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

28997 7590 12/21/2016

HARNESS, DICKEY, & PIERCE, P.L.C
7700 Bonhomme, Suite 400
ST. LOUIS, MO 63105

EXAMINER	
PALENIK, JEFFREY T	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/21/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/183,441	06/15/2016	Fintan Keegan	17040-000029-US-CPB	7401

TITLE OF INVENTION: NASAL DRUG PRODUCTS AND METHODS OF THEIR USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	03/21/2017

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 ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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.

PTOL-85 (Rev. 02/11)

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)

28997 7590 12/21/2016
HARNESS, DICKEY, & PIERCE, P.L.C
7700 Bonhomme, Suite 400
ST. LOUIS, MO 63105

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.
15/183,441	06/15/2016	Fintan Keegan	17040-000029-US-CPB	7401

TITLE OF INVENTION: NASAL DRUG PRODUCTS AND METHODS OF THEIR USE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	03/21/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
PALENIK, JEFFREY T	1615	604-516000

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 credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/183,441	06/15/2016	Fintan Keegan	17040-000029-US-CPB	7401

28997 7590 12/21/2016

HARNESS, DICKEY, & PIERCE, P.L.C
7700 Bonhomme, Suite 400
ST. LOUIS, MO 63105

EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/21/2016

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

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

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.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B 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. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	15/183,441	KEEGAN ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jeffrey T. Palenik*. (3)_____.

(2) *Mr. Gregory DeLassus (Atty)*. (4)_____.

Date of Interview: *13 December 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1, 12, 22 (as allowed)*.

Identification of prior art discussed: *WO 2009/040595 (Wynne)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The Examiner and Mr. DeLassus discussed at length, the teachings and suggestions of Wynne with respect to the disclosure of benzalkonium chloride (BAC) in Table 2. Therein, the Table appears to teach two different things with respect to the 0.4mL aliquot of 50% w/v BAC used in the diluent formulation. On one hand, the Table presents the amount of BAC as: 0.4mL, wherein the "*" is a footnote indicating that the 0.4mL is equivalent to 0.02% w/v BAC, a teaching the Examiner took on its face. However, further discussion with Mr. DeLassus indicates that the amount of BAC present in the diluent formulation is actually 20% w/v (see attached Reasons for Allowance). Mr DeLassus walked the Examiner through their calculations demonstrating their results*.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Jeffrey T. Palenik/ Primary Examiner, Art Unit 1615	

Notice of Allowability	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--

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' Remarks and Amendments filed 21 October 2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
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 *1,3,5-14 and 16-33*. 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).

   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)).

   * 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 11/14/16
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *with Allowance* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Jeffrey T. Palenik/
Primary Examiner, Art Unit 1615

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' filed Amendments and Remarks filed 21 October 2016 in the matter of Application N° 15/183,441. Also acknowledged are Applicants' corrected Terminal Disclaimers (TDs) filed 9 November 2016. Said documents are entered on the record. The Examiner further acknowledges the following:

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

Applicants' Request for TrackOne Status was *granted* on 28 July 2016.

Claims 2, 4, and 15 are newly canceled. Claims 31-33 are newly added and supported by the instant specification.

Claims 1, 3, 5-7, 14, 16, 17, 24, 25, and 28 have been amended. Support for the amendments adding new limitations to the claims has been clearly presented in Applicants' remarks. All other amendments are considered editorial (e.g., change of dependency).

Thus, claims 1, 3, 5-14, and 16-33 are pending allowance for the reasons discussed herein.

INFORMATION DISCLOSURE STATEMENT

One new Information Disclosure Statement (IDS) filed 14 November 2016 is acknowledged and has been considered.

EXAMINER'S AMENDMENT

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 Mr. Gregory S. DeLassus on 14 November 2016.

1. **Please AMEND claim 1 to reads as follows:**

   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 pharmaceutical solution comprises about 4 mg naloxone hydrochloride or a hydrate thereof, between about 0.005% and about 0.015% (w/v) of benzalkonium chloride, and an isotonicity agent.

2. **Please AMEND claim 3 to reads as follows:**

   The method of claim 1, wherein the pharmaceutical solution comprises between about 0.2% and about 1.2% (w/v) of the isotonicity agent.

