PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 15/183,441

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Applicant: Fintan Keegan

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Examiner: Jeffrey Palenik

Art Unit: 1615

Title: NASAL DRUG PRODUCTS AND METHODS OF THEIR USE

Attorney Docket: 17040-000029-US-CPB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

This paper is responsive to the non-final Office Action dated 22 August 2016 in the above referenced application, in which a three-month shortened statutory period was set for reply. Authorization is provided herewith to charge any fee due to Deposit Account No. 08-0750.

* * *

AMENDMENT in the specification begins on page 2 of this paper.

AMENDMENT in the claims begins on page 3 of this paper.

REMARKS on the present amendment begin on page 8 of this paper.

IN THE SPECIFICATION

Please insert the following paragraph after paragraph **[0001]**:

JOINT RESEARCH AGREEMENT

The subject matter disclosed and claimed herein was developed by or on behalf of LightLake Therapeutics Inc. and Adapt Pharma Operations Ltd., as parties to a joint research agreement, and as a result of activities undertaken within the scope of the joint research agreement. The joint research agreement was in effect on or before the effective filing date of the present claims.

IN THE CLAIMS

The following listing of claims will replace all previous listings of claims.

1. (Currently amended) A method of treating opioid overdose, the method comprising:

delivering a **25–200 µL** spray **of a pharmaceutical solution** 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)~~ **pharmaceutical solution comprises about 4 mg** naloxone hydrochloride or a hydrate thereof, and **between about 0.005% and about 0.015% (w/v) of benzalkonium chloride.**

~~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.~~

2. (Cancelled).

3. (Currently amended) The method of ~~claim 2~~ **claim 1**, wherein the pharmaceutical solution further comprises between about 0.2% and about 1.2% (w/v) of an isotonicity agent.

4. (Cancelled).

5. (Currently amended) The method of ~~claim 4~~ **claim 3**, wherein the pharmaceutical solution further comprises between about 0.1% and about 0.5% (w/v) of a stabilizing agent and an amount of an acid sufficient to achieve a pH between about 3.5 and about 5.5.

6. (Currently amended) The method of claim 5, wherein:

the isotonicity agent is sodium chloride;

the stabilizing agent is disodium edetate; **and**

the acid is hydrochloric acid**.** ~~; and~~

~~the preservative is benzalkonium chloride.~~

7. (Currently amended) The method of claim 6, wherein the pharmaceutical solution comprises:

about 4**[[.4]]**% (w/v) naloxone hydrochloride ~~**dihydrate**~~;
about 0.74% (w/v) sodium chloride;
about 0.01% (w/v) benzalkonium chloride; and
about 0.2% (w/v) disodium edetate.

8. (Original) The method of claim 7, wherein the device has a single reservoir containing approximately 125 µL of the pharmaceutical solution.

9. (Original) The method of claim 8, wherein approximately 100 µL of the pharmaceutical solution is delivered by one actuation of the device.

10. (Original) The method of claim 9, wherein the device comprises a reservoir, a piston, and a swirl chamber.

11. (Original) The method of claim 6, further comprising storing the device for about twelve months or less at 25°C and 60% relative humidity prior to actuating the device, wherein the device retains at least about 100% of initial naloxone hydrochloride content at actuation.

12. (Original) The method of claim 1, wherein the patient experiences a geometric mean naloxone C_{max} not less than about 3 ng/mL following a single spray.

13. (Original) The method of claim 12, wherein the patient experiences a plasma naloxone concentration such that the geometric mean of area under a plasma concentration versus time curve ($AUC_{0-\infty}$) is not less than about 8 hr*ng/mL when time is extrapolated to infinity.

14. (Currently amended) A mist comprising droplets ~~**of a naloxone hydrochloride solution**~~,

wherein the ~~**solution has a concentration of about 4% (w/v)**~~ **droplets comprise in aggregate about 4 mg of naloxone hydrochloride or a hydrate**

thereof and between about 0.005% and about 1% (w/v) of benzalkonium chloride, and

wherein no more than about 10% of the droplets have a diameter less than 10 µm.

15. (Cancelled).

16. (Currently amended) The mist of ~~**claim 15**~~ **claim 14**, wherein the mist comprises an isotonicity agent in a concentration between about 0.2% and about 1.2% (w/v).

