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| EXAMINER |
|---|
| PALENIK, JEFFREY T |

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**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):

stldocket@hdp.com

| Office Action Summary | Application No. 15/183,441 | Applicant(s) KEEGAN ET AL. | |
|---|---|---|---|
| | Examiner Jeffrey T. Palenik | Art Unit 1615 | AIA (First Inventor to File) Status Yes |

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

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 June 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

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.

4)☐ 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.

**Disposition of Claims***

5)☒ Claim(s) *1-30* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-30* is/are rejected.

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

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

* If any claims have been determined allowable, 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.

**Application Papers**

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

11)☒ The drawing(s) filed on *5 July 2016* 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).

**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).

**Certified copies:**

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)).

** 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) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *6/15/16; 6/20/16; 6/21/16*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

## DETAILED ACTION

Claims 1-30 are presented and represent all claims currently under consideration on the merits.

**The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.**

### INFORMATION DISCLOSURE STATEMENT

Three Information Disclosure Statements (IDS) filed 15 June 2016, 20 June 2016, and 21 June 2016 are acknowledged and have been considered.

### CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 1 recites a method of treating opioid overdose comprising delivering a spray from a pre-primed device into a nostril of a patient, wherein the device is adapted for nasal delivery, and wherein the device contains a pharmaceutical solution comprising about 4% (w/v) naloxone hydrochloride or a hydrate thereof, and wherein the pharmaceutical solution is delivered in a round spray plume with an ovality ratio less than about 2.0 when measured at 3 cm.

Claim 2 narrows this ratio to less than about 1.5 when measured at 3 cm. Claims 3-9 recite limitations directed to the administered composition.

Claim 11 which depends from claim 6, recites that the method further comprises storing the device for about twelve months or less at 25ºC and 60% relative humidity prior to actuating the device, wherein the device retains at least about 100% of initial naloxone hydrochloride content at actuation.

Claim 12 depends from claim 1 and recites wherein the patient experiences a geometric mean naloxone $C_{max}$ not less than about 3 ng/mL following a single spray.

Claim 13 depends from claim 12 and recites wherein the patient experiences a plasma concentration such that the geometric mean of area under a plasma concentration versus time curve ($AUC_{0\text{-}inf}$) is not less than about 8 hr-ng/mL when time is extrapolated to infinity.

Independent claim 14 is drawn to a "mist" comprising droplets of a naloxone hydrochloride solution wherein the solution has a concentration of about 4% (w/v), and wherein no more than about 10% of the droplets have a diameter less than 10 µm.

Claims 15-17 are directed to limitations which further define the composition.

Claim 18 recites that the mist takes the shape of a round plume with an ovality ratio less than 2.0.

Claim 19 which depends directly from claim 14 recites that the naloxone is at least 40% bioavailable.

Claim 20 recites that the median droplet size is between about 30 µm and about 100 µm.

Claim 21 narrows this range to wherein approximately 50% of the droplets have a diameter between about 30 µm and about 70 µm.

Claim 22 narrows this range further still to wherein approximately 90% of droplets have a diameter less than about 100 µm.

Claim 23 recites wherein no more than approximately 2% of droplets have a diameter less than about 10 µm.

Independent claim 24 recites the same subject matter as claim 1 with the notable exception that the preamble recites treating a different condition.

Claims 25-28 recite compositional limitations directed to the administered formulation.

Claim 29 which depends from claim 24 recites wherein the plasma concentration versus time curve of naloxone in the patient has a $t_{max}$ of less than 30 minutes.

Claim 30 recites the same limitations as claim 2 above.

The Examiner broadly and reasonably interprets from the claimed invention as well as the instant specification, that the claimed methods and composition require two components: 1) the composition being administered, and 2) the device which administers the composition.

