or PVC containers. (*See*, the specification, pp. 18-20, paras. [0086] - [0088]). As described by Table 1, when stored in glass vials or ampoules, the ready to use liquid pharmaceutical composition maintained over 98% potency after 5 months. However, when stored in plastic or PVC containers, which include plastic syringes and plastic bags, the potency was reduced by as much as 20% after only a two-week storage period. (*See* the specification, pp. 19-20, Table 1). Similarly, Example 3 discloses that the potency of the claimed ready to use liquid pharmaceutical composition maintained relatively unchanged after being stored in glass vials and ampoules at 25°C for 9 months. (*See* the specification, Example 3, pp. 22-23, para. [0095]).

In contrast, the Precedex™ label discloses that the concentrated 100 μg/mL dexmedetomidine composition is suitable for storage, and not the diluted 4 μg/mL composition. (*See* the Precedex™ label, p. 13, ¶5-¶7). Furthermore, as described by the FDA Memorandum by Cynthia G. McCormick, M.D., dated November 30, 1999, in connection with the Medical Reviews of the Precedex (dexmedetomidine hydrochloride injection) Application No. 21-038 submitted to the FDA, and available on the FDA website July 26, 2001 (hereafter, "the Memorandum," a copy of which is submitted herewith as Appendix A and in an "Information

Disclosure Statement Not in Support of Accelerated Examination Support Document and Petition to Make Special"), the undiluted dexmedetomidine composition is manufactured through an "aseptic fill and terminal sterilization by autoclave," (*see*, the Memorandum, p. 8, third para.), and as such, is suitable for storage. However, once diluted for administration, the diluted composition is stable for only 24 hours. (*See* the Memorandum, p. 8, para. 4, stating: "The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours" (emphasis added)). Thus, unlike the claimed ready to use liquid pharmaceutical composition, which can be stored for prolonged periods of time, the diluted composition described by the Precedex™ label is prepared for use within a 24 hour period, and is not a formulation suitable for prolonged storage.

Accordingly, while diluting a 100 μg/mL concentrate to a 4 μg/mL dilution produces a composition that is stable and useable for a 24 hour period after dilution, the claimed ready to use liquid pharmaceutical composition can be stored for at least 9 months in a sealed glass container. Such a characteristic is not suggested or disclosed by the cited reference, as evidenced by the Memorandum. Rather, in contrast, an artisan of ordinary skill would understand that a diluted 4 μg/mL composition is only stable and useable for up to 24 hours.

Additionally, in view of the Precedex™ label's disclosure as a whole, an artisan of ordinary skill would understand that the diluted 4 μg/mL formulation is formulated for immediate administration to a subject, and not suitable for prolonged storage. For example, the Precedex™ label discloses that the composition is "preservative-free and contains no additives or chemical stabilizers." (*See* the Precedex™ label, p. 1, ¶2). Thus, the artisan would have had no expectation that the formulation is suitable for storage. Additionally, the diluted composition is intended for a single use only, and further, such a single use can only be for a period of, at most, 24 hours. (*See* the Precedex™ label, p. 12, ¶3-¶4). As such, the artisan would understand that any portion of the diluted composition that is not administered to a subject, or that remains after a 24 hour dosing period, cannot be stored for later use. Finally, contamination with impurities is a greater concern for compositions diluted to a low concentration. "Since the drug is present at such a low concentration 4 μg/mL, even ppb levels of impurities would have a significant contribution toward the impurity limit." (*See* the specification, p. 32, para. [00115]). Accordingly, the skilled artisan would be motivated to immediately use the diluted composition once prepared, and not store the dilution since storage could increase the risk of contamination,

e.g., microbe growth resulting from contamination during dilution. Applicants submit that none of the other cited references, considered alone or in combination with the Precedex™ label, suggests or describes a composition comprising dexmedetomidine formulated as a ready to use liquid for parenteral administration to a subject at the claimed concentrations, that is disposed within a sealed glass container.

With regard to Miyawaki, the reference discloses compounds for local anesthesia comprising a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine (p. 2, ¶24-29), and wherein the composition is formulated as a liquid for parenteral administration to a subject (p. 4, ¶58 p. 5, ¶67-¶68; pp. 7-8, ¶78-81). Miyawaki discloses that the dexmedetomidine can be present at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively.