17. (Currently amended) The mist of claim 16, wherein ~~**the preservative is benzalkonium chloride and**~~ the isotonicity agent is sodium chloride.

18. (Original) The mist of claim 14, wherein the mist takes the shape of a round plume with an ovality ratio less than 2.0.

19. (Original) The mist of claim 14, wherein the naloxone is at least 40% bioavailable.

20. (Original) The mist of claim 19, wherein the median droplet size is between about 30 µm and about 100 µm.

21. (Original) The mist of claim 20, wherein approximately 50% of droplets have a diameter between about 30 µm and about 70 µm.

22. (Original) The mist of claim 21, wherein approximately 90% of droplets have a diameter less than about 100 µm.

23. (Original) The mist of claim 22, wherein no more than approximately 2% of droplets have a diameter less than about 10 µm.

24. (Currently amended) A method of treating narcotic-induced respiratory depression, the method comprising:

delivering a **25–200 µL** spray **of a pharmaceutical solution** from a pre-primed device into a nostril of a patient **in need thereof in a manner that delivers the pharmaceutical solution in a round spray plume with an ovality ratio less than about 2.0 when measured at 3 cm**,

wherein the device is adapted for nasal delivery, and

wherein the ~~device contains a pharmaceutical solution comprising about 4% (w/v)~~ **spray comprises about 4 mg** naloxone hydrochloride or a hydrate thereof, and **between about 0.005% and about 0.015% (w/v) of benzalkonium chloride,**

wherein the patient experiences a geometric mean naloxone C_{max} not less than about 3 ng/mL following a single spray.

~~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.~~

25. (Currently amended) The method of claim 24, wherein the pharmaceutical solution further comprises between ~~about 0.005% and about 0.015% (w/v) of a preservative and~~ about 0.2% and about 1.2% (w/v) of an isotonicity agent.

26. (Original) The method of claim 25, wherein the pharmaceutical solution further comprises between about 0.1% and about 0.5% (w/v) of a stabilizing agent.

27. (Original) The method of claim 26, wherein the pharmaceutical solution further comprises an amount of an acid sufficient to achieve a pH between about 3.5 and about 5.5.

28. (Currently amended) The method of claim **[[27]] 31**, wherein the acid is hydrochloric acid and wherein the pharmaceutical solution comprises:

about 4**[[.4]]**% (w/v) naloxone hydrochloride ~~dihydrate~~;

about 0.74% (w/v) sodium chloride as the isotonicity agent;

about 0.01% (w/v) benzalkonium chloride ~~as the preservative~~; and

about 0.2% (w/v) disodium edetate as the stabilizing agent.

29. (Original) The method of claim 24, wherein the plasma concentration versus time curve of naloxone in the patient has a t_{max} of less than 30 minutes.

30. (Original) The method of claim 24, wherein the ovality ratio is less than about 1.5 when measured at 3 cm.

31. (New) The method of claim 27, wherein:
    the isotonicity agent is sodium chloride;
    the stabilizing agent is disodium edetate; and
    the acid is hydrochloric acid.

32. (New) The method of claim 24, wherein the device comprises a plunger that houses a container closure comprising
    a vial comprising an opening,
    a cannula, and
    a rubber stopper,
    wherein the stopper is configured to occlude the opening of the vial, and
    wherein the cannula is configured such that the cannula can pierce the stopper when the plunger applies sufficient force to the cannula.

33. (New) The mist of claim 14, wherein the mist stands adjacent to an aperture in a single-dose spray device or a bi-dose spray device.

Claim Amendment

Following amendments as requested herein, Claims 1–3, 5–14, and 16–33 are pending in the present application. Claims 4 and 15 are cancelled without prejudice. New Claims 31–33 are added herein.

Support for the amendment "25–200 μL" in Claims 1 and 24 can be found in at least paragraph **[0076]** of the specification as filed. Support for "wherein the pharmaceutical solution about 4 mg naloxone hydrochloride" can be found in at least paragraphs **[0070]**, **[0079]**, **[0084]**, and **[0104]** of the specification as filed. Support for benzalkonium chloride can be found in at least paragraph **[0095]** of the specification as filed. The remaining amendments to Claims 1 and 24 consist of merely in re-arranging limitations already present, and moving the subject matter of Claims 4 and 25 into their respective independent claims. Claim 1 is also amended to remove a limitation.