3. **Please AMEND claim 14 to reads as follows:**

   A mist delivered from a pre-primed device, wherein the mist comprises droplets, wherein the droplets comprise, in aggregate, about 4 mg of naloxone hydrochloride or a hydrate thereof, between about 0.005% and about 1% (w/v) of benzalkonium

chloride, and an isotonicity agent, wherein no more than about 10% of the droplets have a diameter less than 10 μm.

4. **Please AMEND claim 16 to reads as follows:**

The mist of claim 14, wherein the mist comprises the isotonicity agent in a concentration between about 0.2% and about 1.2% (w/v).

5. **Please AMEND claim 24 to reads as follows:**

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 spray comprises about 4 mg naloxone hydrochloride or a hydrate thereof, between about 0.005% and about 0.015% (w/v) of benzalkonium chloride, and an isotonicity agent wherein the patient experiences a geometric mean naloxone C_{max} not less than about 3 ng/mL following a single spray.

6. **Please AMEND claim 25 to reads as follows:**

The method of claim 24, wherein the pharmaceutical solution comprises between about 0.2% and about 1.2% (w/v) of the isotonicity agent.

REASONS FOR ALLOWANCE

The following is the Examiner's statement of reasons for allowance:

Applicants' filed amendments as well as the above, agreed-upon Examiner's Amendments have been fully considered in light of the available prior art. The first of the two references discovered and considered to represent the closest prior art available is published by **Wynne et al. (WO 2009/040595 A1)**.

The reference is drawn to a multi-dose pharmaceutical composition of an analgesic in the form of a nasal spray **(Abstract)**. The device is disclosed as being primed prior to use **(see e.g., claim 20)** and as being primed to administer 2-4, 50-μL doses of the composition contained within the device **(see pg. 10, lines 4-11)**. As such, the reference is considered to teach and suggest the instantly claimed 25-200 μL delivery volume as well as the amounts recited, for example, in claims 8 and 9 (i.e., contain 125 μL to deliver 100 μL). Furthermore, regarding the instantly claimed "mist" possessing delivered droplets wherein no more than about 10% of the droplets have a diameter less than 10 μm, since the Examiner can find no structural differences between the claimed and disclosed devices, the droplet diameter properties which are recited are considered to be met, particularly as the droplet size property of the mist cannot be achieved without such a device. That is, the mist cannot spontaneously form. Devices which are capable of producing the claimed mist properties are known in the art and read on those devices which are discussed as being used by Applicants. See the attached article published by **Makidon et al.**

Regarding the nasally-administered composition, Wynne teaches in **claim 4** that the opioid analgesic which may be administered is selected from the group consisting of "naloxone … and the like". The reference repeatedly employs the phrase "and the like" with regard to the

different compositional components of the practiced formulations, but provides no added clarity as to its true meaning. Certainly, a person of skill in the art at the time the instant invention was filed could divine that the phrase implies at the very least "derivatives thereof". However, based on this alone, the Examiner cannot assume that said artisan would conclude that "and the like" or "derivatives thereof" necessarily means "hydrochloride or hydrate". The only semblance of a suggestion to this effect could be discerned from the **Tables** of the **Example** which are specifically directed to diamorphine hydrochloride. Based on this teaching and with respect to the other of the disclosed opioid analgesics, the skilled artisan might assume that naloxone … and the like, could potentially be directed to naloxone hydrochloride. Thus, with respect to the instantly claimed drug, the Examiner advances that the drug is taught and suggested by the reference. **Table 1** of the **Example (pg. 10)** is considered to teach amounts of drug (in general), presuming the disclosed amounts are applicable to any of the disclosed species. Here, **Formula 1** teaches 144 mg of drug reconstituted in 10 mL (10,000 µL) of diluent and **Formula 4** teaches 380 mg/10 mL. Thus, the reference is considered to specifically teach a formulation ranging in concentration of diamorphine hydrochloride from 14.4 mg/mL to 38 mg/mL. Applicants' claimed range for naloxone hydrochloride or hydrate, ranges in each independent claim from 4 mg/200µL (20 mg/mL) to 4 mg/25µL (160 mg/mL).