Specifically regarding claims: 1, 2, 8, 9, 11-14, 18-24, 29, and 30, the Examiner on review of the instant specification cannot reconcile a structure/function or structure/property relationship for the above limitations. That is, for example, in the case of independent claims 1 and 24, a 4% naloxone solution is administered from a device which is "adapted for nasal

delivery" and which emits a spray plume which has an ovality ratio (ratio of $D_{max}/D_{min}$) of less than 2.0 when measured at 3 cm. While the former limitation is fairly straight forward, the latter limitation pertaining to the plume is a recited function which lacks structure. That is, the instant specification does not appear to provide clear discussion as to what device is relied upon by Applicants to achieve the claimed property. It is noted that the instant specification does discuss several devices which could be used. Such devices include, for example Mucosal Atomization Device (MAD) as well as other single- and bi-dose devices (see e.g., ¶¶[0075]-[0077]). However, none of these devices is clearly discussed or, more critically, described by the instant specification as being responsible for providing the instantly claimed plume property. A similar argument is advanced on behalf of the claimed "mist" composition, specifically, claims 14, 18, and 20-23. These claims recite a mist which is presumably emitted from a nasal delivery device, but recite no device whatsoever. Here again, functional and property limitations are recited with no corresponding structural limitations which give rise to the function/property. Like the method claims above (which at least recite a generic nasal device), there is no discussion or description provided within the instant specification of a device which provides the claimed functions or properties. While it might be argued, for example, that the droplet sizes of the mist are properties of the claimed composition, the Examiner would counter with the fact that the mist is created by actuation through a spray device and thus a spray device must be part of the claimed composition. Further, as mentioned above, the instant claims and specification lack clear description of the device which is responsible for providing the claimed properties.

Herein, for the purposes of examination on the merits, the Examiner will consider any showing in the art of intranasal administration of the claimed composition to meet the instantly claimed functions/properties.

> The following is a quotation of 35 U.S.C. 112(b):
> (b) CONCLUSION — the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
>
> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The instantly claimed limitations are discussed above.

Regarding claims 1-13 and 24-30, each of the independent claims, and therefore, dependent claims, carry the limitation reciting "wherein the pharmaceutical solution is delivered in a round spray plume with an ovality ratio less than about 2.0 when measured at 3 cm." Claims 2 and 30 lower that ratio to 1.5 when measured at 3 cm. As discussed above, the instant specification is not considered to provide adequate written description regarding what device produces the claimed spray properties. Turning to the language employed in the claims, it is noted that the only structural limitations pertaining to a nasal device are directed to a device which is "adapted for nasal delivery" and that the device is "pre-primed". The Examiner considers the claims to be rendered indefinite because that device which Applicants consider to actually accomplish the claimed function or property is not claimed.

Claims 14-23 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See **MPEP §2172.01**. The omitted elements are: the spray device used to produce the mist composition of claim 14 as well as the properties claimed thereafter. As with claims 1-13 and 24-30, the Examiner submits that it is not sufficient to simply amend into the claim a limitation directed to a generic "spray device", particularly where limitations follow which are directed to specific properties such as spray plume size/ratio and droplet size. Properties such as these are considered to be dependent on the particular device which is used to administer the claimed solution. As claims 14-23 do not recite such a device required to create a "mist", they are rendered indefinite.

The limitations of claims 12, 13, and 29 are discussed above and are briefly re-summarized here as being drawn to stability and pharmacokinetic properties of the administered composition.

Herein, the Examiner submits that the claims are rendered indefinite on account of both of the undefined components recited in the claims: 1) the lack of structure of the administering device as discussed above, and 2) the lack of definition of the administered composition. Regarding the former, the Examiner maintains that definition for the administering device is considered critical because the composition administered to the body achieves a particular pharmacokinetic concentration based on the amount delivered and, presumably, the plume which said device creates. Regarding the latter, the Examiner here again submits that it is unclear as to whether the claimed pharmacokinetic properties are due to the composition comprising naloxone alone in solution (as claimed) or if they are due to the composition as a whole (see e.g., claim

11). The Examiner would argue the former citing Wyse (USPN 9,192,570 as evidence). As discussed in the telephone interview conducted 12 August 2016, the reason Wyse was considered to teach away from previously allowed formulations is on the basis of the preservative used; benzalkonium chloride was recited in the independent claim whereas benzyl alcohol was preferred by Wyse. Further, Wyse provided guidance teaching that benzalkonium chloride had been shown to degrade the naloxone active, thereby providing less active to administer/interact with the body. Thus, the Examiner respectfully advances that claims 12, 13, and 29 are indefinite with respect to their recited pharmacokinetic properties because it is unclear what composition Applicants are claiming which gives rise to said properties. Herein, for the purposes of examination on the merits, the Examiner will consider the recited properties met where the composition and/or intranasal methods of administering said compositions is shown in the art.