Support for "a geometric mean naloxone C_{max} not less than about 3 ng/mL following a single spray" in Claim 24 can be found in at least Claim 12 as originally filed.

Support for "droplets comprise in aggregate about 4 mg of naloxone hydrochloride or a hydrate thereof" in Claim 14 can be found in at least paragraphs **[0079]** and **[0084]** of the specification as filed. Support for "about 0.005% to about 1% benzalkonium chloride" can be found in at least paragraph **[0095]** of the specification as filed. The remaining amendments to Claim 14 mere re-arrange limitations already present and move the subject matter of Claim 15 into the independent claim.

Support for new Claim 31 can be found in at least original Claim 6.

Support for new Claims 32 and 33 can be found in at least paragraph **[0077]** of the specification as filed, which names the Becton-Dickinson ACCUSPRAY device and the Aptar UDS UNITDOSE and BDS BIDOSE devices. As the Federal Circuit has recently reaffirmed in *Yeda Res. & Dev. v. Abbott GmbH*, No. 15-1662 (Fed. Cir. Sept. 20, 2016), "when a specification describes an invention that has certain undisclosed yet inherent properties, that specification serves as adequate written description to support a subsequent patent application that explicitly recites the invention's inherent properties," (slip op. at 6). Therefore, the prose description of a unit-dose or bi-dose device is inherently supported by the disclosure of particular spray devices that possess all of these features.

The present amendments contain no new matter. Applicant respectfully requests entry of these amendments and favorable consideration of the pending claims.

RESPONSE TO OFFICE ACTION DATED 22 AUGUST 2016

1. Statement of the substance of the interview

Applicant thanks the Examiner for the courtesy of a telephone interview on 12 August 2016, in which Applicant's representatives Kisuk Lee and Greg DeLassus participated, along with Fintan Keegan and Robert Bell—inventors on the present application—and David Brabazon, a representative of Adapt Pharma, the owner of the present application. Applicant proposed a series of claim amendments focusing on the about 4 mg naloxone aspect of the claimed invention. The inventors explained how the state of the art taught away from this aspect of the claimed invention.

Applicant also thanks the Examiner for the courtesy of a second interview on 5 October 2016, in which Kisuk Lee and Greg DeLassus discussed an additional set of amendments related to the written description and definiteness rejections. These amendments are embodied in the Interview Summary mailed on 12 October 2016.

2. Rejection under 35 U.S.C. §112, written description

Claims 1–30 stand rejected under 35 U.S.C. §112(a) as allegedly failing the written description requirement. Applicant respectfully traverses this rejection.

The Examiner contends (page 5) that "['']a spray plume which has an ovality ratio…['] is a recited function that lacks structure," and that (page 5) the same argument applies broadly to the mist of Claim 14. Applicant's response is two-fold. Firstly, spray plume geometry and particle size distribution are *structural* features of the claim, not functional features. The functional effect of the claimed invention is reversal of opioid overdose. The *structural* features by which this effect is achieved include: (1) choice of drug (naloxone); (2) about 4 mg naloxone; (3) quantity of pharmaceutical solution administered (25–200 μL); (4) choice of excipient (about 0.005% to about 0.015% (w/v) benzalkonium chloride); and (5) form of drug administration (intranasal mist with a particular geometry).

The Examiner protests (page 5) that the "claims recite a mist which is presumably emitted from a nasal delivery device, but recite no device whatsoever." Once again, the chemical and geometric composition of the mist constitutes a *structural* description of the mist, as do the 10 µm diameter limitation and the about 0.005% to about 0.015% (w/v) benzalkonium chloride limitation. Indeed, the 10 µm is a structural feature of the mist that *achieves* a functional outcome—*viz.* preventing droplets from proceeding into narrower portions of the respiratory tract, where the benzalkonium chloride could adversely affect cilia on the airway surface.

A mist is an article of manufacture, just like a hammer or an ibuprofen tablet. *In re Hruby*, 373 F.2d 997, 999 (C.C.P.A. 1967). In the same way that a claim to a hammer does not need to recite the mold in which the hot metal is cast, and the claim to the tablet does not need to recite the die-press with which the tablet is stamped, so too it is equally unnecessary to recite the spray device when claiming the mist. For at least these reasons, Applicant respectfully requests that the present rejections be reconsidered and withdrawn.