In contrast to the claims, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki does not suggest or describe a method of administering a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. None of the other cited references, considered alone or in combination with Miyawaki, suggests or describes a method for administering a composition comprising dexmedetomidine formulated as a ready to use liquid for parenteral administration to a subject at the claimed concentrations that is disposed within a sealed glass container.

With regard to Maze, Maze discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof for use in perioperative care (Col. 1, ll. 12-37; Col. 2, ll. 5-22), wherein the composition is formulated as a liquid for parenteral administration to a subject (Col. 2, ll. 55-61; Col. 4, ll. 9-10). However, in contrast to claim 1, Maze does not suggest or describe methods of administering a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL.

Additionally, in contrast to the claims, Maze does not suggest or describe methods of administering a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. None of the other cited references, considered alone or in combination with Maze, suggests or describes a method for administering a composition comprising dexmedetomidine formulated as a ready to use liquid for parenteral administration to a subject at the claimed concentrations that is disposed within a sealed glass container.

With regard to Aantaa, the reference discloses the use of dexmedetomidine as a sedative agent to be administered to patients in an intensive care unit (ICU) to achieve patient comfort (Col. 3, ll. 35-43). In contrast to the claims, Aantaa does not suggest or describe that the dexmedetomidine or a pharmaceutically acceptable salt thereof are at a concentration of about 0.005 to about 50 μg/mL.

Additionally, in contrast to the claims, Aantaa does not suggest or describe methods of administering a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. None of the other cited references, considered alone or in combination with Aantaa, suggests or describes a method for administering a composition comprising dexmedetomidine formulated as a ready to use liquid for parenteral administration to a subject at the claimed concentrations that is disposed within a sealed glass container.

With regard to Karjalainen, the reference discloses separation of the d and l enantiomers of medetomidine and their salts which can be used for sedation, analgesia, anxiolytic effects and antihypertensive effects, (Col. 3, l. 21 - Col. 4, l. 63). In contrast to the claims, Karjalainen does not suggest or describe that the dexmedetomidine or a pharmaceutically acceptable salt thereof are at a concentration of about 0.005 to about 50 μg/mL.

Additionally, in contrast to the claims, Karjalainen does not suggest or describe methods of administering a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, that is formulated as a ready to use liquid for parenteral administration to a subject and that is disposed within a sealed glass container. None of the other cited references, considered alone or

in combination with Karjalainen, suggests or describes a method for administering a composition comprising dexmedetomidine formulated as a ready to use liquid for parenteral administration to a subject at the claimed concentrations that is disposed within a sealed glass container.

Applicants submit that none of the references described above, considered alone or in any combination, renders claim 1 obvious because none of the references, or any combination thereof, suggests or describes all the elements of claim 1. As described above, none of the cited references, considered alone or in any combination, suggests or describes a method of providing sedation to a patient in need thereof, the method comprising administering to the patient a composition comprising dexmedetomidine formulated as a ready to use liquid for parenteral administration to a subject at the claimed concentrations, that is disposed within a sealed glass container. For example, although Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95), the reference fails to disclose or suggest that such a composition is displaced within a sealed glass container as a ready to use liquid comprising dexmedetomidine at the claimed concentration. Thus, combining the disclosure of Miyawaki with any of the other references, for example, the Precedex™ label, which describes a composition comprising dexmedetomidine, provides an artisan of ordinary skill with no suggestion or motivation to practice the claims.

Dependent Claim 2

Dependent claim 2 depends from claim 1, and recites that the claimed ready to use liquid pharmaceutical composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 ug/mL. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 µg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 2, which is directed to a 0.05 to about 15 µg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 µg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-

¶6).

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that such compositions can comprise dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively. However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 1, ll. 10-31; Col. 3, ll. 35-67; Col. 4, ll. 29-43; Col. 5, ll. 5-15; Col. 14, ll. 12-50). Aantaa discloses the use of dexmedetomidine as a sedative agent to be administered to patients in an intensive care unit (ICU) to achieve patient comfort (Col. 3, ll. 35-43). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral

administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.05 to about 15 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 2. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 2.