## CLAIM REJECTIONS - 35 USC §103

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the Examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the Examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

**Claims 1-5, 12-16, 18-27, 29, and 30 are rejected under 35 U.S.C. 103 as being unpatentable over Wyse et al. (USPN 9,192,570 B2; IDS reference) in view of Djupesland (*Drug Deliv. and Transl. Res.*; 2013).**

The limitations of the recited claims are discussed above.

**Wyse** discloses a nasal spray composition comprising from about 5 mg/mL to about 50 mg/mL naloxone. Such a concentration recalculates to a range of 0.5-5% (w/v) of the composition. Said naloxone compound is further defined in the reference as being embodied by naloxone hydrochloride dihydrate **(see e.g., claim 13)**. The composition is clearly disclosed in the reference as being used to treat opioid overdose **(see e.g., Abstract)** and that said composition is administered nasally **(see e.g., Title, Abstract; claim 1)**. Regarding the "plume" limitations discussed above, the Examiner notes that such devices which are mentioned in the instant specification are disclosed by the reference. Therein, for example, unit dose devices available from Aptar/Pfeiffer are disclosed as being used to administer the practiced naloxone

formulations **(see e.g., col. 10, lines 28-52)**. Thus, as teachings are provided which appear to meet the device limitations as claimed and as defined by the instant specification, the Examiner considers the limitations directed to the plume ratio to also be met. Of particular note, this passage teaches that each container of the device will deliver about 100 µL of spray, each of which can contain, for example, 1-mg or 2-mg of naloxone HCl dihydrate. The passage also teaches that the volume may be modified to deliver between 50-200 µL. Recalculation of a 2 mg dose of naloxone in a 50 µL dose produces a 4% dosage of naloxone (0.04 mg/50µL). Of course when considered in light of the broader teachings of the reference (e.g., above passage and claims), the Examiner advances that a person of skill in the art at the time of the filed invention would have discovered the instantly claimed 4% (w/v) dose through routine experimentation.

Regarding the claimed isotonicity agent, sodium chloride is one such agent which is taught and suggested as being included in such formulations to modify the osmolality of the composition. **Table 13** teaches using it in a concentration of 6.4 mg/mL or 0.64% (w/v).

Regarding the limitations of claim 4 directed to the percentage of preservative used, the reference is considered to teach and suggest the claimed limitation, for example, at claim 8. Therein, it is taught that the spray composition will be "substantially free of" paraben-based preservatives. The term "substantially free" is further defined in the reference as being typically less than 0.1% by weight and also includes zero percent by weight. Table 13, again defines such a preservative as propyl paraben as being present in an amount such as 0.2 mg/mL (or 0.02% (w/v)). Such is considered to teach and suggest the recited limitation of between about 0.005% and ***about 0.015% of a preservative***.

Regarding the stabilizing agent, the reference teaches including disodium EDTA in the practiced composition in an amount ranging from about 2 to about 20 mM. Recalculated, 2 mM EDTA is about 0.0584% (w/v) and 20 mM is about 0.584% (w/v). An EDTA concentration of about 17.12 mM would produce the claimed concentration of 0.5% (w/v). Lastly, regarding claim 5, the Examiner notes that citric acid is added to the composition such that a pH of about 4 is achieved (see e.g., claim 6). Other such compounds which may be used in order to achieve the claimed pH are taught as including hydrochloric acid **(see e.g., col. 8, lines 1-4)**.

The foregoing is considered to also teach and suggest the limitations recited in method claims 24-27. As claim 24 does not recite a particular population to whom the nasal composition is to be administered, the Examiner advances that simply demonstrating its nasal administration in the art is sufficient in meeting the positively recited steps of the claim. However, in the alternative, the Examiner advances that the prior art immediately recognizes the use of intranasally administered naloxone for the purposes of treating opioid-induced respiratory depression. Motivation to use the claimed composition as such stems from, for example, **Green et al. (Abstract)**, which teaches that naloxone is a known opioid antagonist which reverses the effects of opioids and conditions associated therewith. As such, a person of ordinary skill in the art at the time of the filed invention would have found motivation to administer the composition disclosed by Wyse to a person in need thereof, absent a clear showing of evidence to the contrary.