With particular regard to Claims 32 and 33, the Examiner contends (page 5) a particular device must be recited in the claims. Although Applicant does not agree for the reasons specified above, Applicant recites particular devices and device features in Claims 32 and 33, so the present rejection cannot apply to these new claims.

3. Rejection under 35 U.S.C. §112, definiteness

Claims 1–30 stand rejected under 35 U.S.C. §112(b) as allegedly indefinite. Applicant respectfully traverses this rejection.

As with the written description rejection, the present rejection is predicated (page 6) on the lack of a device recitation. However, the definiteness requirement exists to provide the person of ordinary skill with reasonable certainty as to claim scope. See MPEP §2173; "[A]ny description which is sufficient to apprise [competitors] in the language of the art of the definite feature of the invention, and to serve as a warning to others of what the patent claims as a monopoly, is sufficiently definite to sustain the patent." *Nautilus Inc. v. Biosig Instruments*, 134 S. Ct. 2120, 2129 (2014) (quoting *Carnegie Steel Co. v. Cambria Iron Co.*, 185 U.S. 403, 437 (1902)). Even without a

single device being named in the claims, the person of ordinary skill can readily ascertain whether a given device meets the requirements of Claim 1 or 24 (about 4 mg naloxone, about 0.005% to about 0.015% benzalkonium chloride, ovality ratio less than about 2.0 when measured at 3 cm, *etc.*), or whether a given mist comes within the scope of Claim 14. For at least these reasons, Applicant respectfully requests that the present rejections be reconsidered and withdrawn. Additionally, as noted in Section 2 above, Claims 32 and 33 recite devices, so the present rejection is not applicable to these new claims.

4. Rejection under 35 U.S.C. §103 over Wyse in view of Djupesland

Claims 1–5, 12–16, 18–27, 29, and 30 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over US 9,192,570 ("Wyse") in view of Djupesland (2013) *Drug Deliv. & Transl. Res.* 3:42–62 ("Djupesland"). The Examiner contends (page 12) that Wyse reports all elements of the claimed methods and mists except that "Wyse appears to be deficient… with regard to the recited droplet size… ." The Examiner cites (page 13) Djupesland to remedy this deficiency.

Applicant respectfully traverses this rejection because the cited art does not account for all claim limitations. For example, the cited art does not disclose either the feature "about 4 mg naloxone" of Claims 1, 14, and 24 or the feature "between about 0.005% and about 0.015% (w/v) of benzalkonium chloride" of Claims 1 and 24. Moreover, the repeated failure of others in the prior art to develop a naloxone nasal spray formulation demonstrates that Applicant had no reasonable expectation of success from the cited art, which further negates *prima facie* obviousness. Additionally, even if *prima facie* obviousness were established, Applicant's unexpected results, commercial success, and after-the-fact praise from its peers would establish that the methods of Claims 1 and 24 and the mist of Claim 14 are not obvious over the cited art. Each of these points is detailed in turn below.

(a) Benzalkonium chloride: Claims 1, 14, and 24 each require benzalkonium chloride. Wyse, however, teaches strongly and unambiguously against benzalkonium chloride as shown below:

> "The results further surprisingly showed that the use of benzalkonium chloride, a common nasal product preservative, resulted in an additional degradant in formulations 7, 9, 14 and 14A." (col. 27, lines 30–32)
>
> "In this initial study, the preliminary conclusion was that benzyl alcohol and paraben preservatives were acceptable, but benzalkonium chloride was not, due to increased observed degradation." (col. 27, lines 42–44, emphasis added)

The person of ordinary skill would not, therefore, have used benzalkonium chloride, as claimed in the present application.

(b) About 4 mg naloxone hydrochloride of a hydrate thereof: The Examiner purports (pages 9 and 10) to account for an about 4% (w/v) solution as merely the result of routine experimentation within Wyse's broadly disclosed range of 0.5–5% (w/v). However, a broad disclosure does not necessarily render obvious a narrower selection from within a prior art range. MPEP §2144.08.II. Rather, a prior art genus only negatives patentability of a claim to a species within that range if there is some teaching in the art toward the claimed species. Further, the prior art would also need to provide a person of ordinary skill in the art with a reasonable expectation of success as to the claimed invention. MPEP §2143.02. Both a teaching of species covered by the claim, and a reasonable expectation of success as to those species, is absent from the prior art of record.