Dependent Claim 3

Dependent claim 3 depends from claim 1, and recites that the claimed ready to use liquid pharmaceutical composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 ug/mL. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 µg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 3, which is directed to a 0.5 to about 10 µg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 µg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local

anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that such compositions can comprise dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively. However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 1, ll. 10-31; Col. 3, ll. 35-67; Col. 4, ll. 29-43; Col. 5, ll. 5-15; Col. 14, ll. 12-50). Aantaa discloses the use of dexmedetomidine as a sedative agent to be administered to patients in an intensive care unit (ICU) to achieve patient comfort (Col. 3, ll. 35-43). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can

be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.5 to about 10 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 3. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 3.

Dependent Claim 4

Dependent claim 4 depends from claim 1, and recites that the claimed ready to use liquid pharmaceutical composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 ug/mL. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 µg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 4, which is directed to a 1 to about 7 µg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 µg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that such compositions can comprise dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 µg/mL, 0.08 µg/mL, 0.008 µg/mL and 0.0008 µg/mL, respectively.

Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ µg/mL and 0.2 µg/mL, respectively. However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 µg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 1, ll. 10-31; Col. 3, ll. 35-67; Col. 4, ll. 29-43; Col. 5, ll. 5-15; Col. 14, ll. 12-50). Aantaa discloses the use of dexmedetomidine as a sedative agent to be administered to patients in an intensive care unit (ICU) to achieve patient comfort (Col. 3, ll. 35-43). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 1 to about 7 ug/mL, wherein the composition is formulated as a ready to use liquid for

parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 4. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 4.

Dependent Claim 5

Dependent claim 5 depends from claim 1, and recites that the claimed ready to use liquid pharmaceutical composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 ug/mL. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules. In contrast to claim 5, which is directed to a 4 μg/mL dexmedetomidine composition disposed within a sealed glass container that is formulated as a ready to use liquid pharmaceutical composition for administration to a subject upon removal from the sealed glass container, the dexmedetomidine composition of the Precedex™ label must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6).

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that such compositions can comprise dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of $4x10^{-6}$ M, $4x10^{-7}$ M, $4x10^{-8}$ M, or $4x10^{-9}$ M (p. 56, ¶56). Such concentrations correspond to about 0.8 μg/mL, 0.08 μg/mL, 0.008 μg/mL and 0.0008 μg/mL, respectively. Miyawaki also discloses a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of between $1x10^{-15}$ M and $1x10^{-6}$ M (p. 2, ¶26; and Claim 2), which corresponds to about $2x10^{-10}$ μg/mL and 0.2 μg/mL, respectively. However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical

composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof (Col. 1, ll. 10-31; Col. 3, ll. 35-67; Col. 4, ll. 29-43; Col. 5, ll. 5-15; Col. 14, ll. 12-50). Aantaa discloses the use of dexmedetomidine as a sedative agent to be administered to patients in an intensive care unit (ICU) to achieve patient comfort (Col. 3, ll. 35-43). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 4 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 5. For the reasons discussed above, and further, for the reasons discussed previously for claim 1,

none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 5.

Dependent Claim 6

Dependent claim 6 depends from claim 1, and recites that the claimed composition is administered perioperatively. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules, which must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6). However, the Precedex™ label fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient perioperatively. Additionally, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses administering a composition comprising dexmedetomidine to a patient perioperatively (p. 9, ¶92-93). However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses administering a composition comprising dexmedetomidine to a patient perioperatively (Abstract; Col. 2, ll. 11-19; Claim 1). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses administering a composition comprising dexmedetomidine to a patient perioperatively (Col. 5, ll. 46-49; Col. 6, ll. 35-41; Col. 9, ll. 45-65). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically

acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient perioperatively. Additionally, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 6. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 6.

Dependent Claim 7

Dependent claim 7 depends from claim 6, which depends from claim 1. Dependent claim 7 recites that the claimed composition is administered before or after surgery. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules, which must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6). However, the Precedex™ label fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient before or after surgery. Additionally, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof to a patient before or after surgery (p. 9, ¶92-93). However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze describes administration of a composition comprising dexmedetomidine to a patient before or after surgery (Col. 4, ll. 11-18). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient before or after surgery (Col. 5, ll. 46-49; Col. 6, ll. 35-41; Col. 9, ll. 45-65). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient before or after surgery. Additionally, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 7.