Regarding the limitations recited by claim 12 pertaining to the geometric mean naloxone $C_{max}$ being not less than about 3 ng/mL following a single spray, the reference is considered to teach and suggest this limitation as well (see e.g., col. 7, lines 29-39). Therein, peak plasma

concentration is disclosed as ranging as high as about 4 ng/mL. The same passage teaches and suggests the limitations recited by claim 29 whereby the $t_{max}$ is less than 30 minutes.

Regarding the limitations of claim 13, as discussed in the indefiniteness rejection above, the Examiner considers the composition taught and suggested by the reference as meeting the instantly claimed property limitation. Applicants are directed to MPEP **§2112.01** which states that "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established". In the instant case, the Examiner has presented a case of *prima facie* obviousness demonstrating that the composition administered in claims 1 and 12 is taught and suggested by Wyse. Thus, despite not providing an express teaching of the instantly claimed pharmacokinetic $C_{max}$ limitation, the Examiner advances that the disclosed composition would present the ordinarily skilled artisan of meeting the instantly claimed limitations, absent a clear showing of evidence to the contrary.

Regarding the claimed composition, the Examiner again advances that the nasally prepared 4% solution of naloxone is taught and suggested by Wyse. Similarly, disclosed is the preservative component. Claim 1 of the reference, for example, discloses using benzyl alcohol as an antimicrobial agent (aka preserving compound) in amounts ranging from 0.1-2.0 wt%. Other, narrower ranges are also taught and suggested **(e.g., col. 7, lines 21-28)**. The isotonicity agent is taught and suggested above (see e.g., sodium chloride, **Table 13**).

Where Wyse appears to be deficient is with regard to the recited droplet size, despite teaching administering compositions from devices which read on those which are considered to

define the instantly and generically claimed nasal devices. The teachings of Djupesland are considered to remedy this deficiency.

As an initial point, the reference is considered to disclose different forms of pumps and metered-dose inhalers as well as other such devices which are considered useful in administering a small volumes of liquid in spray form. "[N]asal delivery may help address issues related to poor bioavailability, slow absorption, drug degradation, and adverse events in the gastrointestinal tract and avoids the first-pass metabolism in the liver" **(Abstract)**. Recommendation of minimizing the fraction of respirable particles below 9 μm in order to avoid lung inhalation of drugs intended for nasal delivery as well as plume characteristics and dose uniformity are all disclosed as parameters which are governed by the FDA. Discussion pertaining to known metered-dose inhalers as well as single- and duo-dose spray devices are discussed on pages 48-49 of the reference. Therein, the devices are disclosed as possessing vial, a piston, and a swirl chamber and that such devices, in order to emit 100 μL, a volume of 125 μL is filled into the device (e.g., Pfeiffer/Aptar single-dose device) **(see pg. 49, left col.)**. Thus, while the Djupesland reference does not expressly teach or suggest filling single- or duo-dose spray devices with naloxone, the ordinarily skilled artisan would have found motivation to combine the disclosed naloxone composition practiced by Wyse using such a device as is describe by Djupesland. As previously mentioned, the devices disclosed by Djupesland are taught as being used to improve bioavailability of the active ingredient packaged therein. Further, the devices considered to be taught and suggested as being engineered to provide a desired spray cone which may be altered to provide the desired geometry. One such study determined that the ovality ratio measured at 3 cm was 2.52/1.58 or about 1.58. Such ratios appear to change with the change in

the spray angle. As such, the Examiner advances that a person of ordinary skill in the art at the time of the filed invention would have had a reasonable expectation of successfully arriving at the instantly claimed methods and composition.

Based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed methods and composition. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed, absent a clear showing of evidence to the contrary.

**Claims 1, 2, 14, 15, and 24 are rejected under 35 U.S.C. 103 as being unpatentable over Namburi et al. (US Pre-Grant Publication N° 2006/0120967 A1; IDS reference).**

The limitations of the instant claims are discussed above.

**Namburi** discloses a composition suitable for intranasal spray administration comprising, among other ingredients, a respiratory stimulant **(see e.g., Abstract; claim 1; ¶[0026])**. Claim 21 teaches that said stimulant may be naloxone HCl; ¶[0026] further defines the component as being present in the composition in an amount ranging from about 1.0% to about 5.0% w/v. The composition is also disclosed as comprising a preservative, which per ¶[0013] is present, most preferably in a range of about 0.01% to about 0.05% w/v.