As amended herein, Applicant is not merely claiming an about 4% solution. Applicant is claiming about **4 mg** naloxone hydrochloride or a hydrate thereof. There is no teaching in the cited art toward about 4 mg. The highest intranasal dose reported in Wyse is 2 mg, and Djupesland is totally unconcerned with dose strengths. Indeed, the art as a whole taught away from an about 4 mg naloxone. Before the demonstrated success of Applicant's product showed otherwise, it was widely believed that a 4 mg initial dose could trigger precipitous withdrawal symptoms. Fiore *et al.* (2015) *MedPage Today*, "Naloxone for Opioid Overdose: New Questions Arise in 2015" (Exhibit A). Therefore, the art cannot be said to guide the ordinary artisan toward about 4 mg naloxone.

(c) Failure of others: In light of the problem facing the person of ordinary skill at the time of invention (accidental opioid overdose), naloxone is the sort of drug that one only needs in occasional emergencies, not for daily use. Therefore, a naloxone spray device must be able to sit unused for extended periods, but be certain to be usable at a moment's notice when it is needed. Maintaining product viability in long-term storage typically requires preservatives. For regulatory registration and approval, the FDA requires comparable or higher systemic exposure and comparable or quicker onset of action than the approved reference listed drug given by an intramuscular (IM) route of administration in a comparative pharmacokinetic study. The preservatives necessary to achieve storage stability tend to be incompatible with naloxone nasal formulations and their associated container closure systems, which can lead to reduced absorption and decreased and variable bioavailability, making stable, compatible, bioequivalent nasal formulations and delivery systems difficult to achieve.

Applicant was the first to conceive of a formulation with the right dose of naloxone and the right concentration of excipients to break through this barrier. Applicant's pharmaceutical formulations can sit unused at room temperature for up to 24 months (2 years), but still achieve pharmacokinetic outcomes that meet and even exceed those achieved with injectable naloxone. Applicant's success where others have repeatedly tried and failed shows that there was no reasonable expectation of success at the time of invention. "[T]here can be little better evidence negating an expectation of success than actual reports of failure." *In re Cyclobenzaprine HCl*, 676 F.3d 1063, 1081 (Fed. Cir. 2012). Without a reasonable expectation of success, there can be no *prima facie* obviousness. "A party seeking to [establish] obviousness must demonstrate… that the skilled artisan would have had a reasonable expectation of success… ." *Procter & Gamble Co. v. Teva Pharma.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

As shown in Tables 17–20 and 25 of the application as filed, Applicant's formulation has demonstrated naloxone stability under both accelerated (40℃/75% relative humidity) for six (6) months and room temperature conditions at twelve (12) months (25℃/60% relative humidity) and is stable through the 24-month (2-year) expiry shelf life throughout the product's expected shelf life. Furthermore, Applicants'

formulation spray characteristics (over the shelf life) deliver 100% of the dose with a consistent and reproducible plume geometry, droplet size distribution, spray pattern, and ovality (Tables 21–24) sufficient to assure reproducible pharmacokinetics and clinical effects (Tables 10–13) throughout the product's 24-month expiry.

Here, the prior art contains reports of others who have tried and failed to achieve an intranasal naloxone that is both acceptably stable and acceptably bioavailable. For example, Dowling *et al.* (2008) *Ther. Drug Monit.* 30(4):490–96 reports (page 493) that "naloxone has a very poor bioavailability… by the IN route and large doses that are physically impossible to administer intranasally… are required to produce similar concentrations to those following [intravenous] naloxone." Similarly, the AntiOp inventors (such as Wyse) were working essentially contemporaneously with the inventors of the present application, but the FDA determined that AntiOp's (Wyse's) intranasal product did not achieve an acceptable bioavailability. *See*, enclosed timeline of AntiOp IN development and failure (Exhibit B). In view of the failure of others, *prima facie* obviousness cannot be established because there was no reasonable expectation of success as to the claimed formulations.