For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 7.

Dependent Claim 8

Dependent claim 8 depends from claim 1, and recites that the claimed composition is administered to the patient in an intensive care unit. The Precedex™ label discloses administering a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof to a patient in an intensive care unit (p. 4, ¶4; p. 6, ¶4). However, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient in an intensive care unit. Additionally, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Miyawaki also fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, Maze fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient in an intensive care unit. Additionally, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a

subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses administration of a composition comprising dexmedetomidine to a patient in an intensive care unit (Col. 3, ll. 35-51; Col. 4, ll. 1-7; Col. 4, ll. 29-48; Col. 5, ll. 46-58; Col. 6, ll. 35-44; Col. 7, ll. 44-56). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient in an intensive care unit. Additionally, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 8. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 8.

Dependent Claim 9

Dependent claim 9 depends from claim 1 and recites that the patient is non-ventilated or intubated. The Precedex™ label discloses administration of a composition comprising dexmedetomidine to a patient that is intubated (p. 4, ¶4). However, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that the composition for local anesthesia comprising dexmedetomidine enhances an anesthetic action due to local anesthesia and is applicable to surgeries and to the control and palliative care of cancer pain (p. 9, ¶92-93). However, Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is non-ventilated or intubated. Miyawaki also fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses administration of a composition comprising dexmedetomidine to a patient that is intubated (Col. 2, ll. 23-33). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses administration of a composition comprising dexmedetomidine to a patient that is non-ventilated or intubated (Col. 4, ll. 49-66; Col. 5, ll. 45-58; Col. 6, ll. 35-55; Col. 8, ll. 2-5). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to disclose or suggest administration of a

composition comprising dexmedetomidine to a patient that is non-ventilated or intubated. Additionally, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 9. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 9.

Dependent Claim 10

Dependent claim 10 depends from claim 1, and recites that the claimed composition is administered to a patient that is critically ill. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules, which must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6). However, the Precedex™ label fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is critically ill. Additionally, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that the composition for local anesthesia comprising dexmedetomidine enhances an anesthetic action due to local anesthesia and is applicable to surgeries and to the control and palliative care of cancer

pain (p. 9, ¶92-93). However, Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is critically ill. Miyawaki also fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, Maze fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient that is critically ill. Additionally, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses administration of a composition comprising dexmedetomidine to a patient that is critically ill (Col. 4, ll. 49-66; Col. 13, ll. 41-42). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine to a patient that is critically ill. Additionally, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 10. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 10.

Dependent Claim 11

Dependent claim 11 depends from claim 1, and recites that the claimed composition is administered by an intravenous infusion. The Precedex™ label describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (p. 6, ¶4; p. 7, ¶3-¶5; p. 12, ¶2-¶4). However, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). Miyawaki discloses that the composition for local anesthesia comprising dexmedetomidine enhances an anesthetic action due to local anesthesia and is applicable to surgeries and to the control and palliative care of cancer pain (p. 9, ¶92-93). However, Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion. Miyawaki also fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (Col. 4, ll. 9-11). However, Maze does not suggest or

describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (Col. 5, ll. 5-30). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen describes administration of a composition comprising dexmedetomidine to a patient by an intravenous infusion (Col. 4, ll. 64-67). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 10. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 10.

Dependent Claim 12

Dependent claim 12 depends from claim 1, and recites that the claimed composition is administered as an anxiolytic. The Precedex™ label discloses administration of a composition comprising dexmedetomidine as an anxiolytic (p. 4, ¶3). However, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses a kit for local anesthesia including a local anesthetic agent, such as

lidocaine, and a composition for local anesthesia, such as dexmedetomidine, as components of the kit, wherein an amount of the composition for local anesthesia may be mixed into the local anesthetic agent in advance of its use (p. 2, ¶24-29; p. 9, ¶ 95). However, Miyawaki fails to suggest or describe administration of a composition comprising dexmedetomidine as an anxiolytic. Miyawaki also fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses administration of a composition comprising dexmedetomidine as an anxiolytic (Col. 1, ll. 38-41; Claim 2). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa discloses administration of a composition comprising dexmedetomidine as an anxiolytic (Col. 3, ll. 35-51; Col. 3, ll. 43-51; Col. 3, ll. 59-67; Col. 4, ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses administration of a composition comprising dexmedetomidine as an anxiolytic (Col. 3, l. 61 - Col. 4, 1. 40; Claims 2-4). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim

12. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 12.