Where Namburi appears to be deficient is with respect to the instantly recited spray plume ratio. However, as discussed above, with respect to the teachings of different devices by Djupesland (e.g., single- and duo-dose devices), the Examiner respectfully advances that it

would have been prima facie obvious to a person of ordinary skill in the art at the time the instant invention was filed to prime such a device with the intranasal compositions taught and suggested by Namburi. Said artisan would reasonably expect success in producing methods and compositions absent a clear showing of evidence to the contrary.

**DOUBLE PATENTING**

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 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); *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 nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See **MPEP §717.02** for applications subject to examination

under the first inventor to file provisions of the AIA as explained in **MPEP §2159**. See **MPEP §§706.02(l)(1) - 706.02(l)(3)** for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with **37 CFR 1.321(b)**.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used.

***A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.***

Claims 14-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of **Crystal et al. (USPN 9,211,253 B2)**. Although the claims at issue are not identical, they are not patentably distinct from each other. The limitations of claims 14-23 are discussed above. Claim 1 of the 253 patent discloses:

A single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising a pharmaceutical composition which is an aqueous solution of about 100 μL comprising:

about 4 mg naloxone hydrochloride or a hydrate thereof;

between about 0.2 mg and about 1.2 mg of an isotonicity agent;

between about 0.005 mg and about 0.015 mg of a preservative;

about 0.2 mg of a stabilizing agent;

an amount of an acid sufficient to achieve a pH or 3.5-5.5.

The key differences between the instantly claimed and patented compositions are as follows:

- The instant composition does not recite the stabilizing agent, the pH-adjusting acid, or the pre-primed device which holds 100 μL of the formulation; and
- The '253 patent though disclosing the above pre-primed device, does not disclose the instantly claimed droplet size distribution limitations, the spray plume property, or the bioavailability property.

Despite these key differences, the Examiner advances that the compositions would be considered obvious variants of one another primarily given that the administered compositions are clear variants of one another. The instant claims, while not reciting a spray device, must be associated with such a device in order to achieve the recited spray plume and droplet size limitations. The '253 patent does teach that the device is a single-use, pre-primed nasal administration device, interpreted from the specification as being selected from the same type of devices as are mentioned in the instant specification. When considering this point, a person of ordinary skill in the art at the time the instant invention was filed would have reasonably expected to achieve the claimed composition and properties therewith.

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-45 of copending **US Application No. 14/950,707**. Although the claims at issue are not identical, they are not patentably distinct from each other.

The limitations of method claims 1 and 24 as well as claim 14 are discussed above.

Claim 1 of the allowed copending '707 application discloses as follows:

A method of treatment of opioid overdose or a symptom thereof, comprising nasally administering to a patient in need thereof a dose of naloxone hydrochloride using a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising a pharmaceutical composition which is an aqueous solution of about 100 μL comprising: about 4 mg naloxone hydrochloride or a hydrate thereof; between about 0.2 mg and about 1.2 mg of an isotonicity agent; between about 0.005 mg and about 0.015 mg of a compound which is at least one of a preservative, a cationic surfactant, and a permeation enhancer; between about 0.1 mg and about 0.5 mg of a stabilizing agent; and an amount of an acid sufficient to achieve a pH of 3.5-5.5.

Claims 16-18 of the '707 application disclose that the treated patient exhibits respiratory depression.

Instant claims 1-5, 9, and 24-27 recite the same limitations as above, including the treatment of the same conditions.

Claim 2 of the '707 application discloses the same limitations as instant claim 6.

Claims 3 and 33 disclose the same compositional limitations as instant claim 7.

Claims 5, 6, and 30 disclose that the volume of the reservoir is not more than 140 µL which is considered to read on instant claims 8 and 9 which recite that the device will contain 125 µL of formulation to administer 100 µL.

Instant claims 14-17 recite the same compositional limitations as are disclosed in the methods discussed above as well as the compositional limitations disclosed in claim 30 of the '707 application.

The key differences between the two applications lay with the instant recitation of spray volume geometry, droplet size distribution, stability, peak plasma concentration ($C_{max}$), and $t_{max}$ properties. The allowed '707 application discloses in far greater detail, property limitations drawn to both $C_{max}$ and $t_{max}$. However, the '707 makes no mention of any of the first three properties. Despite these differences in properties, the Examiner advances that a person in possession of the allowed '707 application would have had a reasonable expectation of success in arriving at the instantly claimed composition as well as deriving the instantly claimed methods of treatment. Properties aside, the two applications are clear obvious variants of one another in terms of the composition which is claimed and nasally administered.