The active is diluted in a "composition of diluent for reconstitution" which is disclosed in **Table 2 (pp. 10-11)**. Here, the Examiner notes that the instantly claimed ingredients: benzalkonium chloride, disodium edetate, NaCl, and hydrochloric acid are used. However, with respect to the instantly claimed composition and methods, the amount of benzalkonium chloride used by Wynne, immediately and significantly departs from the instantly claimed range. The

mist composition and composition administered by the instant methods require benzalkonium to be present at a concentration ranging from 0.005% to 0.015% (w/v) in the primed solution which is then administered in volumes ranging from 25-200 μL. The disclosure of Table 2 of Wynne is somewhat confusing in that the disclosed 0.4mL is stated as being equivalent to 0.02% w/v benzalkonium chloride. However, in calculating the %w/v using the information provided in the Table and what the skilled artisan understands about the solution, the Examiner and Applicants agree that this cannot be the case.

As an initial point, the densities of benzalkonium chloride (BAC) and water are both about 1 g/mL, so a 100-mL solution of 50% (w/v) BAC will have a mass of about 100 grams, 50 grams of which are due to BAC. Thus, a 50% w/v solution of BAC will have a BAC concentration of 50g/100 mL. The 1-mL formulation set forth in Table 2 uses 0.4 mL of this 50% solution which proportionately contains 0.2 grams of BAC or 200 mg of BAC per mL or about 20% w/v.

Thus, while the Wynne reference discloses and suggests each of the compounds used in the instant invention, discussion with Applicants reveals that the amount of preservative employed by the reference is substantially higher than that which is instantly claimed. Wynne is thus considered to teach away from the instant invention.

The second of the two references discovered and considered to represent the closest prior art available is published by **Wyse et al. (USPN 9,192,570 B2)**.

Like Wynne, Wyse is directed a naloxone intranasal spray composition. The naloxone active is disclosed as being naloxone HCl dihydrate (claims 1 and 11) and the concentration

range disclosed 5-50 mg/mL is considered to read on the instantly claimed amount. Similarly, the disclosed concentration range of disodium EDTA (aka disodium edetate), about 2mM to about 20mM is also considered to read on the instantly claimed concentration range. These calculations are based on the instantly claimed volume of 100 μL and molecular weights of disodium edetate (336.21 g/mol) and naloxone HCl dihydrate (399.87 g/mol). Hydrochloric acid can also be used as a buffering agent.

The reference is considered to teach away from the instantly claimed composition on two points. The first and lesser critical of the two points is the presence of citric acid in the disclosed composition. Since the instantly claimed composition recites a composition "comprising…", inclusion of citric acid in the disclosed compositions is not considered to wholly teach away. The more critical of the two teachings away is the disclosure of benzyl alcohol as an antimicrobial agent (e.g., claims). Initial consideration of the reference notes that benzalkonium chloride is in fact taught in the examples of the reference (see Table 13; Examples 7, 9, 14, and 14A). However, the reference is considered to expressly exclude the use of benzalkonium chloride stating that benzalkonium chloride, a common nasal product preservative, results in increased degradation of the naloxone active and teaches outright that apart from the preservative (i.e., benzalkonium chloride) the formulation of Example 7 is suitable for nasal administration (see col. 27, lines 18-37). This is considered to be a direct departure from the instantly claimed composition. Thus, despite the teaching of **Wynne et al.** at **claim 11** teaching benzalkonium chloride and benzyl alcohol as functionally equivalent preservatives **(pg. 7, lines 1-5)**, motivation to combine and or modify such teachings are considered to be overcome by the teachings of Wyse.

Thus, the search has elicited no results which either anticipate or render obvious (e.g., by way of teaching *or* suggesting), the instantly amended invention. **This is to say that the instant pending claims are immediately free and clear of the prior art.**

Furthermore, Applicants have filed terminal disclaimers against **USPNs 9,211,253** and **9,468,747**, as well as copending applications **14/942,344** and **14/795,403**. The TDs were filed electronically and thus approved on submission. This negates any potential double patenting issues.

Any comments considered necessary by Applicants 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."

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.

/Jeffrey T. Palenik/
Primary Examiner, Art Unit 1615