(d) Unexpected results: While previous attempts to formulate naloxone for intranasal use have failed, Applicant's device worked. This success—where others had repeatedly failed—is an unexpected result that demonstrates nonobviousness. As noted above, there is a trade-off in the prior art between stability and bioavailability. Wyse Table 4 is shown below, alongside Applicant's own data. As can be seen, when Wyse uses 2 mg intranasally, Wyse achieves a C_{max} of 1.95 ng/mL and an $AUC_{0-\infty}$ of 3.47 ng•hr/mL. This is pharmacokinetically inferior to the results that Wyse achieves from 1 mg intramuscular injection of a smaller naloxone dose (C_{max}=2.54 ng/mL and $AUC_{0-\infty}$=4.43 ng•hr/mL). By contrast, Applicant's 2 mg intranasal achieves better pharmacokinetics (C_{max}=3.11 ng/mL and $AUC_{0-\infty}$=4.86 ng•hr/mL) than the FDA-approved 0.4 mg intramuscular injectable (C_{max}=0.906 ng/mL and $AUC_{0-\infty}$=1.83 ng•hr/mL), and Applicant's 4 mg intranasal is even better still (C_{max}=5.34 ng/mL and $AUC_{0-\infty}$=8.87 ng•hr/mL). There is nothing in the art to suggest to the ordinary artisan that

bioavailability could be so significantly improved—to achieve an intranasal comparable to the intramuscular injection, just as the art had so long sought but failed to achieve—by reducing excipient concentrations and increasing the naloxone dose. Therefore, these unexpected results constitute objective indicia of the nonobviousness of the methods of Claims 1 and 24 and the mist of Claim 14.

TABLE 4

PK Parameters from Study
Median ± SD

	Arm	t_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng-hr/mL)	$t_{1/2}$ (hr)
A	0.4 mg IV	0.03 ± 0.06	3.87 ± 2.72	1.67 ± 0.54	1.28 ± 0.17
B	1 mg IM	0.33 ± 0.52	2.54 ± 1.04	4.43 ± 1.16	1.41 ± 0.32
C	1 mg SC	0.17 ± 0.29	2.72 ± 0.79	4.15 ± 1.07	1.59 ± 0.60
D	2 mg NNS	0.42 ± 0.25	1.95 ± 1.05	3.47 ± 0.80	1.53 ± 0.17
E	1 mg NNS	0.50 ± 0.20	0.84 ± 0.49	1.52 ± 0.45	1.41 ± 0.31
F	2 mg IN/MAD	0.27 ± 0.11	0.53 ± 0.16	0.90 ± 0.17	1.64 ± 0.30

Adapted Table 11 of Application as Filed

0.4 mg IM	0.42	0.906±0.285	1.83±0.42	1.19
Adapt 2 mg NNS	0.33	3.11±1.13	4.86±1.46	1.70
Adapt 4 mg NNS	0.50	5.34±2.66	8.87±3.30	2.00

- Arm B: on-label injectable
- Arm F: off-label intranasal atomization; relative exposure ≈ 20–25% of Arm B
- Arm D: AntiOp 2 mg spray; relative exposure ≈ 80–100% of Arm B
- Table 11 data: relative exposure ~300–1000% > IM from Wyse Table 4

(e) Commercial success: As noted in the enclosed Rule 132 declaration (Exhibit C), Adapt Pharma's NARCAN nasal spray, which embodies the claimed invention, launch in February 2016. In this short time, over 180,000 NARCAN units have been sold. Kaleo's EVZIO brand injectable naloxone has been on the market since April 2014, but in that time it has only sold about 56,000 packages. That is to say, NARCAN has sold approximately three times as units as EVZIO in approximately one third of the time.

(f) Community praise: It is difficult for untrained individuals to administer injectable naloxone, because such a formulation requires use of a needle on a person who may have previously injected illicit opioid drugs as heroin, and thus is at increased risk of,

e.g., infection. Accordingly, the market and the FDA have long wanted an intranasal naloxone delivery system, which does not require use of a needle to administer. To this end, the FDA took the unusual step of designating Adapt Pharma's new drug application (NDA) for both fast-track and priority review statuses. *See*, FDA 18 November 2015 press release announcing the approval of Adapt Pharma's NDA (Exhibit D). Meanwhile, the National Institutes of Health hailed the approval of Adapt Pharma's NDA as "life-saving science… that changes how we practice medicine… ." This acclaim from those working in the field is yet more objective evidence of nonobviousness.

For at least these reasons, Applicant respectfully requests that the present rejection be reconsidered and withdrawn.