**This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims while having been allowed, have not yet received a US Patent Number.**

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 2, 33-35, 37-39, and 45-57 of allowed copending **US Application No. 14/942,344**. Although the claims at issue are not identical, they are not patentably distinct from each other. The limitations of claims 1, 14, and 24 are discussed above.

Claims 1 and 2 of the allowed '344 application disclose

A single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising a pharmaceutical composition which is an aqueous solution of about 100 μL comprising: about 2 mg naloxone hydrochloride or a hydrate thereof; between about 0.2 mg and about 1.2 mg of an isotonicity agent; between about 0.005 mg and about 0.015 mg of a compound which is at least one of a preservative, a cationic surfactant, and a permeation enhancer; between about 0.1 mg and about 0.5 mg of a stabilizing agent; and an amount of an acid sufficient to achieve a pH of 3.5-5.5.

The device of claim 1 wherein: the isotonicity agent is NaCl; the compound which is at least one of a preservative, a cationic surfactant, and a permeation enhancer is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid.

Such is considered to be an obvious variant to instant claims 14-23. The key differences between the two compositions are as discussed above. Notably the instantly claimed composition, while being recited as a "mist" having various droplet size distribution limitations does not actually recite a spray of any kind as part of the composition. Similarly, the instant composition recites a bioavailability limitation which is not disclosed in the '344 claims. Despite these properties not being disclosed by the '344 claims, the Examiner advances that the compositions are obvious variants of one another, if not duplicates of one another.

Claims 33-35, 37-39, and 45-57 are considered to be obvious variants of the limitations of claims 1-13 and 24-30. Of note is that both are drawn to methods of intranasally administering the same composition to treat the same conditions (i.e., opioid overdose and

narcotic-induced respiratory depression). Claim 48 of the '344 application discloses an obvious variant to instant claim 29 regarding the $t_{max}$ time limit of less than 30 minutes. The method of the '344 application is deficient, however, with respect to the instantly claimed stability, AUC, $C_{max}$, and spray plume properties. Conversely, the instantly claimed methods are deficient where it pertains to the "drainage" limitations disclosed in claims 45-47 as well as the limitations pertaining to being "free from respiratory depression" as disclosed in claims 53-57.

As with the '707 application, the '344 application is considered to be an obvious variant to a person of ordinary skill in the art on the basis of the shared compositions and the methods of treating the same conditions. Thus, a person in possession of the '344 application would have had a reasonable expectation of arriving at the instantly claimed methods and composition.

**This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims while having been allowed, have not yet received a US Patent Number.**

Claims 1-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 195-201, 205-208, 210-222, 225, 226, 228-232, 235, and 236 of copending **US Application No. 14/795,403**. Although the claims at issue are not identical, they are not patentably distinct from each other.

The limitations of claims 1 and 14 are discussed above. Regarding the composition instantly recited in claims 14-23, the compositional limitations recited in claims 195-201, 205-208, and 210-215 are considered to read on the instant composition. However, the composition of the '403 application does not recite the instant bioavailability limitation nor does it recite the instant droplet size distribution limitations for the instantly claimed "mist". Conversely, the

instant composition claims do not recite any of the device limitations as are recited in the copending '403 application. Despite these deficiencies, the Examiner advances that the copending compositions are obvious variants of one another and would have been viewed as such by a person of ordinary skill in the art at the time the instant invention was filed.

Regarding the instantly claimed method of treating an opioid overdose, copending claims 216-222, 225, 226, 228-232, 235, and 236 are considered to again teach and suggest the compositional metes and bounds associated with the instantly claimed method. The instantly recited method is less specific in terms of the recited device and recites stability, peak plasma concentration, and AUC limitations which are not recited in the copending claims. However, such properties are considered to be tied to the composition which is administered from the nasal spray device. Again, as the compositions are essentially indistinct and obvious variants of one another, a person of skill in the art at the time of the instantly filed invention would have had a reasonable expectation of arriving at the same methods of treatment as well

**This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not yet been allowed.**

All claims have been rejected; no claims are allowed.

## CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The Examiner can normally be reached on **9:30 am - 7:00 pm; M-F (EST)**.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. 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.

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