Dependent Claim 13

Dependent claim 13 depends from claim 1, and recites that the claimed composition is administered as an adjunct to an anesthetic. The Precedex™ label describes administration of a composition comprising dexmedetomidine as an adjunct to an anesthetic. (p. 8, ¶4). However, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof as an adjunct to an anesthetic (p. 2, ¶24-29; pp. 2-3, ¶37; p. 3, ¶43; p. 4, ¶56; p. 4, ¶58; p. 9, ¶ 95). However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze describes administration of a composition comprising dexmedetomidine to a patient as an adjunct to an anesthetic (Col. 1, ll. 12-20; Col. 2, ll. 23-26; Claims 2 and 3). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient as an adjunct to an anesthetic (Col. 7, ll. 33-41). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt

thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to disclose or suggest administration of a composition comprising dexmedetomidine as an adjunct to an anesthetic. Additionally, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 13. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 13.

Dependent Claim 14

Dependent claim 14 depends from claim 1, and recites that the claimed composition is administered as an analgesic. The Precedex™ label describes administration of a composition comprising dexmedetomidine as an analgesic (p. 5, ¶2-¶3, p. 6, ¶2). However, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki describes administration of a composition comprising dexmedetomidine as an analgesic (p. 2, ¶24-29; pp. 2-3, ¶37; p. 3, ¶43; p. 4, ¶56; p. 4, ¶58; p. 9, ¶ 95). However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a

concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze describes administration of a composition comprising dexmedetomidine to a patient as an analgesic (Claims 2 and 3). However, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient as an analgesic (Col. 3, ll. 35-51; Col. 3, ll. 43-51; Col. 3, ll. 59-67; Col. 4, ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen describes administration of a composition comprising dexmedetomidine as an analgesic (Col. 3, l. 61 - Col. 4, 1. 40; Claims 2-4). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 14. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 14.

Dependent Claim 15

Dependent claim 15 depends from claim 1, and recites that the claimed composition is administered as an anti-hypertensive agent. The Precedex™ label discloses a pharmaceutical composition comprising dexmedetomidine hydrochloride at a concentration of 100 μg/mL disposed within 2 mL clear glass vials and 2 mL ampoules, which must be removed from the 2 mL vial or ampoule and diluted to a concentration of 4 μg/mL prior to administration to a subject (p. 12, ¶6-¶8; p. 13, ¶5-¶6). However, the Precedex™ label fails to suggest or describe administration of a composition comprising dexmedetomidine as an anti-hypertensive agent. Additionally, the Precedex™ label fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Miyawaki discloses administration of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof as an anti-hypertensive agent (p. 2, ¶32). However, Miyawaki fails to suggest or disclose a method of providing sedation to a patient in need thereof. Additionally, Miyawaki fails to suggest or describe a ready to use liquid pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Maze discloses the use of compositions comprising dexmedetomidine in perioperative care to reduce the amount of anesthetic necessary to administer to achieve surgical anesthesia (Col. 1, ll. 12-20). However, fails to suggest or describe administration of a composition comprising dexmedetomidine as an anti-hypertensive agent. Additionally, Maze does not suggest or describe a pharmaceutical composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Aantaa describes administration of a composition comprising dexmedetomidine to a patient as an anti-hypertensive agent (Col. 3, ll. 35-51; Col. 3, ll. 43-51; Col. 3, ll. 59-67; Col. 4,

ll. 1-12; Col. 4, ll. 30-45; Claims 1 and 3). However, Aantaa fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 ug/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

Karjalainen discloses d- and l-enantiomers of medetomidine, and their non-toxic pharmaceutically acceptable acid addition salts. Karjalainen discloses that such compounds can be administered for sedation, analgesia, treatment of anxiety or treatment of hypertension (Col. 3, l. 21 - Col. 4, l. 63). However, Karjalainen fails to suggest or describe a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 μg/mL, wherein the composition is formulated as a ready to use liquid for parenteral administration to a subject, and wherein the composition is disposed within a sealed glass container.