5. Rejection under 35 U.S.C. §103 over Namburi in view of Djupesland

Claims 1, 2, 14, 15, and 24 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over US 2006/0120967 ("Namburi") in view of Djupesland. Applicant respectfully traverses this rejection.

Claims 4 and 25 do not stand rejected over Namburi and Djupesland. As amended herein, Claims 1 and 24 now include the limitations of Claims 4 and 25, so the present rejection is moot with regard to Claims 1 and 24.Claim 14 is amended herein to require about 4 mg naloxone. Namburi teaches nothing about naloxone dosage, but rather merely mentions naloxone as one among over 100 optional components that can be added to Namburi's sprays, with no particular guidance toward naloxone. P*rima facie* obviousness is not established on this record for Claim 14 as amended herein.

For at least these reasons, and the reasons summarized in section 4 above, Claims 1, 14, and 24 are not obvious over Namburi and Djupesland. Applicant respectfully requests that the present rejection be reconsidered and withdrawn.

6. Rejection for obviousness type double-patenting

Claims 14–23 stand rejected under the judicially created doctrine of obviousness type double-patenting as allegedly claiming obvious variants of claims in US 9,211,253. Claims 1–30 stand provisionally rejected as allegedly claiming obvious variants of

claims in US 14/950,707 (now issued as US 9,468,747), US 14/942,344 (to be issued as US 9,480,644), and US 14/795,403. Applicant respectfully traverses this rejection.

Terminal disclaimers are enclosed herewith to moot each of these rejections. The filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Techs. v. Union Sanitary Dist.*, 946 F.2d 870, 874 (Fed. Cir. 1991) ("[A] terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection,"). Reconsideration and withdrawal of this double patenting rejection are respectfully requested.

7. Conclusion

As such it is believed that all of the stated grounds of rejections are properly traversed, accommodated or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding objection and rejections. It is believed that a full and complete response has been made to the outstanding Office Action and that the application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested.

Also, should the Examiner conclude that one or more claims (but less than all claims) are allowable, Applicant again respectfully requests the Examiner to call the undersigned directly at 314-446-7670 to discuss the possible cancellation/amendment of claims by an Examiner's amendment in a Notice of Allowance.

Respectfully submitted,

Dated: 21 October 2016

By: /Kisuk Lee/
Kisuk Lee, Reg. No. 66,861

HARNESS, DICKEY & PIERCE, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
314-446-7670 (telephone)

Enclosures: Exhibit A: Fiore *et al.* (2015) *MedPage Today*
Exhibit B: AntiOp timeline
Exhibit C: Rule 132 declaration
Exhibit D: FDA press release and NIH press release

Exhibit A

medpagetoday.com

Naloxone for Opioid Overdose: New Questions Arise in 2015

Kristina Fiore

Last winter, public health and harm reduction groups raised concerns about the skyrocketing price of an off-label version of nasal naloxone. Since then, two on-label formulations have been developed, and one was approved. This follow-up story looks at how the new product will play out in the real world.

First responders and harm reduction groups have long been cobbling together a nasal delivery system for the opioid overdose reversal agent naloxone. They'd pop atomizers atop cartridges that held a higher dose of the drug than the one used for regular injection, to make it easier for emergency teams and bystanders to save someone from an overdose. No need to find a clear injection site, no risk of needle sticks.

The problem: nasal delivery was an off-label use, which meant manufacturing issues and reimbursement challenges when dealing with insurers.

But last month the FDA approved the first on-label nasal-spray naloxone, which will be marketed under the very first brand name

for naloxone, Narcan. Drugmaker Adapt Pharma licensed the name from Endo Pharmaceuticals.

The reaction in the public health community was initially positive: "Another option is always welcome," Fred Brason, executive director of Project Lazarus, told *MedPage Today*. "Hopefully this will provide an easier avenue to obtain intranasal naloxone than putting naloxone kits together and adding an off-label nasal atomizer like we have had to do and then provide to pharmacy/patient/person."

But several experts contacted by *MedPage Today* on the day the Adapt product was approved noted that they were eager for real-world results, because only pharmacokinetic and usability data were needed for FDA approval. Adapt didn't have to conduct any field trials.

"Because it was approved with no field testing to get it approved quickly, we don't know how it works in the real world," said Caleb Banta-Green, PhD, MPH, of the University of Washington.