None of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, discloses or suggests all of the elements as claimed in dependent claim 15. For the reasons discussed above, and further, for the reasons discussed previously for claim 1, none of the Precedex™ label, Miyawaki, Maze, Aantaa or Karjalainen, considered alone or in any combination, suggests or describes a composition as recited by dependent claim 15.

Statement of Disqualification of Prior Art

None of the above references may be disqualified under 35 U.S.C. § 103(c).

Statement of Utility:

The present invention, as set forth in independent claim 1 and the claims depending therefrom, is directed to a method of providing sedation to a patient in need thereof, the method comprising administering a pharmaceutical composition comprising dexmedetomidine that is formulated as a ready to use liquid for parenteral administration to a subject and is disposed within a sealed glass container.

Showing of Support of Each Claim Limitation:

CLAIM LIMITATION	SUPPORT FOR CLAIM LIMITATION IN THE PRESENT APPLICATION	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/541,524	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/343,672
1. A method of providing sedation to a patient in need thereof, the method comprising	See, for example, p. 3, ¶15; p. 7, ¶36; and p. 14, ¶66.	See, for example, p. 3, ¶15; p. 7, ¶36; and p. 14, ¶66.	See, for example, p. 3, ¶15; p. 7, ¶36; and p. 14, ¶66.
administering to the patient an effective amount of a composition, wherein the composition comprises dexmedetomidine or a pharmaceutically acceptable salt thereof	See, for example, p. 2, ¶¶6-9; p. 3, ¶14; pp. 4-5, ¶23; pp. 10-11, ¶¶46-49; Examples 1-6.	See, for example, p. 2, ¶¶6-9; p. 3, ¶14; pp. 4-5, ¶23; pp. 10-11, ¶¶46-49; Examples 1-6.	See, for example, p. 2, ¶¶6-9; p. 3, ¶14; pp. 4-5, ¶23; pp. 10-11, ¶¶46-49; Examples 1-6.
at a concentration of about 0.005 to about 50 μg/mL,	See, for example, p. 10, ¶46.	See, for example, p. 10, ¶46.	See, for example, p. 10, ¶46.

CLAIM LIMITATION	SUPPORT FOR CLAIM LIMITATION IN THE PRESENT APPLICATION	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/541,524	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/343,672
wherein the composition is a ready to use liquid pharmaceutical composition for parenteral administration to the patient	See, for example, p. 2, ¶4; p. 2, ¶¶6-8; p.3, ¶19; p. 5, ¶25; p. 6, ¶30; p. 8, ¶37; pp. 9-10, ¶¶42-44; p. 11, ¶50; Examples 1-6.	See, for example, p. 2, ¶4; p. 2, ¶¶6-8; p.3, ¶19; p. 5, ¶25; p. 6, ¶30; p. 8, ¶37; pp. 9-10, ¶¶42-44; p. 11, ¶50; Examples 1-6.	See, for example, pp. 1-2, ¶4; p. 2, ¶¶6-8; p.3, ¶19; p. 5, ¶25; p. 6, ¶30; p. 8, ¶37; pp. 9-10, ¶¶42-44; p. 11, ¶50; Examples 1-6.
disposed within a sealed glass container.	See, for example, p. 2, ¶6; p. 5, ¶12; p. 12; ¶¶57-58; p. 13, ¶60; and Examples 1-6.	See, for example, p. 2, ¶6; p. 5, ¶12; p. 12; ¶¶57-58; p. 13, ¶60; and Examples 1-6.	See, for example, p. 2, ¶6; p. 2, ¶12; p. 12; ¶¶57-58; p. 13, ¶60; and Examples 1-6.
2. The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.05 to about 15 ug/mL.	See, for example, p. 2, ¶7; and p. 3, ¶13.	See, for example, p. 2, ¶7; and p. 3, ¶13.	See, for example, p. 2, ¶7; and pp. 2-3, ¶13.
3. The method of claim 1, wherein the	See, for example, p. 11, ¶47.	See, for example, p. 11, ¶47.	See, for example, p. 11, ¶47.

CLAIM LIMITATION	SUPPORT FOR CLAIM LIMITATION IN THE PRESENT APPLICATION	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/541,524	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/343,672
dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 0.5 to about 10 ug/mL.			
4. The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is at a concentration of about 1 to about 7 ug/mL.	See, for example, p. 11, ¶47.	See, for example, p. 11, ¶47.	See, for example, p. 11, ¶47.
5. The method of claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt	See, for example, p. 2, ¶8; p. 3, ¶14; p. 11, ¶¶48-49; p. 12, ¶¶55-56; Examples 1-6.	See, for example, p. 2, ¶8; p. 3, ¶14; p. 11, ¶¶48-49; p. 12, ¶¶55-56; Examples 1-6.	See, for example, p. 2, ¶8; p. 3, ¶14; p. 11, ¶¶48-49; p. 12, ¶¶55-56; Examples 1-6.

CLAIM LIMITATION	SUPPORT FOR CLAIM LIMITATION IN THE PRESENT APPLICATION	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/541,524	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/343,672
thereof is at a concentration of about 4 ug/mL.			
6. The method of claim 1, wherein the composition is administered perioperatively.	See, for example, p. 3, ¶16; and p. 15, ¶68.	See, for example, p. 3, ¶16; and p. 15, ¶68.	See, for example, p. 3, ¶16; and p. 15, ¶68.
7. The method of claim 6, wherein the composition is administered before or after surgery.	See, for example, p. 15, ¶71.	See, for example, p. 15, ¶71.	See, for example, p. 15, ¶71.
8. The method of claim 1, wherein the composition is administered to the patient in an intensive care unit.	See, for example, p. 1, ¶3; and pp. 14-15, ¶67.	See, for example, p. 1, ¶3; and pp. 14-15, ¶67.	See, for example, p. 1, ¶3; and pp. 14-15, ¶67.
9. The method of claim 1, wherein the patient is non-ventilated or intubated.	See, for example, p. 18, ¶84; and pp. 14-15, ¶67.	See, for example, p. 18, ¶84; and pp. 14-15, ¶67.	See, for example, p. 18, ¶84; and pp. 14-15, ¶67.

CLAIM LIMITATION	SUPPORT FOR CLAIM LIMITATION IN THE PRESENT APPLICATION	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/541,524	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/343,672
10. The method of claim 1, wherein the patient is critically ill.	See, for example, p. 15, ¶70.	See, for example, p. 15, ¶70.	See, for example, p. 15, ¶70.
11. The method of claim 1, wherein the composition is administered by an intravenous infusion.	See, for example, p. 2, ¶4; p. 3, ¶19; p. 8, ¶¶37-38; pp. 9-10, ¶¶43-44; p. 10, ¶45; and p. 16, ¶75.	See, for example, p. 2, ¶4; p. 3, ¶19; p. 8, ¶¶37-38; pp. 9-10, ¶¶43-44; p. 10, ¶45; and p. 16, ¶75.	See, for example, pp. 1-2, ¶4; p. 3, ¶19; p. 8, ¶¶37-38; pp. 9-10, ¶¶43-44; p. 10, ¶45; and p. 16, ¶75.
12. The method of claim 1, wherein the composition is administered as an anxiolytic.	See, for example, p. 3, ¶15; p. 7, ¶36; p. 14, ¶66; and p. 16, ¶72.	See, for example, p. 3, ¶15; p. 7, ¶36; p. 14, ¶66; and p. 16, ¶72.	See, for example, p. 3, ¶15; p. 7, ¶36; p. 14, ¶66; and p. 16, ¶72.
13. The method of claim 1, wherein the composition is administered as an adjunct to an anesthetic.	See, for example, p. 15, ¶ 69.	See, for example, p. 15, ¶ 69.	See, for example, p. 15, ¶ 69.
14. The method of claim 1, wherein the composition is administered as an analgesic.	See, for example, p. 3, ¶15; p. 7, ¶36; p. 14, ¶66; and p. 16, ¶72.	See, for example, p. 3, ¶15; p. 7, ¶36; p. 14, ¶66; and p. 16, ¶72.	See, for example, p. 3, ¶15; p. 7, ¶36; p. 14, ¶66; and p. 16, ¶72.