Within a few weeks, researchers started raising questions about the dose of the new nasal formulation: 4 mg. The off-label nasal naloxone was given at a dose of 1 mg, and the injectable at 0.4 mg.

"My concern is that withdrawal symptoms might be much more substantial at this dose than at our traditionally administered dose," Phillip Coffin, MD, of the San Francisco Department of Public Health, told *MedPage Today*. "It may be more challenging to manage those symptoms in the lay environment."

Experts have also questioned why a competing nasal naloxone product made by Indivior (formerly Reckitt Benckiser Pharmaceuticals), at a dose of 1.8 mg, was denied approval just days after Adapt's product was given the green light. In a press release announcing a complete response letter from the FDA, Indivior said it was denied because "early stage uptake of naloxone nasal spray did not fully meet the FDA's threshold as determined by the reference product," which was the 0.4 mg intramuscular injection dose.

Injectable naloxone came on the market in the 1970s and has been available as an inexpensive generic. But the rising toll of the nation's opioid addiction woes, paired with concerns about bystanders having difficulty with needles, provided an incentive to get companies back into the labs to develop alternate delivery strategies.

The first new naloxone formulation was Evzio, an auto-injector approved in April 2014. But many groups, including first responders and harm reduction community groups, couldn't afford its wholesale $700 price tag, and so they stuck with regular injectables or an off-label nasal formulation.

The nasal formulation, made by Amphastar, was preferred because it was easier to administer. But after Evzio hit the market, its price started to climb as well -- more than doubling from $13 to $30 per dose in fall 2014.

Adapt Pharma was keen to put the price for first responders and

community groups right in its press release announcing approval: $37.50 per dose, rivaling the current price for off-label nasal naloxone.

Christy Maginn, a spokesperson for Adapt Pharma, said the 4-mg nasal dose was "selected in collaboration with NIDA, which supported the work, for its balance between an adequate dose for rapid restoration of respiratory function (to potentially avoid death or CNS side effects) and the known potential risk of opioid withdrawal symptoms."

Maginn noted that injectable naloxone "has been available since 1971 and approved at significantly larger doses" up to 10 mg -- although this dose is rarely used in overdose reversal settings.

"We have seen in just the past year how changes in the opioids consumed -- like nonpharmaceutical fentanyl or fentanyl-laced heroin -- can significantly impact opioid overdose death," Maginn said, referencing recent CDC data on rising opioid overdose deaths, many linked to illicit fentanyl. "Indeed, CDC recommended first responders stock extra naloxone as fentanyl is much more potent than heroin."

Indivior's nasal naloxone would be delivered at about half the dose, at 1.8 mg, given as two sprays of 0.9 mg -- one in each nostril.

That drug was originally developed by Daniel Wermeling, a pharmacist at the University of Kentucky, and his company AntiOp, but he sold the drug to Indivior in June 2015. Indivior was granted priority review a month later, but received its complete response

letter in November.

As Reckitt Benckiser, the company had clashed with FDA when it tried to block generic versions of its best-selling addiction therapy drug Suboxone, a combination of buprenorphine and naloxone.

The FDA referred the company to the Federal Trade Commission over the matter, saying it acted disingenuously when it decided to stop selling tablets and switch all patients to a sublingual film instead, right around the time its patent was set to expire.

The film was supposed to be less prone to accidental use by children -- but the FDA didn't buy those claims and ended up approving Suboxone generics.

Federal officials raided Reckitt's Virginia headquarters in December 2013. A year later, the company changed the name of its pharmaceuticals business to Indivior.

While Indivior may have lost the race to be first to market with an on-label nasal naloxone -- and it lost access to the brand-name Narcan, too -- questions remain about which product will ultimately be the most widely used for preventing opioid overdose: Will Adapt's drug become the favorite? Will the Indivior product ever be approved? Will Amphastar discontinue its off-label naloxone?

Banta-Green warned it could be hard to measure "if people are reversing overdose, getting extreme behavioral or medical consequences [such as withdrawal] and start to warn others not to use naloxone and those people not distinguishing which product

was used. And, ultimately LESS naloxone gets used and fewer overdoses reversed."

While he said he doesn't think that's a likely outcome, it's "important to consider that it is unlikely that this is a one size fits all product."