CLAIM LIMITATION	SUPPORT FOR CLAIM LIMITATION IN THE PRESENT APPLICATION	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/541,524	SUPPORT FOR CLAIM LIMITATION IN PRIORITY DOCUMENT U.S. SER. NO. 13/343,672
15. The method of claim 1, wherein the composition is administered as an anti-hypertensive agent.	See, for example, p. 3, ¶15; and p. 14, ¶66.	See, for example, p. 3, ¶15; and p. 14, ¶66.	See, for example, p. 3, ¶15; and p. 14, ¶66.

No means plus function claim elements are present in the above claims.

Thus, claims 1-15 satisfy the requirements of 35 U.S.C. § 112, ¶1.

Conclusion:

In view of this Accelerated Examination Support Document, Applicants respectfully request that the Examiner grant the Petition for Accelerated Examination in the above-referenced patent application. Applicant respectfully submits that the claims of the above-referenced patent application are in condition for allowance, and respectfully request that the Examiner allow the claims of the above-referenced patent application to issue in a U.S. patent.

Applicants believe that no additional fee is due in connection with the filing of this submission other than the fees submitted herewith, which include the fee under 37 C.F.R. 1.17(h), and the basic filing fee, search fee, and examination fee in connection with the application filed herewith under 35 U.S.C. § 111(a). However, if any additional fee is required, or if any overpayment has been made, Applicant authorizes the Director to charge any fees, or credit or any overpayments made, to Deposit Account 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

November 15, 2012
Date

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30 Rockefeller Plaza
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§ 2
’527 PATENT NOTICE OF ALLOWANCE (JAN. 11, 2013)

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

62965 7590 01/11/2013

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

EXAMINER
POLANSKY, GREGG

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 01/11/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/678,148	11/15/2012	Priyanka Roychowdhury	077350.0359	9687

TITLE OF INVENTION: METHODS OF TREATMENT USING A DEXMEDETOMIDINE PREMIX FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	04/11/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

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B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/678,148	11/15/2012	Priyanka Roychowdhury	077350.0359	9687

TITLE OF INVENTION: METHODS OF TREATMENT USING A DEXMEDETOMIDINE PREMIX FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	04/11/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
POLANSKY, GREGG	1629	514-396000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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2 _____
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

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❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/678,148	11/15/2012	Priyanka Roychowdhury	077350.0359	9687

62965 7590 01/11/2013

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

EXAMINER	
POLANSKY, GREGG	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 01/11/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/678,148	ROYCHOWDHURY ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the 12/20/2012 telephone interview and the filing of Terminal Disclaimers*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *1-15*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/15/2012
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20121221* .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Gregg Polansky/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

DETAILED ACTION

Information Disclosure Statement

1. Applicants' Information Disclosure Statement, filed 11/15/201, is acknowledged and has been reviewed.

Terminal Disclaimer

2. The terminal disclaimer filed on 12/20/2012 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Patent Nos. 8,242,158 and 8,338,470, and on any patent granted on Application No. 13/678,260 has been reviewed and is accepted. The terminal disclaimers have been recorded.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: Although the prior art teaches providing sedation and analgesia to a patient in need thereof, and treating hypertension or anxiety, comprising administration to the patient an effective amount of a composition comprising dexmedetomidine or a pharmaceutically acceptable salt thereof, the prior art does not teach or reasonably suggest the use of dexmedetomidine disposed within a sealed glass container *as a ready to use formulation* for parenteral use at the instantly claimed concentrations. Additionally, the

Examiner concurs with Applicants' detailed explanation of patentability as set forth at pages 44-73 of the Examination Support Document filed by Applicants on 11/15/2008.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 10:00 A.M. - 8:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie L. McCormick can be reached on (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629

EXHIBIT 5

DECLARATION OF JONATHAN M. EDWARDS

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY