UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NALOX-1 PHARMACEUTICALS, LLC,

Petitioner

v.

OPIANT PHARMACEUTICALS, INC.,
Patent Owner

IPR2019-00685
U.S. Patent No. 9,211,253

DECLARATION OF MAUREEN DONOVAN, Ph.D.

TABLE OF CONTENTS

I, Maureen D. Donovan, Ph.D., do hereby declare as follows:

I. OVERVIEW

1. I am over the age of 18 and otherwise competent to make this Declaration. This Declaration is based on my personal knowledge as an expert in the fields of pharmaceutical formulation, in particular intranasal formulation. I understand that this Declaration is being submitted together with a petition for *Inter Partes* Review ("IPR") of certain claims of U.S. Patent No. 9,211,253 ("the '253 patent") (Nalox1001).

2. I have been retained as an expert witness on behalf of Nalox-1 Pharmaceuticals, LLC ("Nalox-1") for this IPR.

3. I understand that the '253 patent issued on December 15, 2015, and resulted from U.S. Patent Application No. 14/659,472, filed on March 16, 2015. I also understand that the U.S. Patent and Trademark Office ("USPTO") records state that the '253 patent is currently assigned to Opiant Pharmaceuticals, Inc.

4. The face page of the '253 patent lists other patent applications. I understand that the '253 patent is related to a patent application which was filed on March 14, 2014. As discussed below, it is my opinion that the '253 patent cannot claim priority to the March 14, 2014 application, and it is only entitled to its filing date of March 16, 2015.

5. In preparing this Declaration, I have reviewed the '253 patent and its file history. I have also considered each of the documents listed in the table below, in light of general knowledge in the art as of March 16, 2015.

Exhibit No.	Description
Nalox1001	U.S. Patent No. 9,211,253 (the '253 patent)
Nalox1003	Expert Declaration of Günther Hochhaus
Nalox1005	Excerpt of File History of U.S. Patent No. 9,561,177, Oct. 21, 2016 Amendment and Response to Office Action (Oct. 21, 2016 Response to Office Action)
Nalox1006	Excerpt of File History of U.S. Patent No. 9,561,177, Dec. 21, 2016 Office Action, Notice of Allowance and Fees Due (Notice of Allowance)
Nalox1007	U.S. Patent No. 9,192,570 (Wyse)
Nalox1008	Chinese Patent No. 1,575,795 (Wang)
Nalox1009	PCT International App. Pub. No. WO00/62757 (Davies)
Nalox1010	Djupesland, P., *Nasal Drug Delivery Device: Characteristics and Performance in a Clinical Perspective - A Review*, 3 Drug Deliv. & Transl. Res. 42–62 (2013) (Djupesland)
Nalox1011	Grassin-Delyle, S. et al., *Intranasal Drug Delivery: An Efficient and Non-invasive Route for Systemic Administration, Focus on Opioids*, 134 Pharm. & Ther. 366–79 (2012) (Grassin-Delyle)
Nalox1012	Handbook of Pharmaceutical Excipients, 56–60, 64–66, 78–81, 220–22, 242–44, 270-72, 441–45, 517–22, 596–98 (Rowe, R. et al. eds., 6th ed. 2009) (HPE)
Nalox1013	Kushwaha, S. et al., *Advances in Nasal Trans-Mucosal Drug Delivery*, (1)7 J. Applied Pharm. Sci. 21–28 (2011) (Kushwaha)

Exhibit No.	Description
Nalox1014	U.S. Patent No. 5,866,154 (Bahal)
Nalox1015	U.S. Patent No. 8,198,291 (the '291 patent)
Nalox1016	Wermeling, D., *A Response to the Opioid Overdose Epidemic: Naloxone Nasal Spray*, 3 Drug Deliv. & Transl. Res. 63–74 (2013) (Wermeling 2013)
Nalox1018	Aptar Pharma, Press Release, Aptar Pharma Provides Unit-Dose Nasal Spray Technology for Treatment of Opioid Overdose (Apr. 20, 2016) (Aptar Press Release)
Nalox1021	Barton, E. et al., *Efficacy of Intranasal Naloxone as a Needleless Alternative for Treatment of Opioid Overdose in the Prehospital Setting*, 29(3) J. Emerg. Med. 265–71 (2005) (Barton 2005)
Nalox1022	Bitter, C. et al., *Nasal Drug Delivery in Humans*, 40 Curr. Probl. Dermatol. 20–35 (2011) (Bitter)
Nalox1023	Boyer, E., *Management of Opioid Analgesic Overdose*, 367(2) N. Engl. J. Med. 146–55 (2012) (Boyer)
Nalox1027	Dowling, J. et al., *Population Pharmacokinetics of Intravenous, Intramuscular, and Intranasal Naloxone in Human Volunteers*, 30(4) Ther. Drug. Monit. 490–96 (2008) (Dowling)
Nalox1028	FDA, Center for Drug Evaluation and Research, Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (2002) (2002 FDA Guidance)
Nalox1029	FDA, Center for Drug Evaluation and Research, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (2003) (2003 FDA Guidance)

Exhibit No.	Description
Nalox1031	Glende, O., *Development of non-injectable naloxone for pre-hospital reversal of opioid overdose: A Norwegian project and a review of international status* (May 2016) (unpublished M.A. thesis, Norwegian University of Science and Technology) (on file with Norwegian University of Science and Technology) (Glende)
Nalox1032	Hertz, S., Naloxone for Outpatient Use: Data Required to Support an NDA, Powerpoint Presentation (Hertz Presentation)
Nalox1034	Kelly, A-M. et al., *Randomised Trial of Intranasal Versus Intramuscular Naloxone in Prehospital Treatment for Suspected Opioid Overdose*, 182(1) Med. J. Austl. 24–27 (2005) (Kelly)
Nalox1035	Kerr, D. et al., *Intranasal Naloxone for the Treatment of Suspected Heroin Overdose*, 103 Addiction 379–86 (2008) (Kerr 2008)
Nalox1036	Kerr, D. et al., *Randomized Controlled Trial Comparing the Effectiveness & Safety of Intranasal & Intramuscular Naloxone for the Treatment of Suspected Heroin Overdose*, 104 Addiction 2067–74 (2009) (Kerr 2009)
Nalox1038	Marple, B. et al., *Safety Review of Benzalkonium Chloride Used as a Preservative in Intranasal Solutions: An Overview of Conflicting Data and Opinions*, 130 Otolaryngol Head Neck Surg. 131–41 (2004) (Marple)
Nalox1039	Merck Index, *Isotonic Solutions*, MISC-47–69 (Windholz, M. et al. eds., 10th ed. 1983) (Merck Index)
Nalox1041	Middleton, L. et al., *The Pharmacodynamic & Pharmacokinetic Profile of Intranasal Crushed Buprenorphone & Buprenorphine/Naloxone Tablets in Opioid Abusers*, 106(8) Addiction 1460–73 (2011) (Middleton)
Nalox1043	*Pharmacodynamic Agents, in* Foye's Principles of Medicinal Chemistry, 670 (Lemke, T. et al. eds., 6th ed. 2008) (Lemke)

Exhibit No.	Description
Nalox1044	Physicians' Desk Reference, *NARCAN [Naloxone Hydrochloride Injection, USP]*, *IMITREX Nasal Spray [Sumatriptan]*, 1300–02, 1546–50 (57th ed., 2003) (PDR 2003)
Nalox1045	Physicians' Desk Reference, *ZOMIG Nasal Spray [Zolmitriptan]*, 768–78 (64th ed., 2010) (PDR 2010)
Nalox1049	*Role of Naloxone in Opioid Overdose Fatality Prevention* FDA Meeting Transcript (Apr. 12, 2012) (2012 FDA Meeting)
Nalox1050	Rosanske, T., *Morphine*, *in* Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists, 604–11 (Connors, K. et al. eds., 2d ed. 1986) (Rosanske)
Nalox1051	Sabzghabaee, A. et al., *Naloxone Therapy in Opioid Overdose Patients: Intranasal or Intravenous? A Randomized Clinical Trial*, 10(2) Arch. Med. Sci. 309–14 (2014) (Sabzghabaee)
Nalox1053	Trows, S. et al., *Analytical Challenges and Regulatory Requirements for Nasal Drug Products in Europe and the U.S.*, 6 Pharm. 195–219 (2014) (Trows)
Nalox1054	United States Pharmacopeia and National Formulary (USP 36-NF 31) Vol 1., 54–55, 930–33 (2013) (USP)
Nalox1055	U.S. Patent Appl. No. 61/918,802 (the '802 Appl.)
Nalox1058	U.S. Provisional Patent Appl. No. 61/953,379 (the '379 provisional)

6. Generally, the '253 patent claims are directed to a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition comprising naloxone hydrochloride or a hydrate thereof, a preservative, an

isotonicity agent, a stabilizing agent, and an acid sufficient to achieve a pH of 3.5 to 5.5.

7. It is my opinion that a person of ordinary skill in the art ("POSA") reading Wyse in view of Handbook of Pharmaceutical Excipients ("HPE") would have had ample reason and know-how to arrive at the subject matter of claims 1–3 and 16–24 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

8. It is my opinion that a POSA reading Wyse in view of Djupesland and HPE would have had ample reason and know-how to arrive at the subject matter of claims 4–7 and 10–14 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

9. It is my opinion that a POSA reading Wyse in view of Djupesland, HPE, and the '291 patent would have had ample reason and know-how to arrive at the subject matter of claims 8–9 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

10. It is my opinion that a POSA reading Wang in view of Djupesland, HPE, Bahal, and Kushwaha would have had ample reason and know-how to arrive at the subject matter of claims 1–7, 12–14, and 16 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

11. It is my opinion that a POSA reading Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse would have had ample reason and know-how to arrive at the subject matter of claims 10–11 and 17–24 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

12. It is my opinion that a POSA reading Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent would have had ample reason and know-how to arrive at the subject matter of claims 8–9 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

13. It is my opinion that a POSA reading Davies in view of HPE, Bahal, and Kushwaha would have had ample reason and know-how to arrive at the subject matter of claims 1–4 and 16–24 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

14. It is my opinion that a POSA reading Davies in view of Djupesland, HPE, Bahal, and Kushwaha would have had ample reason and know-how to arrive at the subject matter of claims 5–7 and 10–14 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

15. It is my opinion that a POSA reading Davies in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent would have had ample reason and know-how to arrive at the subject matter of claims 8–9 of the '253 patent with a reasonable expectation of success, as discussed in this Declaration below.

16. I have reviewed the opinion of Dr. Günther Hochhaus, an expert in clinical pharmacology, and it is my understanding that he has rendered an opinion that claims 15 and 25–29 of the '253 patent are obvious over the prior art. I offer no opinion regarding the obviousness of these claims.

II. MY BACKGROUND AND QUALIFICATIONS

17. I am a Professor in the Division of Pharmaceutics and Translational Therapeutics at the University of Iowa College of Pharmacy. I have more than 25 years of experience working and consulting in the field of pharmaceutics. My curriculum vitae is attached to this report as Exhibit A.

18. I am an expert in pharmaceutics. I received my Bachelor of Science in Pharmacy from the University of Minnesota College of Pharmacy in 1983 and my Ph.D. in Pharmaceutics from the University of Michigan in 1989.

19. My professional experience includes working as a Staff Pharmacist for Clark Professional Pharmacy from 1986 until 1989 and as a Visiting Scholar for SmithKline Beecham Pharmaceuticals in 1991. From 1989 through the present, I have held various positions at the University of Iowa College of Pharmacy. Specifically, in the Division of Pharmaceutics, I was an Assistant Professor from 1989 until 1996, and an Associate Professor from 1996 until 2008. I was promoted to the rank of Professor in 2008 in the College of Pharmacy, and I currently hold this position. From 2008 until 2013, I was the Division Head for the Division of

Pharmaceutics. In 2013, I became the Associate Dean for Undergraduate Programs at the College of Pharmacy, and I currently hold this position.

20. I have over 25 years of experience in pharmaceutical research and development including actively teaching drug delivery, pharmaceutical preformulation, and compounding to pharmacy students and graduate students, and directing research programs focused on drug absorption, nasal drug delivery, and alternative routes of drug delivery and delivery systems.

21. I have published numerous articles, book chapters, and abstracts in the area of pharmaceutics, drug absorption, drug delivery, and materials characterization, and have conducted research related to the absorption of compounds from the nasal cavity as well as the properties of nasal sprays that influence the deposition of nasal sprays in the nasal cavity as well as the absorption of active ingredients through nasal tissues. Of particular relevance to this proceeding, I have co-authored numerous publications related to systemic delivery of compounds through intranasal administration, including such papers as

- Al-Ghabeish M, Scheetz T, Assem M, Donovan MD. Microarray Determination of Expression of Drug Transporters in Humans and Animal Species Used in the Investigation of Nasal Absorption. *Mol. Pharm.* 12(8), 2742–54, 2015.
- Zhang H, Lin C-W, Donovan MD. Correlation between Nasal Membrane Permeability and Nasal Absorption Rate. *AAPS PharmSciTech* 14(1), 60–63, 2013.
- Foo M-Y, Cheng Y-S, Su W-C, and Donovan MD. The Influence of

Spray Geometry on Intranasal Deposition and Distribution. *J. Aerosol Med.* 20 (4), 495–508, 2007

- Chemuturi NV, Hayden P, Klausner M, and Donovan MD. Comparison of Human Tracheal/bronchial Epithelial Cell Cultures (EpiAirway) and Bovine Nasal Respiratory Explants for Nasal Drug Transport Studies. *J. Pharm. Sci.* 94, 1976–85, 2005.

I also belong to several professional societies for pharmaceutical science and technology, including the American Association of Pharmaceutical Scientists.

22. I am being compensated for my work at $400 per hour in this matter. No part of this compensation due or received is contingent upon the outcome of this matter or the pending proceeding.

23. In addition to my knowledge, education, and experience in the field of pharmaceutical formulation, in forming the opinions I express in this report, I reviewed the full list of materials cited in paragraph 5 above.

III. LEGAL STANDARDS

24. I am neither a patent lawyer nor an expert in patent law. It has been explained to me by counsel for Petitioner that the following law is applicable to patent validity and I have relied upon these legal principles in forming opinions set forth in this Declaration.

A. Person of ordinary skill in the art

25. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA may work as part of a multi-disciplinary

team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team, to solve a given problem. In evaluating who constitutes a POSA, one should take into account the types of problems encountered in the art, solutions to those problems disclosed in the prior art, the speed of innovation in the field, the sophistication of the technology, and the education level of the persons working in the field.

26. In my opinion, with regard to the '253 patent, a POSA would comprise a team of individuals having experience in drug development, and specifically the development of solution-based dosage forms such as intranasal dosage forms. Such a team would include at least one formulator with experience in preformulation testing for and selection of excipients for a solution-based dosage form (including intranasal dosage forms) to achieve a target pharmaceutical profile. Such a formulator would likely have a Ph.D. in pharmacy, pharmaceutics, pharmaceutical chemistry, or a similar field involving pharmaceutical formulations, and would have several years of experience in pharmaceutical formulation development, including development of solution-based dosage forms, including intranasal dosage forms. Alternatively, such a formulator would have a Bachelor's or Master's degree in pharmacy, pharmaceutical chemistry, or a similar field involving pharmaceutical formulations, and would have 3–5 years of experience developing and testing pharmaceutical formulations with specific

experience with solution dosage forms, such as intranasal sprays and drops. Such a formulator would also have an understanding of the importance, use, and component elements of certain commercially-available delivery systems for dosage forms, including inhalers, metered-dose nasal sprayers, and single-dose nasal sprayers, as well as the importance of the properties of the spray emitted from such devices (including droplet size and spray plume geometry).

27. Within the POSA "team," such a formulator would routinely collaborate with others, such as clinical pharmacologists, to discuss issues regarding safety, efficacy, and pharmacokinetic profiles and requirements of a new dosage form, and with mechanical, chemical or biomedical engineers with experience in the design and development of new devices for delivering drugs, such as autoinjectors and spray applicators.

28. I have at least the ordinary skill of the "formulator" who forms part of the POSA team (i.e, the "Formulator POSA") in the relevant art with respect to the '253 patent, and I possessed such ordinary skill as of the March 16, 2015, priority date of the '253 patent, as well as on March 14, 2014 (the date U.S. Patent Provisional Application No. 61/953,379 was filed) .

B. Claim construction

29. I understand from counsel that, prior to conducting an analysis of a patent claim's validity, the claim terms must be properly construed. I have been

advised that claim terms are generally interpreted in accordance with the ordinary and customary meaning they would have to a person of ordinary skill in the art at the time of the invention. I have also been advised that the skilled person would read the claim terms in the context of the claims as well as the entire patent, including the specification of the patent. I further understand that the skilled person, when interpreting claim terms, would consider the record of a patentee's communications with the patent office during prosecution to obtain the patent (the "prosecution history"). Together, the patent claims, specification, and prosecution history make up the "intrinsic evidence" in light of which the claims are construed.

30. Finally, I understand that it is also appropriate to consult other sources contemporaneous with the filing of the patent (such as dictionaries, published articles, other patents, or other materials written by those of skill in the art or with interest in the art to which the patent pertains) that shed light on the proper meaning of a particular claim term. Such other sources are considered "extrinsic evidence." It is my understanding that the intrinsic evidence will generally be more pertinent to the construction of a claim term than the extrinsic evidence.

C. Anticipation and obviousness

31. I understand that a patent claim is unpatentable as "anticipated" when a single piece of prior art describes every element of the claimed inventions, either expressly or inherently, arranged in the same way as the claim. I further understand

that, for inherent anticipation to be found, it is required that the missing descriptive material is necessarily present in the cited prior art.

32. I also understand that a patent claim is unpatentable as "obvious" if the subject matter of the claim as a whole would have been obvious to a Formulator POSA as of the time of the invention at issue. I further understand that the following factors must be evaluated to determine whether the claimed subject matter is obvious: (1) the scope and content of the prior art; (2) the difference or differences, if any, between each claim of the patent and the prior art; (3) the level of ordinary skill in the art at the time of the invention; and (4) "objective indicia of non-obviousness."

33. As just noted, I understand that the so-called "objective indicia of non-obviousness," also known as "secondary considerations," are to be considered, if present, when assessing obviousness. These include commercial success, long-felt but unresolved needs, failure of others to solve the problem that the inventor solved, unexpected results, copying of the invention by others, and industry recognition or expressions of disbelief by experts in the field of the claimed invention. I also understand that a nexus, i.e., a tie, must exist between any "secondary considerations" and the novel aspects of the claimed subject matter. Along those same lines, I understand that secondary considerations cannot be

based on features (and their related benefits and/or advantages) that were already known in the prior art.

34. I understand that obviousness may be shown by considering more than one prior art reference as well as the Formulator POSA's common knowledge. I further understand that the reason or reasons for combining multiple prior art references can come from a variety of sources, such as the specific teachings in the cited prior art, teachings in the prior art collectively, known needs or problems in the art, substituting one known element in the art for another to obtain predictable results, the use of a known technique or feature to improve a similar devices, a Formulator POSA's common sense, etc. I further understand that a combination of multiple prior art references or teachings needs to have a reasonable expectation of success from the perspective of a Formulator POSA. I further understand that, when performing an obviousness analysis, a Formulator POSA should be viewed as person of ordinary creativity, not an automaton.

35. I have evaluated the scope and content of the prior art based on the knowledge of a Formulator POSA at the time of the alleged invention date for the '253 patent. Below in section VII is a comparison of certain prior art references to claims 1–14 and 16–24 of the '253 patent. I also considered "secondary considerations" as part of my analysis, but for organizational purposes, I placed that discussion in section VIII below.

D. Written description and priority

36. I understand from counsel that a patent that claims priority to the filing date of an earlier application can only properly do so if the earlier application provides written description support for the claims of the patent as of the date the earlier application was filed. I further understand that, although the earlier application need not describe exactly the subject matter claimed, the description must allow a Formulator POSA to recognize that the applicant invented what is claimed. Further, I understand that, while the description requirement does not demand any particular form of disclosure, or that the earlier application recite the claimed invention in the exact claim terms used, a description that merely renders the invention obvious does not satisfy the requirement. Rather, it is my understanding from counsel that the specification of a patent must have 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.

IV. THE ’253 PATENT AND ITS CLAIMS

37. I understand that this Declaration is being submitted together with a petition for IPR of claims 1–29 of the ’253 patent.

38. I have considered the disclosure of the ’253 patent in light of the general knowledge in the art as of the priority date of the ’253 patent.

39. For the purposes of determining the priority date of the claims, I have evaluated the disclosure of each application in what I understand is termed the “chain of priority” set forth in the ’253 patent specification. It is my understanding from counsel that a patent claim cannot claim priority to an earlier application and its filing date unless the patent claim finds adequate written description in the disclosure of that earlier priority document.

40. The ’253 patent specification is generally directed towards drug products adapted for nasal delivery comprising a pre-primed device and a pharmaceutical composition comprising an opioid receptor antagonist, pharmaceutical compositions comprising an opioid receptor antagonist, and methods of use thereof. Nalox1001 at 1:8–12. In particular, the device is a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device into the nostril of the patient. *Id.* at 21:5–8. The pharmaceutical composition, most specifically, is one containing about 4.4 mg naloxone hydrochloride dihydrate, 0.74 mg sodium chloride as an isotonicity agent, 0.01 mg benzalkonium chloride as a preservative, and about 0.2 mg disodium edetate as a stabilizing agent, hydrochloric acid in an amount sufficient

to achieve a pH between 3.5 and 5.5, in an aqueous solution of about 100 µL. *See id*. at 21:5–39.

A. Background of the art pertinent to the ’253 Patent

41. The ’253 patent generally relates to drug products for the intranasal administration of naloxone hydrochloride, an opioid antagonist, for the reversal of opioid overdose. Nalox1001. The naloxone hydrochloride is administered as an aqueous solution from a pre-primed, single-use device that, when actuated, forms a spray plume in the nose that deposits on the nasal tissues.

1. Opioid overdose

42. Opioid overdose has become a major medical problem in the United States. In 2008, “poisonings” surpassed motor vehicle accidents as the leading cause of injury deaths in the United States, 90% of which are caused by drugs. Wermeling 2013 (Nalox1016) at 63. Of the 36,500 poisoning deaths in the United States, approximately 18,000, or nearly half, involved prescription opioids or heroin. *Id.* The Center for Disease Control has referred to prescription drug overdose deaths as having reached epidemic proportions in the United States. *Id.*

43. Naloxone is an opioid antagonist that acts as an antidote for opioid overdose. It is a competitive mu-opioid receptor antagonist that reverses the signs of opioid intoxication. Boyer (Nalox1023) at 150. Narcan® (naloxone hydrochloride injection) is indicated for the “complete or partial reversal of opioid

depression, including respiratory depression" and "diagnosis of suspected or [known] acute opioid overdosage." PDR 2003 (Nalox1044) at 1300. The injection is available in two strengths, 0.4 mg/mL and 1.0 mg/mL. *Id.* at 1301. The initial parenteral dose of naloxone for adults with known or suspected narcotic overdose is 0.4 to 2 mg, which may be repeated as needed to a total dose of 10 mg. *Id.* The injectable formulations of naloxone are approved for intravenous (IV), intramuscular (IM) and subcutaneous (SC) injection. *See id.*

44. However, administration of injectable naloxone to opioid overdose patients carries risk. Opioid users frequently self-administer opioids, such as heroin, intravenously, and the resultant damage to the opioid user's veins can make it difficult for health professionals (including paramedics) to access peripheral veins in such patients, thus delaying intravenous administration of the antidote. *See* Sabzghabaee (Nalox1051) at 309; *see also* Kerr 2008 (Nalox1035) at 381. Likewise, drug users can be infected with blood-borne viruses, such as human immunodeficiency virus (HIV) and hepatitis C (HCV), and needlestick injuries to emergency personnel or healthcare workers can result in transmission of these diseases. *See* Kerr 2009 (Nalox1036) at 2067. Finally, some amount of prior experience using needles or clinical expertise is required to use needles and syringes to inject naloxone via parenteral routes, making it unlikely that bystanders

such as family and friends can administer naloxone quickly and easily in the case of an overdose or suspected overdose. *See* Kerr 2008 (Nalox1035) at 381.

2. Prior intranasal formulations of naloxone

45. To address this problem, several authors published papers discussing administration of the injectable naloxone formulation via an intranasal route. *See, e.g.*, Barton 2005 (Nalox1021) at 267–68; Kelly (Nalox1034) at 26–27. Prior to 2013, several emergency medical systems in the United States had moved towards intranasal administration of naloxone instead of intravenous administration, in order to minimize needlestick injuries to personnel. *See* Wermeling 2013 (Nalox1016) at 64. Some of these EMS systems administered the injectable formulation of naloxone (at a 1 mg/mL concentration) intranasally via a syringe with a Luer-fitted tip with a marketed device called the Mucosal Atomizer Device. *See id.* Generally, 1 mL of this formulation is administered per nostril, for a total dose of 2 mg. *See id*.

46. Even then, the prior art recognized problems with intranasal administration of the naloxone injection formulation. The injectable formulation was insufficiently concentrated to deliver an effective dose in a small enough volume to be easily retained in the nasal cavities, thus leading to loss of naloxone from drainage via the front of the nose or via the nasopharynx. *See, e.g.*, Kelly (Nalox1034) at 26; Kerr 2008 (Nalox1035) at 383; Dowling (Nalox1027) at 494;

Wermeling 2013 (Nalox1016) at 64; Wyse (Nalox1007) at 2:34–63. One author specifically noted that a "significant barrier" to greater access to intranasal naloxone was the lack of a "concentrated formulation and a nasal delivery device." Nalox1016 at 64; *see also* Nalox1007 at 3:17–23 ("Further, there is a need for one-step, needle-free, portable naloxone delivery drug products that contain a sufficiently high concentration of naloxone but are capable of long term storage in a variety of different conditions, such that the naloxone is intact and effective when needed, and safe to deliver to a patient either by a professional or by an untrained layperson."). Thus, the prior art provided ample motivation for a Formulator POSA to design an improved intranasal formulation of naloxone in a nasal delivery device.

3. Development of a new intranasal naloxone formulation

47. A Formulator POSA would have taken several considerations into account when designing an improved intranasal formulation of naloxone in a nasal delivery device. These include: (a) the physical and chemical properties of naloxone; (b) the stability of the formulation, (c) the nasal physiology; (d) the drug exposure attributes for the improved intranasal formulation of naloxone one wished to obtain; (e) the choice of pharmaceutical excipients to achieve the desired exposure and stability attributes; (f) the choice of delivery device; and (g) the

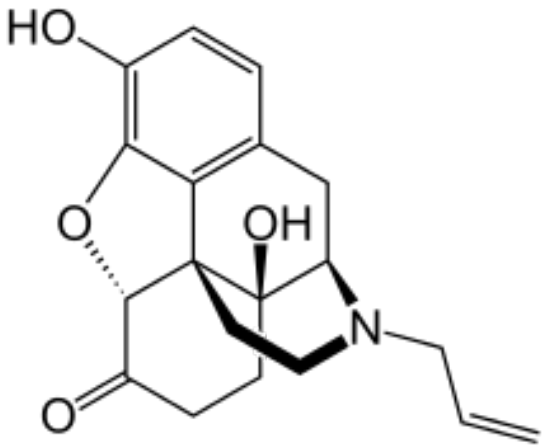
properties of the spray that results when the formulation is delivered by the spray device.

(a) Physical and chemical properties of naloxone

48. The physical and chemical properties of naloxone would have motivated a Formulator POSA to include the drug in an intranasal formulation, with a reasonable expectation of success. Lipophilic drugs with molecular weight less than 1 kD, a logP of less than 5, and a high water solubility (of which naloxone is an example) are generally well absorbed from the nasal cavity at a dose of up to 20 mg. Bitter (Nalox1022) at 26–28; Wermeling 2013 (Nalox1016) at 66. The prior art also discloses administering intranasal naloxone solutions containing up to 50 mg/mL of naloxone (Wyse (Nalox1007) at 6:50–51), at doses of up to 5 mg (Davies (Nalox1009) at 3:2) or even 10 mg (Wang[1] (Nalox1008) at 6, claim 9). Thus, based on the prior art, a Formulator POSA would have had a reasonable expectation of success in designing an intranasal formulation of naloxone that could be administered at doses of up to 10 mg.

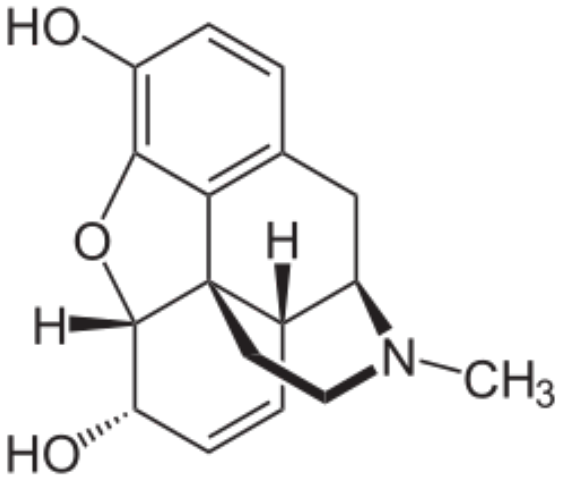
49. Naloxone, however, was also likely subject to oxidative degradation. Naloxone has the following chemical structure:

[1] All cites to Wang are to English translation provided in Nalox1008.



Naloxone

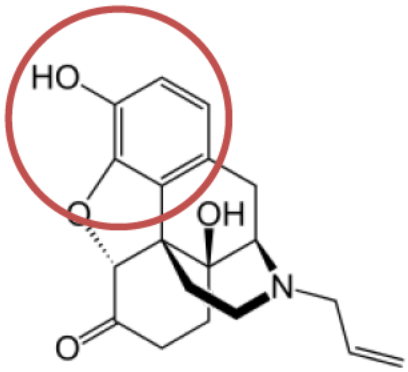
Other opiates that include similar functional groups to those present in naloxone are subject to oxidative degradation. For instance, morphine has the following structure:



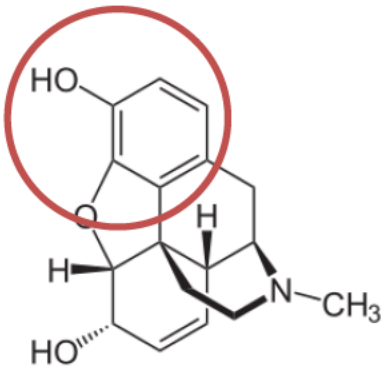
Morphine

Morphine was known to undergo oxidative degradation in solution. *See* Rosanske (Nalox1050) at 605. The functional group primarily responsible for its instability in aqueous solutions is the phenolic moiety, which readily undergoes oxidation in

solution to produce pseudomorphine and morphine N-oxide. *See id.* As can be seen below, both naloxone and morphine contain this phenolic moiety (circled in red):



Naloxone



Morphine

See Lemke (Nalox1043) at 670 (showing that both morphine and naloxone have similar ring structures and a hydrogen at position R_1, giving them both a phenolic group). The prior art (Wyse) also specifically discloses that naloxone solutions are more stable at lower pH values, just as morphine solutions are (*compare* Nalox1007 at 27:18–24 *with* Rosanske (Nalox1050) at 605), and that naloxone solutions, like morphine solutions, turn yellow or brown upon degradation (*compare* Nalox1007, Table 12 *with* Rosanske (Nalox1050) at 605). A Formulator POSA would take these principles into account when making a solution-based formulation of naloxone hydrochloride, including one for a nasal spray, and would seek to choose excipients, packaging, and manufacturing processes that prevented oxidative degradation of naloxone.

(b) Stability of the Formulation.

50. An ideal intranasal formulation of naloxone would have been stable. Stable formulations are those which "retain, within specified limits, and throughout its period of storage and use (i.e., its shelf life), the same properties and characteristics that it possessed at the time of manufacture." *See* USP (Nalox1054) at 930. Generally speaking, five types of stability are recognized for a pharmaceutical product, including chemical (i.e., the active ingredient retains its chemical integrity and labeled potency within specified limits), physical (the original physical properties, including appearance, palatability, uniformity, and the like are retained), microbiological (i.e., sterility or resistance to microbial growth is retained according to specified requirements), therapeutic (i.e., the product retains its therapeutic activity) and toxicological (i.e., no significant increase in toxicity occurs). *Id.* Such general formulation requirements would apply to a naloxone nasal spray: namely, it would need to be physically, chemically, and microbiologically stable and compatible with its delivery system. *See* Wermeling 2013 (Nalox1016) at 73. Ideally, nearly all of the naloxone active ingredient would have been present after storage; the solution would have resisted any changes in color or formation of particulate matter; and the solution would have been free of microbial growth or ingress.

51. In the case of naloxone, a Formulator POSA would have been concerned with stabilizing the active ingredient against oxidation. *See* paragraph 49, *supra.* A Formulator POSA would have considered several possible avenues to improving the stability of the drug substance, including a) removing oxygen from the container and replacing it with a nitrogen overlay; b) including antioxidants or other stabilizing excipients to improve the overall stability of the active ingredient (e.g., chelators to prevent heavy metal ions from contributing to oxidation); c) using opaque external packaging to prevent exposure to light; and d) modifying the pH of the solution to retard oxidation. *See* USP (Nalox1054) at 931. One obvious choice for a naloxone formulation would have been to include sodium edetate as a chelating agent, as this had been used in previous intranasal and injectable formulations of naloxone to stabilize it against oxidation. *See, e.g.*, Wyse (Nalox1007) at 27:35–40 (disclosing that disodium EDTA, i.e., disodium edetate was included to "prevent oxidation" and that it "did not adversely impact Naloxone in formulations"); Bahal (Nalox1014) at 5:60–64 (disclosing that the addition of sodium edetate stabilized naloxone formulations in the presence and absence of oxygen). Yet another obvious choice would have been to reduce the pH of the formulation to below 5, as Wyse disclosed that naloxone exhibited "the most degradation" at a pH of about 5. *See* Nalox1007 at 25:8–40 and FIG. 3. This is consistent with other, chemically similar opiates such as morphine, which exhibit

greater stability to oxidation at pH values below 5.5. *See* Rosanske (Nalox1050) at 607 (disclosing that, for morphine "there is a rapid increase in reaction rate [for oxidation] between pH 5.5 and 7.").

52. Similarly, a Formulator POSA would have been motivated to render the formulation microbiologically stable—i.e., to maintain sterility of the product and freedom from microbiological growth. FDA states that "if preservatives are used in the formulation, the minimum content limit should be demonstrated as microbiologically effective by performing a microbial challenge assay of the drug formulated with an amount of preservative equal to or less than the minimum amount specified." 2002 FDA Guidance (Nalox1028) at 36. Several prior art intranasal naloxone formulations disclosed include antimicrobial agents. *See, e.g.*, Wyse (Nalox1007) at 7:21–28 and Table 1 (disclosing a formulation containing benzyl alcohol); Davies (Nalox1009) at 3:27–4:2 (disclosing use of benzalkonium chloride as a preservative); Wang (Nalox1008) at 8:13–14 (disclosing use of ethylparaben as a preservative). One reasonable choice for an antimicrobial preservative would have been benzalkonium chloride, which was known to be effective at retarding growth of a broad range of bacteria at low concentrations, and whose antimicrobial activity is improved by disodium edetate. *See* HPE (Nalox1012) at 56.

(c) Nasal physiology.

53. An intranasal spray should be concentrated enough and delivered at a small enough volume (100–150 µL per spray) to be retained in the nasal cavity without causing runoff out of the nose (either down the nostril or down the nasopharynx). *See*, *e.g.*, Bitter (Nalox1022) at 27–28; Wermeling 2013 (Nalox1016) at 65; Grassin-Delyle (Nalox1011) at 368. The prior art also discloses the use of 20–200 µL of an intranasal naloxone solution, and specifically 100 µL per spray. Wyse (Nalox1007) at 10:53–56; Wang (Nalox1008) at 8:13–14; Davies (Nalox1009) at 3:3–4; Wermeling 2013 (Nalox1016) at 65. Previously, intranasal administration of dilute naloxone solutions (2 mg of naloxone in 5 mL of solution) had been attempted, and the large volume of liquid administered was thought to be at least partially responsible for the low bioavailability observed (4% as compared to IV), as the healthy subjects to which it had been administered swallowed a large portion of the formulation, and the oral bioavailability of naloxone is low. *See* Dowling (Nalox1027) at 493–95; Middleton (Nalox1041) at 8; Wermeling 2013 (Nalox1016) at 67; Sabzghabaee (Nalox1051) at 311. Prior to the priority date of the ’253 patent, at least one reference (Wyse) had disclosed more concentrated solutions (2 mg naloxone in 200 µL of solution), which has a higher bioavailability (about 40% as compared to IV). *See* Wyse (Nalox1007), Table 4. Based on the prior art, a Formulator POSA would have been motivated to further concentrate the

naloxone to achieve a higher dose than Wyse in a single 100 µL spray to avoid runoff problems and increase bioavailability, and would have had a reasonable expectation of success in doing so.

(d) Drug exposure attributes for an improved intranasal formulation of naloxone.

54. A Formulator POSA would have been motivated to develop an intranasal naloxone formulation that was bioavailable and rapidly absorbed. A Formulator POSA would have been motivated to concentrate the dose of naloxone into a small enough volume so that the drug was retained in the nasal cavity without excessive drainage from the nostrils or into the nasopharynx in order to minimize loss of drug upon administration. As discussed above in section IV.A.3(c), a Formulator POSA would have had a reasonable expectation of success that he or she could do so by concentrating the naloxone dose in an appropriately small volume—e.g., 100 µL per spray.

55. Second, a Formulator POSA would have considered selecting an appropriate naloxone HCl dose for use in such a formulation. Based on the prior art, a Formulator POSA would have been highly motivated to choose an intranasal naloxone dose that correlated with the exposure parameters of a 2 mg naloxone dose administered IM, IV or SC, based on the directions provided by the U.S. Food and Drug Administration ("FDA") regarding the development of naloxone-containing formulations, including intranasal formulations. In 2012 FDA held a

public meeting to discuss the regulatory pathway for intranasal naloxone formulations. *See generally* 2012 FDA Meeting (Nalox1049) at 164–73; Hertz Presentation (Nalox1032). The FDA stated that, in order to meet certain streamlined regulatory requirements, an intranasal naloxone formulation must *meet or exceed* the exposure levels of an approved parenteral naloxone formulation administered by an approved route (i.e., 0.4 to 2 mg naloxone administered IM, IV or SC). 2012 FDA Meeting (Nalox1049) at 166, 169–70, 172; Hertz Presentation (Nalox1032) at 8, 14–15. The goal in naloxone therapy is to achieve rapid onset of action (*see*, *e.g.*, Kerr 2008 (Nalox1035) at 382), and a Formulator POSA would have recognized that, as the goal is to reverse the effects of respiratory depression and restore breathing in the patient, one would naturally seek to get the drug to the patient as quickly as possible. In addition, the prior art discloses that serious adverse events are reportedly rare. *See, e.g.*, Kerr 2008 (Nalox1035) at 381; 2012 FDA Meeting (Nalox1035) at 58–59, 167 ("[I]f [the relative exposure is] high…in this instance, [safety is] not too much of a concern.").

56. Given these teachings, a Formulator POSA would have been motivated to design an improved intranasal formulation of naloxone targeting the exposure levels of the highest approved dose (i.e., 2 mg). Furthermore, a Formulator POSA would have recognized that such a dose would have to be higher than 2 mg, because the prior art disclosed that prior intranasal naloxone

formulations had bioavailabilities of no more than ~42%. *See* paragraph 53, *supra*. In order to achieve sufficient drug exposure, a Formulator POSA thus would have considered doses of between about 4 and about 6 mg. Based on the prior art, a Formulator POSA would have been able to do so with a reasonable expectation of success, as the prior art disclosed formulating solutions of up to 50 mg/mL naloxone hydrochloride (i.e., 5 mg in a 100 μL dose). *See* Wyse (Nalox1007) at 6:50–61.

(e) Choice of pharmaceutical excipients to achieve the desired exposure and stability attributes.

57. As discussed above, a Formulator POSA would have been motivated to choose excipients for an intranasal naloxone formulation that would render the formulation stable and serve to improve, or at least not hinder, absorption and exposure of naloxone. Such excipients would potentially have included isotonicity agents, stabilizing agents, antimicrobial agents, and pH-adjusting agents (i.e., acids and bases).

(i) Sodium chloride as an isotonicity agent

58. The prior art discloses that an intranasal drug formulation can be isotonic to slightly hypertonic (e.g., 290–500 mOsm/kg). Bitter (Nalox1022) at 28; Wermeling 2013 (Nalox1016) at 65. The prior art also discloses the use of sodium chloride to adjust the tonicity of an intranasal naloxone solution. *See, e.g.*, Wyse (Nalox1007) at 7:64–66; Wang (Nalox1008) at 6, claim 2; Davies (Nalox1009) at

2:23–26. A Formulator POSA would have had a reasonable expectation of success that an improved intranasal formulation of naloxone containing sodium chloride to adjust the tonicity from isotonic to slightly hypertonic would work for the intended purpose.

(ii) Hydrochloric acid to adjust pH

59. The prior art discloses that an intranasal drug formulation may have a pH of 4-7.5 (Bitter (Nalox1022) at 28), and that nasal irritation can be minimized when the pH is 4.5-6.5 (*see* Kushwaha (Nalox1013) at 23). Furthermore, Wyse discloses that the stability of naloxone improves as pH decreases. *See* Wyse (Nalox1007) at 27:20–24. This is consistent with other, chemically similar opiates, which show greater stability against oxidation at lower pH values. *See* Rosanske (Nalox1050) at 607 (disclosing that, for morphine "there is a rapid increase in reaction rate [for oxidation] between pH 5.5 and 7."). The prior art discloses an intranasal naloxone solution having a "slightly acid" pH (for example, pH 6.5) (Davies (Nalox1009) at 2:28; 4:2) and the use of hydrochloric acid to adjust the pH of an intranasal naloxone solution within the range of about 3 to about 5.5 (Wyse (Nalox1007) at 8:1–4; Wang (Nalox1008) at 8:3–8). Therefore, a Formulator POSA would have been motivated to adjust the pH to about 3 to about 5.5 from both the disclosure of Wyse and the knowledge that naloxone HCl is likely more stable to oxidation at lower pH levels, but would also aim to adjust the pH from

around 4.5 or above in order to minimize nasal irritation. Further still, a Formulator POSA would have been motivated to choose hydrochloric acid as an acidifying agent, as the counterion (Cl^-) is the same as that of naloxone hydrochloride, and thus would not be expected to result in any insoluble precipitates on combination with cationic (i.e., protonated) naloxone that otherwise may have negative effects on the stability of the formulation.

(iii) Disodium edetate as a chelating agent

60. Disodium edetate is a chelating agent that can help to stabilize active ingredients, as well as promote absorption from nasal formulations. *See* Kushwaha (Nalox1013) at 25. The prior art discloses the use of disodium edetate as a stabilizing agent or preservative in IV[2] and intranasal naloxone solutions. Wyse (Nalox1007) at 7:17–20; Wang (Nalox1008) at 6, claim 3; Bahal (Nalox1014) at 2:44–50.[3] Bahal, specifically, disclosed that injectable solutions of naloxone containing sodium edetate were more stable to oxidation than solutions without it. *See* Nalox1014 at 2:44–50.

[2] A Formulator POSA would have applied the teachings of an IV solution to an intranasal solution, with a reasonable expectation of success.

[3] The HPE discloses that disodium ethylenediamenetetraacetate, disodium EDTA, and other terms are synonymous with disodium edetate. *See also* HPE (Nalox1012) at 242.

61. A Formulator POSA thus would have had a reasonable expectation of success that an intranasal formulation of naloxone containing disodium edetate would have been more stable against oxidation than one without it, and thus would have had motivation to include it in an intranasal naloxone formulation.

(iv) Benzalkonium chloride as an antimicrobial preservative

62. As noted above in paragraph 52, a Formulator POSA would have been motivated to include an antimicrobial preservative in an intranasal naloxone formulation in order to render the formulation stable against microbial growth. Although single-use devices can be sterile-filled, and thus do not require preservatives (*see* Djupesland (Nalox1010) at 49), several formulations of intranasal naloxone include antimicrobial preservatives, including benzyl alcohol, ethylparaben, and benzalkonium chloride. *See* paragraph 52, *supra*. Other preservatives that a formulator may have considered would include methylparaben, propylparaben, and mixtures of the two, particularly since a mixture of the two was used as a preservative in the prior injectable formulation of Narcan®. *See* PDR 2003 (Nalox1044) at 1300. For the following reason, a Formulator POSA would have been motivated to choose benzalkonium chloride as the preservative.

1) A Formulator POSA would have been motivated to use benzalkonium chloride as a preservative.

63. When a preservative is included in a formulation, the formulation will likely undergo antimicrobial effectiveness testing to determine that the preservative is sufficiently active against a range of bacteria and other pathogens. This is usually done by inoculating a number of different sterile, capped container of the drug product with a prepared, standard inoculum of each of at least five different types of bacteria and fungi (namely, *Eschericia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus niger*), and evaluating whether the bacteria quantity decreases (and whether the yeast and mold quantity fails to increase) over several time periods. *See* USP (Nalox1054) at 54–55. In order to meet the requirement for antimicrobial effectiveness in a nasal formulation, each sample including a bacteria strain should demonstrate a 10-fold decrease in the number of colony-forming units (cfu) over 7 days, a 1000-fold decrease in the number of colony-forming units over 14 days, and no increase in the number of cfu from the 14 days' count at 28 days. *See id*. Similarly, in order to meet the requirement for antimicrobial effectiveness in a nasal formulation, there must be no increase from the initial calculated count of yeasts and molds at each of the 7, 14, and 28 day time points.

64. Thus, the potency and wide range of antimicrobial activity of benzalkonium chloride would make it attractive as an antimicrobial preservative, specifically because it has a broad range of antimicrobial activities at low concentrations. Benzalkonium chloride is a commonly used antimicrobial preservative in FDA-approved nasal formulations (Kushwaha (Nalox1013) at 24), was disclosed in the FDA's inactive ingredients database for nasal preparations (HPE (Nalox1012) at 57), and has been utilized in intranasal naloxone solutions (Wang (Nalox1008) at 6, claim 3; Davies (Nalox1009) at 3:27–4:2). One review concluded that "intranasal products containing the preservative [benzalkonium chloride] are safe and well tolerated for both short- and long-term use." Marple (Nalox1038) at 140. Benzalkonium chloride solutions are active against a wide range of bacteria, yeasts, and fungi in pharmaceutical solutions at low concentrations, particularly when combined with disodium edetate. *See* HPE (Nalox1012) at 56. In addition, benzalkonium chloride has been proposed to enhance drug penetration in intranasal formulations. Marple (Nalox1038) at 140.

65. Other preservatives are less effective against some of the bacteria or molds used in the antimicrobial effectiveness testing. For instance, benzyl alcohol is only moderately active against Gram-positive organisms and less active against Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *E. coli*. HPE (Nalox1012) at 64. Benzyl alcohol is usually used at concentrations such as 5

mg/mL (0.5 % w/v) (HPE (Nalox1012) at 64), as used in the formulations disclosed in Wyse. *See, e.g.*, Nalox1007, Table 1. Other preservatives, such as methylparaben or propylparaben, are slightly more potent, and are used at lower concentrations of 0.033% w/v (methylparaben) and 0.017% w/v (propylparaben) in nasal solutions. *See* HPE (Nalox1012) at 442 (methylparaben), 596 (propylparaben). However, parabens—including methylparaben, ethylparaben, and propylparaben—are somewhat less active against *Pseudomonas aeruginosa* (minimum inhibitory concentrations of >2000 µg/mL for methylparaben and ethylparaben, and >1000 µg/mL of propylparaben), which is one of the organisms used in the antimicrobial effectiveness testing. *See* HPE (Nalox1012) at 221, 442, 597.

66. Benzethonium chloride and benzalkonium chloride are more effective than benzyl alcohol, methylparaben, or propylparaben against a number of bacteria, as is shown by a comparison of their respective minimum inhibitory concentrations against various bacteria and fungi. *Compare* HPE (Nalox1012) at 57 (benzalkonium chloride) and 59 (benzethonium chloride) *with* 64 (benzyl alcohol), 442 (methylparaben), and 597 (propylparaben). For this reason, benzethonium chloride is typically used at concentrations of 0.01%–0.02% w/v, and benzalkonium chloride is typically used at concentrations of 0.002%–0.02 %

w/v.[4] *See id*. at 56, 60. More notably, benzalkonium chloride is noted to have minimum inhibitory concentrations in the range of 1–30 µg/mL against *Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus aureus*, all of which are listed in the antimicrobial effectiveness testing protocol set forth in the United States Pharmacopoeia, whereas the minimum inhibitory concentrations for these organisms tend to be higher for methylparaben, propylparaben, and benzyl alcohol. *Compare id.* at 57 (benzalkonium chloride) *with* 64 (benzyl alcohol), 271 (ethylparaben), 442 (methylparaben), and 597 (propylparaben). As such, benzalkonium chloride would have been a reasonable choice for inclusion as an antimicrobial preservative in an intranasal naloxone formulation.

2) Wyse would not have directed a Formulator POSA away from using benzalkonium chloride in an intranasal naloxone formulation.

67. During prosecution of an application that, I understand from counsel, is related to the ’253 patent, the Examiner stated that Wyse “is considered to teach away from the instantly claimed composition” specifically because Wyse “is considered to expressly exclude the use of benzalkonium chloride[.]” *See* Notice of Allowance (Nalox1006) at 8. Specifically, the Examiner stated as follows:

[4] These quantities would equate to 0.01–0.02 mg benzethonium chloride per 100 µL of solution, or between 0.002–0.02 mg benzalkonium chloride per 100 µL of solution.

> [Wyse (Nalox1007)] 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.

Id. I disagree with the Examiner in this regard. Wyse, in my opinion, does not teach away from the use of benzalkonium chloride in a naloxone nasal spray.

68. Wyse discloses that the formulation can contain an antimicrobial agent—i.e., a preservative—in an amount of 0.1% to 2% by weight of the formulation. Nalox1007 at 7:21–28. While Wyse discloses that the preservative may be benzyl alcohol, "other suitable antimicrobial agents may be readily understood by one of ordinary skill in the art." Benzalkonium chloride would have been one such antimicrobial agent. *See* HPE (Nalox1012) at 56–57.

69. Wyse, in fact, discloses naloxone nasal spray formulations that contain benzalkonium chloride. Specifically, Wyse discloses an experiment to evaluate excipients in naloxone hydrochloride formulations in Example 5. *See*

Wyse (Nalox1007) at 26:18–28:35. In that experiment, several different combinations of excipients were evaluated in combination with naloxone hydrochloride at a concentration of 20 mg/mL. *Id.* at 26:23–29. The formulations were at pH 5.0 to accelerate degradation (except as otherwise noted in Table 13) and stored at 60 ºC for 4 weeks in sealed 5 mL vials with 1 mL fill volumes. *Id.* at 26:29–34. The composition of the formulations that were being investigated is shown below (modified slightly such that the table fits on one page):

TABLE 13

Preliminary Formulation Screening Studies

	Formulation No.												
	4	5	6	7	8	9	10	11 (pH 4.0)	12	13	13A (pH 4.5)	14	14A (pH 4.5)
Citric Acid (25 mM)	x	x	x	x									
Citric Acid (2.0 mg/mL)										x	x	x	x
Sodium Citrate (3.1 mg/mL)										x	x	x	x
EDTA (10 mM)	x	x		x			x	x		x	x	x	x
Ascorbic Acid (10 mM)		x	x										
Hypromellose (0.1%)				x			x	x	x				
Polyethylene Glycol 400 (20%)						x							
Sorbitol (5%)				x		x			x				
Glycerine (2.0%)						x				x	x	x	x
Propylene Glycol (1.0%)										x	x	x	x
Methylparaben (1.8 mg/mL)					x		x	x					
Propylparaben (0.2 mg/mL)					x		x	x					
Benzalkonium Chloride (0.125%)				x		x			x			x	x
Benzyl Alcohol (0.5%)										x	x		
Sodium Chloride (6.4 mg/mL)				x	x	x				x	x	x	x
Polysorbate 20 (0.02%)										x	x	x	x
Nitrogen Gas					x	x	x	x	x	x	x	x	x

*Formulation was examined at three different pH values and at two storage conditions for a total of six different formulations (FIGS. 1 and 2).
**Nitrogen gas will be sparged in the bulk solution in addition to a nitrogen overlay. All other formulations with nitrogen will be an overlay.

See id., Table 13.

70. As can be seen from Table 13 above, five formulations—7, 9, 12, 14, and 14A—contained benzalkonium chloride at a concentration of 0.125% (w/v).[5] Wyse discloses the following regarding certain formulations containing benzalkonium chloride:

> The results further surprisingly show that the use of benzalkonium chloride, a common nasal product preservative, resulted in an additional degradant in formulations 7, 9, 14 and 14A. Apart from the preservative, Formulation 7 was believed to be ideal for nasal delivery because the excipients were expected to increase the residence time in the nasal cavity (HPMC), prevent oxidation (EDTA), and create a hyperosmotic solution that facilitates diffusion across the cell membrane.
>
> This screening study indicated the following: the formulation should be buffered and a citric-acid based buffer system was acceptable and disodium EDTA did not adversely impact Naloxone in formulations. 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.

Nalox1007 at 27:29–44.

71. There are three specific reasons a Formulator POSA would not regard this disclosure as "teaching away" from the use of benzalkonium chloride in a naloxone nasal spray. First, the testing disclosed in Wyse would not necessarily permit a Formulator POSA to conclude any one ingredient was the cause of an instability issue in the formulation. Second, nothing in the disclosure of Wyse

[5] Generally, the concentration of benzalkonium chloride in aqueous solution, when expressed as a percentage, refers to the weight/volume concentration.

would permit a Formulator POSA to conclude that the "additional degradant" in Formulations 7, 9, 14, and 14A was a naloxone degradant. Third, Wyse itself discloses a formulation (Formulation 12) that includes benzalkonium chloride, but was not disclosed to result in an additional degradant, indicating that benzalkonium chloride was not necessarily the cause of the "additional degradant."

72. First, I note that one cannot conclude from the disclosure of Wyse that any individual excipient is responsible for any instability issue in the disclosed formulations. Rather, the excipient compatibility studies disclosed in Example 5 of Wyse are performed on combinations of multiple excipients, rather than different combinations of naloxone and different, single excipients in isolation. Generally, if one wishes to determine if a particular excipient will cause degradation of an active ingredient upon long-term storage of the combination, one would combine the excipient and the active in a container and allow them to sit for a period of time under controlled conditions (i.e., controlled for temperature, humidity, pH, ionic strength, the presence or absence of oxygen, etc.) in order to analyze if any additional degradation products form, or increased degradation is observed, upon storage relative to control samples (i.e., samples of the active and excipient alone at the same control parameters). The compatibility studies in Wyse, however, do not permit a Formulator POSA to single out any one inactive ingredient as causing degradation of the active/API. For this reason alone, a Formulator POSA would

have recognized that the disclosure of Wyse does not teach away from combining benzalkonium chloride and naloxone in a nasal spray formulation.

73. Of note, others of skill in the art reading the disclosure in Example 5 have also reached the same conclusion. For instance, a graduate thesis published in 2016, which reviewed the WIPO Publication equivalent of Wyse, stated as follows:

> Although the AntiOp patent describes better observed degradation properties for a formulation lacking commonly used excipients in IN formulations (i.e. absorption promotors and viscosity increasing agents), these excipients should not be depreciated based on this patent solely. The selection of formulation was based on comparison of "cocktails" of excipients, and not systematic examination of one by one excipient. Excipients such as the benzalkonium chloride (preservative) and glycerine (preservative, co-solvent and viscosity enhancer) may have been identified as unsuitable on wrong basis.

Glende (Nalox1031) at 76. This is consistent with how I, and other POSAs, would have read Example 5 in Wyse. As such, this further confirms my opinion that Wyse did not teach away from use of benzalkonium chloride in naloxone nasal sprays.[6]

74. Second, I note that none of the testing in Wyse specifically indicates that the formulations containing benzalkonium chloride resulted in additional degradation of *naloxone*. Rather, Wyse discloses that inclusion of benzalkonium

[6] Further, other prior art disclosed naloxone nasal sprays containing benzalkonium chloride at or around these concentrations. For instance, Davies discloses a naloxone nasal spray containing 0.025% w/v benzalkonium chloride. *See* Davies (Nalox1009) at 3:27–4:5.

chloride "resulted in an additional degradant" in Formulations 7, 9, 14, and 14A. Nalox1007 at 27:30–32. There is no specific indication that the "additional degradant" is a naloxone degradant or derivative.[7] This specifically shows that the Examiner's assumption that "benzalkonium chloride results in increased degradation of the naloxone active" was unwarranted. *See* Notice of Allowance (Nalox1006) at 8.

[7] While Wyse discloses that "one or more [sic] ascorbic acid, hypromellose, propylene glycol 400, sorbitol, glycerine, polypropylene glycol, methylparaben, propylparaben, benzalkonium chloride, were found to increase degradation of naloxone[,]" a Formulator POSA would regard this with some skepticism. *See* Nalox1007 at 28:23–30. Notably, a Formulator POSA would need some evidence that the "additional degradant" was a result of the combination of naloxone and the inactive ingredient, rather than due to other factors—e.g., incompatibility between two different inactive ingredients. This could be shown by providing evidence that the quantity of naloxone drug substance decreased in an assay when the additional degradant appeared, or by conducting a degradation study of naloxone to identify the relative retention times of the naloxone degradants in an HPLC assay, and then note these degradants' appearance in the HPLC assays of the samples that underwent stability testing.

Wyse discloses that naloxone exhibits degradants with relative retention times of 0.52 and 1.2 in an HPLC analysis of the results of a degradation study. *See* Nalox1007 at 26:15–17. Further, Wyse discloses in Example 5 that "[i]ncreasing the pH of the solution accelerated the degradation of naloxone HCl resulting in the formation of a major degradant at a relative retention time (RRT) of 0.52." *Id*. at 27:20–23. The fact that Wyse refers to the degradant in test formulations 7, 9, 14, and 14A as an "additional degradant" leads me to believe it was one not previously observed in the naloxone degradation study. Further, Wyse does not disclose that the assay of naloxone hydrochloride decreased in formulations 7, 9, 14, and 14A; as such, a Formulator POSA could not conclude from the evidence presented in Wyse that the "additional degradant" is a degradant of naloxone.

75. Third, I note that Wyse itself discloses a formulation that includes benzalkonium chloride, but was not disclosed to result in an additional degradant. Formulation 12 includes the same excipients as Formulation 7, except it does not include EDTA or citric acid, and it was put under a nitrogen overlay as opposed to Formulation 7, which was not. *See* paragraph 69, *supra.* Critically, this indicates that the combination of benzalkonium chloride and naloxone did not result in an additional degradant.

76. Furthermore, a Formulator POSA reading Wyse in view of HPE would have been able to identify that Formulations 7, 14, and 14A potentially showed the presence of an "additional degradant" because they combined a citrate buffer with benzalkonium chloride. HPE discloses that benzalkonium chloride is "incompatible with…citrates" and that citrate buffers decrease its antimicrobial activity. *See* HPE (Nalox1012) at 56–57. This may be due to the citrate anion forming an ion pair with the quaternary amine of benzalkonium chloride.

77. Likewise, a Formulator POSA reading Wyse in view of HPE would have recognized that polyethylene glycol 400 in formulation 9—which lacks a citrate buffer—could contribute to the oxidative degradation of the naloxone active ingredient. HPE explicitly discloses that "all grades [of polyethylene glycol] can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation." *See* Nalox1012 at 520. A Formulator

POSA would have recognized that naloxone is sensitive to oxidative degradation (*see supra* section IV.A.3(a)) and may have limited incompatibility with polyethylene glycol due to the presence of such peroxides.

78. The fact that Formulation 12—which contains benzalkonium chloride—was not disclosed to contain the "additional degradant" further supports my opinion. Of note, Formulation 12 contains hypromellose, sorbitol, and benzalkonium chloride, like formula 7, but does not contain citric acid, EDTA, or a nitrogen overlay. As Wyse discloses that the naloxone drug substance is compatible with both disodium EDTA, i.e., disodium edetate and a citrate buffer (Nalox1007 at 27:38–41 ("This screening study indicated the following:…a citric acid based buffer system was acceptable and disodium EDTA did not adversely impact Naloxone in formulations")) and HPE discloses that benzalkonium chloride is frequently combined with disodium edetate (i.e., disodium EDTA) (Nalox1012 at 57), a Formulator POSA would reasonably conclude that the source of the additional degradant in Formulation 7 was either (a) the lack of a nitrogen overlay to remove ambient oxygen; or (b) an interaction between citric acid and benzalkonium chloride. A Formulator POSA, however, would not have concluded that an interaction between benzalkonium chloride and naloxone was the cause of the presence of an additional degradant.

(f) Choice of delivery device

79. The choice of delivery device is a critical consideration for development of a nasal spray formulation. Several intranasal spray devices are available, including spray bottles, multi-dose sprayers, single- and duo-dose devices, and syringe-based devices. *See generally* Djupesland (Nalox1010). The choice of device will generally depend on factors such as the intended use of the formulation, the intended setting in which the formulation is to be administered, the stability of the drug formulation, and others.

80. Naloxone, as a drug, is used to treat an acute condition (i.e., opioid overdose), rather than a chronic one. A Formulator POSA would generally recognize that multidose sprayers, which require priming prior to use, are less suited to drugs that are intended for sporadic use. *See* Djupesland (Nalox1010) at 48–49. This is because the process of priming—which is required to ensure that an accurate dose is delivered—results in loss of the drug substance because one has to actuate the sprayer repeatedly until a spray forms. Likewise, spray bottles that lack metering devices are unsuitable for use in administering potent, systemically absorbed medications. Wermeling 2013 (Nalox1016) at 66. Single-use intranasal devices, such as those used for the migraine medications zolmitriptan (Zomig®, approved by FDA in 2003) and sumatriptan (Imitrex®, approved by FDA in 1997) would have been a natural choice, as such devices require no priming and are thus

ready to use when needed. Several prior art intranasal naloxone formulations—e.g., those disclosed in Wyse, Wang, and Davies—recommend such single-use devices for naloxone nasal sprays. One recommended device (which is used in Wyse) is the Aptar/Pfeiffer Unitdose device. Nalox1007 at 10:53–58. This is, in fact, the device in which Narcan® nasal spray is packaged. *See* Aptar Press Release (Nalox1018).

81. A Formulator POSA thus would have been highly motivated to choose a single-use, pre-primed device such as the Aptar/Pfeiffer Unitdose device, for use with a naloxone nasal spray, as doing so would minimize the loss of drug and permit accurate dosing of an intranasal naloxone formulation.

(g) The properties of the nasal spray delivered by the spray device.

82. A Formulator POSA would also want to take into account how the formulation would perform when placed in the chosen device. Properties a Formulator POSA would need to take into account for a single-dose nasal spray include the delivered dose uniformity from one spray device to the next, the spray pattern emitted from the device, and the droplet size distribution in the spray. *See* Trows (Nalox1053) at 197.

83. The droplet size distribution is one parameter a Formulator POSA would characterize for a nasal spray, particularly since the FDA requires manufacturers to specify the droplet size distribution of a delivered plume

subsequent to spraying. *See* 2002 FDA Guidance (Nalox1028) at 15. Generally speaking, the droplet size is a measure of how much of the total volume of the spray is present in droplets of a defined diameter. The droplet size and distribution of the spray can influence the *in vivo* deposition of the drug in the nasal cavity. Trows (Nalox1053) at 200.

84. Ideally, the prevalent median droplet size is between 30 and 120 μm in diameter. If too much of the spray is present in droplets larger than 120 μm, those droplets will deposit mainly in the anterior part of the nose where drug is not absorbed as well. *See id.* However, droplets that are too small (<10 μm) can possibly be inhaled and reach the lungs; if too much of the spray is present in droplets that small, safety issues can result. *See id.* at 200–01; *see also* Grassin-Delyle (Nalox1011) at 368 ("For drugs in solution administered as a nasal spray, the aerodynamic diameter of the particles emitted by the spray device must be greater than or equal to 10 μm, in order to ensure impaction of the particles on the nasal mucosae and to prevent them from being drawn into the lower airways by inspiratory flow."). For this reason, FDA requires specifying the percentage of droplets below 10 μm in diameter, and minimizing the fraction of such droplets. *See* 2002 FDA Guidance (Nalox1028) at 15; *see also* Djupesland (Nalox1010) at 42 ("[FDA guidance] primarily addresses *in vitro* testing of nasal sprays and pressurized aerosols for local action. The reference to in vivo performance is

limited to the recommendation of minimizing the fraction of respirable particles below 9 μm in order to avoid lung inhalation of drugs intended for nasal delivery."); *and* 2003 FDA Guidance (Nalox1029) at 14:572–578 (which is the Guidance document cited by Djupesland).[8]

85. Several factors can influence the droplet size, including formulation factors (namely viscosity); the design of the device; and actuation parameters of the device such as actuation force, stroke length, and actuation velocity. *See* Trows (Nalox1053) at 201. As for formulation factors, viscosity has a significant influence on the droplet size distribution of a spray from a specific device, while the surface tension has only a minor to no effect. *Id.* at 202–03. Furthermore, while actuation force, actuation velocity, and stroke length can all modify the droplet size distribution of a nasal spray, *id.* at 206–07, single-use devices often include a pressure-point mechanism to ensure reproducibility of the actuation force and spray characteristics. *See* Djupesland (Nalox1010) at 49.

86. In addition, the spray pattern is another factor that FDA requires to be characterized for an intranasal formulation. *See* 2002 FDA Guidance (Nalox1028) at 36; *see also id.* at 20 (describing methods for characterizing plume geometry).

[8] Although naloxone is intended for systemic absorption, and this guidance is primarily directed to nasal sprays for local action, a Formulator POSA would have taken this teaching into account as it would have been relevant for a Formulator POSA to consider safety issues that could result from excessive quantities of drugs being present in respirable particles.

The spray pattern is, in effect, the shape of the spray plume, and is generally defined by an axial cross-section of the plume at a defined distance from the spray nozzle. *See* Trows (Nalox1053) at 207. Such measurements of the spray pattern are evaluated by spraying onto a plate at a distance (generally 3 to 7 cm from the actuator tip) and characterized by identifying the approximate center of mass for the spray plume and the maximum (D_{max}) and minimum diameters (D_{min}) drawn through this center to determine the size of the pattern. *Id*. at 208. The ratio of the maximum and minimum diameters, $D_{max}/D_{min,}$ is the "ovality ratio" of the plume. *Id*. A uniform, circular plume with an ovality ratio close to one has been reported to be ideal. *Id.*

87. Delivered dose uniformity is another parameter that would need to be considered. If the dose delivered varies significantly from one spray to the next (or, in the case of a single-use device, from one device to the next), there will be potential issues of overdosing or underdosing patients.

88. A Formulator POSA would have recognized that it would have been possible to control the dose uniformity, both droplet size distribution and the shape of the spray plume (including the ovality ratio) of a nasal spray through careful evaluation of devices used with similar formulations. For instance, U.S. Patent No. 8,198,291 to Wermeling (the "'291 patent") discloses intranasal opioid compositions that can be delivered with a Pfeiffer Unitdose Second Generation

Spray Device, which is a commercially-available single-use nasal sprayer. *See* Nalox1015 at 6:51–60. Furthermore, the '291 patent discloses various properties of the spray pattern produced by a butorphanol formulation emitted from the Pfeiffer Unitdose Second Generation device. Specifically, the '291 patent discloses preparing a formulation comprising 1 mg butorphanol tartrate, 0.65 mg sodium chloride, and 0.1 mg citric acid, with 0.12 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0, in an amount of water sufficient to give 100 µL of solution. *See id.* at 7:61–8:11, 8:16–26, 11:46–48.[9] The droplet size distribution (in terms of Dv10, Dv50, and Dv90 values, i.e., a volume-weighted distribution) from this sprayer was measured via laser diffraction at spray distances from the laser beam of 1, 3, and 5 cm; the results are reported in the table below.

[9] The '291 patent specifically discloses that the formulation contains "10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0." *Id.* at 7:63–67. However, it also discloses pharmacokinetic results obtained from "Administration of a 2 mg dose of butorphanol tartrate" in this formulation from a Pfeiffer Unitdose Second Generation spray device (*id.* at 8:2–6), and that the Pfeiffer Unitdose Second Generation spray device was "charged with sufficient liquid to deliver a 0.1 mL dose of the butorphanol test formulation." *Id.* at 8:16–18. Further, the '291 patent discloses that two such devices were used to administer the dose to each patient. *See id*. at 8:23–24. Based on these combined disclosures, it appears that the formulation as prepared above was dissolved sufficient water to give a 1 mL solution, which was then subdivided into sufficient quantities to deliver a 1 mg dose of butorphanol tartrate in 100 µL of solution in each sprayer. Furthermore, for the spray testing, the '291 applicants disclosed that the formulation did not include benzethonium chloride. *See id.* at 11:46–48.

Distance	Mean Dv10 in μm (range)	Mean Dv50 in μm (range)	Mean Dv90 in μm (range)
1 cm	15.45 (13.70–19.98)	41.46 (35.74–55.67)	93.88 (69.55–117.15)
3 cm	13.83 (11.84–15.68)	35.29 (29.46–41.69)	90.80 (71.2–122.42)
5 cm	15.82 (14.38–17.17)	32.96 (31.03–35.32)	71.85 (61.64–83.68)

See id. at 11:64–12:15. Likewise, when sprayed from a Pfeiffer Unitdose Second Generation device onto an impaction plate at a distance of 3 cm, the spray plume had an average ovality of about 1.1 (range of 1.0–1.3), and when measured at 5 cm, the sprayer had an average ovality of about 1.1 (range of 1.0 to 1.2). *Id.* at 11:55–63. A Formulator POSA would reasonably expect two formulations emitted from the same device to have roughly the same droplet size distribution and spray characteristics, so long as there were no excipients or ingredients resulting in significant differences between the viscosities of the formulation. *See* Trows (Nalox1053) at 202–03 (noting that viscosity has a major influence on the droplet size distribution, whereas the surface tension has a minor to no effect).

89. As such, a Formulator POSA would have been highly motivated, from the disclosure of the ’291 patent, to omit ingredients that increase the viscosity of an improved intranasal naloxone formulation, as similar formulations of opioids in a single-use device without viscosity enhancers had droplet sizes that were larger than 10 μm but, in large part, smaller than 100 μm. In addition, a Formulator

POSA would have been motivated to use such a formulation in a commercially-available device to ensure these spray characteristics were maintained.

90. Similarly, the ’291 patent discloses a study to compare bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. Nalox1015 at 7:60–62. The formulation contained 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0. *Id.* at 7:63–67. This composition was loaded into the Pfeiffer Unitdose Second Generation Sprayer in quantities sufficient to deliver 0.1 mL (100 µL) of the butorphanol test formulation. *Id.* at 8:13–18. The applicators were weighed prior to and after delivery of one dose into a subject’s nostril, with each patient receiving a total of two doses from two separate devices. *See id*. at 8:20–27. The weight of the pair of devices before and after delivery was compared and the difference was calculated to determine the dose delivered. *See id*. at 8:27–36. For the 23 sets of two Pfeiffer Unitdose spray devices weighed before and after actuation, it was found that the two sprayers together had delivered a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams, (*id.* at 8:39–47), and a 95% confidence interval of (0.203 g, 0.209 g). This corresponds to a 95% CI for the dose delivered over two sprays of about ±1.5% and a 90% CI for dose delivered over the two

sprays of about ±0.9%.[10] From these results, it was concluded that this sprayer demonstrated a higher degree of accuracy in intranasally administering 100 µL of solution than the other sprayer tested. *See id*. at 9:15–19. Thus, a Formulator POSA could have confidence that such unit dose sprayers consistently and reproducibly administer the same volume of drug solution, and thus the same dose of drug.

B. Claim 1 of the ’253 patent

91. Claim 1 of the ’253 patent, from which claims 2–29 depend explicitly or implicitly, in general recites a single-use, pre-primed nasal sprayer containing a naloxone hydrochloride solution.

92. In particular, claim 1 recites the following:

> 1. 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;

[10] This was calculated from the standard deviation, mean, and number of sprays, using an online calculator for the 90% confidence interval.

an amount of an acid sufficient to achieve a pH of[11] 3.5-5.5.

Nalox1001, claim 1.

93. The chart below lays out the limitations of claim 1:

Limitation	Claim 1
Preamble	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
1.1	a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:
1.2	about 4 mg naloxone hydrochloride or a hydrate thereof;
1.3	between about 0.2 mg and about 1.2 mg of an isotonicity agent;
1.4	between about 0.005 mg and about 0.015 mg of a preservative;
1.5	about 0.2 mg of a stabilizing agent;
1.6	an amount of an acid sufficient to achieve a pH of 3.5-5.5.

C. Dependent claims 2–29 of the '253 patent

94. The remaining claims of the '253 patent, which depend either directly or indirectly from claim 1, are reproduced below:

> 2. The device as recited in claim 1 wherein: the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid.

[11] The patent recites "a pH ***or*** 3.5-5.5." (emphasis added). Petitioner believes this is a typographical error and reads the claim as reciting "a pH of 3.5-5.5."

3. The device of claim 2, wherein the aqueous solution comprises: about 4.4 mg naloxone hydrochloride dihydrate; about 0.74 mg NaCl; about 0.01 mg benzalkonium chloride; about 0.2 mg disodium edetate; and an amount of hydrochloric acid sufficient to achieve a pH of[12] 3.5-5.5.

4. The device of claim 2, wherein said device is actuatable with one hand.

5. The device of claim 4, wherein the volume of said reservoir is not more than about 140 μL.

6. The device of claim 5, wherein about 100 μL of said aqueous solution in said reservoir is delivered to said patient in one actuation.

7. The device of claim 6, wherein the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate.

8. The device of claim 7, wherein the 90% confidence interval for dose delivered per actuation is ±about 2%.

9. The device of claim 7, wherein the 95% confidence interval for dose delivered per actuation is ±about 2.5%.

10. The device of claim 7, wherein the delivery time is less than about 25 seconds.

11. The device of claim 7, wherein the delivery time is less than about 20 seconds.

12. The device of claim 7, wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.

13. The device of claim 12, wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of

[12] *See supra* n.11.

said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.

14. The device of claim 13, wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.

15. The device of claim 7, wherein the plasma concentration versus time curve of said naloxone hydrochloride in said patient has a T_{max} of between about 20 and about 30 minutes.

16. The device of claim 1, wherein said patient is an opioid overdose patient or a suspected opioid overdose patient.

17. The device of claim 16, wherein the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia, sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting.

18. The device of claim 17, wherein the patient exhibits respiratory depression.

19. The device of claim 18, wherein said respiratory depression is caused by the illicit use of opioids, or by an accidental misuse of opioids during medical opioid therapy.

20. The device of claim 19, wherein said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist.

21. The device of claim 20, wherein said patient is free from respiratory depression for at least about 2 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist.

22. The device of claim 21, wherein said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist.

23. The device of claim 22, wherein said patient is free from respiratory depression for at least about 6 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist.

24. The device of claim 16, wherein said patient is in a lying, supine, or recovery position.

25. The device of claim 7, wherein said single actuation yields a plasma concentration of ≥0.2 ng/mL within 2.5 minutes in said patient.

26. The device of claim 7, wherein said single actuation yields a plasma concentration of ≥1 ng/mL within 5 minutes in said patient.

27. The device of claim 7, wherein said single actuation yields a plasma concentration of ≥3 ng/mL within 10 minutes in said patient.

28. The device of claim 3, wherein said single actuation yields a plasma concentration of ≥0.2 ng/mL within 2.5 minutes in said patient.

29. The device of claim 3, wherein said single actuation yields a plasma concentration of ≥1 ng/mL within 5 minutes in said patient.

D. The ’253 patent lacks priority to U.S. Provisional Application No. 61/953,379.

95. The ’253 patent, on its face, claims priority to U.S. Provisional Application No. 61/953,379 (“the ’379 provisional”), which was filed on March 14, 2014. Nalox1001, Cover.

96. I have reviewed the ’379 provisional. It is my opinion that the ’379 provisional does not provide adequate written description support for the claims of

the ’253 patent, and thus that the earliest filing date to which the ’253 patent can claim priority is March 16, 2015.

97. The ’253 patent’s one independent claim recites delivery of a spray that contains the following ingredients in the following amounts:

> 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 of 3.5-5.5.

Nalox1001, claim 1.

98. The ’379 provisional does not disclose these limitations implicitly or explicitly. Rather, the ’379 provisional only provides general disclosure regarding the composition of the naloxone hydrochloride nasal spray, without reciting specific combinations of excipients or disclosing the quantities or concentrations in which those excipients are to be included. *See, e.g.*, ’379 provisional (Nalox1058) at [083]–[088]. Furthermore, the only specific reference to a pharmaceutical formulation of naloxone hydrochloride containing benzalkonium chloride is in paragraph 121 of the ’379 provisional, which is reproduced below:

> Pharmaceutical compositions comprising naloxone hydrochloride (10 mg/mL) were stored at 25 °C and 60% relative humidity in upright clear glass vials (200 µL) stoppered with a black plunger. Vials were either nude (Batch 1), or mounted in the Pfeiffer BiDose device (Batch 2). In addition to naloxone hydrochloride, the pharmaceutical

> compositions further comprised water, benzalkonium chloride, and disodium edetate.

99. *Id.*, ¶ 121. This does not disclose or otherwise suggest using any particular quantity of benzalkonium chloride in a formulation containing the recited quantity of naloxone, or that the formulation contains benzalkonium chloride, naloxone, and an isotonicity agentI understand from counsel that a description that merely renders the invention obvious does not satisfy the written description requirement. Thus, because the '379 provisional does not provide any description from which a Formulator POSA could conclude that the applicants had possession of the claimed subject matter at the time of filing of the '379 provisional, I conclude that no claim of the '253 patent can claim priority to the filing date of the '379 provisional.

100. Based on the above, I find that the priority date of the '253 patent is no earlier than March 16, 2015, which is the filing date of the application from which the '253 patent issued.

E. Orange Book listing of the '253 patent

101. From my professional activities, I am familiar with the United States Food and Drug Administration's compilation of Approved Drug Products With Therapeutic Equivalence Evaluations, otherwise known as the "Orange Book." I am also familiar with the Orange Book as a source of listings of patents that are associated with a particular drug product. I have used, in the past, the Orange

Book's patent listings to identify patent information regarding particular drug products.

102. The '253 patent is listed in the United States Food and Drug Administration's electronic publication known as the "Orange Book" in conjunction with the prescription intranasal drug product Narcan® Nasal Spray.

V. CLAIM CONSTRUCTION

103. I have discussed the legal standard for claim construction in paragraphs 29 and 30 above. Generally, I have given the claim terms their plain and ordinary meaning to a Formulator POSA in light of the specification and file history of the '253 patent, which I have reviewed. It is also my understanding that a dependent claim contains all the limitations of the claim from which it depends. The patentee has specifically defined certain terms in the specification of the '253 patent, and I have generally applied those definitions unless otherwise specified below.

104. I have been informed that certain claim terms were proposed to be construed in the case captioned *Adapt Pharma Operations Limited v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 2:16-cv-07721 (JLL)(JAD) (D.N.J.), which involves the '253 patent. I have been informed that none of the proposed constructions conflicts with my opinions below.

105. In addition, below, I note how I have construed particular claim terms.

1. "pre-primed"

106. The patentee has given the term "pre-primed" a definition in the specification, which I have applied in analyzing the claims. In particular, the '253 patent defines "pre-primed" as follows: "The term 'pre-primed,' as used herein, refers to a device, such as a nasal spray which is capable of delivering a pharmaceutical composition to a patient in need thereof with the first actuation of the spray pump, i.e., without the need to prime the pump prior to dosing, such as by actuating the pump one or more times until a spray appears." Nalox1001 at 11:60–65.

2. "delivery time"

107. The patentee has given the term "delivery time" a definition in the specification, which I have applied in analyzing the claims. In particular, the '253 patent defines "delivery time" as follows: "The term 'delivery time,' as used herein, refers to the amount of time that elapses between a determination made by a healthcare professional, or an untrained individual that an individual is in need of nasal delivery of an opioid antagonist and completion of the delivery." *Id.* at 8:52–56.

3. "90% confidence interval for dose delivered per actuation is ±about 2.0%," and "95% confidence interval for dose delivered per actuation is ±about 2.5%"

108. There is no explicit definition of these terms in the specification or the file history of the '253 patent. There is a definition of "confidence interval" as "a

range of values which will include the true average value of a parameter of a specified percentage of the time." *Id.* at 8:47–49. Applying this definition, in my opinion a Formulator POSA would interpret the terms "90% confidence interval for dose delivered per actuation is ±about 2.0%," and "95% confidence interval for dose delivered per actuation is ±about 2.5%" as ranges covering devices that had a 90% or 95% confidence interval for dose delivered per actuation within the claimed range, rather than exactly at the recited number, as greater consistency between dose delivered per actuation is desirable.

VI. PUBLIC ACCESSIBILITY OF THE PRIOR ART

109. I understand that something is only considered a printed publication if it has been disseminated or otherwise made available to the extent that persons interested in and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.

VII. BASIS OF MY ANALYSIS WITH RESPECT TO OBVIOUSNESS

A. A Formulator POSA reading Wyse in view of HPE would have had ample reason and know-how to arrive at the subject matter of claims 1–3 and 16–24.

110. In my opinion, claims 1–3 and 16–24 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

111. The claim charts and discussion below show where each and every limitation of claims 1–3 and 16–24 are disclosed in Wyse (Nalox1007) and HPE (Nalox1012).

112. It is my opinion that claims 1–3 and 16–24 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse (Nalox1007) in view of HPE (Nalox1012).

1. Claim 1

113. It is my opinion that claim 1 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

114. Claim 1 recites the following:

> 1. 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 of 3.5-5.5.

(a) Preamble: "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"

115. The preamble of claim 1 recites "[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."

116. Wyse discloses this element. Wyse discloses that "in one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products…." Wyse (Nalox1007) at 10:53–58. A Formulator POSA would have understood that this is a device adapted for nasal delivery of a pharmaceutical composition to a patient. Wyse further discloses that "[t]he disclosed nasal spray device…may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof," *id.* at 10:29–33, and suggests that the Aptar/Pfeiffer Unitdose device is an example of such a device containing those features. *Id*. at 10:45–48. The fact that the device is both single-use and ready-to-use indicates that it is pre-primed, as other nasal spray devices require priming prior to use in order to deliver the correct dosage amounts. *See* Djupesland (Nalox1010) at 48–49 ("Metered-dose spray pumps require priming

and some degree of overfill to maintain dose conformity for the labeled number of doses."). This indicates that the device is "pre-primed" as defined in the '253 patent. *See* section V.1 above.

117. Finally, the fact that it is "single-use" further indicates that it is both pre-primed and that it only provides one spray, as there are bi-dose devices that are also pre-primed. *See, e.g.*, *id.* at 48–49. In the case of the Aptar/Pfeiffer Unitdose device, the single spray has a volume of 100 µL. *See id*.

118. I, personally, have previously evaluated the Aptar/Pfeiffer Unitdose device, and it is my opinion that it is a single-use, pre-primed device adapted for the nasal delivery of a pharmaceutical composition to a patient by one actuation of said device in one nostril of said patient.

119. Wyse further discloses that the Aptar/Pfeiffer Unitdose delivery device "may comprise a container (glass vial)," which would constitute a single reservoir. Nalox1007 at 10:58–59; *see also id*. at 10:35–37 ("The device may comprise one or more unit dose containers, each container delivering about one 100 µL spray[.]"). Wyse thus discloses this element.

Claim 1	Wyse in view of HPE
"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"	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris." (10:29–35). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products." (10:53–57).

120. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(b) 1.1: "a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:"

121. Element 1.1 of claim 1 recites "a pharmaceutical composition which is an aqueous solution of about 100 µL."

122. Wyse discloses solutions containing naloxone hydrochloride or naloxone hydrochloride dihydrate for intranasal administration, which are useful in treating opioid overdose in a subject in need thereof. *See* Nalox1007 at 6:50–65

and 9:17–21. Wyse discloses that this composition may be placed in an Aptar/Pfeiffer Unitdose Delivery Device to deliver 100 µL of this intranasal solution per actuation to a patient's nostril. *See id.* at 10:53–56. Wyse further discloses that "the compositions are formulated with a suitable carrier to form a pharmaceutically acceptable nasal spray. In one aspect, the carrier may comprise water, saline, dextrose, or other suitable aqueous…carriers suitable for application to the nasal mucosa." *Id.* at 8:25–30. This element is thus disclosed in the prior art.

123. The below claim chart shows the relevant disclosures related to this element.

Claim 1	Wyse in view of HPE
"a pharmaceutical composition which is an aqueous solution of about 100 µL comprising"	**WYSE (Nalox1007)** "In one aspect, the disclosed compositions may comprise from about 5 mg/mL to about 50 mg/mL…of an opioid antagonist…. The opioid antagonist may be naloxone or a pharmaceutically acceptable salt thereof. In one aspect, the opioid antagonist may be naloxone, naloxone HCl, or naloxone HCL dihydrate. Unless otherwise specified, the term 'naloxone,' as used herein, refers to naloxone, naloxone HCl, naloxone HCl dihydrate, any pharmaceutically acceptable salt of naloxone, or combinations thereof." (6:50–65). "The compositions are formulated with a suitable carrier to form a pharmaceutically acceptable nasal spray. In one aspect, the carrier may comprise water, saline, dextrose, or other suitable aqueous or non-aqueous carriers suitable for application to the nasal mucosa. In one aspect, the nasal spray is formed with an aqueous carrier, such as water or saline. Other suitable carriers will be readily understood by one of ordinary skill in the art." (8:25–32).

Claim 1	Wyse in view of HPE
	"In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products…." (10:53–57).

124. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(c) 1.2: "about 4 mg naloxone hydrochloride or a hydrate thereof;"

125. Element 1.2 of claim 1 recites that the pharmaceutical composition comprises "about 4 mg naloxone hydrochloride or a hydrate thereof."

126. Wyse discloses this element. Wyse discloses solutions for intranasal administration containing between 5 mg/mL and 50 mg/mL of an opioid antagonist. Nalox1007 at 6:50–65, 9:17–21. The opioid antagonist may be naloxone hydrochloride or naloxone hydrochloride dihydrate. *Id.* at 6:60–61. Wyse discloses that this composition may be placed in an Aptar/Pfeiffer Unitdose

delivery device to deliver 100 µL of this intranasal solution per actuation to a patient's nostril. *See id*. at 10:53–56. Given that volume, Wyse discloses an amount of about 0.5 mg to 5 mg naloxone hydrochloride or naloxone hydrochloride dihydrate in 100 µL of solution.

127. The below claim chart shows the relevant disclosures of Wyse related to this element.

Claim 1	Wyse in view of HPE
"about 4 mg naloxone hydrochloride or a hydrate thereof"	**WYSE (Nalox1007)** "In one aspect, the disclosed compositions may comprise from about 5 mg/mL to about 50 mg/mL…of an opioid antagonist…. The opioid antagonist may be naloxone or a pharmaceutically acceptable salt thereof. In one aspect, the opioid antagonist may be naloxone, naloxone HCl, or naloxone HCL dihydrate. Unless otherwise specified, the term 'naloxone,' as used herein, refers to naloxone, naloxone HCl, naloxone HCl dihydrate, any pharmaceutically acceptable salt of naloxone, or combinations thereof." (6:50–65). "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This

Claim 1	Wyse in view of HPE
	delivery system is used in other approved nasal spray drug products." (10:53–57).

128. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(d) 1.3: "between about 0.2 mg and about 1.2 mg of an isotonicity agent;"

129. Element 1.3 of claim 1 recites that the pharmaceutical composition comprises "between about 0.2 mg and about 1.2 mg of an isotonicity agent."

130. Wyse discloses this element. Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg using sodium chloride. Nalox1007 at 7:64–67. Further, Example 5 of Wyse discloses a naloxone formulation containing 6.4 mg/mL of sodium chloride, which is approximately 0.64 mg per a 100 µL solution. *See id.,* Table 13.

131. The below claim chart shows the relevant disclosures of Wyse related to this element.

Claim 1	Wyse in view of HPE
"between about 0.2 mg and about 1.2 mg of an isotonicity agent"	**WYSE (Nalox1007)** "In one aspect, the composition may comprise sodium chloride in an amount sufficient to adjust the osmolality of the compositions from about 300 to about 500, or from about 350 to about 450, or about 400." (7:64–67). Table 13 discloses use of a concentration of 6.4 mg/mL sodium chloride in various naloxone formulations. (*See* 26:23–27:17).

132. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(e) 1.4: "between about 0.005 mg and about 0.015 mg of a preservative;"

133. Element 1.4 of claim 1 recites that the pharmaceutical composition comprises "between about 0.005 mg and about 0.015 mg of a preservative."

134. It would have been obvious to a Formulator POSA to include between about 0.005 to 0.015 mg of a preservative in such a formulation from the disclosure of Wyse. Wyse discloses using an antimicrobial agent—i.e., a preservative—in an amount of 0.1% to 2% by weight of the formulation. Nalox1007 at 7:20–28. While Wyse generally discloses that the formulation may include an "antimicrobial agent," Wyse does not specifically identify the range of antimicrobial agents that may be used, which would have motivated a Formulator POSA to consult compendiums of pharmaceutical excipients, such as HPE, to determine what other antimicrobial agents he or she should consider in developing a nasal formulation of naloxone.

135. A Formulator POSA, in reviewing HPE, would also have known that antimicrobial agents have differing potencies, and thus may be included in aqueous compositions in different concentrations. For instance, Wyse discloses that "the composition may comprise…from about 0.1 weight % to about 2 weight %, or about 0.2 weight % to about 1.0 weight %, or about 0.5 weight % of an

antimicrobial agent," which can be benzyl alcohol. *See* Nalox1007 at 7:21–28. Benzyl alcohol is only moderately active against Gram-positive organisms and less active against Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *E. coli* species, (HPE (Nalox1012) at 64), which generally are included in antimicrobial challenge tests for parenteral drug products. *See* USP (Nalox1054) at 55. For this reason, benzyl alcohol is usually used at concentrations such as 5 mg/mL (0.5 % w/v) (HPE (Nalox1012) at 64), as used in the formulations disclosed in Wyse. *See, e.g.*, Nalox1007, Table 1. Other preservatives, such as methylparaben or propylparaben, have increased activity compared to benzyl alcohol against some microorganisms, and can be used at lower concentrations of 0.033% w/v (methylparaben) and 0.017% w/v (propylparaben) in nasal solutions. *See* HPE (Nalox1012) at 442 (methylparaben), 596 (propylparaben).

136. Other preservatives, such as benzethonium chloride and benzalkonium chloride, have increased activity against key microorganisms compared to methylparaben, propylparaben, and benzyl alcohol. Notably, the minimum inhibitory concentrations (MIC) of benzalkonium chloride and benzethonium chloride tend to be lower against a broad range of bacteria and fungi than those of methylparaben, propylparaben, or benzyl alcohol. *Compare* HPE (Nalox1012) at 57 (benzalkonium chloride) and 59 (benzethonium chloride) *with* 64 (benzyl alcohol), 442 (methylparaben), and 597 (propylparaben). For this reason,

benzethonium chloride is typically used at concentrations of 0.01%–0.02% w/v in ophthalmic, otic, and injectable formulations, and benzalkonium chloride is typically used at concentrations of 0.002%–0.02% w/v in nasal formulations.[13] *See* HPE (Nalox1012) at 56–60. More notably, benzalkonium chloride is noted to have minimum inhibitory concentrations in the range of 1-30 μg/mL against *Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus aureus*, indicating it is effective against each of these microorganisms, which are all listed in the antimicrobial effectiveness testing protocol set forth in the United States Pharmacopoeia. *See* USP (Nalox1054) at 55. Therefore, a Formulator POSA would have been motivated to choose benzalkonium chloride as a preservative for an intranasal formulation, and would have been motivated to include it in an amount between about 0.005 mg and about 0.015 mg per 100 μL of solution, with a reasonable expectation of success.

137. While Wyse discloses using quantities of preservative between 0.1% w/v and 2% w/v, a Formulator POSA would have recognized from the disclosure of HPE that this was based on the specific choice of preservative—i.e., benzyl alcohol—and that different preservatives commonly used in nasal sprays will function at lower concentrations—particularly benzalkonium chloride—of between

[13] These quantities would equate to 0.01 – 0.02 mg benzethonium chloride per 100 μL of solution, or between 0.002 – 0.02 mg benzalkonium chloride per 100 μL of solution.

0.002% w/v and 0.02% w/v (i.e., 0.002 mg/100 µL to 0.02 mg/100 µL).[14] The prior art thus discloses this element.

138. The below claim chart shows the relevant disclosures of Wyse and HPE related to this element.

Claim 1	Wyse in view of HPE
"between about 0.005 mg and about 0.015 mg of a preservative"	**WYSE (Nalox1007)** "In certain aspect, the composition may further comprise from about 0.1 weight % to about 2 weight %, or about 0.2 weight % to about 1.0 weight %, or about 0.5 weight % of an antimicrobial agent. The antimicrobial agent may comprise an alcohol antimicrobial agent. In one aspect, the antimicrobial agent may comprise benzyl alcohol. Other suitable antimicrobial agents may be readily understood by one of ordinary skill in the art." (7:21–28). **HPE (Nalox1012)** "Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative…. In nasal, and otic formulations a concentration of 0.002–0.02% w/v is used…Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products." (56).

[14] Further, other prior art disclosed naloxone nasal sprays containing benzalkonium chloride at or around these concentrations. For instance, Davies discloses a naloxone nasal spray containing 0.025% w/v benzalkonium chloride. *See* Davies (Nalox1009) at 3:27–4:5.

Claim 1	Wyse in view of HPE

Table II: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

(57).

"Benzethonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative. Typically, it is used for this purpose in injections, ophthalmic and otic preparations at concentrations 0.01–0.02% w/v." 59.

Table II: Minimum inhibitory concentration (MIC) for benzethonium chloride.

Microorganism	MIC (μg/mL)
Aspergillus niger	128
Candida albicans	64
Escherichia coli	32
Penicillium notatum	64
Proteus vulgaris	64
Pseudomonas aeruginosa	250
Pseudomonas cepacia	250
Pseudomonas fluorescens	250
Staphylococcus aureus	0.5
Streptococcus pyogenes	0.5

(*Id.*).

"Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations, including oral and parenteral preparations, at concentrations up to 2.0% v/v. The typical concentration used is 1% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use

Claim 1	Wyse in view of HPE
	has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006." (64).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.[43]

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

(*Id.*).

Table I: Uses of methylparaben.

Use	Concentration (%)
IM, IV, SC injections[a]	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18

[a] See Section 14.

(442).

Claim 1	Wyse in view of HPE

Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[4]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. mycoides ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

(*Id.*).

Table I: Uses of propylparaben in pharmaceutical preparations.

Use	Concentration (%)
IM, IV, SC injections	0.005–0.2
Inhalation solutions	0.015
Intradermal injections	0.02–0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005–0.01
Oral solutions and suspensions	0.01–0.02
Rectal preparations	0.02–0.01
Topical preparations	0.01–0.6
Vaginal preparations	0.02–0.1

(596).

Claim 1	Wyse in view of HPE
	Table III: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.[2] **Microorganism** / **MIC (µg/mL)** *Aerobacter aerogenes* ATCC 8308 — 1000 *Aspergillus niger* ATCC 9642 — 500 *Aspergillus niger* ATCC 10254 — 200 *Bacillus cereus* var. *mycoides* ATCC 6462 — 125 *Bacillus subtilis* ATCC 6633 — 500 *Candida albicans* ATCC 10231 — 250 *Enterobacter cloacae* ATCC 23355 — 1000 *Escherichia coli* ATCC 8739 — 500 *Escherichia coli* ATCC 9637 — 100 *Klebsiella pneumoniae* ATCC 8308 — 500 *Penicillium chrysogenum* ATCC 9480 — 125 *Penicillium digitatum* ATCC 10030 — 63 *Proteus vulgaris* ATCC 13315 — 250 *Pseudomonas aeruginosa* ATCC 9027 — >1000 *Pseudomonas aeruginosa* ATCC 15442 — >1000 *Pseudomonas stutzeri* — 500 *Rhizopus nigricans* ATCC 6227A — 125 *Saccharomyces cerevisiae* ATCC 9763 — 125 *Salmonella typhosa* ATCC 6539 — 500 *Serratia marcescens* ATCC 8100 — 500 *Staphylococcus aureus* ATCC 6538P — 500 *Staphylococcus epidermidis* ATCC 12228 — 500 *Trichophyton mentagrophytes* — 65 (597).

139. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(f) 1.5: "about 0.2 mg of a stabilizing agent;"

140. Element 1.5 of claim 1 recites that the pharmaceutical composition comprises "about 0.2 mg of a stabilizing agent."

141. Wyse discloses this element. Wyse discloses including in the pharmaceutical composition "from about 2 mM to about 20 mM, or from about 5 mM to about 15 mM, or from about 8 mM to about 12 mM, or about 10 mM disodium ethylene diamine tetraacetic acid (EDTA)." Nalox1007 at 7:17–20. Disodium ethylene diamine tetraacetic acid is disodium edetate, which is defined

as a stabilizing agent in the '253 patent. *See, e.g.*, Nalox1001 at 21:30. For a 100 µL spray volume as disclosed by Wyse, this would equate to between about 0.07 mg to 0.67 mg of anhydrous disodium edetate, with narrower ranges corresponding to between about 0.17 and about 0.50 mg, about 0.27 mg and about 0.40 mg, and about 0.34 mg.[15] "About 0.2 mg" of a disodium edetate would fall within "from about 2 mM to about 20 mM, or from about 5 mM to about 15 mM," and is reasonably close to the other ranges. Further, there is no evidence, in the '253 specification or otherwise, that the claimed range of "about 0.2 mg" is critical to the performance of the claimed formulation.

142. The below claim chart shows the relevant disclosures of Wyse related to this element.

Claim 1	Wyse in view of HPE
"about 0.2 mg of a stabilizing agent"	**WYSE (Nalox1007)** "In one aspect, the composition may comprise from about 2 mM to about 20 mM, or from about 5 mM to about 15 mM, or from about 8 mM to about 12 mM, or about 10 mM disodium ethylene diamine tetraacetic acid (EDTA)." (7:17–20).

143. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

[15] Disodium edetate is also supplied in a dihydrate form, which has a molecular weight of 372.2 mg/mmol as compared to 336.2 mg/mmol for the anhydrous form. For the dihydrate, the corresponding ranges are 0.07 mg to 0.74 mg, 0.19 mg to 0.56 mg, 0.30 mg to 0.45 mg, and 0.37 mg, respectively.

(g) 1.6: "an amount of an acid sufficient to achieve a pH of 3.5-5.5."

144. Element 1.6 of claim 1 recites that the pharmaceutical composition comprises "an amount of an acid sufficient to achieve a pH of 3.5-5.5."

145. Wyse discloses this element. Wyse specifically discloses that "the compositions may further comprise…hydrochloric acid in an amount sufficient to adjust the pH to from about 3 to about 5.5, or from about 3.5 to about 5, or about 4±0.5." Nalox1007 at 8:1–4. Wyse further discloses compositions in which the pH is adjusted to about 4.25 using hydrochloric acid. *See id*. at 14:51–52. As such, Wyse discloses this element.

146. The below claim chart shows the relevant disclosures of Wyse related to this element.

Claim 1	Wyse in view of HPE
"an amount of an acid sufficient to achieve a pH of 3.5-5.5."	**WYSE (Nalox1007)** "The compositions may further comprise sodium hydroxide or hydrochloric acid in an amount sufficient to adjust the pH to from about 3 to about 5.5, or from about 3.5 to about 5, or about 4±0.5." (8:1–4). "Verify pH to 4.25 and adjust if necessary, with 1 N NaOH or 1 N HCl solutions…." (14:51–52).

147. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

2. Claim 2

148. It is my opinion that claim 2 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

149. Claim 2 depends from claim 1 and recites the limitations that "the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid." '253 patent (Nalox1001), claim 2. The disclosures of the prior art in regard to the limitations of claim 1 are discussed above in section VII.A.1.

(a) "the isotonicity agent is NaCl;"

150. As discussed above in section VII.A.1(d), Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg using sodium chloride. Nalox1007 at 7:64–67. Further, Example 5 of Wyse discloses a naloxone formulation containing 6.4 mg/mL of sodium chloride, which is approximately 0.64 mg per a 100 µL solution. *See id.*, Table 13. Wyse thus discloses this element.

(b) "the preservative is benzalkonium chloride;"

151. Wyse discloses that the formulation can contain an antimicrobial agent—i.e., a preservative—in an amount of 0.1% to 2% by weight of the formulation. Nalox1007 at 21–28. While Wyse discloses that the preservative may be benzyl alcohol, "[o]ther suitable antimicrobial agents may be readily understood by one of ordinary skill in the art." Benzalkonium chloride would have been one such antimicrobial agent. *See* HPE (Nalox1012) at 56–57. It is my opinion that a

Formulator POSA would have recognized that Wyse did not teach away from using benzalkonium chloride in combination with naloxone, particularly in view of the combined disclosure of HPE and Wyse, for the reasons discussed above in section IV.A.3(e)(iv)2). Furthermore, a Formulator POSA would have been motivated to choose benzalkonium chloride as an antimicrobial preservative, with a reasonable expectation of success, for the reasons discussed above in sections IV.A.3(e)(iv)1) and VII.A.1(e).

152. For the foregoing reasons, the use of benzalkonium chloride in the claimed amounts would have been obvious. A Formulator POSA would have recognized that different preservatives are used at different concentrations; HPE discloses that benzalkonium chloride is usually used in nasal sprays at a concentration of 0.002–0.02% w/v. Nalox1012 at 56. The claimed weight range of 0.005 mg to 0.015 mg in 100 µL of solution falls squarely within this range.[16] Moreover, a Formulator POSA would have been able to immediately envision using a concentration of 0.01% w/v (i.e., 0.01 mg per 100 µL of solution) of benzalkonium chloride from the disclosure of HPE, as it discloses that such concentrations are frequently used in small-volume parenteral products. *See id.* It would have been obvious to incorporate benzalkonium chloride into a nasal spray naloxone formulation in an amount of 0.005 mg to about 0.15 mg in a 100 µL

[16] *See also* footnote 13, *supra.*

solution—particularly an amount of 0.01 mg—from the disclosure of Wyse in combination with HPE.

153. The below claim chart shows the relevant disclosures of Wyse and HPE related to this element.

Claim 2	Wyse in view of HPE
"the preservative is benzalkonium chloride"	**WYSE (Nalox1007)** "In certain aspect, the composition may further comprise from about 0.1 weight % to about 2 weight %, or about 0.2 weight % to about 1.0 weight %, or about 0.5 weight % of an antimicrobial agent. The antimicrobial agent may comprise an alcohol antimicrobial agent. In one aspect, the antimicrobial agent may comprise benzyl alcohol. Other suitable antimicrobial agents may be readily understood by one of ordinary skill in the art." (7:21–28). **HPE (Nalox1012)** "Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative…. In nasal, and otic formulations a concentration of 0.002–0.02% w/v is used…Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products." (56).

Claim 2	Wyse in view of HPE

Table II: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

(57).

"Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations, including oral and parenteral preparations, at concentrations up to 2.0% v/v. The typical concentration used is 1% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006." (64).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.[49]

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

(*Id.*).

154. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

(c) "the stabilizing agent is disodium edetate;"

155. As discussed above in section VII.A.1(f), Wyse discloses the use of disodium edetate within ranges overlapping the claimed amount. Wyse thus discloses this element.

(d) "and the acid is hydrochloric acid."

156. As discussed above in section VII.A.1(g), Wyse discloses using hydrochloric acid to adjust the pH of the solution to within the claimed range of 3.5 to 5.5. Wyse thus discloses this element.

3. Claim 3

157. It is my opinion that claim 3 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

158. Claim 3 depends from claim 2 and recites the limitations that "the aqueous solution comprises: about 4.4 mg naloxone hydrochloride dihydrate; about 0.74 mg NaCl; about 0.01 mg benzalkonium chloride; about 0.2 mg disodium edetate; and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5." '253 patent (Nalox1001), claim 3. The disclosures of the prior art in regard to the limitations of claim 2 are discussed above in section VII.A.2.

(a) "about 4.4 mg naloxone hydrochloride dihydrate;"

159. As discussed above in section VII.A.1(c), Wyse discloses solutions for intranasal administration containing between 5 mg/mL and 50 mg/mL of an opioid antagonist. Nalox1007 at 6:50–65, 9:17–21. The opioid antagonist may be

naloxone hydrochloride or naloxone hydrochloride dihydrate. *Id.* at 6:60–61. Wyse discloses that this composition may be placed in an Aptar/Pfeiffer Unitdose delivery device to deliver 100 µL of this intranasal solution per actuation to a patient's nostril. *See id*. at 10:53–56. Given that volume, Wyse discloses an amount of about 0.5 mg to 5 mg naloxone hydrochloride or naloxone hydrochloride dihydrate. This would encompass the claimed amount of about 4.4 mg naloxone hydrochloride dihydrate. Further, a Formulator POSA would have recognized that one would have to modify the dose of naloxone hydrochloride (anhydrous) on a weight basis to account for the presence of the two water molecules associated with the naloxone in the crystalline solid.[17] Moreover, a Formulator POSA would have expected the anhydrous and dihydrate forms of naloxone hydrochloride, once dissolved in aqueous medium, to behave identically.

(b) "about 0.74 mg NaCl;"

160. Wyse suggests this element. Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg using sodium chloride. Nalox1007 at 7:64–67. Further, Example 5 of Wyse discloses a naloxone formulation

[17] Naloxone hydrochloride dihydrate has a molecular weight of 399.9 g/mol, and water has an approximate molecular weight of 18.02. The molecular weight of the anhydrous naloxone hydrochloride would therefore be about 363.8 g/mol, indicating that a Formulator POSA would need to include about 1.1 times as much of the dihydrate as the anhydrous naloxone hydrochloride to achieve an identical quantity of naloxone.

containing 6.4 mg/mL of sodium chloride, which is approximately 0.64 mg per a 100 µL solution. *See id.*, Table 13. As Wyse discloses adjusting the tonicity of the solution to between 300 and 500 mOsm/kg, or more particularly to "within 365–425 mOsm," (*id.* at 14:55–56)), it would have been obvious to arrive at the quantity of sodium chloride through routine optimization of a result-effective variable, particularly because a Formulator POSA would have known that the function of adding sodium chloride to the solution was to adjust the tonicity, which would take into account the total quantity of solute particles in the solution (including from other ingredients).

161. The Merck Index discloses, for the purpose of calculating approximate solution tonicity, sodium chloride equivalents for each of naloxone hydrochloride, disodium edetate, and benzalkonium chloride. Nalox1039. Specifically, the Merck Index discloses that 1 mg disodium edetate in sufficient water to make up a 0.5% (w/v) solution contributes a tonicity equivalent to 0.24 mg sodium chloride in the same volume of solution, and that 1 mg naloxone hydrochloride in sufficient water to make up a 3 or 5% solution contributes a tonicity equivalent to 0.13 mg sodium chloride. *Id*. (One would have expected the contribution of hydrochloric acid and benzalkonium chloride to be negligible based on their relatively low concentrations).

162. Based on these values, a Formulator POSA would have been able to approximate the tonicity of a 4% (w/v) naloxone hydrochloride solution including 0.2% (w/v) disodium edetate and 0.01% (w/v) benzalkonium chloride for the purposes of determining how much sodium chloride to add to achieve the tonicity values disclosed in Wyse. A Formulator POSA would have expected a 4% (w/v) (or 4 mg/100 µL) naloxone hydrochloride solution including 0.2% (w/v) (or 0.2 mg/100 µL) disodium edetate and 0.01% (w/v) benzalkonium chloride (0.01 mg / 100 µL) adjusted to a pH of between 3.5 and 5.5 using hydrochloric acid to be approximately osmotically equivalent to a 0.57% (w/v) NaCl solution (i.e., (4 mg naloxone hydrochloride * 0.13 NaCl equivalents + 0.2 mg disodium edetate * 0.24 NaCl equivalents)/ 100 µL H_2O), or the equivalent of 570 µg of NaCl per 100 µL of water.

163. From there, a Formulator POSA would have approximated the quantity of sodium chloride required to reach the tonicity values disclosed in Wyse. A 0.9% (w/v) sodium chloride solution has a tonicity of approximately 300 mOsm/kg , and a 300 to 500 mOsm/kg solution would have between about 900 and about 1500 µg of sodium chloride per 100 µL of water. Thus, to adjust the tonicity of a solution already having a tonicity equivalent to a solution of 570 µg NaCl in 100 µL water, a Formulator POSA would have expected to add approximately

between 300 and 900 µg NaCl per 100 µL of water to adjust the tonicity to between 300 mOsm/kg and 500 mOsm/kg.

164. Likewise, a sodium chloride solution with a tonicity of between 365 mOsm/kg and 425 mOsm/kg would have between about 1100 µg and 1300 µg of NaCl per 100 µL water, meaning that a Formulator POSA would have expected to have to add about 500 to about 700 µg of sodium chloride per 100 µL of aqueous solution to adjust the tonicity between these targets.

165. Of course, there is some degree of approximation in these calculations. Alternately, a Formulator POSA would have optimized within this range by measuring the tonicity of the naloxone hydrochloride/disodium edetate/benzalkonium chloride solution and determining the appropriate amount of sodium chloride to add from that measurement in order to achieve the desired tonicity.

166. As such, a Formulator POSA would have known how to add a quantity of sodium chloride sufficient to achieve an osmolality within the range disclosed in Wyse, in light of the concentrations of other components he or she chose to include in the formulation.

167. The below claim chart shows the relevant disclosures of Wyse related to this element.

Claim 3	Wyse in view of HPE
"about 0.74 mg NaCl"	**WYSE (Nalox1007)** "In one aspect, the composition may comprise sodium chloride in an amount sufficient to adjust the osmolality of the compositions from about 300 to about 500, or from about 350 to about 450, or about 400." (7:64–67). Table 13 discloses use of a concentration of 6.4 mg/mL sodium chloride in various naloxone formulations. (26:23–27:17).

168. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

(c) "about 0.01 mg benzalkonium chloride;"

169. As discussed above in section VII.A.2(b), the disclosures of Wyse in view of HPE would have made it obvious to include 0.01 mg benzalkonium chloride in the pharmaceutical composition.

(d) "about 0.2 mg disodium edetate;"

170. As discussed above in sections VII.A.2(c), the disclosures of Wyse in view of HPE would have made it obvious to include 0.2 mg disodium edetate in the pharmaceutical composition.

(e) "and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5."

171. As discussed above in section VII.A.2(d), the disclosures of Wyse in view of HPE would have made it obvious to include an amount of hydrochloric acid sufficient to achieve a pH of 3.5 to 5.5 in the pharmaceutical composition.

4. Claim 16

172. It is my opinion that claim 16 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

173. Claim 16 depends from claim 1 and recites the limitation that "wherein said patient is an opioid overdose patient or a suspected opioid overdose patient." '253 patent (Nalox1001), claim 16. The disclosures of the prior art in regard to the limitations of claim 1 are discussed above in section VII.A.1.

174. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21.

175. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 16	Wyse in view of HPE
"wherein said patient is an opioid overdose patient or a suspected opioid overdose patient."	**WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intransally via the nasal membranes to the subject."

Claim 16	Wyse in view of HPE
	(9:17–21).

176. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

5. Claim 17

177. It is my opinion that claim 17 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

178. Claim 17 depends from claim 16 and recites the limitation that "the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia, sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting." '253 patent (Nalox1001), claim 17. The disclosures of the prior art in regard to the limitations of claim 16 are discussed above in section VII.A.4.

179. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses that, "[i]n one aspect, the known or suspected

opioid overdose is manifested by respiratory and/or central nervous system depression." *Id.* at 9:33–35.

180. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 17	Wyse in view of HPE
"wherein the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia; sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting."	**WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression." (9:33–35). "In one aspect, the known or suspected opioid overdose may be manifested by respiratory and/or central nervous system depression." (10:1–3).

181. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

6. Claim 18

182. It is my opinion that claim 18 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

183. Claim 18 depends from claim 17 and recites the limitation that "the patient exhibits respiratory depression." '253 patent (Nalox1001), claim 18.

184. The disclosures of the prior art in regard to the limitations of claim 17 are discussed above in section VII.A.5. As discussed in that section, Wyse discloses administering the compositions to patients experiencing opioid overdose, which may be manifested by respiratory depression.

185. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

7. Claim 19

186. It is my opinion that claim 19 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

187. Claim 19 depends from claim 18 and recites the limitation that "said respiratory depression is caused by the illicit use of opioids, or by an accidental misuse of opioids during medical opioid therapy." '253 patent (Nalox1001), claim 19. The disclosures of the prior art in regard to the limitations of claim 18 are discussed above in section VII.A.6.

188. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses that, "of the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose." *Id.* at 1:41–44. A Formulator POSA would have understood that naloxone could be used to reverse the effects of opioid overdose resulting from both abuse of prescription opioid analgesics and heroin, as well as the accidental misuse of prescription opioid analgesics.

189. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 19	Wyse in view of HPE
"wherein said respiratory depression is caused by the illicit use of opioids or by an accidental misuse of opioids during medical opioid therapy"	**WYSE (Nalox1007)** "In 2008, poisoning surpassed motor vehicle accidents as the leading cause of 'injury deaths' in the United States (Warner 2011). Nearly 90% of poisoning deaths are caused by drugs. During the past 3 decades, the number of drug poisoning deaths increased six-fold from about 6,100 in 1980 to 36,500 in 2008. Of the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose (Warner 2011)." (1:36–44). "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition

Claim 19	Wyse in view of HPE
	as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression." (9:33–35). "In one aspect, the known or suspected opioid overdose may be manifested by respiratory and/or central nervous system depression." (10:1–3).

190. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

8. Claims 20–23

191. It is my opinion that claims 20–23 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

192. Claim 20 depends from claim 19 and recites the limitation that "said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." '253 patent (Nalox1001), claim 20. Claim 21 depends from claim 20 and recites the limitation that "said patient is free from respiratory depression for at least about 2 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid

antagonist." *Id.*, claim 21. Claim 22 depends from claim 21 and recites the limitation that "said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id*., claim 22. Claim 23 depends from claim 22 and recites that "said patient is free from respiratory depression for at least about 6 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 23.

193. The disclosures of the prior art in regard to the limitations of claim 19 are discussed above in section VII.A.7.

194. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses that "the phrase 'treating an opioid overdose' includes 'reversing the effects of an opioid overdose." *Id.* at 9:35–37. Reversal of an opioid overdose would include ensuring that the patient was free of respiratory depression for an indefinite period after the opioid overdose—that is, administration of naloxone would reverse the effects of the overdose such that they do not recur and the patient resumes normal breathing activity.

195. Wyse further discloses a method for reversing the effects of opioid overdose by administering 200 µL of a 10 mg/mL naloxone solution divided into two half-doses (i.e., two 100 µL doses of 1 mg each, for a total dose of 2 mg), where each half-dose is administered intranasally. Nalox1007 at 10:13–24.

196. A Formulator POSA would have had a reasonable expectation of success that such intranasal administration of naloxone would reverse opioid overdose. Wermeling 2013 (Nalox1016) indicates that, when naloxone is administered according to standard practice, only 15–20% of cases require a repeat dose of naloxone due to overt toxicity such as central nervous system and respiratory depression recurring, which indicates that approximately 80–85% of opioid overdose patients have respiratory depression reversed without a second dose of naloxone. *See* Nalox1016 at 71. A Formulator POSA further would have expected that intranasal doses higher than the 2 mg dose discussed in paragraph 195 above would have been equally, if not more, likely to reverse the effects of opioid overdose, including respiratory depression. As a result, this claim is obvious.

197. The below claim chart shows the relevant disclosures of each reference related to this element.

Claims 20–23	**Wyse in view of HPE**
"wherein said patient is free from respiratory depression for at least	**WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in

Claims 20–23	Wyse in view of HPE
about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." (claim 20) "wherein said patient is free from respiratory depression for at least about about 2 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." (claim 21) "wherein said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist" (claim 22) "wherein said patient is free from respiratory depression for at least about 6 hours following treatment comprising delivery of said therapeutically effective amount of said opioid antagonist"(claim 23)	need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression. The phrase 'treating an opioid overdose' includes 'reversing the effects of an opioid overdose'." (9:33–37). "In one aspect, a method for reversing the effects of an opioid overdose in an individual in need thereof is disclosed, which may comprise the step of administering intranasally a dose of a naloxone composition, wherein the naloxone composition may comprise about 10 mg/mL naloxone HCl dihydrate, about 25 mM citric acid, about 10 mM EDTA, and about 0.5% benzyl alcohol; wherein said dose comprises about 200 µL of said naloxone composition; and wherein said dose is divided into two half doses; wherein each said half dose comprises about 100 µL of said composition; and wherein each said half dose may be administered intranasally to a subject in need thereof." (10:13–24). *See also* **WERMELING 2013 (Nalox1016)** "Due to naloxone's high metabolic clearance and the fact that most opioids have a longer persistence in the blood stream, the symptoms of withdrawal dissipate, and in about 15–20 % of cases, administration of a repeat dose of naloxone may become necessary if overt toxicity such as central nervous system and respiratory depression recur." (71).

198. Accordingly, it is my opinion that the prior art suggests these limitations of these claims.

9. Claim 24

199. It is my opinion that claim 24 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of HPE.

200. Claim 24 depends from claim 16 and recites the limitation that "said patient is in a lying, supine, or recovery position." '253 patent (Nalox1001), claim 24. The disclosures of the prior art in regard to the limitations of claim 16 are discussed above in section VII.A.4.

201. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses a kit comprising a naloxone nasal spray composition with "instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) placing the individual on their back…" *Id.* at 12:12–17. Placing the individual on their back would put the individual in a lying position.

202. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 24	Wyse in view of HPE
"wherein said patient is in a lying, supine, or recovery position"	**WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the kit may comprise a device as disclosed herein, and may further comprise instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) ***placing the individual on their back;*** b) inserting a first sprayer into the individual's nostril; c) aiming the nozzle towards the side of the individual's nose and away from the center of the nose; d) pressing a plunger of the device firmly with the thumb of the administrator; e) repeating steps b through d with a second sprayer in the second nostril of the individual's nose;

Claim 24	Wyse in view of HPE
	f) monitoring the individual and the breaths of the individual, wherein if the individual does not improve or if signs of opioid overdose reappear 3-5 minutes after administering the composition, the administrator repeats the steps of b through e with a second device. The term 'does not improve' means wherein the individual does not exhibit increased breathing rates, for example, wherein an individual does not achieve 10 to 12 breaths per minute within about 3 to about 5 minutes after administration." (12:12–33) (emphasis added).

203. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

B. A Formulator POSA reading Wyse in view of Djupesland and HPE would have had ample reason and know-how to arrive at the subject matter of claims 4–7 and 10–14.

204. In my opinion, claims 4–7 and 10–14 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

205. The claim charts and discussion below show where each and every limitation of claims 4–7 and 10–14 are disclosed in Wyse (Nalox1007), Djupesland (Nalox1010), and HPE (Nalox1012).

206. It is my opinion that claims 4–7 and 10–14 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse (Nalox1007) in view Djupesland (Nalox1010) and HPE (Nalox1012).

1. Claim 4

207. It is my opinion that claim 4 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of Djupesland and HPE.

208. Claim 4 depends from claim 2 and recites the limitation that "said device is actuatable with one hand." '253 patent (Nalox1001), claim 4. The disclosure of Wyse and HPE with regard to the limitations of claim 2 are discussed above in section VII.A.2.

209. Wyse further discloses that intranasal naloxone compositions may be placed in an Aptar/Pfeiffer Unitdose delivery device to deliver 100 μL of this intranasal solution per actuation to a patient's nostril. Nalox1007 at 10:53–56. Wyse does not explicitly disclose that the Aptar/Pfeiffer Unitdose delivery device is actuatable with one hand; however, Djupesland does. Djupesland specifically states that "[t]he single- and duo-dose devices mentioned above…are held between the second and the third fingers with the thumb on the actuator." *See* Nalox1010 at 49. A Formulator POSA would have been motivated to combine these teachings because both Wyse and Djupesland refer to the same single-use nasal spray device, and Djupesland provides further direction and details on how to use the commercial Aptar single-use device that a Formulator POSA would look to in order to achieve predictable results.

210. The below claim chart shows the relevant disclosures of Wyse and Djupesland related to this element.

Claim 4	Wyse in view of Djupesland and HPE
"wherein said device is actuatable with one hand"	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers…." (10:29–36). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products in the U.S. (Imitrex nasal spray NDA #20-626). The direct product contact components of the container closure may comprise a container (glass vial)…." (10:53–59). **DJUPESLAND (Nalox1010)** "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. ***These devices are held between the second and the third fingers with the thumb on the actuator.*** A pressure point mechanism incorporated in some devices secures reproducibility of the actuation

Claim 4	Wyse in view of Djupesland and HPE
	force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49) (emphasis added).

211. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

2. Claim 5

212. It is my opinion that claim 5 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of Djupesland and HPE.

213. Claim 5 depends from claim 4 and recites the limitation that "the volume of said reservoir is not more than about 140 µL." '253 patent (Nalox1001), claim 5. The disclosures of the prior art in regard to the limitations of claim 4 are discussed above in section VII.B.1.

214. Wyse further discloses that intranasal naloxone compositions may be placed in an Aptar/Pfeiffer Unitdose delivery device to deliver 100 µL of this intranasal solution per actuation to a patient's nostril. Nalox1007 at 10:53–56.

Wyse further discloses that the Aptar/Pfeiffer Unitdose delivery device "may comprise a container (glass vial)," which would constitute a single reservoir. *Id.* at 10:58–59.

215. Djupesland further discloses that a volume of 125 µL is filled into Aptar/Pfeiffer single-dose devices to deliver a 100 µL spray volume. Nalox1010 at 49. Djupesland further discloses that single-use nasal spray devices, including the Aptar device, include a single reservoir. *See id*. A Formulator POSA would have been motivated to combine these teachings because both Wyse and Djupesland refer to the same single-use nasal spray device, and Djupesland provides further direction and details on how to use the commercial Aptar single-use device that a Formulator POSA would look to in order to achieve predictable results.

216. Further, a Formulator POSA would have recognized from the combined disclosures of Wyse and Djupesland that the volume of the reservoir could be as little as 125 µL to accommodate the necessary overfill to deliver a 100 µL volume of spray. Thus, a Formulator POSA would have recognized that the volume of the reservoir could be as small as 125 µL.

217. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 5	Wyse in view of Djupesland and HPE
"wherein the volume of said reservoir is not more than 140 µL."	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers…." (10:29–36). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products in the U.S. (Imitrex nasal spray NDA #20-626). The direct product contact components of the container closure may comprise a container (glass vial)…." (10:53–59). **DJUPESLAND (Nalox1010)** "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed

Claim 5	Wyse in view of Djupesland and HPE
	influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, ***a volume of 125 µl is filled in the device*** (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49) (emphasis added).

218. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

3. Claim 6

219. It is my opinion that claim 6 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of Djupesland and HPE.

220. Claim 6 depends from claim 5 and recites the limitation that "wherein about 100µL of said aqueous solution in said reservoir is delivered to said patient in one actuation." '253 patent (Nalox1001), claim 6. The disclosures of the prior art in regard to the limitations of claim 5 are discussed above in section VII.B.2.

221. As discussed above in section VII.A.1(a) (paragraphs 116-119), Wyse discloses this element. Wyse discloses that "in one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products…."

Nalox1007 at 10:53–58. A Formulator POSA would have understood that this is a device adapted for nasal delivery of a pharmaceutical composition to a patient. Wyse further discloses that "[t]he disclosed nasal spray device…may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof," *id.* at 10:29–33, and suggests that the Aptar/Pfeiffer Unitdose device is an example of such a device containing those features. *Id*. at 10:45–48. As the device is both "single use" and "delivers a volume of about 100 µL per spray," Wyse discloses this element and claim 6 would have been obvious to a Formulator POSA.

4. Claim 7

222. It is my opinion that claim 7 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of Djupesland and HPE.

223. Claim 7 depends from claim 6 and recites the limitation that "the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate." '253 patent (Nalox1001), claim 7. The disclosures of the prior art in regard to the limitations of claim 6 are discussed above in section VII.B.3.

224. Wyse discloses this element, as is discussed above in sections VII.A.3(a) and VII.A.1(c). Accordingly, claim 7 would have been obvious to a Formulator POSA.

5. Claims 10–11

225. It is my opinion that claims 10–11 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of Djupesland and HPE.

226. Claim 10 depends from claim 7 and recites the limitation that "the delivery time is less than about 25 seconds." '253 patent (Nalox1001), claim 10. Claim 11 depends from claim 7 and recites the limitation that "the delivery time is less than about 20 seconds." *Id.*, claim 11. The disclosures of the prior art in regard to the limitations of claim 7 are discussed above in section VII.B.4.

227. I have previously discussed the construction of the term "delivery time" in section V.2 above. The '253 patent defines "delivery time" as follows: "The term 'delivery time,' as used herein, refers to the amount of time that elapses between a determination made by a healthcare professional, or an untrained individual that an individual is in need of nasal delivery of an opioid antagonist and completion of the delivery." '253 patent (Nalox1001), 8:52–56. I have applied this definition in analyzing this claim element.

228. Wyse suggests this element. Wyse discloses that "there is a need for integrating compositions, methods, and devices that can allow for an effective reversal of opioid overdose, but which eliminates or minimizes the use of needles." Nalox1007 at 2:67–3:3. Further, Wyse discloses that there is a need for "effective

formulations and methods of providing such compositions to an individual…for reversing opioid overdose, that can be quickly and easily used[.]" *Id.* at 3:3–6. Wyse further discloses that the devices used for administering the compositions are "ready-to-use" and can be "assembled in the Unitdose delivery devices and packaged in 4" by 4" foil pouches, one device/pouch, heat-sealed and labeled as appropriate." *Id.* at 10:31–33, 11:4–6. Each of these factors indicates that Wyse was seeking to minimize the delivery time of naloxone to a patient to a matter of mere seconds, which comports with the most fundamental goal of the treatment: when a patient is not breathing due to an opioid overdose, every second counts in getting the patient the naloxone antidote and breathing again.

229. The below claim chart shows the relevant disclosures of each reference related to this element.

Claims 10–11	Wyse in view of HPE and Djupesland
"wherein the delivery time is less than about 25 seconds." (claim 10) "wherein the delivery time is less than about 20 seconds." (claim 11)	**WYSE (Nalox1007)** "[T]here is a need for integrating compositions, methods, and devices that can allow for an effective reversal of opioid overdose, but which eliminates or minimizes the use of needles. There is further a need for effective formulations and methods of providing such compositions to an individual, for rapid absorption into the nasal mucosa and for reversing opioid overdose, that can be quickly and easily used, but which minimize sudden and severe side effects of rapid reversal of opioid overdose." (2:67–3:8). "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or

Claims 10–11	Wyse in view of HPE and Djupesland
	more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof." (10:29–33). "Naloxone HCl dihydrate nasal spray, 10 mg/mL, 100 µL/spray, assembled into the Aptar/Pfeiffer Unitdose delivery device or in vials (not assembled into the delivery device) may be stored protected from light. Bulk vials and assembled Unitdose delivery device units of drug product may be stored in bulk sealed containers pending further processing. The disclosed compositions may be assembled in the Unitdose delivery devices and packaged in 4"x4" foil pouches, one device/pouch, heat-sealed and labeled as appropriate." (10:65–11:6).

230. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

6. Claims 12–14

231. It is my opinion that claim 12–14 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse in view of Djupesland and HPE.

232. Claim 12 depends from claim 7 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." '253 patent (Nalox1001), claim 12. Claim 13 depends from claim 12 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about

10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." *Id.*, claim 13. Claim 14 depends from claim 13 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." *Id.*, claim 14. The disclosures of the prior art in regard to the limitations of claim 7 are discussed above in section VII.B.4.

233. These limitations are met by Wyse's disclosure of administration of a single 100 µL spray to a naris of a patient. Specifically, Wyse discloses placing the naloxone compositions in a nasal spray device, which may be "configured to administer the disclosed compositions as a single spray per naris." Nalox1007 at 10:33–35. That "single spray" may have a volume of 100 µL. *See id*. at 10:35–39. Wyse specifically discloses using the Aptar/Pfeiffer Unitdose delivery device to deliver the disclosed compositions in a volume of about 100 µL per spray; this device is configured to deliver a single spray per naris. *See id*. at 10:53–56.

234. 100 µL of liquid spray will not drip out or drain when placed on the surface of the nasal cavity. Several references show that this volume is small enough to be retained in the nasal cavity: for instance, Wermeling 2013 (Nalox1016) discloses that "[t]he nasal cavity can retain 100–150µL without causing immediate runoff out the front of the nose or down the nasopharynx."

Nalox1016 at 65; *see also* Grassin-Delyle (Nalox1011) at 368 ("The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff."). Furthermore, other intranasal products frequently use shot volumes of 100 µL. *See, e.g.*, PDR 2003 (Nalox1044) at 1546; PDR 2010 (Nalox1045) at 772. Thus, Wyse discloses this limitation to a Formulator POSA.

235. The below claim chart shows the relevant disclosures of the prior art related to these elements.

Claims 12–14	Wyse in view of Djupesland and HPE
"wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally" (claim 12) "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally" (claim 13) "wherein upon nasal	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers, each container delivering about one 100 µL spray containing about 1 mg naloxone HCl dihydrate (a 10 mg/mL solution) or a 2 mg naloxone hydrochloride dihydrate in 100 µL." (10:29–39). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products…." (10:53–57). *See also* **WERMELING 2013 (Nalox1016)** "The dose must have sufficient solubility to be

Claims 12–14	Wyse in view of Djupesland and HPE
delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally" (claim 14)	administered in approximately 100–200 µL (one spray per naris) of solution. The nasal cavity can retain 100–150 µL without causing immediate runoff out the front of the nose or down the nasopharynx []." (65). *See also* **GRASSIN-DELYLE (Nalox1011)** "The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff. For insulin preparations of between 80 and 160 µL in volume, it has been shown that the entire administered dose is deposited in the nasal cavities, with no passage to the lungs (Newman et al., 1994). The unit volume administered is also important because it appears that the administration of a single volume of 100 µL leads to deposition over a greater surface area than that obtained with the administration of two 50 µL volumes (Newman et al., 1994; Kundoor & Dalby 2011)." (368).

236. Accordingly, it is my opinion that the prior art discloses these limitations of these claims.

C. A Formulator POSA reading Wyse in view of Djupesland, HPE, and the '291 patent would have had ample reason and know-how to arrive at the subject matter of claims 8–9.

237. In my opinion, claims 8–9 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

238. The claim charts and discussion below show where each and every limitation of claims 8–9 are disclosed in Wyse (Nalox1007), Djupesland (Nalox1010), HPE (Nalox1012), and the '291 patent (Nalox1015).

239. It is my opinion that claims 8–9 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wyse (Nalox1007) in view of Djupesland (Nalox1010), HPE (Nalox1012), and the ’291 patent (Nalox1015).

240. Claim 8 depends from claim 7 and recites the limitation that “the 90% confidence interval for dose delivered per actuation is ±about 2%.” ’253 patent (Nalox1001), claim 8. Claim 9 depends from claim 7 and recites the limitation that “the 95% confidence interval for dose delivered per actuation is ±about 2.5%.” *Id.*, claim 9.

241. The disclosure of Wyse, Djupesland and HPE with regard to the limitations of claim 7 are discussed above in section VII.B.4.

242. A person of ordinary skill in the art would have combined the disclosure of the ’291 patent disclosure with the disclosure of Wyse to arrive at the claimed device and formulation with a reasonable expectation of success. As discussed above, Wyse discloses placing a naloxone nasal spray into an “Aptar/Pfeiffer Unitdose” nasal sprayer. Wyse, however, does not explicitly disclose the 90% or 95% confidence intervals of the dose delivered per actuation from this device.

243. A Formulator POSA looking for information on the 90% or 95% confidence intervals of the dose delivered per actuation from the Aptar/Pfeiffer Unitdose device of an intranasal naloxone formulation would have looked to the

'291 patent. The '291 patent also discloses intranasal opioid compositions that can be delivered with a Pfeiffer Unitdose Second Generation Spray Device, which is a single-use, pre-primed device like the Aptar/Pfeiffer Unitdose device disclosed in Wyse. *See* Nalox1015 at 8:2–4, 8:30–9:19.

244. The '291 patent discloses a study to compare bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. *Id.* at 7:60–62. The formulation contained "10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0." *Id.* at 7:63–67. This composition was loaded into a Pfeiffer "Unitdose Second Generation" in quantities sufficient to deliver 0.1 mL (100 µL) of the butorphanol test formulation. *Id.* at 8:13–18. The applicators were weighed prior to and after delivery of one dose into a subject's nostril, with each patient receiving a total of two doses from two separate devices. The weight of the pair of devices before and after delivery was compared and the difference was calculated to determine the dose delivered. *See id*. at 8:20–27.

245. For the 23 sets of two Pfeiffer Unitdose spray devices weighed before and after actuation, it was found that the two sprayers together had delivered a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams, (*id.* at 8:39–47), and a 95% confidence interval of (0.203 g, 0.209

g). This corresponds to a 95% CI for the dose delivered over two sprays of about ±1.5% and a 90% CI for dose delivered over the two sprays of about ±0.9%. This indicates that, for the Pfeiffer Unitdose Spray device in combination with the formulation disclosed in the '291 patent, the 90% confidence interval for dose delivered is within ±about 2%, and that the 95% confidence interval for dose delivered is within ±about 2.5%. A Formulator POSA would have been motivated to achieve similar results through selection of an appropriate delivery device that reproducibly and consistently delivered the same dose upon each actuation, and the '291 patent evidences that such devices were available to a Formulator POSA prior to March 16, 2015. *See* paragraphs 87–88, *supra*.

246. A Formulator POSA would reasonably have expected the device to behave similarly when used in combination with other formulations (including those suggested and taught by Wyse), as the reliability and repeatability of dose delivery is a function of the device and the reproducibility of loading into the device. *See* '291 patent (Nalox1015) at 6:51–56 ("Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J.… These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition.").

247. The below claim chart shows the relevant disclosures of Wyse in view of Djupesland, HPE and the '291 patent related to this element.

Claims 8–9	Wyse in view of Djupseland, HPE and the '291 patent.
"wherein the 90% confidence interval for dose delivered per actuation is ±about 2%" (claim 8) "wherein the 95% confidence interval for dose delivered per actuation is ±about 2.5%" (claim 9)	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers…." (10:29–36). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products in the U.S. (Imitrex nasal spray NDA #20-626). The direct product contact components of the container closure may comprise a container (glass vial)…." (10:53–59). **'291 PATENT (Nalox1015)** "In accordance with one embodiment of the present invention, it has now been surprisingly found that intranasal pharmaceutical compositions can be made having improved bioavailability in terms of plasma opioid levels….

Claims 8–9	Wyse in view of Djupseland, HPE and the '291 patent.
	Opioids as herein include any substance naturally or synthetically derived from opium. Suitable opioids for use in the present invention include, but are not limited to, morphine, apomorphine, hydromorphone, oxymorphone, dihydromorphine, levorphanol, levallorphan, levophenacylmorphan, norlevorphanol, nalorphine, nalbuphine, buprenorphine, butorphanol, naloxone, naltrexone, nalmexone, oxilorphan, cyclorphan, ketobemidone, fentanyl, sufentanil, alfentanyl, or combinations thereof." (3:51–4:6) "Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J. and Valois of America, Inc. of Greenwich, Conn. These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition. These devices are easily operable by the patient, leave virtually no opioid remaining in the device after use and can thereafter be discarded without concern that others may abuse the opioid or other controlled substance." (6:51–60). "This example compares bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. The formulation contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0…. The second delivery system employed to administer the butorphanol compositions was a unit-dose disposable intranasal applicator that is commercially available from Pfeiffer of America under the designation 'Unitdose Second Generation.' Each of the Pfeiffer spray applicators was charged with sufficient

Claims 8–9	Wyse in view of Djupseland, HPE and the '291 patent.
	liquid to deliver a 0.1 mL dose of the butorphanol test formulation. The glass containers were filled using a pipette under clean conditions, sealed and assembled to the applicator. Each of the applicators was weighed prior to use and after use. Qualified medical personnel administered, one dose into each nostril, after which the applicator was recovered for weighing. In the case of the unit-dose applicators (test formulation), two devices were used for each patient, both of which were discarded following the post-use weighing. The results of these studies of the method and system of the invention and the comparative prior art method follow…. Unit-Dose: The statistical comparison of dose 1 and dose 2 for the test formulation unit dose delivery system was done using a paired t-test. Analysis of the data indicated that the difference between the mean, sprays of the two applications using the Pfeiffer device was not statistically significant (t=1.0; p=0.3). The sample of 23 sprayers (actually 23 sets of 2 sprayers, since they were single-dose) had a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams. … A t-test was used in each case to compare the observed sample mean to the desired weight of 0.2 grams. The unit-dose sprayer dispensed a mean total weight that was significantly higher than the goal of 0.2 grams (t=4.4; p<0.001). A 95% confidence interval for the mean total weight dispensed by the unit-dose sprayer is (0.203, 0.209)." (7:60–9:11)

248. Accordingly, it is my opinion that the prior art discloses these limitations of these claims.

D. A Formulator POSA reading Wang in view of Djupesland, HPE, Bahal, and Kushwaha would have had ample reason and know-how to arrive at the subject matter of claims 1–7, 12–14, and 16.

249. In my opinion, claims 1–7, 12–14, and 16 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

250. The claim charts and discussion below show where each and every limitation of claims 1–7, 12–14, and 16 are disclosed in Wang (Nalox1008), Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), and Kushwaha (Nalox1013).

251. It is my opinion that claims 1–7, 12–14, and 16 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang (Nalox1008) in view of Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), and Kushwaha (Nalox1013).

1. Claim 1

252. It is my opinion that claim 1 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

253. Claim 1 recites the following:

> 1. 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 of 3.5-5.5.

'253 patent (Nalox1001), claim 1.

(a) Preamble: "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"

254. The preamble of claim 1 recites "[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."

255. Wang discloses that the nasal spray disclosed therein is "used in a single-dose or multi-dose form, and the administration amount of the nasal spray is [between] 20–200 μL each time." Nalox1008 at 8:13–14.

256. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the

device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device (*id.* at 49), which would have been considered a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient via a single actuation. These devices comprise "a vial, a piston, and a swirl chamber." *Id*. A Formulator POSA would have understood that the vial is a single reservoir.

257. A Formulator POSA would have been motivated to look to Djupesland's disclosure of single-use devices from the disclosure in Wang that the compositions therein can be used in "single-dose" form, and particularly because opioid overdose is an acute condition, making medications for treating it best suited to use in single-use devices. *See id.* at 48 ("For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred."). Combining the devices disclosed in Djupesland with the formulations disclosed in Wang would have been little more than the use of known elements to achieve predictable results.

258. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 1	**Wang in view of Djupesland, HPE, Bahal, and Kushwaha**
"a single-use, pre-primed device adapted for nasal	**WANG (Nalox1008)** "The nasal spray of the present invention is used in a

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
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"	single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time." (8:13–14). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	(zolmitriptan) and about half of that for a duo-dose design." (49).

259. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(b) 1.1: "a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:"

260. Element 1.1 of claim 1 recites "a pharmaceutical composition which is an aqueous solution of about 100 µL."

261. Wang discloses that "[n]aloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning…." Nalox1008 at 7:8–9. Wang further discloses that "[t]he object of the present invention is to overcome the shortcomings of current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others[.]" *Id* at 7:15–19. Wang further discloses that "[a]nother aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." *Id*. at 7:31–33.

262. Wang discloses that the nasal spray disclosed therein is "used in a single-dose or multi-dose form, and the administration amount of the nasal spray is [between] 20–200 µL each time." Nalox1008 at 8:13–14.

263. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device (*id.* at 49), which can emit a 100 µL volume. *See id.* This would have motivated a Formulator POSA to deliver the nasal spray as a 100 µL solution and to consider the ingredients delivered in 100 µL of such a solution.

264. The below claim chart shows the relevant disclosures related to this element.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"a pharmaceutical composition which is an aqueous solution of about 100 µL comprising"	**WANG (Nalox1008)** "Naloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning, rescue for acute alcoholism and the like." (7:8–9). "The object of the present invention is to overcome the shortcomings of the current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others, with rapid absorption, high bioavailability, convenient use, and no need of special conditions." (7:15–20).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	"Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." (7:31–33). "The nasal spray of the present invention is used in a single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time." (8:13–14). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

265. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(c) 1.2: "about 4 mg naloxone hydrochloride or a hydrate thereof;"

266. Element 1.2 of claim 1 recites that the pharmaceutical composition comprises "about 4 mg naloxone hydrochloride or a hydrate thereof."

267. Wang discloses this element. Specifically, Wang discloses preparing naloxone nasal spray formulations "wherein naloxone hydrochloride is administered in a single dose of 0.1 to 10 mg." Nalox1008 at 6, claim 9. A Formulator POSA would have recognized this as encompassing a dose of about 4 mg.

268. Although Wang does not explicitly disclose using the dihydrate form, a Formulator POSA would have recognized that the dihydrate form of naloxone existed and was useful in the disclosed nasal sprays. It was well-known that naloxone hydrochloride is frequently supplied as the dihydrate form. *See*

Nalox1016 at 66 ("Naloxone is supplied as naloxone HCl dihydrate"). Further, a Formulator POSA would have recognized that one would have to modify the amount of naloxone hydrochloride (anhydrous) on a weight basis to account for the presence of the two water molecules associated with the crystalline solid form of the dihydrate.[18] As Wang discloses using "naloxone hydrochloride dry product" in the examples, a Formulator POSA would have recognized that the doses disclosed in Wang are on the basis of the anhydrous naloxone hydrochloride, and would need to be adjusted upwards when using the common dihydrate form. *See* Nalox1008 at 8, Examples 1 and 2. Moreover, a Formulator POSA would have expected the anhydrous and dihydrate forms of naloxone hydrochloride, once dissolved in aqueous medium, to behave identically.

269. The below claim chart shows the relevant disclosures of Wang related to this element.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"about 4 mg naloxone hydrochloride or a hydrate thereof"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative, and water." (6,

[18] Naloxone hydrochloride dihydrate has a molecular weight of 399.9 g/mol, and water has an approximate molecular weight of 18.02. The molecular weight of the anhydrous naloxone hydrochloride would therefore be about 363.8 g/mol, indicating that a Formulator POSA would need to include about 1.1 times as much of the dihydrate as the anhydrous naloxone hydrochloride to achieve an identical quantity of naloxone.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	claim 1). "The nasal spray of any of claims 1–4, wherein the naloxone hydrochloride is administered in a single dose of 0.1–10 mg." (6, claim 9). "Example 1 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use. Example 2 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which 20 g of propylene glycol was added and then an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use." (8:17–41).

270. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(d) 1.3: "between about 0.2 mg and about 1.2 mg of an isotonicity agent;"

271. Element 1.3 of claim 1 recites that the pharmaceutical composition comprises "between about 0.2 mg and about 1.2 mg of an isotonicity agent."

272. Wang discloses this element. Wang discloses "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative and water." Nalox1008 at 6, claim 1. A Formulator POSA would have understood that the osmotic pressure regulator is the same thing as an isotonicity agent in the case of a solution for nasal administration. Furthermore, Wang discloses two examples in which a naloxone nasal spray is prepared that includes 0.9 g of sodium chloride—a well-known tonicity agent—in 100 mL of an aqueous solution. *See id*. at 8:17–41. Were one

supplying a volume of a liquid dose of 100 µL (as discussed above in section (b) (paragraphs 260-265)), this would constitute about 0.9 mg of sodium chloride per 100 µL dose.

273. The below claim chart shows the relevant disclosures of Wang related to this element.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"between about 0.2 and about 1.2 mg of an isotonicity agent"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative and water." (6, claim 1). "Accordingly, a first aspect of the invention relates to a naloxone-containing nasal spray preparation for nasal administration, comprising naloxone hydrochloride, an osmotic pressure regulator, a preservative, a penetration enhancer and water." (7:27–30). "Example 1 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 µm microporous filter membrane until the

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use. Example 2 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which 20 g of propylene glycol was added and then an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use." (8:17–41).

274. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(e) 1.4: "between about 0.005 mg and about 0.015 mg of a preservative;"

275. Element 1.4 of claim 1 recites that the pharmaceutical composition comprises "between about 0.005 mg and about 0.015 mg of a preservative."

276. It would have been obvious to a Formulator POSA to include between about 0.005 to 0.015 mg of a preservative in such a formulation from the disclosure of Wang, particularly in view of HPE. Wang discloses including a preservative in the naloxone nasal spray formulation disclosed therein, which preservative may be benzalkonium chloride. *See* Nalox1008 at 6, claim 3; *see also id.* at 7:34–40. Further, Wang discloses incorporating ethyl parahydroxybenzoate (i.e., ethylparaben)—a preservative—in the formulation of example 1 in a concentration of 0.03 g per 100 mL of water, which would constitute 0.03 mg in 100 μL of water. *Id.* at 8:17–28.

277. Wang discloses a range of preservatives that may be used in a naloxone nasal spray, which would have motivated a Formulator POSA to consult compendia of pharmaceutical excipients, such as HPE, to determine the properties of these preservatives such that he or she could make a rational selection of a preservative.

278. A Formulator POSA, in reviewing HPE, would also have known that preservatives have differing potencies against bacteria, fungi, and other microbes, and thus may be included in aqueous compositions in different concentrations. For instance, Wang discloses a naloxone nasal spray containing 0.03 g of ethylparaben in 100 mL of water (i.e., a 0.03% (w/v) concentration). *See id.* at 8:17–28. Other preservatives disclosed include methyl, propyl, and butylparabens, benzoic acid,

sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol, and sodium ethylenediamine tetraacetate (i.e., disodium edetate). *Id.* at 7:34–40.

279. While Wang discloses using ethylparaben at a concentration of 0.03 % (w/v), a Formulator POSA would have recognized from the disclosure of HPE that this choice of concentration was based on the specific choice of preservative—i.e., ethylparaben—and that different preservatives commonly used in nasal sprays will function at lower concentrations—particularly benzalkonium chloride—of between 0.002 % w/v and 0.02 % w/v in nasal sprays (i.e., 0.002 mg/100 µL to 0.02 mg/100 µL). Further, a Formulator POSA would have been motivated to select benzalkonium chloride as a preservative, with a reasonable expectation of success, because it has activity against a broad spectrum of microorganisms and greater efficacy in that regard than ethylparaben. *See* section IV.A.3(e)(iv)1) (paragraphs 63-66), *supra*. The prior art thus discloses this element.

280. The below claim chart shows the relevant disclosures of Wang and HPE related to this element.

Claim 1	**Wang in view of Djupesland, HPE, Bahal, and Kushwaha**
"between about 0.005 mg and about 0.015 mg of a preservative"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative and water." (6, claim 1).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	"The nasal spray of claim 1 or 2, wherein the preservative is selected from methyl, ethyl, propyl, or butyl para-hydroxybenzoate, sorbic acid, sodium sorbate, benzoic acid, sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol and sodium ethylenediamine tetraacetate." (6, claim 3). "Accordingly, a first aspect of the invention relates to a naloxone-containing nasal spray preparation for nasal administration, comprising naloxone hydrochloride, an osmotic pressure regulator, a preservative, a penetration enhancer and water." (7:27–30). "According to the present invention, the preservative used in the nasal spray of the present invention is selected from methyl, ethyl, propyl, or butyl para-hydroxybenzoate, sorbic acid, benzoic acid, sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol, sodium ethylenediamine tetraacetate and the like…." (7:34–38). "Example 1 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use. Example 2 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which 20 g of propylene glycol was added and then an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use." (8:17–41). **HPE (Nalox1012)** "Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative… In nasal, and otic formulations a concentration of 0.002–0.02% w/v is used…Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products." (56).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha

Table II: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

(57).

"Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations, including oral and parenteral preparations, at concentrations up to 2.0% v/v. The typical concentration used is 1% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006." (64).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.[44]

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

(*Id.*).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha

Table III: Minimum inhibitory concentrations (MICs) for butylparaben in aqueous solution.[2]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	400
Aspergillus niger ATCC 9642	125
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	63
Bacillus subtilis ATCC 6633	250
Candida albicans ATCC 10231	125
Enterobacter cloacae ATCC 23355	250
Escherichia coli ATCC 8739	5000
Escherichia coli ATCC 9637	5000
Klebsiella pneumoniae ATCC 8308	250
Penicillium chrysogenum ATCC 9480	70
Penicillium digitatum ATCC 10030	32
Proteus vulgaris ATCC 13315	125
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	63
Saccharomyces cerevisiae ATCC 9763	35
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	125
Staphylococcus epidermidis ATCC 12228	250
Trichophyton mentagrophytes	35

(79).

"Ethylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations.

It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives.

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; see Section 10.

Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used. However, this may cause the pH of poorly buffered formulations to become more alkaline.

See Methylparaben for further information." (270).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha

Table II: Minimum inhibitory concentrations (MICs) for ethylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1200
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	400
Bacillus cereus var. *mycoides* ATCC 6462	1000
Bacillus subtilis ATCC 6633	1000
Candida albicans ATCC 10231	500
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	250
Penicillium digitatum ATCC 10030	250
Proteus vulgaris ATCC 13315	500
Pseudomonas aeruginosa ATCC 9027	>2000
Pseudomonas aeruginosa ATCC 15442	>2000
Pseudomonas stutzeri	1000
Rhizopus nigricans ATCC 6227A	250
Saccharomyces cerevisiae ATCC 9763	500
Salmonella typhosa ATCC 6539	1000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	1000
Staphylococcus epidermidis ATCC 12228	1000
Trichophyton mentagrophytes	125

(271).

Table I: Uses of methylparaben.

Use	Concentration (%)
IM, IV, SC injections[a]	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18

(a) See Section 14.

(442).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha

Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[14]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. mycoides ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

(*Id.*).

Table I: Uses of propylparaben in pharmaceutical preparations.

Use	Concentration (%)
IM, IV, SC injections	0.005–0.2
Inhalation solutions	0.015
Intradermal injections	0.02–0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005–0.01
Oral solutions and suspensions	0.01–0.02
Rectal preparations	0.02–0.01
Topical preparations	0.01–0.6
Vaginal preparations	0.02–0.1

(596).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha

Table III: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1000
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	200
Bacillus cereus var. mycoides ATCC 6462	125
Bacillus subtilis ATCC 6633	500
Candida albicans ATCC 10231	250
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	500
Escherichia coli ATCC 9637	100
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	125
Penicillium digitatum ATCC 10030	63
Proteus vulgaris ATCC 13315	250
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	125
Saccharomyces cerevisiae ATCC 9763	125
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	500
Staphylococcus epidermidis ATCC 12228	500
Trichophyton mentagrophytes	65

(597).

281. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(f) 1.5: "about 0.2 mg of a stabilizing agent;"

282. Element 1.5 of claim 1 recites that the pharmaceutical composition comprises "about 0.2 mg of a stabilizing agent."

283. Wang discloses this element. Wang discloses sodium ethylenediamine tetraacetate (i.e., sodium edetate) as a preservative. *See, e.g.*, Nalox1008 at claim 3; *see also* HPE (Nalox1012) at 242 (disclosing that disodium

ethylenediaminetetraacetate is synonymous with disodium edetate).[19] However, a Formulator POSA would have understood that disodium edetate is not itself an antimicrobial preservative, but rather a *chemical* preservative, i.e., a chelating agent that can sequester metal ions in aqueous solution in order to preserve the chemical stability of the solution.[20] *See* HPE (Nalox1012) at 243. A Formulator POSA would have been motivated to include disodium edetate in a naloxone nasal spray for three reasons: first, the combination of benzalkonium chloride and disodium edetate improves the antimicrobial activity of benzalkonium chloride; second, disodium edetate was known to stabilize naloxone against oxidative degradation in solution; and third, disodium edetate can act as a permeation enhancer in nasal sprays.

284. First, disodium edetate was known to improve the antimicrobial activity of benzalkonium chloride. A Formulator POSA would have been motivated to include benzalkonium chloride as a preservative in a naloxone nasal spray for the reasons discussed in section VII.D.1(e). Furthermore, HPE discloses that, in ophthalmic solutions, benzalkonium chloride is often "used in combination

[19] Although disodium edetate and monosodium edetate are not entirely identical, a Formulator POSA would have understood them to be effectively equivalent, and would be able to take into account their differences in molecular weight in determining the quantity to add to a formulation.

[20] Disodium edetate, however, can improve the antimicrobial action of other antimicrobial agents, as discussed below.

with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*," particularly in ophthalmic solutions. *See* Nalox1012 at 56. Likewise, HPE also discloses that "Benzalkonium chloride is ineffective against some *Pseudomonas aeruginos*a strains, *Mycobacterium tuberculosis*, *Trichophyton interdigitale*, and *T. rubrum*. However, combined with disodium edetate (0.01–0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against *Pseudomonas aeruginosa* is increased." *Id.* These disclosures would have motivated a Formulator POSA to include disodium edetate in a nasal spray formulation of naloxone including benzalkonium chloride.

285. Second, it was known that disodium edetate specifically was useful in stabilizing naloxone against oxidative degradation. Specifically, Bahal discloses that chelating agents, such as disodium edetate, can prevent degradation of naloxone in solution. Specifically, Bahal discloses the following:

> Instability of naloxone solution has been observed in the manufactured product. Autoclaving of currently available formulations of naloxone caused significant degradation of naloxone and formation of noroxymorphone. The degradation rates depended on headspace oxygen content. When non-autoclaved samples were sparged/flushed with nitrogen, no significant changes were observed in naloxone and bisnaloxone levels. However, noroxymorphone level increased from 0.08% to 0.4% over a six-week period at 60° C. It has now been found that addition of a chelating agent, such as sodium edetate, to the commercial formulation prevents naloxone degradation, even in the presence of oxygen and after autoclaving.

Nalox1014 at 1:45–57. Bahal further discloses incorporating a stabilizing agent, which ca, in a concentration of 0.0001 to 1%. *See id*. at 2:48–51 and 2:63–67.

286. Although Bahal is directed to an injectable solution of naloxone, a Formulator POSA would have been motivated to combine the teachings of this reference with Wang because both relate to solution formulations of naloxone, and a Formulator POSA would have been motivated to add ingredients to a naloxone nasal spray known to stabilize naloxone against oxidative degradation in solution.

287. A Formulator POSA would have further had a reasonable expectation of success that addition of disodium edetate to a naloxone nasal spray would have been safe for patients, as it is a commonly-used excipient in injectable and other formulations. Both Wang and Kushwaha disclose use of disodium EDTA in nasal sprays.

288. Third, a Formulator POSA would have been motivated to add disodium edetate to a nasal spray formulation as it is a known permeation enhancer. Wang discloses that the naloxone nasal spray should include a "penetration enhancer." *See* Nalox1008 at 7:4–6. A Formulator POSA reading the disclosure of Wang would have been motivated to look at the full range of options of penetration enhancers available in nasal sprays, and would have looked to Kushwaha, which discloses a list of excipients that can serve as permeation enhancers in intranasal dosage forms, such as those disclosed by Wang. *See*

Nalox1013 at 25–26. Kushwaha discloses that EDTA (which a Formulator POSA would have understood to be edetic acid and can be used as an equivalent to disodium edetate after adjusting for the additional sodium ions included in the crystalline solid form of disodium edetate) is a chelator that can serve as a permeation enhancer for small-molecule and large molecule drugs. *Id.* at 25–26.

289. These combined disclosures would have motivated a Formulator POSA to include disodium edetate and benzalkonium chloride together in a naloxone nasal spray, as the combination of these ingredients would have been expected to have synergistic antimicrobial activity based on the combination of Wang and HPE. The combination of Wang and Bahal would have led a Formulator POSA to conclude that disodium edetate stabilized naloxone and prevented its oxidative degradation in solution. Finally, the combination of Wang and Kushwaha would have taught a Formulator POSA that disodium edetate can serve as both a preservative and a penetration enhancer in a naloxone nasal spray in solution.

290. A Formulator POSA would further have been motivated to include disodium edetate in the claimed amount of 0.2 mg per 100 μL. Bahal discloses that preferred concentrations of stabilizing agents (including sodium edetate) are between 0.0001% by weight to 1% by weight. Nalox1014 at 2:65–67. Bahal discloses that concentrations of as low as 0.1% by weight of sodium edetate were sufficient to stabilize low concentrations of naloxone (0.04%) from degradation

during autoclaving and exposure to oxygen. *See id.* at 7:1–8:67 A Formulator POSA would reasonably have expected that higher concentrations, such as 0.2%, 0.3%, 0.4%, etc. would also serve to stabilize naloxone.

291. The below claim chart shows the relevant disclosures of Wang, Bahal, HPE, and Kushwaha related to this element.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"about 0.2 mg of a stabilizing agent"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative and water." (6, claim 1). "The nasal spray of claim 1 or 2, wherein the preservative is selected from methyl, ethyl, propyl, or butyl para-hydroxybenzoate, sorbic acid, sodium sorbate, benzoic acid, sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol and sodium ethylenediamine tetraacetate." (6, claim 3). "Accordingly, a first aspect of the invention relates to a naloxone-containing nasal spray preparation for nasal administration, comprising naloxone hydrochloride, an osmotic pressure regulator, a preservative, a penetration enhancer and water." (7:27–30). "According to the present invention, the preservative used in the nasal spray of the present invention is selected from methyl, ethyl, propyl, or butyl para-hydroxybenzoate, sorbic acid, benzoic acid, sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol, sodium ethylenediamine tetraacetate and the like…." (7:34–38). **HPE (Nalox1012)** "In ophthalmic preparations, benzalkonium chloride is one of the most widely used preservatives, at a concentration of

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	0.01–0.02% w/v. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of Pseudomonas." (56). "Benzalkonium chloride is ineffective against some Pseudomonas aeruginosa strains, Mycobacterium tuberculosis, Trichophyton interdigitale, and T. rubrum. However, combined with disodium edetate (0.01–0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against Pseudomonas aeruginosa is increased." (*Id.*). **Bahal (Nalox1014)** "Instability of naloxone solution has been observed in the manufactured product. Autoclaving of currently available formulations of naloxone caused significant degradation of naloxone and formation of noroxymorphone. The degradation rates depended on headspace oxygen content. When non-autoclaved samples were sparged/flushed with nitrogen, no significant changes were observed in naloxone and bisnaloxone levels. However, noroxymorphone level increased from 0.08% to 0.4% over a six-week period at 60° C. It has now been found that addition of a chelating agent, such as sodium edetate, to the commercial formulation prevents naloxone degradation, even in the presence of oxygen and after autoclaving." (1:45–57). "Ready-to-use injectable solution formulations of naloxone with improved chemical and physical stability are preferably composed of an effective amount of naloxone hydrochloride, an acid or a buffer to yield a final solution pH of 3–3.5, one or more tonicity adjusting agents, and a stabilizing agent selected from sodium edetate, citrate and/or ethylenediamine tetraacetic acid and its other salts Said compositions are autoclaved for sterilization." (2:44–51). "Preferred concentrations of the stabilizing agents are 0.0001 to 1% . Specifically preferred concentrations are 0.001 to 0.1%." (2:65–67).

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha

See also Example 2, 7:1–8:65.

Kushwaha (Nalox1013)

"Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show insufficient bioavailability. Their permeation can improve by being administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier. **(Table-1)**."

Table 1: Mucosal penetration enhancers and mechanisms of action.

Classification	Examples	Mechanism
Surfactants	Anionic: Sodium lauryl sulphate Cationic:Cetylpyridiniu m Chloride Nonionic:Poloxamer,Spa n,Tween	Perturbation of intercellular lipids, Protein domain integrity, Distrusts membrane
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate	Distrusts membrane, Open tight junctions, Mucolytic activity
Cyclodextrins	α,β,γ Cyclodextrin, Methylated β–Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Fatty acids	Oleic acid, Methyloleate, Lauric acid, Caprylic acid, Phosphotidylcholine	Increase fluidity of phospholipid domains, Distrusts membrane
Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface
Chelators	EDTA, Citric Acid, Sodium citrate, Sodium Salicylate	Interfere with Ca Polyacrylates
+ve charged polymers	Chitosan,Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Bioadhesive Materials	Carbopol, Starch, Chitosan	Reduce nasal clearance, Open tight junctions

(25–26).

292. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(g) 1.6: "an amount of an acid sufficient to achieve a pH of 3.5-5.5."

293. Element 1.6 of claim 1 recites that the pharmaceutical composition comprises "an amount of an acid sufficient to achieve a pH of 3.5-5.5."

294. Wang discloses this element. Wang specifically discloses adjusting the nasal spray solution to a pH value of 3.8 +/- 0.8. with hydrochloric acid. (Nalox1008 at 8:17-41) As such, Wang discloses this element.

295. The below claim chart shows the relevant disclosures of Wang related to this element.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"an amount of an acid sufficient to achieve a pH of 3.5-5.5."	**WANG (Nalox1008)** "Example 1 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use.

Claim 1	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	(8:17–41).

296. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

2. Claim 2

297. It is my opinion that claim 2 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

298. Claim 2 depends from claim 1 and recites the limitations that "the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid." '253 patent (Nalox1001), claim 2. The disclosures of the prior art in regard to the limitations of claim 1 are discussed above in section VII.D.1.

(a) "the isotonicity agent is NaCl;"

299. As discussed above in section VII.D.1(d), Wang discloses including the recited amount of sodium chloride as an isotonicity agent.

(b) "the preservative is benzalkonium chloride;"

300. As discussed above in section VII.D.1(e), Wang discloses including benzalkonium chloride as a preservative, and the prior art as a whole would have suggested its use in the recited amounts in the pharmaceutical composition.

(c) "the stabilizing agent is disodium edetate;"

301. As discussed above in section VII.D.1(f), Wang discloses including sodium diethylamine tetraacetate (sodium edetate) as a preservative, and a Formulator POSA would have been motivated from this disclosure to include disodium edetate in the recited amount based on the disclosures of the prior art.

(d) "and the acid is hydrochloric acid."

302. As discussed above in section VII.D.1(g) (paragraphs 293-296), Wang discloses adjusting the pH of the composition within the claimed pH range of 3.5 to 5.5 using hydrochloric acid.

3. Claim 3

303. It is my opinion that claim 3 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

304. Claim 3 depends from claim 2 and recites the limitations that "the aqueous solution comprises: about 4.4 mg naloxone hydrochloride dihydrate; about 0.74 mg NaCl; about 0.01 mg benzalkonium chloride; about 0.2 mg disodium edetate; and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5." '253 patent (Nalox1001), claim 3. The disclosures of the prior art in regard to the limitations of claim 2 are discussed above in section VII.D.2.

(a) "about 4.4 mg naloxone hydrochloride dihydrate;"

305. Wang suggests this element. Specifically, Wang discloses preparing naloxone nasal spray formulations "wherein naloxone hydrochloride is administered in a single dose of 0.1 to 10 mg." Nalox1008 at 6, claim 9. A Formulator POSA would have recognized this as encompassing a dose of about 4 mg.

306. Although Wang does not explicitly disclose using the dihydrate form, a Formulator POSA would have recognized that the dihydrate form of naloxone hydrochloride existed and was useful in the disclosed nasal sprays. It was well-known that naloxone hydrochloride is frequently supplied as the dihydrate form. *See* Wermeling 2013 (Nalox1016) at 66 ("Naloxone is supplied as naloxone HCl dihydrate"). Further, a Formulator POSA would have recognized that one would have to modify the amount of naloxone hydrochloride (anhydrous) on a weight basis to account for the presence of the two water molecules associated with the crystalline solid form of the dihydrate.[21] As Wang discloses using "naloxone hydrochloride dry product" in the examples, a Formulator POSA would have

[21] Naloxone hydrochloride dihydrate has a molecular weight of 399.9 g/mol, and water has an approximate molecular weight of 18.02. The molecular weight of the anhydrous naloxone hydrochloride would therefore be about 363.8 g/mol, indicating that a Formulator POSA would need to include about 1.1 times as much of the dihydrate as the anhydrous naloxone hydrochloride to achieve an identical quantity of naloxone.

recognized that the doses disclosed in Wang are on the basis of the anhydrous naloxone hydrochloride, and would need to be adjusted upwards when using the common dihydrate form. *See* Nalox1008 at 8:17–41. Moreover, a Formulator POSA would have expected the anhydrous and dihydrate forms of naloxone hydrochloride, once dissolved in aqueous medium, to behave identically.

307. The below claim chart shows the relevant disclosures of Wang related to this element.

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"about 4.4 mg naloxone hyhdrochloride dihydrate"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative, and water." (6, claim 1). "The nasal spray of any of claims 1–4, wherein the naloxone hydrochloride is administered in a single dose of 0.1–10 mg." (6, claim 9). "Example 1 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use. Example 2 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which 20 g of propylene glycol was added and then an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use." (8:17–41).

308. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(b) "about 0.74 mg NaCl;"

309. Wang discloses this element. Wang discloses two examples in which a naloxone nasal spray is prepared that includes 0.9 g of sodium chloride—a well-

known tonicity agent—in 100 mL of an aqueous solution. *See* Nalox1008 at 8:17-41. Were one supplying a volume of a liquid dose of 100 µL (as discussed above in section VII.D.1(b)) (paragraphs 260-265), this would constitute about 0.9 mg of sodium chloride per 100 µL of solution. As a Formulator POSA would have known that a range of tonicities are acceptable in nasal formulations (*see* paragraph 58) and would have recognized that a 0.9 g sodium chloride in 100 mL of aqueous solution also containing the drug and additional excipients would have been at least slightly hypertonic. A Formulator POSA seeking to make an isotonic or less hypertonic nasal spray, in accordance with the disclosures in the prior art, would have been motivated to adjust the concentration of sodium chloride downwards slightly to arrive at an approximately isotonic or slightly hypertonic solution.

310. The below claim chart shows the relevant disclosures of Wang related to this element.

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"about 0.74 mg NaCl"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative and water." (6, claim 1). "The nasal spray of claim 1, wherein the osmotic pressure regulator is selected from sodium chloride, potassium nitrate, boric acid, and glucose." (6, claim 2). "Accordingly, a first aspect of the invention relates to

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	a naloxone-containing nasal spray preparation for nasal administration, comprising naloxone hydrochloride, an osmotic pressure regulator, a preservative, a penetration enhancer and water." (7:27–30). "Example 1 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use. Example 2 Preparation of a nasal spray of naloxone hydrochloride. 0.03 g of ethyl para-hydroxybenzoate was weighed, and placed in a 100 ml volumetric flask, to which 20 g of propylene glycol was added and then an appropriate amount of water for injection was added, followed by dissolving them by heating in a warm water bath, cooling to room temperature, then adding 1.0 g of naloxone hydrochloride dry product and 0.9 g of sodium chloride, shaking to dissolve, adding water for

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	injection close to the scale mark, shaking uniformly, adjusting to a pH value of 3.8 ± 0.8 with 0.1 mol/L hydrochloric acid, adding water for injection to the scale mark, shaking uniformly, and filtering with 0.25 μm microporous filter membrane until the drug liquid is clear, thereby obtaining the nasal spray liquid of naloxone hydrochloride. Subsequently, single-dose and multi-dose nasal spray devices were filled with the nasal spray liquid separately and packaged for later use." (8:17–41).

311. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

(c) "about 0.01 mg benzalkonium chloride;"

312. As discussed above in section VII.D.1(e), the use of benzalkonium chloride would have been obvious from the disclosure of Wang. Further, the use of 0.01% (w/v) benzalkonium chloride would have been obvious from the disclosure of Wang, particularly in view of HPE. HPE discloses using between 0.002% (w/v) and 0.02% (w/v) benzalkonium chloride in nasal spray solutions as a preservative, and that it is used in 0.01% (w/v) concentrations in concentrated injectable solutions. *See* Nalox1012 at 56. A Formulator POSA would have immediately envisaged that one could use a concentration of about 0.01 % (w/v) in a nasal spray from this disclosure, which would be about 0.01 mg in 100 µL of aqueous solution.

313. The below claim chart shows the relevant disclosures of Wang and HPE related to this element.

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"about 0.01 mg benzalkonium chloride"	**WANG (Nalox1008)** "A nasal spray of naloxone hydrochloride, comprising naloxone hydrochloride, an osmotic pressure regulator, a penetration enhancer, a preservative and water." (6, claim 1). "The nasal spray of claim 1 or 2, wherein the preservative is selected from methyl, ethyl, propyl, or butyl para-hydroxybenzoate, sorbic acid, sodium sorbate, benzoic acid, sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol and sodium ethylenediamine tetraacetate." (6, claim 3). "Accordingly, a first aspect of the invention relates to a naloxone-containing nasal spray preparation for nasal administration, comprising naloxone hydrochloride, an osmotic pressure regulator, a preservative, a penetration enhancer and water." (7:27–30). "According to the present invention, the preservative used in the nasal spray of the present invention is selected from methyl, ethyl, propyl, or butyl para-hydroxybenzoate, sorbic acid, benzoic acid, sodium benzoate, benzyl alcohol, benzalkonium chloride, benzalkonium bromide, chlorobutanol, resorcinol, sodium ethylenediamine tetraacetate and the like…." (*Id*. at 34–38). **HPE (Nalox1012)** "Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative… In nasal, and otic formulations a concentration of 0.002–0.02% w/v is used…Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-

Claim 3	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	volume parenteral products." (56).

314. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(d) "about 0.2 mg disodium edetate;"

315. As discussed above in section VII.D.1(f), Wang discloses including sodium diethylamine tetraacetate (sodium edetate) as a preservative, and a Formulator POSA would have been motivated from this disclosure to include disodium edetate[22] in the recited amount based on the disclosures of the prior art.

(e) "and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5."

316. As discussed above in section VII.D.1(g), Wang discloses adjusting the pH of the composition within the claimed pH range of 3.5 to 5.5 using hydrochloric acid.

4. Claim 4

317. It is my opinion that claim 4 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

318. Claim 4 depends from claim 2 and recites the limitation that "said device is actuatable with one hand." '253 patent (Nalox1001), claim 4. The

[22] *See also supra* n.17

disclosures of the prior art in regard to the limitations of claim 2 are discussed above in section VII.D.2.

319. Wang discloses that the nasal spray disclosed therein is "used in a single-dose or multi-dose form, and the administration amount of the nasal spray is [between] 20–200 µL each time." Nalox1008 at 8:13–14.

320. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device (*id.* at 49), which can emit a 100 µL volume. *See id.*

321. Further, Djupesland specifically states that "[t]he single- and duo-dose devices mentioned above…are held between the second and the third fingers with the thumb on the actuator." *See id*. at 48–49. This indicates the device is actuatable with one hand.

322. The below claim chart shows the relevant disclosures of Wang and Djupesland related to this element.

Claim 4	**Wang in view of Djupesland, HPE, Bahal, and Kushwaha**
"wherein said device is actuatable with one hand"	**WANG (Nalox1008)** "The nasal spray of the present invention is used in a single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time." (8:13–14).

Claim 4	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	DJUPESLAND (Nalox1010) "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

323. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

5. Claim 5

324. It is my opinion that claim 5 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of in view of Djupesland, HPE, Bahal, and Kushwaha.

325. Claim 5 depends from claim 4 and recites the limitation that "the volume of said reservoir is not more than about 140 µL." '253 patent (Nalox1001), claim 5. The disclosures of the prior art in regard to the limitations of claim 4 are discussed above in section VII.D.4.

326. Wang discloses that the nasal spray disclosed therein is "used in a single-dose or multi-dose form, and the administration amount of the nasal spray is [between] 20–200 µL each time." Nalox1008 at 8:13–14.

327. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device. *Id*. at 49. These devices comprise "a vial, a piston, and a swirl chamber." *Id*. A Formulator POSA would have understood that the vial is a reservoir. Djupesland further discloses that a volume of 125 µL is filled into Aptar/Pfeiffer single dose devices to deliver a 100

µL spray volume. *Id*. A Formulator POSA would have recognized from the disclosure of Wang and Djupesland that the volume of the reservoir could be as little as 125 µL to accommodate the necessary overfill to deliver a 100 µL volume of spray.

328. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 5	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"wherein the volume of said reservoir is not more than about 140 µL."	**WANG (Nalox1008)** "The nasal spray of the present invention is used in a single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time." (8:13–14). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in

Claim 5	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

329. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

6. Claim 6

330. It is my opinion that claim 6 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

331. Claim 6 depends from claim 5 and recites the limitation that "wherein about 100µL of said aqueous solution in said reservoir is delivered to said patient in one actuation." '253 patent (Nalox1001), claim 6. The disclosures of the prior art in regard to the limitations of claim 5 are discussed above in section VII.D.5.

332. Wang discloses that the nasal spray disclosed therein is "used in a single-dose or multi-dose form, and the administration amount of the nasal spray is [between] 20–200 µL each time." Nalox1008 at 8:13–14.

333. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device (*id.* at 49), which can emit a 100 µL volume upon a single actuation. *See id.*

334. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 6	Wang in view of Djupesland, HPE, Bahal and Kushwaha
"wherein about 100 µL of said aqueous solution in said reservoir is delivered to said patient in one actuation"	**WANG (Nalox1008)** "The nasal spray of the present invention is used in a single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time." (8:13–14). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred

Claim 6	Wang in view of Djupesland, HPE, Bahal and Kushwaha
	(www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

335. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

7. Claim 7

336. It is my opinion that claim 7 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

337. Claim 7 depends from claim 6 and recites the limitation that "the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate." Nalox1001, claim 7. The disclosures of the prior art in regard to the limitations of claim 6 are discussed above in section VII.D.6.

338. Wang, in view of the prior art, suggests this element, as is discussed above in sections VII.D.1(c) and VII.D.3(a). Accordingly, claim 7 would have been obvious to a Formulator POSA.

8. Claims 12–14

339. It is my opinion that claim 12 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

340. Claim 12 depends from claim 7 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." '253 patent (Nalox1001), claim 12. Claim 13 depends from claim 12 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." *Id.*, claim 13. Claim 14 depends from claim 13 and

recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." *Id.*, claim 14. The disclosures of the prior art in regard to the limitations of claim 7 are discussed above in section VII.D.7.

341. Wang discloses that the nasal spray disclosed therein is "used in a single-dose or multi-dose form, and the administration amount of the nasal spray is [between] 20–200 μL each time." Nalox1008 at 8:13–14.

342. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device (*id.* at 49), which can emit a 100 μL volume. *See id.*

343. This limitation is met by Djupesland's disclosure of administration of a single 100 μL spray from a single-dose device. 100 μL of liquid spray will not drip out or drain when placed on the surface of the nasal cavity. Several references show that this volume is small enough to be retained in the nasal cavities: for instance, Wermeling 2013 (Nalox1016) discloses that "[t]he nasal cavity can retain 100–150μL without causing immediate runoff out the front of the nose or down the nasopharynx." Nalox1016 at 65; *see also* Grassin-Delyle (Nalox1011) at 368 ("The

nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff."). Furthermore, other intranasal products frequently use shot volumes of 100 µL. *See, e.g.*, PDR 2003 (Nalox1044); PDR 2010 (Nalox1045). Thus, Wang, in view of Djupesland, discloses this limitation to a Formulator POSA.

344. The below claim chart shows the relevant disclosures of each reference related to this element.

Claims 12–14	**Wang in view of Djupesland, HPE, Bahal, and Kushwaha**
"wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally" (claim 12) "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally" (claim 13)	**WANG (Nalox1008)** "The nasal spray of the present invention is used in a single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time." (8:13–14). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The

Claims 12–14	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
"wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally" (claim 14)	spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49). *See also* **WERMELING 2013 (Nalox1016)** "The dose must have sufficient solubility to be administered in approximately 100–200 µL (one spray per naris) of solution. The nasal cavity can retain 100–150 µL without causing immediate runoff out the front of the nose or down the nasopharynx []." (65). *See also* **GRASSIN-DELYLE (Nalox1011)** "The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff. For insulin preparations of between 80 and 160 µL in volume, it has been shown that the entire administered dose is deposited in the nasal cavities, with no passage to the lungs

Claims 12–14	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	(Newman et al., 1994). The unit volume administered is also important because it appears that the administration of a single volume of 100 µL leads to deposition over a greater surface area than that obtained with the administration of two 50 µL volumes (Newman et al., 1994; Kundoor & Dalby 2011)." (368).

345. Accordingly, it is my opinion that the prior art discloses these limitations of these claims.

9. Claim 16

346. It is my opinion that claim 16 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, and Kushwaha.

347. Claim 16 depends from claim 1 and recites the limitation that "wherein said patient is an opioid overdose patient or a suspected opioid overdose patient."'253 patent (Nalox1001), claim 16. The disclosures of the prior art in regard to the limitations of claim 1 are discussed above in section VII.D.1.

348. Wang discloses this element. Wang discloses that "[n]aloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning." Nalox1008 at 7:8–9. A Formulator POSA would have recognized that "morphine poisoning" was a form of opioid overdose.

349. Wang further discloses that "[t]he object of the present invention is to overcome the shortcomings of current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others[.]" *Id.* at 7:15–19. Wang further discloses that "[a]nother aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism and the like." *Id* at 7:31–33. It thus would have been obvious to use the naloxone nasal spray disclosed in Wang to treat opioid overdoses or suspected opioid overdoses.

350. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 16	**Wang in view of Djupesland, HPE, Bahal, and Kushwaha**
"wherein said patient is an opioid overdose patient or a suspected opioid overdose patient."	**WANG (Nalox1008)** "Naloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning, rescue for acute alcoholism and the like." (7:8–9). "The object of the present invention is to overcome the shortcomings of the current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others, with rapid absorption, high bioavailability, convenient use, and no need of special conditions." (7:15–20).

Claim 16	Wang in view of Djupesland, HPE, Bahal, and Kushwaha
	"Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." (7:31–33).

351. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

E. A Formulator POSA reading Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse would have had ample reason and know-how to arrive at the subject matter of claims 10–11 and 17–24.

352. In my opinion, claims 10–11 and 17–24 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

353. The claim charts and discussion below show where each and every limitation of claims 10–11 and 17–24 are disclosed in Wang (Nalox1008), Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), Kushwaha (Nalox1013), and Wyse (Nalox1007).

354. It is my opinion that claims 10–11 and 17–24 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang (Nalox1008) in view of Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), Kushwaha (Nalox1013), and Wyse (Nalox1007).

1. Claims 10–11

355. It is my opinion that claims 10–11 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse.

356. Claim 10 depends from claim 7 and recites the limitation that "the delivery time is less than about 25 seconds." '253 patent (Nalox1001), claim 10. Claim 11 depends from claim 7 and recites the limitation that "the delivery time is less than about 20 seconds." *Id.*, claim 11. The disclosures of the prior art in regard to the limitations of claim 7 are discussed above in section VII.D.7 (paragraphs 336-338).

357. I have previously discussed the construction of the term "delivery time" in section V.2 (paragraph 107) above. The '253 patent defines "delivery time" as follows: "The term 'delivery time,' as used herein, refers to the amount of time that elapses between a determination made by a healthcare professional, or an untrained individual that an individual is in need of nasal delivery of an opioid antagonist and completion of the delivery." '253 patent (Nalox1001), 8:52–56. I have applied this definition in analyzing this claim element.

358. Wyse suggests this element. Wyse discloses that "there is a need for integrating compositions, methods, and devices that can allow for an effective reversal of opioid overdose, but which eliminates or minimizes the use of needles."

Nalox1007 at 2:67–3:3. Further, Wyse discloses that there is a need for "effective formulations and methods of providing such compositions to an individual…for reversing opioid overdose, that can be quickly and easily used[.]" *Id.* at 3:3–6. Wyse further discloses that the devices used for administering the compositions are "ready-to-use" (*id.* at 10:31–33) and can be "assembled in the Unitdose delivery devices and packaged in 4"x4" foil pouches, one device/pouch, heat-sealed and labeled as appropriate." *Id.* at 11:3–6. Each of these factors indicates that Wyse was seeking to minimize the delivery time of naloxone to a patient to a matter of mere seconds, which comports with the most fundamental goal of the treatment: when a patient is not breathing due to an opioid overdose, every second counts in getting the patient the naloxone antidote and breathing again.

359. A Formulator POSA would further recognize that placing the solution for administration in a single-use, pre-primed device, such as the Aptar/Pfeiffer Unitdose device disclosed in Djupesland, would further minimize delivery time as defined by the '253 patent (*see* section V.1 (paragraph 106)) to a matter of seconds.

360. The below claim chart shows the relevant disclosures of each reference related to this element.

Claims 10–11	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
"wherein the delivery time is less than about 25 seconds" (claim 10) "wherein the delivery time is less than about 20 seconds" (claim 11)	**WYSE (Nalox1007)** "[T]here is a need for integrating compositions, methods, and devices that can allow for an effective reversal of opioid overdose, but which eliminates or minimizes the use of needles. There is further a need for effective formulations and methods of providing such compositions to an individual, for rapid absorption into the nasal mucosa and for reversing opioid overdose, that can be quickly and easily used, but which minimize sudden and severe side effects of rapid reversal of opioid overdose." (2:67–3:8). "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof." (10:29–33). "Naloxone HCl dihydrate nasal spray, 10 mg/mL, 100 µL/spray, assembled into the Aptar/Pfeiffer Unitdose delivery device or in vials (not assembled into the delivery device) may be stored protected from light. Bulk vials and assembled Unitdose delivery device units of drug product may be stored in bulk sealed containers pending further processing. The disclosed compositions may be assembled in the Unitdose delivery devices and packaged in 4"x4" foil pouches, one device/pouch, heat-sealed and labeled as appropriate." (10:65–11:6).

361. Accordingly, it is my opinion that the prior art suggests these limitations of these claims.

2. Claim 17

362. It is my opinion that claim 17 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse.

363. Claim 17 depends from claim 16 and recites the limitation that "the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia, sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting." '253 patent (Nalox1001), claim 17. The disclosures of Wang, HPE, Bahal, and Kushwaha are discussed above in regard to the limitations of claim 16 are discussed above in section VII.D.9.

364. Wang discloses that "Naloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning." Nalox1008 at 7:8–9. A Formulator POSA would have recognized that "morphine poisoning" was a form of opioid overdose.

365. Wang further discloses that "the object of the present invention is to overcome the shortcomings of current preparations of naloxone hydrochloride

injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others[.]" *Id* at 7:15–20. Wang further discloses that "Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning…and the like." *Id*. at 7:31–33.

366. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses that, "[i]n one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression." *Id.* at 9:33–35.

367. A Formulator POSA would have been motivated to combine the teachings of Wang with Wyse. Wang specifically discloses that the intranasal naloxone compositions that are disclosed are useful for treatment of morphine poisoning. Wyse more broadly discloses that intranasal naloxone is useful in reversing both respiratory depression and depressive effects on the central nervous system caused by opioid overdose. A Formulator POSA would have understood that morphine poisoning is a specific form of opioid overdose, and would reasonably expect that the formulations of Wang would have been effective in

reversing the symptoms of opioid overdose, as naloxone was well-known to be effective in reversing the effects of opioid overdose, including respiratory depression.

368. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 17	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
"wherein the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia; sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting"	**WANG (Nalox1008)** "Naloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning…and the like." (7:8–9). "The object of the present invention is to overcome the shortcomings of the current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others, with rapid absorption, high bioavailability, convenient use, and no need of special conditions." (7:15–20). "Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." (7:31–33). **WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed

Claim 17	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
	herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression." (9:33–35) "In one aspect, the known or suspected opioid overdose may be manifested by respiratory and/or central nervous system depression." (10:1–3).

369. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

3. Claim 18

370. It is my opinion that claim 18 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse.

371. Claim 18 depends from claim 17 and recites the limitation that "the patient exhibits respiratory depression." '253 patent (Nalox1001), claim 18. The disclosures of the prior art in regard to the limitations of claim 17 are discussed above in section VII.E.2. As discussed in that section, Wyse discloses administering intranasal naloxone compositions to patients experiencing opioid overdose, which may be manifested by respiratory depression.

372. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

4. Claim 19

373. It is my opinion that claim 19 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse.

374. Claim 19 depends from claim 18 and recites the limitation that "said respiratory depression is caused by the illicit use of opioids, or by an accidental misuse of opioids during medical opioid therapy." '253 patent (Nalox1001), claim 19. The disclosures of the prior art in regard to the limitations of claim 18 are discussed above in section VII.E.3.

375. Wang discloses that "the object of the present invention is to overcome the shortcomings of current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others[.]" Nalox1008 at 7:15–20. Wang further discloses that "Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." *Id*. at 7:31–33.

376. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses that, "[o]f the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose." *Id.* at 1:41–44. A Formulator POSA would have understood that naloxone could be used to reverse the effects of opioid overdose resulting from both abuse of prescription opioid analgesics and heroin, as well as the accidental misuse of prescription opioid analgesics.

377. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 19	**Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse**
"wherein said respiratory depression is caused by the illicit use of opioids or by an accidental misuse of opioids during medical opioid therapy"	**WANG (Nalox1008)** "Naloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning, rescue for acute alcoholism and the like." (7:8–9). "The object of the present invention is to overcome the shortcomings of the current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others, with rapid absorption, high bioavailability, convenient use, and no need of special conditions." (7:15–20). "Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for

Claim 19	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
	the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." (7:31–33). **WYSE (Nalox1007)** "In 2008, poisoning surpassed motor vehicle accidents as the leading cause of 'injury deaths' in the United States (Warner 2011). Nearly 90% of poisoning deaths are caused by drugs. During the past 3 decades, the number of drug poisoning deaths increased six-fold from about 6,100 in 1980 to 36,500 in 2008. Of the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose (Warner 2011)." (1:36–44). "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression." (9:33–35). "In one aspect, the known or suspected opioid overdose may be manifested by respiratory and/or central nervous system depression." (10:1–3).

378. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

5. Claims 20–23

379. It is my opinion that claims 20–23 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse.

380. Claim 20 depends from claim 19 and recites the limitation that "said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." '253 patent (Nalox1001), claim 20. Claim 21 depends from claim 20 and recites the limitation that "said patient is free from respiratory depression for at least about 2 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 21. Claim 22 depends from claim 21 and recites the limitation that "said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 22. Claim 23 depends from claim 22 and recites that "said patient is free from respiratory depression for at least about 6 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 23. The disclosures of the prior art in regard to the limitations of claim 19 are discussed above in section VII.E.4.

381. Wyse discloses these limitations. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses that "the phrase 'treating an opioid overdose' includes 'reversing the effects of an opioid overdose." *Id.* at 9:35–37. Reversal of an opioid overdose would include ensuring that the patient was free of respiratory depression for an indefinite period after the opioid overdose—that is, administration of naloxone would reverse the effects of the overdose such that they do not recur and the patient resumes normal breathing activity.

382. Wyse further discloses a method for reversing the effects of opioid overdose by administering 200 µL of a 10 mg/mL naloxone solution divided into two half-doses (i.e., two 100 µL doses of 1 mg each, for a total dose of 2 mg), where each half-dose is administered intranasally. Nalox1007 at 10:13–24.

383. A Formulator POSA would have had a reasonable expectation of success that such intranasal administration of naloxone would reverse opioid overdose. Wermeling 2013 (Nalox1016) indicates that only 15–20% of cases require a repeat dose of naloxone due to overt toxicity such as central nervous system and respiratory depression recurring, which indicates that approximately

80–85% of opioid overdose patients have respiratory depression reversed indefinitely without a second dose of naloxone. *See* Nalox1016 at 71.

384. The below claim chart shows the relevant disclosures of each reference related to this element.

Claims 20–23	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
"wherein said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist" (claim 20) "wherein said patient is free from respiratory depression for at least about 2 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist" (claim 21) "wherein said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said	**WANG (Nalox1008)** "Naloxone hydrochloride is a morphine antagonist and can be used for first aid for morphine drug poisoning, rescue for acute alcoholism and the like." (7:8–9). "The object of the present invention is to overcome the shortcomings of the current preparations of naloxone hydrochloride injections and sublingual tablets, and to develop a novel single-dose and multi-dose nasal spray of naloxone hydrochloride which can be used by the patients themselves or used with the aid of others, with rapid absorption, high bioavailability, convenient use, and no need of special conditions." (7:15–20). "Another aspect of the invention relates to the use of the naloxone hydrochloride-containing nasal spray for the relief or treatment in first aid for morphine drug poisoning, acute alcoholism, and the like." (7:31–33). **WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject."

Claims 20–23	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
opioid antagonist" (claim 22) "wherein said patient is free from respiratory depression for at least about 6 hours following treatment comprising delivery of said therapeutically effective amount of said opioid antagonist" (claim 23)	(9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression. The phrase 'treating an opioid overdose' includes 'reversing the effects of an opioid overdose'." (9:33–37). "In one aspect, a method for reversing the effects of an opioid overdose in an individual in need thereof is disclosed, which may comprise the step of administering intranasally a dose of a naloxone composition, wherein the naloxone composition may comprise about 10 mg/mL naloxone HCl dihydrate, about 25 mM citric acid, about 10 mM EDTA, and about 0.5% benzyl alcohol; wherein said dose comprises about 200 µL of said naloxone composition; and wherein said dose is divided into two half doses; wherein each said half dose comprises about 100 µL of said composition; and wherein each said half dose may be administered intranasally to a subject in need thereof." (10:13–24). *See also* **WERMELING 2013 (Nalox1016)** "Due to naloxone's high metabolic clearance and the fact that most opioids have a longer persistence in the blood stream, the symptoms of withdrawal dissipate, and in about 15–20 % of cases, administration of a repeat dose of naloxone may become necessary if overt toxicity such as central nervous system and respiratory depression recur." (71).

385. Accordingly, it is my opinion that the prior art suggests these limitations of these claims.

6. Claim 24

386. It is my opinion that claim 24 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse.

387. Claim 24 depends from claim 16 and recites the limitation that "said patient is in a lying, supine, or recovery position." '253 patent (Nalox1001), claim 24. The disclosures Wang, Djupesland, HPE, Bahal, and Kushwaha in regard to the limitations of claim 16 are discussed above in section VII.D.9.

388. Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses a kit comprising a naloxone nasal spray composition with "instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) placing the individual on their back…" *Id*. at 12:12–17. Placing the individual on their back would put the individual in a lying position.

389. Again, it would have been obvious that a Formulator POSA could do the same with the intranasal naloxone compositions disclosed or suggested by Wang.

390. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 24	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
"wherein said patient is in a lying, supine, or recovery position"	**WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the kit may comprise a device as disclosed herein, and may further comprise instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) ***placing the individual on their back;*** b) inserting a first sprayer into the individual's nostril; c) aiming the nozzle towards the side of the individual's nose and away from the center of the nose;

Claim 24	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and Wyse
	d) pressing a plunger of the device firmly with the thumb of the administrator; e) repeating steps b through d with a second sprayer in the second nostril of the individual's nose; f) monitoring the individual and the breaths of the individual, wherein if the individual does not improve or if signs of opioid overdose reappear 3-5 minutes after administering the composition, the administrator repeats the steps of b through e with a second device. The term 'does not improve' means wherein the individual does not exhibit increased breathing rates, for example, wherein an individual does not achieve 10 to 12 breaths per minute within about 3 to about 5 minutes after administration." (12:12–33) (emphasis added).

391. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

F. A Formulator POSA reading Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent would have had ample reason and know-how to arrive at the subject matter of claims 8–9.

392. In my opinion, claims 8–9 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

393. The claim charts and discussion below show where each and every limitation of claims 8–9 are disclosed in Wang (Nalox1008), Djupesland

(Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), Kushwaha (Nalox1013), and the ’291 patent (Nalox1015).

394. It is my opinion that claims 8–9 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Wang (Nalox1008) in view of Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), Kushwaha (Nalox1013), and the ’291 patent (Nalox1015).

395. Claim 8 depends from claim 7 and recites the limitation that “the 90% confidence interval for dose delivered per actuation is ±about 2%.” ’253 patent (Nalox1001), claim 8. Claim 9 depends from claim 7 and recites the limitation that “the 95% confidence interval for dose delivered per actuation is ±about 2.5%.” *Id.*, claim 9. The disclosures of Wang, Djupesland, HPE, Bahal, and Kushwaha, with regard to the limitations of claim 7, are discussed above in section VII.D.7.

396. A Formulator POSA looking for information on the 90% or 95% confidence intervals of the dose delivered per actuation from single-use, pre-primed devices like the Aptar/Pfeiffer Unitdose device would have looked to the ’291 patent. The ’291 patent also discloses intranasal opioid compositions that can be delivered with a Pfeiffer Unitdose Second Generation Spray Device, which is a single-use, pre-primed device like the Aptar/Pfeiffer Unitdose device disclosed in Djupesland. *See* Nalox1015 at 8:2–4, 8:30–9:19.

397. The ’291 patent discloses a study to compare bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. *Id.* at 7:61–63. The formulation contained “10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0.” *Id.* at 7:63–67. This composition was loaded into a Pfeiffer “Unitdose Second Generation” in quantities sufficient to deliver 0.1 mL (100 µL) of the butorphanol test formulation. *Id.* at 8:13–18. The applicators were weighed prior to and after delivery of one dose into a subject’s nostril, with each patient receiving a total of two doses from two separate devices. *See id*. at 8:20–27. The weight of the pair of devices before and after delivery was compared and the difference was calculated to determine the dose delivered. *See id*. at 8:27–37.

398. For the 23 sets of two Pfeiffer Unitdose spray devices weighed before and after actuation, it was found that the two sprayers together had delivered a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams, (*id.* at 8:39–47), and a 95% confidence interval of (0.203 g, 0.209 g). *Id*. at 9:9–11. This corresponds to a 95% CI for the dose delivered over two sprays of about ±1.5% and a 90% CI for dose delivered over the two sprays of about ±0.9%. This indicates that, for the Pfeiffer Unitdose Spray device in combination with the formulation disclosed in the ’291 patent, the 90% confidence

interval for dose delivered is within ±about 2%, and that the 95% confidence interval for dose delivered is within ±about 2.5%. A Formulator POSA would have been motivated to achieve similar results through selection of an appropriate delivery device that reproducibly and consistently delivered the same dose upon each actuation, and the '291 patent evidences that such devices were available to a Formulator POSA prior to March 16, 2015. *See* paragraphs 87–88, *supra*.

399. A Formulator POSA would reasonably have expected the device to behave similarly when used in combination with the formulations suggested and taught by Wang, as the reliability and repeatability of dose delivery is a function of the device and the reproducibility of loading into the device. *See* '291 patent (Nalox1015) at 6:51–56 ("Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J.… These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition.").

400. The below claim chart shows the relevant disclosures of Wang in view of HPE, Djupesland, and the '291 patent related to this element.

Claims 8–9	**Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent**
"wherein the 90% confidence interval for dose delivered per actuation is ±about 2%"	**WANG (Nalox1008)** "The nasal spray of the present invention is used in a single dose or multi-dose form, and the administration amount of the nasal spray is 20–200 µl each time."

Claims 8–9	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent
(claim 8) "wherein the 95% confidence interval for dose delivered per actuation is ±about 2.5%" (claim 9)	(8:13–14). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

Claims 8–9	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent
	'291 PATENT (Nalox1015) "In accordance with one embodiment of the present invention, it has now been surprisingly found that intranasal pharmaceutical compositions can be made having improved bioavailability in terms of plasma opioid levels…. Opioids as herein include any substance naturally or synthetically derived from opium. Suitable opioids for use in the present invention include, but are not limited to, morphine, apomorphine, hydromorphone, oxymorphone, dihydromorphine, levorphanol, levallorphan, levophenacylmorphan, norlevorphanol, nalorphine, nalbuphine, buprenorphine, butorphanol, naloxone, naltrexone, nalmexone, oxilorphan, cyclorphan, ketobemidone, fentanyl, sufentanil, alfentanyl, or combinations thereof." (3:51–4:6). "Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J. and Valois of America, Inc. of Greenwich, Conn. These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition. These devices are easily operable by the patient, leave virtually no opioid remaining in the device after use and can thereafter be discarded without concern that others may abuse the opioid or other controlled substance." (6:51–60). "This example compares bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. The formulation contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0…. The second delivery system employed to administer

Claims 8–9	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent
	the butorphanol compositions was a unit-dose disposable intranasal applicator that is commercially available from Pfeiffer of America under the designation 'Unitdose Second Generation.' Each of the Pfeiffer spray applicators was charged with sufficient liquid to deliver a 0.1 mL dose of the butorphanol test formulation. The glass containers were filled using a pipette under clean conditions, sealed and assembled to the applicator. Each of the applicators was weighed prior to use and after use. Qualified medical personnel administered, one dose into each nostril, after which the applicator was recovered for weighing. In the case of the unit-dose applicators (test formulation), two devices were used for each patient, both of which were discarded following the post-use weighing. The results of these studies of the method and system of the invention and the comparative prior art method follow…. Unit-Dose: The statistical comparison of dose 1 and dose 2 for the test formulation unit dose delivery system was done using a paired t-test. Analysis of the data indicated that the difference between the mean, sprays of the two applications using the Pfeiffer device was not statistically significant (t=1.0; p=0.3). The sample of 23 sprayers (actually 23 sets of 2 sprayers, since they were single-dose) had a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams. … A t-test was used in each case to compare the observed sample mean to the desired weight of 0.2 grams. The unit-dose sprayer dispensed a mean total weight that was significantly higher than the goal of 0.2 grams

Claims 8–9	Wang in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent
	(t=4.4; p<0.001). A 95% confidence interval for the mean total weight dispensed by the unit-dose sprayer is (0.203, 0.209)." (7:60–9:11).

401. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

G. A Formulator POSA reading Davies in view of HPE, Bahal, and Kushwaha would have had ample reason and know-how to arrive at the subject matter of claims 1–4 and 16–24.

402. In my opinion, claims 1–4 and 16–24 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

403. The claim charts and discussion below show where each and every limitation of claims 1–4 and 16–24 are disclosed in Davies (Nalox1009), HPE (Nalox1012), Bahal (Nalox1014), and Kushwaha (Nalox1013).

404. It is my opinion that claims 1–4 and 16–24 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies (Nalox1009) in view of HPE (Nalox1012), Bahal (Nalox1014), and Kushwaha (Nalox1013).

1. Claim 1

405. It is my opinion that claim 1 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

406. Claim 1 recites the following:

> 1. 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 of 3.5-5.5.

'253 patent (Nalox1001), claim 1.

(a) Preamble: "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"

407. The preamble of claim 1 recites "[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."

408. Davies discloses this element. Davies discloses naloxone formulations that may be delivered through "[s]uitable spray applicators" which "are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." Nalox1009 at 2:1–3. Davies further discloses that such devices function as follows: "With the

part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. by placing the fore-finger and second finger on the surfaces 13,14 and the thumb on the end of the reservoir and squeezing. This forces liquid from the reservoir along passage 11, out of cross bore 12 and into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6." *Id.* at 5:14–19.

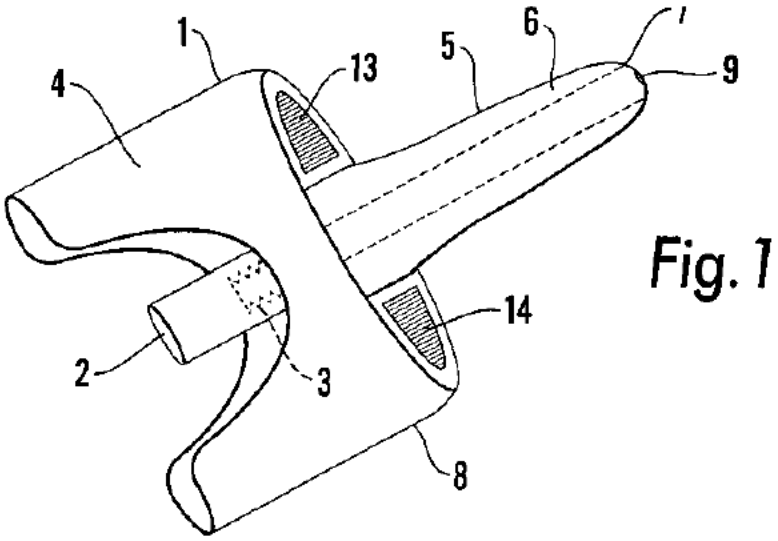
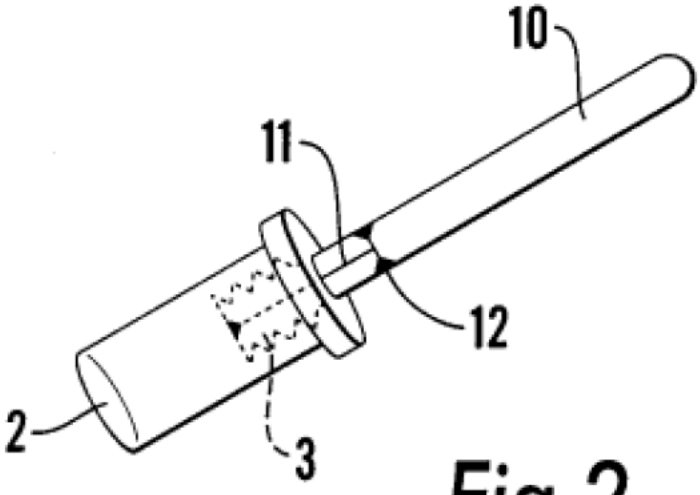
409. Davies discloses that "A solution of the drug to be dispensed is contained in reservoir 2…" Nalox1009 at 5:4. Davies further discloses that "[t]he assembly consisting of the reservoir 2 and piston 3 and piston rod 10 are fitted into the body 4 of the applicator by introducing the rod 10 into the tube 6." *Id.* at 5:10–14. A Formulator POSA would have understood this as being a single reservoir, as Davies does not disclose that the device contains another reservoir.

410. A Formulator POSA would have recognized Davies as disclosing a single-use, pre-primed device adapted for nasal delivery having a single reservoir. In particular, a Formulator POSA would have recognized the device as "single-use" from the fact that the device may be a "single-trip" device that delivers the pharmaceutical composition upon actuation. Furthermore, a Formulator POSA would have recognized that such a device would inherently have to be "pre-primed," because it could only be actuated once, and would thus be "capable of delivering a pharmaceutical composition to a patient in need thereof with the first

actuation of the spray pump," as the patentee defined "pre-primed" in the '253 patent. *See* section V.1, above.

411. The below claim chart shows the relevant disclosures of Davies in view of HPE, Bahal, and Kushwaha related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"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"	**DAVIES (Nalox1009)** "According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:14–19). "Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." (2:1–3). "A solution of the drug to be dispensed is contained in reservoir 2…." (5:4). "The assembly consisting of the reservoir 2 and piston 3 and piston rod 10 are fitted into the body 4 of the applicator by introducing the rod 10 into the tube 6." (5:10–12). "The device works as follows. With the part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. by placing the fore-finger and second finger on the surfaces 13,14 and the thumb on the end of the reservoir and squeezing. This forces liquid from the reservoir along passage 11, out of cross bore 12 and

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6. Tube 6 may be tapered slightly towards the orifice so that higher pressure can be developed within its distal end. It will be appreciated that by shaping the projecting part 5 as a tapering fit in the nostril, a major amount of the composition is retained in the nasal passages." (5:14–22).  Fig. 1  Fig.2

412. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(b) 1.1: "a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:"

413. Element 1.1 of claim 1 recites "a pharmaceutical composition which is an aqueous solution of about 100 µL comprising."

414. Davies discloses this element. Davies discloses naloxone formulations that may be delivered through "[s]uitable spray applicators" which "are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." Nalox1009 at 2:1–3. Davies further discloses that "Preferably, naloxone is used as a sprayable liquid composition." *Id.* at 2:16–17. Davies further discloses that "Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g., approximately isotonic salt solution." *Id.* at 2:22–26. Davies further discloses that, for intranasal administration of a solution, "the shot volume could vary between 20µl and 100µl…." (*Id.* 3:3–4). A Formulator POSA would have immediately envisaged a 100 µL spray volume from this disclosure, as this is a fairly standard volume delivered from single-dose nasal spray devices. *See, e.g.*, Nalox1010 at 49.

415. The below claim chart shows the relevant disclosures related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"a pharmaceutical composition which is an aqueous solution of about 100 µL comprising"	**DAVIES (Nalox1009)** "According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:14–19). "Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." (2:1–3). "Preferably, naloxone is used as a sprayable liquid composition…." (2:16–17). "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µ1 and 100µ1, with the dose per shot preferably varying between 200 and 1200µg." (2:19–3:4).

416. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(c) 1.2: "about 4 mg naloxone hydrochloride or a hydrate thereof;"

417. Element 1.2 of claim 1 recites that the pharmaceutical composition comprises "about 4 mg naloxone hydrochloride or a hydrate thereof."

418. Davies discloses this element. Davies discloses that "a preferred opioid antagonist for use in the compositions of this invention is naloxone…" Nalox1009 at 2:11–12. Davies further discloses that the naloxone is soluble in water when in the form of the hydrochloride salt. *See id.* at 2:28–29. Davies further discloses that "Suitable dosage units are in the range of 0.2 to 5 mg…" *Id*. at 3:2. A Formulator POSA would have recognized this as encompassing a dose of about 4 mg.

419. Although Davies does not explicitly disclose using the dihydrate form, a Formulator POSA would have recognized that the dihydrate form of naloxone existed and was useful in the disclosed nasal sprays. It was well-known that naloxone hydrochloride is frequently supplied as the dihydrate form. *See* Wermeling 2013 (Nalox1016) at 66 ("Naloxone is supplied as naloxone HCl dihydrate"). Further, a Formulator POSA would have recognized that one would have to modify the dose of naloxone hydrochloride (anhydrous) on a weight basis to account for the presence of the two water molecules associated with the

crystalline solid.[23] Moreover, a Formulator POSA would have expected the anhydrous and dihydrate forms of naloxone hydrochloride, once dissolved in aqueous medium, to behave identically.

420. The below claim chart shows the relevant disclosures of Davies related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"about 4 mg naloxone hydrochloride or a hydrate thereof"	**DAVIES (Nalox1009)** "Preferably, naloxone is used as a sprayable liquid composition…." (2:16–17). "Naloxone and naltrexone are both freely soluble and water and aqueous alcohol when in the form of a salt, such as a hydrochloride." (2:28–29). "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µl

[23] Naloxone hydrochloride dihydrate has a molecular weight of 399.9 g/mol, and water has an approximate molecular weight of 18.02. The molecular weight of the anhydrous naloxone hydrochloride would therefore be about 363.8 g/mol, indicating that a Formulator POSA would need to include about 1.1 times as much of the dihydrate as the anhydrous naloxone hydrochloride to achieve an identical quantity of naloxone.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	and 100µ1, with the dose per shot preferably varying between 200 and 1200µg." (2:19–3:4).

421. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(d) 1.3: "between about 0.2 mg and about 1.2 mg of an isotonicity agent;"

422. Element 1.3 of claim 1 recites that the pharmaceutical composition comprises "between about 0.2 mg and about 1.2 mg of an isotonicity agent."

423. Davies discloses this element. Davies discloses that "the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution. A concentration of about 0.9% weight/volume NaCl in purified water is suitable." Nalox1009 at 2:23–26. About 0.9% weight/volume in 100 µL of solution would have been about 0.9 mg.

424. The below claim chart shows the relevant disclosures of Davies related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"between about 0.2 mg and about 1.2 mg of an isotonicity agent"	**DAVIES (Nalox1009)** "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution,

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µl and 100µl, with the dose per shot preferably varying between 200 and 1200µg." (2:19–3:4).

425. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(e) 1.4: "between about 0.005 mg and about 0.015 mg of a preservative;"

426. Element 1.4 of claim 1 recites that the pharmaceutical composition comprises "between about 0.005 mg and about 0.015 mg of a preservative."

427. It would have been obvious to a Formulator POSA to include between about 0.005 to 0.015 mg of a preservative in such a formulation from the disclosure of Davies. Davies discloses, in Example 1, a sprayable aqueous liquid composition of naloxone hydrochloride for a nasal applicator in which "Benzalkonium chloride was added to the hydrochloride solution in an amount of 0.025% weight/volume as a preservative." Nalox1009 at 3:30–4:2.

428. A Formulator POSA would have known that a lower concentration of benzalkonium chloride could be used in a nasal formulation, particularly from the disclosure of HPE. HPE—a standard compendium of monographs regarding various pharmaceutical excipients—discloses that benzalkonium chloride is useful as an antimicrobial preservative in nasal formulations in concentrations of 0.002%

to 0.02% (w/v). Nalox1012 at 56. A Formulator POSA reviewing Davies would have been motivated to review the HPE's monograph regarding benzalkonium chloride from Davies's disclosure of its use in a nasal formulation, and would have been motivated to reduce the concentration of benzalkonium chloride accordingly for any number of reasons (including cost savings, making the formulation appear more acceptable to regulatory authorities, or others). Furthermore, HPE discloses that "Benzalkonium chloride 0.01% is also employed as a preservative in small-volume parenteral products," which indicates that a Formulator POSA would have immediately envisaged that such an amount could be used in a nasal formulation from the disclosure of HPE. *Id*.

429. The below claim chart shows the relevant disclosures of Davies and HPE related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"between about 0.005 mg and about 0.015 mg of a preservative"	**DAVIES (Nalox1009)** "Example 1 Sprayable aqueous liquid composition for a nasal applicator. Naloxone hydrochloride was dissolved in a solution of purified water to form a solution containing 0.8% weight/volume of the naloxone. Benzalkonium chloride was added to the hydrochloride solution in an amount of 0.025% weight/volume as a preservative. The solution may be buffered to a pH of about 6.5 using a phosphate buffer (sodium or potassium hydrogen phosphate). The solution was packaged into a dispenser as shown in the accompanying drawing,

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	giving a shot volume of 50 µL (microlitre) which is equivalent to a unit dose of 400 µg (microgram) per shot." (3:27–4:5). **HPE (Nalox1012)** "Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative… In nasal, and otic formulations a concentration of 0.002–0.02% w/v is used…Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products." (56).

430. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(f) 1.5: "about 0.2 mg of a stabilizing agent;"

431. Element 1.5 of claim 1 recites that the pharmaceutical composition comprises "about 0.2 mg of a stabilizing agent."

432. It would have been obvious to include a stabilizing agent in the formulation from the combined disclosures of Davies, HPE, Bahal, and Kushwaha. Davies discloses using benzalkonium chloride as a preservative in a naloxone nasal spray formulation. *See, e.g.*, Nalox1009 at 3:30–4:2. While Davies does not disclose including a stabilizing agent, such as disodium edetate,[24] to the nasal spray solution, a Formulator POSA would have been motivated to add disodium edetate

[24] The '253 patent notes that disodium edetate is a "stabilizing agent." *See, e.g.*, '253 patent (Nalox1001) at 21:30.

to the solution disclosed in Davies for at least three reasons: the addition of disodium edetate was known to improve the antimicrobial activity of benzalkonium chloride; second, disodium edetate was known to stabilize naloxone against oxidative degradation in solution; and third, disodium edetate can act as a permeation enhancer in nasal sprays.

433. First, disodium edetate was known to improve the antimicrobial activity of benzalkonium chloride. HPE discloses that, in ophthalmic solutions, benzalkonium chloride is often "used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*," particularly in ophthalmic solutions. *See* Nalox1012 at 56. Likewise, HPE also discloses that "Benzalkonium chloride is ineffective against some *Pseudomonas* aeruginosa strains, *Mycobacterium tuberculosis*, *Trichophyton interdigitale*, and *T. rubrum*. However, combined with disodium edetate (0.01–0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against *Pseudomonas aeruginosa* is increased." *Id.* These disclosures would have motivated a Formulator POSA to include disodium edetate in a nasal spray formulation of naloxone including benzalkonium chloride.

434. Second, it was known that disodium edetate specifically was useful in stabilizing naloxone against oxidative degradation. Bahal discloses that chelating

agents, such as disodium edetate, can prevent degradation of naloxone in solution. Specifically, Bahal discloses the following:

> Instability of naloxone solution has been observed in the manufactured product. Autoclaving of currently available formulations of naloxone caused significant degradation of naloxone and formation of noroxymorphone. The degradation rates depended on headspace oxygen content. When non-autoclaved samples were sparged/flushed with nitrogen, no significant changes were observed in naloxone and bisnaloxone levels. However, noroxymorphone level increased from 0.08% to 0.4% over a six-week period at 60° C. It has now been found that addition of a chelating agent, such as sodium edetate, to the commercial formulation prevents naloxone degradation, even in the presence of oxygen and after autoclaving.

Nalox1014 at 1:45–57. Bahal further discloses incorporating a stabilizing agent, which can be sodium edetate, in a concentration of 0.0001 to 1%. *See id*. at 2:48–51 and 2:63–67.

435. Although Bahal is directed to an injectable solution of naloxone, a Formulator POSA would have been motivated to combine the teachings of this reference with Davies because both relate to solution formulations of naloxone, and a Formulator POSA would have been motivated to add ingredients to a naloxone nasal spray known to stabilize naloxone against oxidative degradation and oxidation.

436. A Formulator POSA would have further had a reasonable expectation of success that addition of disodium edetate to a naloxone nasal spray would have been safe for patients, as it is a commonly-used excipient in injectable and other

formulations. Both Kushwaha and HPE disclose use of disodium EDTA in nasal sprays.

437. Third, a Formulator POSA would have been motivated to add disodium edetate to a nasal spray formulation as it is a known permeation enhancer. Kushwaha, discloses a list of excipients that can serve as permeation enhancers in intranasal dosage forms, such as that disclosed by Davies. *See* Nalox1013 at 25–26. Kushwaha discloses that EDTA (which a Formulator POSA would have understood to be edetic acid and can be used as an equivalent to disodium edetate after adjusting for the additional sodium ions included in the crystalline solid form of disodium edetate) is a chelator that can serve as a permeation enhancer for small-molecule and large molecule drugs. *Id.* at 25–26. Based on this disclosure, a Formulator POSA would have reasonably expected disodium EDTA, i.e., disodium edetate, not to have any detrimental effects on naloxone absorption or bioavailability at the concentrations given in Bahal, and possibly a beneficial effect.

438. These combined disclosures would have motivated a Formulator POSA to include disodium edetate and benzalkonium chloride together in a naloxone nasal spray, as the combination of these ingredients would have been expected to have synergistic antimicrobial activity, based on the combination of Davies and HPE, and the combination of Davies and Bahal would have led a

Formulator POSA to conclude that disodium edetate stabilized naloxone and prevented its oxidative degradation in solution.

439. A Formulator POSA would further have been motivated to include disodium edetate in the claimed amount of 0.2 mg per 100 µL (or 0.2% by weight). Bahal discloses that preferred concentrations of stabilizing agents (including sodium edetate) are between 0.0001% by weight to 1% by weight. Nalox1014 at 2:65–67. As Bahal discloses that concentrations of as low as 0.1% by weight of sodium edetate were sufficient to stabilize low concentrations of naloxone (0.04%) from degradation during autoclaving and exposure to oxygen. *See id.* at 7:1–8:67. A Formulator POSA would reasonably have expected that higher concentrations, such as 0.2%, 0.3%, 0.4%, etc. would also serve to stabilize naloxone.

440. The below claim chart shows the relevant disclosures of Davies, HPE, Bahal, and Kushwaha related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"about 0.2 mg of a stabilizing agent"	**DAVIES (Nalox1009)** "Example 1 Sprayable aqueous liquid composition for a nasal applicator. Naloxone hydrochloride was dissolved in a solution of purified water to form a solution containing 0.8% weight/volume of the naloxone. Benzalkonium chloride was added to the hydrochloride solution in an amount of 0.025% weight/volume as a preservative. The solution may be buffered to a pH of about 6.5 using a phosphate buffer (sodium or potassium hydrogen phosphate). The solution was packaged into a dispenser as shown in the accompanying

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	drawing, giving a shot volume of 50 µL (microlitre) which is equivalent to a unit dose of 400 µg (microgram) per shot." (3:27–4:5). **HPE (Nalox1012)** "In ophthalmic preparations, benzalkonium chloride is one of the most widely used preservatives, at a concentration of 0.01–0.02% w/v. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of Pseudomonas." (56). "Benzalkonium chloride is ineffective against some Pseudomonas aeruginosa strains, Mycobacterium tuberculosis, Trichophyton interdigitale, and T. rubrum. However, combined with disodium edetate (0.01–0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against Pseudomonas aeruginosa is increased." (*Id.*). **BAHAL (Nalox1014)** "Instability of naloxone solution has been observed in the manufactured product. Autoclaving of currently available formulations of naloxone caused significant degradation of naloxone and formation of noroxymorphone. The degradation rates depended on headspace oxygen content. When non-autoclaved samples were sparged/flushed with nitrogen, no significant changes were observed in naloxone and bisnaloxone levels. However, noroxymorphone level increased from 0.08% to 0.4% over a six-week period at 60° C. It has now been found that addition of a chelating agent, such as sodium edetate, to the commercial formulation prevents naloxone degradation, even in the presence of oxygen and after autoclaving." (1:45–57). "Ready-to-use injectable solution formulations of naloxone with improved chemical and physical stability are preferably composed of an effective amount of naloxone hydrochloride, an acid or a buffer to yield a final solution pH of 3–3.5, one or

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	more tonicity adjusting agents, and a stabilizing agent selected from sodium edetate, citrate and/or ethylenediamine tetraacetic acid and its other salts Said compositions are autoclaved for sterilization." (2:44–51). "Preferred concentrations of the stabilizing agents are 0.0001 to 1% . Specifically preferred concentrations are 0.001 to 0.1%." (2:65–67). *See also* 7:1–8:67. **KUSHWAHA (Nalox1013)** "Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show insufficient bioavailability. Their permeation can improve by being administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier. **(Table-1)**."

Claim 1	Davies in view of HPE, Bahal, and Kushwaha

Table 1: Mucosal penetration enhancers and mechanisms of action.

Classification	Examples	Mechanism
Surfactants	Anionic: Sodium lauryl sulphate Cationic:Cetylpyridiniu m Chloride Nonionic:Poloxamer,Spa n,Tween	Perturbation of intercellular lipids, Protein domain integrity, Distrusts membrane
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate	Distrusts membrane, Open tight junctions, Mucolytic activity
Cyclodextrins	α,β,γ Cyclodextrin, Methylated β–Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Fatty acids	Oleic acid, Methyloleate, Lauric acid, Caprylic acid, Phosphotidylcholine	Increase fluidity of phospholipid domains, Distrusts membrane
Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface
Chelators	EDTA, Citric Acid, Sodium citrate, Sodium Salicylate	Interfere with Ca Polyacrylates
+ve charged polymers	Chitosan,Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Bioadhesive Materials	Carbopol, Starch, Chitosan	Reduce nasal clearance, Open tight junctions

(25–26).

441. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

(g) 1.6: "an amount of an acid sufficient to achieve a pH of 3.5-5.5."

442. Element 1.6 of claim 1 recites that the pharmaceutical composition comprises "an amount of an acid sufficient to achieve a pH of 3.5-5.5."

443. This would have been obvious in view of the combination of Davies, Bahal, and Kushwaha. Davies discloses that "[t]he composition may include a buffering agent to maintain the opioid in solution in the salt form, e.g. a phosphate buffer, such as sodium hydrogen phosphate to maintain the solution at a slightly acid pH." Nalox1009 at 2:26–28. While Davies does not disclose using hydrochloric acid to reach the target pH, Bahal teaches adjusting the pH of naloxone solutions with hydrochloric acid to a pH of 3–3.5. *See* Nalox1014 at 2:44–53. A Formulator POSA specifically would have been motivated to use hydrochloric acid to adjust the pH, as Bahal discloses that it can be used with naloxone hydrochloride, while HPE teaches that the other pH-adjusting agents (specifically, phosphates and citrates) taught by Bahal and Davies can reduce the antimicrobial activity of benzalkonium chloride against *Pseudomonas*. *See* Nalox1012 at 56 ("In the presence of citrate and phosphate buffers (but not borate), activity against *Pseudomonas* can be reduced."). Furthermore, as discussed above in paragraph 59, a Formulator POSA would have been motivated to choose hydrochloric acid as an acidifying agent, as the counterion (Cl^-) is the same as that of naloxone hydrochloride, and thus would not be expected to result in any insoluble precipitates on combination with cationic naloxone that otherwise may have negative effects on the stability of the formulation.

444. A Formulator POSA further would have been motivated to adjust the pH to between 3.5 and 5.5. As discussed above in paragraphs 49–51, a Formulator POSA would have been motivated to select a pH of below 5.5 to minimize the susceptibility of naloxone to oxidation. However, as discussed in paragraph 59, Kushwaha disclosed that nasal irritation is minimized when products are delivered with pH in the range of 4.5 to 6.5, which would have motivated a Formulator POSA to adjust the pH to somewhere within the range of 4.5 to 5.5, in order to render the formulation less irritating while maintaining stability of the naloxone active ingredient against oxidation. *See* Nalox1013 at 23 (disclosing that nasal irritation is minimized when the pH is 4.5–6.5). A Formulator POSA thus would have considered it obvious to adjust the pH to between 3.5 and 5.5.[25]

445. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
"an amount of an acid sufficient to achieve a pH of 3.5-5.5."	**DAVIES (Nalox1009)** "The composition may include a buffering agent to maintain the opioid in solution in the salt form, e.g. a phosphate buffer, such as sodium hydrogen phosphate to maintain the solution at a slightly acid pH." (2:26–28).

[25] Further, as noted above, both Wang and Wyse disclose using hydrochloric acid to acidify naloxone hydrochloride nasal sprays to a pH between 3.5 and 5.5. *See* sections VII.A.1(g) (paragraphs 144-147) and VII.D.1(g) (paragraphs 293-295).

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	"Example 1 Sprayable aqueous liquid composition for a nasal applicator. Naloxone hydrochloride was dissolved in a solution of purified water to form a solution containing 0.8% weight/volume of the naloxone. Benzalkonium chloride was added to the hydrochloride solution in an amount of 0.025% weight/volume as a preservative. The solution may be buffered to a pH of about 6.5 using a phosphate buffer (sodium or potassium hydrogen phosphate). The solution was packaged into a dispenser as shown in the accompanying drawing, giving a shot volume of 50 µL (microlitre) which is equivalent to a unit dose of 400 µg (microgram) per shot." (3:27–4:5). **HPE (Nalox1012)** "In the presence of citrate and phosphate buffers (but not borate), activity against Pseudomonas can be reduced." (56). **BAHAL (Nalox1014)** "Preferred compositions use dilute hydrochloric acid, acetate, citrate or phosphate [sic] to adjust the pH to 3–3.5. Specifically preferred compositions use dilute hydrochloric acid to adjust the pH to about 3.2." (2:52–55, *see also* Example 1, 3:1–5:52). *See also* Rosanske at 605; Nalox1013 at 23 ("[n]asal irritation is minimized when products are delivered with pH, in the range of 4.5 to 6.5"); and Nalox1015 at 6:18–24 ("[G]enerally for nasal administration a mildly acid pH will be preferred. The pH ranges from about 3 to 6 are preferred, more preferred pH ranges are from about 3 to about 5, and most preferred ranges are from about 4 to about 5. If adjustment of the pH is needed, it can be achieved by the addition of an

Claim 1	Davies in view of HPE, Bahal, and Kushwaha
	appropriate acid, such as hydrochloric acid[.]").

446. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

2. Claim 2

447. It is my opinion that claim 2 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

448. Claim 2 depends from claim 1 and recites the limitations that "the isotonicity agent is NaCl; the preservative is benzalkonium chloride; the stabilizing agent is disodium edetate; and the acid is hydrochloric acid." The disclosures of the prior art in regard to the limitations of claim 1 are discussed above in section VII.G.1.

(a) "the isotonicity agent is NaCl;"

449. As discussed above in section VII.G.1(d), Davies discloses including the recited amount of sodium chloride as an isotonicity agent.

(b) "the preservative is benzalkonium chloride;"

450. As discussed above in section VII.G.1(e), Davies discloses including benzalkonium chloride as a preservative, and the prior art as a whole would have suggested its use in the recited amounts in the pharmaceutical composition.

(c) "the stabilizing agent is disodium edetate;"

451. As discussed above in section VII.G.1(f), a Formulator POSA would have been motivated from the disclosures of HPE, Bahal, and Kushwaha to include disodium edetate in the recited amount in an intranasal naloxone composition.

(d) "and the acid is hydrochloric acid."

452. As discussed above in section VII.G.1(g), the combination of Bahal, Kushwaha, and HPE with Davies would have motivated a Formulator POSA to adjust the pH of the pharmaceutical composition to 3.5 to 5.5 with hydrochloric acid.

3. Claim 3

453. It is my opinion that claim 3 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

454. Claim 3 depends from claim 2 and recites the limitations that "the aqueous solution comprises: about 4.4 mg naloxone hydrochloride dihydrate; about 0.74 mg NaCl; about 0.01 mg benzalkonium chloride; about 0.2 mg disodium edetate; and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5." The disclosures of the prior art in regard to the limitations of claim 2 are discussed above in section VII.G.2.

(a) "about 4.4 mg naloxone hydrochloride dihydrate;"

455. Davies suggests this element. Davies discloses that "a preferred opioid antagonist for use in the compositions of this invention is naloxone…" Nalox1009 at 2:11–12. Davies further discloses that the naloxone is soluble in water when in the form of the hydrochloride salt. *See id.* at 2:28–29. Davies further discloses that "Suitable dosage units are in the range of 0.2 to 5 mg…" *Id*. at 3:2. A Formulator POSA would have recognized this as encompassing a dose of about 4 mg.

456. Although Davies does not explicitly disclose using the dihydrate form, a Formulator POSA would have recognized that the dihydrate form of naloxone existed and was useful in the disclosed nasal sprays. It was well-known that naloxone hydrochloride is frequently supplied as the dihydrate form. *See* Wermeling 2013 (Nalox1016) at 66 ("Naloxone is supplied as naloxone HCl dihydrate"). Further, a Formulator POSA would have recognized that one would have to modify the dose of naloxone hydrochloride (anhydrous) on a weight basis to account for the presence of the two water molecules associated with the crystalline solid.[26] Moreover, a Formulator POSA would have expected the

[26] Naloxone hydrochloride dihydrate has a molecular weight of 399.9 g/mol, and water has an approximate molecular weight of 18.02. The molecular weight of the anhydrous naloxone hydrochloride would therefore be about 363.8 g/mol, indicating that a Formulator POSA would need to include about 1.1 times as much of the dihydrate as the anhydrous naloxone hydrochloride to achieve an identical quantity of naloxone.

anhydrous and dihydrate forms of naloxone hydrochloride, once dissolved in aqueous medium, to behave identically.

457. The below claim chart shows the relevant disclosures of Davies related to this element.

Claim 3	Davies in view of HPE, Bahal, and Kushwaha
"about 4.4 mg naloxone hydrochloride dihydrate"	**DAVIES (Nalox1009)** "Preferably, naloxone is used as a sprayable liquid composition…." (2:16–17). "Naloxone and naltrexone are both freely soluble and water and aqueous alcohol when in the form of a salt, such as a hydrochloride." (2:28–29). "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µl and 100µl, with the dose per shot preferably varying between 200 and 1200µg." (2:19–3:4).

458. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

(b) "about 0.74 mg NaCl;"

459. Davies suggests this element. Davies discloses that "the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution. A concentration of about 0.9% weight/volume NaCl in purified water is suitable." Nalox1009 at 2:23–26. About 0.9% weight/volume in 100 µL of solution would have been about 0.9 mg. As a Formulator POSA would have known that a range of tonicities are acceptable in nasal formulations (*see supra* paragraph 58) and would have recognized that a 0.9% w/v sodium chloride solution also containing the drug and additional excipients would have been at least slightly hypertonic. As such, a Formulator POSA who was seeking to make an isotonic or less hypertonic nasal spray, in accordance with the disclosures in the prior art, would have been motivated to adjust the concentration of sodium chloride downwards slightly to arrive at an approximately isotonic or slightly hypertonic solution.

460. The below claim chart shows the relevant disclosures of Davies related to this element.

Claim 3	Davies in view of HPE, Bahal, and Kushwaha
"about 0.74 mg NaCl"	**DAVIES (Nalox1009)** "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in

Claim 3	Davies in view of HPE, Bahal, and Kushwaha
	water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µ1 and 100µ1, with the dose per shot preferably varying between 200 and 1200µg." (2:19–3:4).

461. Accordingly, it is my opinion that the prior art suggests this limitation of the claim.

(c) "about 0.01 mg benzalkonium chloride;"

462. As discussed above in section VII.G.1(e), the use of benzalkonium chloride would have been obvious from the combined disclosures of Davies, HPE, Bahal and Kushwaha. Further, the use of 0.01% (w/v) benzalkonium chloride would have been obvious from the disclosure of Davies, particularly in view of HPE. HPE discloses using between 0.002% (w/v) and 0.02% (w/v) benzalkonium chloride in nasal spray solutions as a preservative, and that it is used in 0.01% (w/v) concentrations in concentrated injectable solutions. *See* Nalox1012 at 56. A Formulator POSA would have immediately envisaged that one could use a concentration of about 0.01 % (w/v) in a nasal spray from this disclosure.

(d) "about 0.2 mg disodium edetate;"

463. The combination of Davies, HPE, Bahal, and Kushwaha would have motivated a Formulator POSA to use disodium edetate in a naloxone nasal spray in the amount recited, as discussed above in section VII.G.1(f).

(e) "and an amount of hydrochloric acid sufficient to achieve a pH of 3.5-5.5."

464. As discussed above in section VII.G.1(g), the combination of Bahal, Kushwaha, and HPE with Davies would have motivated a Formulator POSA to adjust the pH of the pharmaceutical composition to 3.5 to 5.5 with hydrochloric acid.

4. Claim 4

465. It is my opinion that claim 4 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

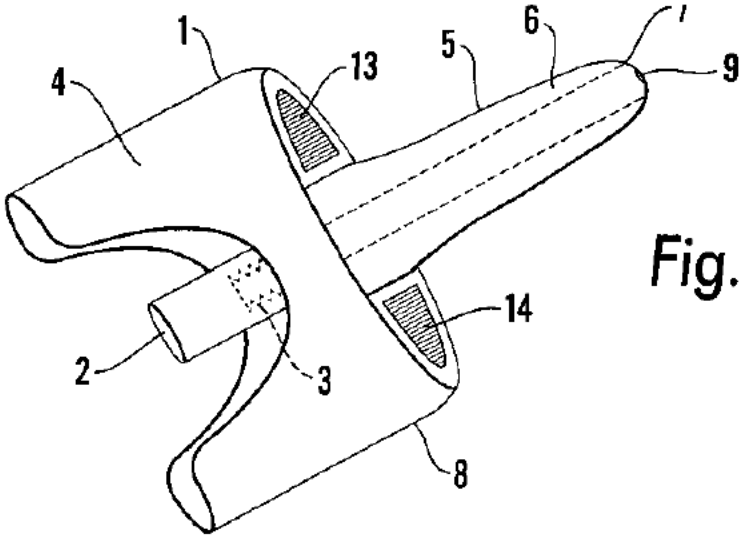
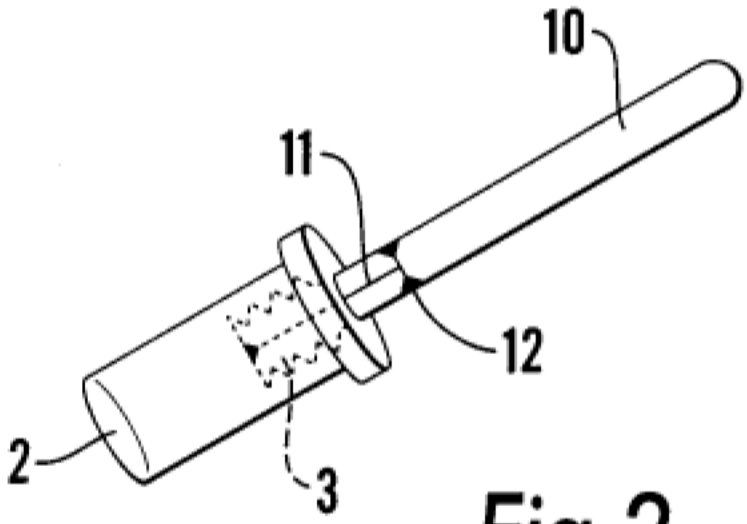
466. Claim 4 depends from claim 2 and recites the limitation that "said device is actuatable with one hand." The disclosures of the prior art in regard to the limitations of claim 2 are discussed above in section VII.G.2.

467. Davies further discloses that the devices therein are actuatable with one hand. Specifically, Davies discloses that "With the part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. ***by placing the fore-finger and second finger on the surfaces 13,14 and the thumb on the end of the***

reservoir and squeezing. This forces liquid from the reservoir along passage 11, out of cross bore 12 and into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6." Nalox1009 at 5:14–19 (emphasis added). This describes a single-handed actuation of the device.

468. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 4	Davies in view of HPE, Bahal, and Kushwaha
"wherein said device is actuatable with one hand"	**DAVIES (Nalox1009)** "According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:14–19). "Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." (2:1–3). "The device works as follows. With the part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. by placing the fore-finger and second finger on the surfaces 13,14 and the thumb on the end of the reservoir and squeezing. This forces liquid from the reservoir along passage 11, out of cross bore 12 and into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6. Tube 6 may be tapered slightly towards the orifice so that higher pressure can be

Claim 4	Davies in view of HPE, Bahal, and Kushwaha
	developed within its distal end. It will be appreciated that by shaping the projecting part 5 as a tapering fit in the nostril, a major amount of the composition is retained in the nasal passages." (5:14–22).  Fig. 1  Fig.2

469. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

5. Claim 16

470. It is my opinion that claim 16 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

471. Claim 16 depends from claim 1 and recites the limitation that "wherein said patient is an opioid overdose patient or a suspected opioid overdose patient." The disclosures of the prior art in regard to the limitations of claim 16 are discussed above in section VII.G.1.

472. Davies discloses this element. Davies discloses that "[a]ddicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage." Nalox1009 at 1:4–12. Davies further discloses that the "invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal

administration for treatment of patients suffering from opioid over-dosage." *Id.* at 1:1–3.

473. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 16	Davies in view of HPE, Bahal, and Kushwaha
"wherein said patient is an opioid overdose patient or a suspected opioid overdose patient."	**DAVIES (Nalox1009)** "This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage. Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage. According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator

Claim 16	Davies in view of HPE, Bahal, and Kushwaha
	comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:1–18).

474. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

6. Claim 17

475. It is my opinion that claim 17 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

476. Claim 17 depends from claim 16 and recites the limitation that "the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia, sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting." '253 patent (Nalox1001), claim 17. The disclosures of the prior art in regard to the limitations of claim 16 are discussed above in section VII.G.5.

477. Davies discloses this element. Davies discloses that "[a]ddicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists

may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage." Nalox1009 at 1:4–12. Davies further discloses that the "invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage." *Id.* at 1:1–3.

478. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 17	Davies in view of HPE, Bahal, and Kushwaha
"wherein the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia; sedation, hypotension,	**DAVIES (Nalox1009)** "This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage. Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out

Claim 17	Davies in view of HPE, Bahal, and Kushwaha
unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting."	successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage. According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:1–18).

479. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

7. Claim 18

480. It is my opinion that claim 18 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

481. Claim 18 depends from claim 17 and recites the limitation that "the patient exhibits respiratory depression." '253 patent (Nalox1001), claim 18. The disclosures of the prior art in regard to the limitations of claim 17 are discussed above in section VII.G.6. As discussed in that section, Davies discloses

administering intranasal naloxone compositions to patients experiencing opioid overdose, which may be manifested by respiratory depression.

482. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

8. Claim 19

483. It is my opinion that claim 19 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

484. Claim 19 depends from claim 18 and recites the limitation that "said respiratory depression is caused by the illicit use of opioids, or by an accidental misuse of opioids during medical opioid therapy." '253 patent (Nalox1001), claim 19. The disclosures of the prior art in regard to the limitations of claim 18 are discussed above in section VII.G.7.

485. Davies discloses this element. Davies discloses that "[a]ddicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of

administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage." Nalox1009 at 1:4–12. Davies further discloses that the "invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage." *Id.* at 1:1–3. A Formulator POSA would have understood that heroin use is an "illicit use of opioids."

486. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 19	Davies in view of HPE, Bahal, and Kushwaha
"wherein said respiratory depression is caused by the illicit use of opioids or by an accidental misuse of opioids during medical opioid therapy"	**DAVIES (Nalox1009)** "This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage. Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be

Claim 19	Davies in view of HPE, Bahal, and Kushwaha
	carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage. According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:1–18).

487. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

9. Claims 20–23

488. It is my opinion that claims 20–23 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

489. Claim 20 depends from claim 19 and recites the limitation that "said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." '253 patent (Nalox1001), claim 20. Claim 21 depends from claim 20 and recites the limitation that "said patient is free from respiratory depression for at least about 2 hours following treatment comprising

essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 21. Claim 22 depends from claim 21 and recites the limitation that "said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 22. Claim 23 depends from claim 22 and recites that "said patient is free from respiratory depression for at least about 6 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist." *Id.*, claim 23.

490. The disclosures of the prior art in regard to the limitations of claim 19 are discussed above in section VII.G.8.

491. Davies discloses this element. Davies discloses that "[a]ddicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage." Nalox1009 at 1:4–12. Davies further discloses that the

"invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage." *Id.* at 1:1–3.

492. A Formulator POSA would have had a reasonable expectation of success that such intranasal administration of naloxone would reverse opioid overdose. Wermeling 2013 (Nalox1016) indicates that only 15–20% of cases require a repeat dose of naloxone due to overt toxicity such as central nervous system and respiratory depression recurring, which indicates that approximately 80–85% of opioid overdose patients have respiratory depression reversed indefinitely without a second dose of naloxone. *See* Nalox1016 at 71. Further, Davies discloses that "suitable dosage units [of naloxone or naltrexone] are in the range of 0.2 to 5 mg[.]" Nalox1009 at 3:2. A Formulator POSA seeking to have longer-lasting effects would have recognized that the higher the dose of naloxone, the longer it was likely to maintain a therapeutic blood level and the more likely it was to maintain the patient as free from respiratory depression for a longer period of time. As a result, this claim is obvious.

493. The below claim chart shows the relevant disclosures of each reference related to these elements.

Claims 20–23	Davies in view of HPE, Bahal, and Kushwaha
"wherein said patient is free from respiratory depression for at least about 1 hour following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist" (claim 20) "wherein said patient is free from respiratory depression for at least about 2 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist" (claim 21) "wherein said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist" (claim 22) "wherein said patient is free from respiratory depression for at least about 6 hours following treatment comprising essentially of delivery of	**DAVIES (Nalox1009)** "This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage. Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage. According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:1–18). "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol.

Claims 20–23	Davies in view of HPE, Bahal, and Kushwaha
said therapeutically effective amount of said opioid antagonist" (claim 23)	Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg…." (2:19–3:4). *See also* **WERMELING 2013 (Nalox1016)** "Due to naloxone's high metabolic clearance and the fact that most opioids have a longer persistence in the blood stream, the symptoms of withdrawal dissipate, and in about 15–20 % of cases, administration of a repeat dose of naloxone may become necessary if overt toxicity such as central nervous system and respiratory depression recur." (71).

494. Accordingly, it is my opinion that the prior art discloses these limitations of these claims.

10. Claim 24

495. It is my opinion that claim 24 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of HPE, Bahal, and Kushwaha.

496. Claim 24 depends from claim 16 and recites the limitation that "said patient is in a lying, supine, or recovery position." '253 patent (Nalox1001), claim 24. The disclosures Davies, HPE, Bahal, and Kushwaha in regard to the limitations of claim 16 are discussed above in section VII.G.5.

497. Davies discloses this element. Davies discloses that "[a] single dose of the antagonist can readily be sprayed into the nose or mouth of an addict who is having difficulty breathing, while undertaking standard resuscitation procedures." Nalox1009 at 5:28–30. A Formulator POSA (as well as most adults) would have recognized that "standard resuscitation procedures" would include rescue breathing and cardio-pulmonary resuscitation (or CPR), both of which require placing the patient on his or her back—i.e., in a lying or supine position.

498. Alternately, Wyse discloses this element. Wyse discloses "methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." Nalox1007 at 9:17–21. Wyse further discloses a kit comprising a naloxone nasal spray composition with "instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) placing the individual on their back…" (*Id.* at 12:12–17). Placing the individual on their back would put the individual in a lying position. It would have been obvious that a Formulator POSA could do the same with the intranasal naloxone compositions disclosed or suggested by Davies.

499. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 24	Davies in view of HPE, Bahal, and Kushwaha
"wherein said patient is in a lying, supine, or recovery position"	**DAVIES (Nalox1009)** "A single dose of the antagonist can readily be sprayed into the nose or mouth of an addict who is having difficulty breathing, while undertaking standard resuscitation procedures." (5:28–30). *See also* **WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the kit may comprise a device as disclosed herein, and may further comprise instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) ***placing the individual on their back;*** b) inserting a first sprayer into the individual's nostril; c) aiming the nozzle towards the side of the individual's nose and away from the center of the nose; d) pressing a plunger of the device firmly with the

Claim 24	Davies in view of HPE, Bahal, and Kushwaha
	thumb of the administrator; e) repeating steps b through d with a second sprayer in the second nostril of the individual's nose; f) monitoring the individual and the breaths of the individual, wherein if the individual does not improve or if signs of opioid overdose reappear 3-5 minutes after administering the composition, the administrator repeats the steps of b through e with a second device. The term 'does not improve' means wherein the individual does not exhibit increased breathing rates, for example, wherein an individual does not achieve 10 to 12 breaths per minute within about 3 to about 5 minutes after administration." (12:12–33) (emphasis added).

500. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

H. A Formulator POSA reading Davies in view of Djupesland, HPE, Bahal, and Kushwaha would have had ample reason and know-how to arrive at the subject matter of claims 5–7 and 10–14.

501. In my opinion, claims 5–7 and 10–14 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

502. The claim charts and discussion below show where each and every limitation of claims 5–7 and 10–14 are disclosed in Davies (Nalox1009), Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), and Kushwaha (Nalox1013).

503. It is my opinion that claims 5–7 and 10–14 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies (Nalox1009) in view of Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), and Kushwaha (Nalox1013).

1. Claim 5

504. It is my opinion that claim 5 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of in view of Djupesland, HPE, Bahal, and Kushwaha.

505. Claim 5 depends from claim 4 and recites the limitation that "the volume of said reservoir is not more than about 140 μL." '253 patent (Nalox1001), claim 5. The disclosures of the prior art in regard to the limitations of claim 4 are discussed above in section VII.G.4.

506. Davies discloses naloxone formulations that may be delivered through "[s]uitable spray applicators" which "are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." Nalox1009 at 2:1–3.

507. Djupesland discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device. *Id*. at 49. These devices

comprise "a vial, a piston, and a swirl chamber." *Id*. A Formulator POSA would have understood that the vial is a reservoir. Djupesland further discloses that a volume of 125 µL is filled into Aptar/Pfeiffer single dose devices to deliver a 100 µL spray volume. *Id*.

508. Further, a Formulator POSA would have recognized from the combined disclosures of Davies and Djupesland that the volume of the reservoir could be as little as 125 µL to accommodate the necessary overfill to deliver a 100 µL volume of spray. Thus, a Formulator POSA would have recognized that the volume of the reservoir could be as small as 125 µL.

509. A Formulator POSA would have been motivated to look to Djupesland's disclosure of single-use devices from the disclosure in Davies that the compositions therein may be delivered through "[s]uitable spray applicators" which "are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." Nalox1009 at 2:1–3. Combining the devices disclosed in Djupesland with the formulations disclosed in Davies would have been little more than the use of known elements to achieve predictable results.

510. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 5	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
"wherein the volume of said reservoir is not more than 140 µL."	**DAVIES (Nalox1009)** "Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." (2:1–3). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar

Claim 5	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
	single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

511. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

2. Claim 6

512. It is my opinion that claim 6 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of Djupesland, HPE, Bahal, and Kushwaha.

513. Claim 6 depends from claim 5 and recites the limitation that "wherein about 100μL of said aqueous solution in said reservoir is delivered to said patient in one actuation." '253 patent Nalox1001, claim 6. The disclosures of the prior art in regard to the limitations of claim 5 are discussed above in section VII.H.1.

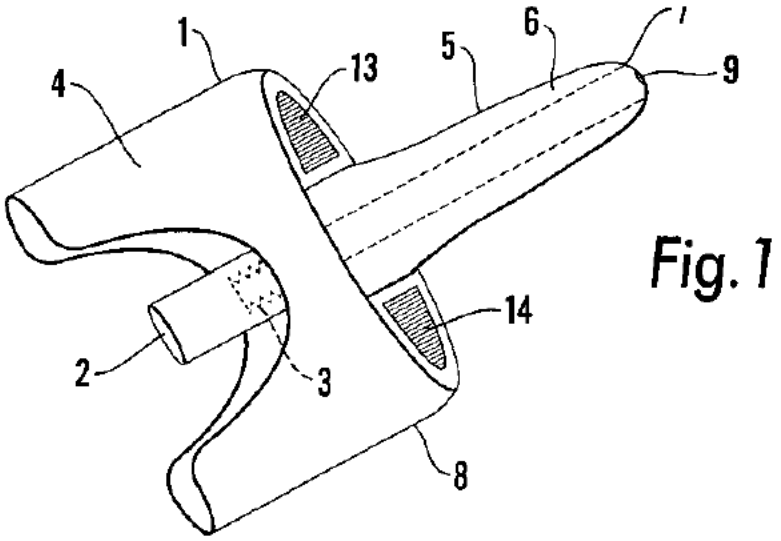
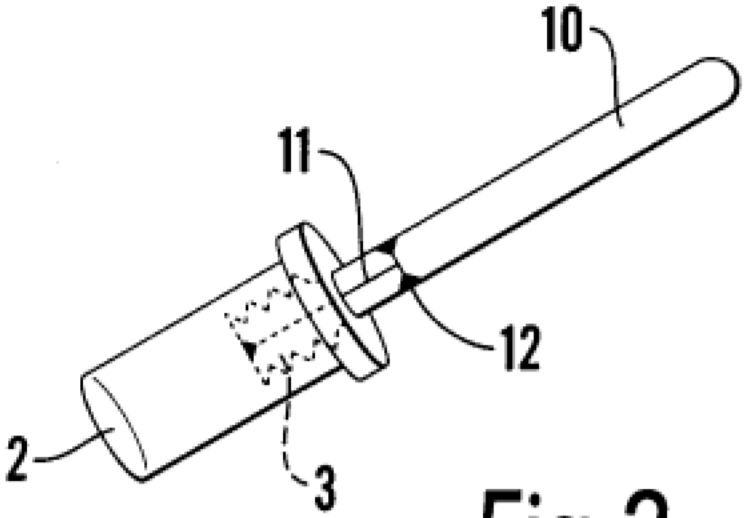
514. Davies discloses this element. Davies discloses naloxone formulations that may be delivered through "[s]uitable spray applicators" which "are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." Nalox1009 at 2:1–3. Davies further discloses that such devices function as follows: "With the part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. by placing the fore-finger and second finger on the surfaces 13,14 and the thumb

on the end of the reservoir and squeezing. This forces liquid from the reservoir along passage 11, out of cross bore 12 and into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6." *Id.* at 5:14–22. Finally, Davies discloses that, for devices delivering an opiate antagonist in the form of a liquid composition, "[f]or example, the shot volume could vary between 20µl and 100µl…." *Id.* at 2:19–3:4. A Formulator POSA would have understood from the fact that such devices are "single trip" and that they deliver the pharmaceutical composition upon actuation, that the entire shot volume is delivered in a single actuation.

515. Djupesland further discloses single-use, pre-primed devices adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of the device. *See* Nalox1010 at 48–49. Specifically, Djupesland discloses single-dose devices such as the Pfeiffer/Aptar single-use device. *Id*. at 49. These devices comprise "a vial, a piston, and a swirl chamber." *Id*. A Formulator POSA would have understood that the vial is a reservoir. Djupesland further discloses that a volume of 125 µL can be filled into Aptar/Pfeiffer single dose devices to deliver a 100 µL spray volume. *Id*.

516. The below claim chart shows the relevant disclosures of each reference related to this element.

Claim 6	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
"wherein about 100 µL of said aqueous solution in said reservoir is delivered to said patient in one actuation"	**DAVIES (Nalox1009)** "According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:14–19). "Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the opioid antagonist out of a nozzle." (2:1–3). "Where the antagonist is in the form of a liquid composition, it may be a solution in a pharmaceutically acceptable carrier or co-solvent such as water or an alcohol, such as ethanol, e.g. giving an aqueous solution containing about 5% of ethanol. Naloxone and naltrexone are both freely soluble in water and aqueous alcohol when in the form of a salt, such as a hydrochloride. Alternatively, the opioid antagonist may be dissolved in dilute saline solution, e.g. approximately isotonic salt solution…. Suitable dosage units are in the range of 0.2 to 5 mg, preferably 0.2 to 2 mg, especially 0.4 to 1.6 mg. For example, the shot volume could vary between 20µ1 and 100µ1, with the dose per shot preferably varying between 200 and 1200µg." (2:19–3:4). "The device works as follows. With the part 5 in the patient's nostril, pressure is applied to the free end of the reservoir, e.g. by placing the fore-finger and second finger on the surfaces 13,14 and the thumb on the end of the reservoir and squeezing. This forces

Claim 6	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
	liquid from the reservoir along passage 11, out of cross bore 12 and into the tube 6. Continued pressure forces liquid in a spray out of orifice 9 by the rod 10 acting as a piston in the tube 6. Tube 6 may be tapered slightly towards the orifice so that higher pressure can be developed within its distal end. It will be appreciated that by shaping the projecting part 5 as a tapering fit in the nostril, a major amount of the composition is retained in the nasal passages." (5:14–22).  Fig. 1  Fig.2

Claim 6	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
	DJUPESLAND (Nalox1010) "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

517. Accordingly, it is my opinion that the prior art discloses this limitation of the claim.

3. Claim 7

518. It is my opinion that claim 7 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of Djupesland, HPE, Bahal, and Kushwaha.

519. Claim 7 depends from claim 6 and recites the limitation that "the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate." '253 patent Nalox1001, claim 7. The disclosures of the prior art in regard to the limitations of claim 6 are discussed above in section VII.H.2.

520. Davies, in view of the prior art, suggests this element, as is discussed above in sections VII.G.1(c) and VII.G.3(a). Accordingly, claim 7 would have been obvious to a Formulator POSA.

4. Claims 10–11

521. It is my opinion that claims 10–11 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of Djupesland, HPE, Bahal, and Kushwaha.

522. Claim 10 depends from claim 7 and recites the limitation that "the delivery time is less than about 25 seconds." '253 patent Nalox1001, claim 10.

Claim 11 depends from claim 7 and recites the limitation that "the delivery time is less than about 20 seconds." *Id.*, claim 11. The disclosures of the prior art in regard to the limitations of claim 7 are discussed above in section VII.H.3.

523. I have previously discussed the construction of the term "delivery time" in section V.2 above. The '253 patent defines "delivery time" as follows: "The term 'delivery time,' as used herein, refers to the amount of time that elapses between a determination made by a healthcare professional, or an untrained individual that an individual is in need of nasal delivery of an opioid antagonist and completion of the delivery." '253 patent Nalox1001 at 8:52–56. I have applied this definition in analyzing this claim element.

524. Davies suggests this element. Davies discloses that "Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of administering an opioid antagonist which can be carried out by an unskilled person, *rapidly* and with a good chance of successfully reviving a patient suffering from opioid over-dosage." Nalox1009 at 1:4–12 (emphasis added). Davies further

discloses that "a single dose of the antagonist can readily be sprayed into the nose or mouth of an addict who is having difficulty breathing, *while undertaking standard resuscitation procedures*." Nalox1009 at 5:28–30 (emphasis added). Each of these disclosures indicates that Davies was seeking to minimize the delivery time of naloxone to a patient to a matter of mere seconds by formulating it as an intranasal or buccal dosage form, which comports with the most fundamental goal of the treatment: when a patient is not breathing due to an opioid overdose, every second counts in getting the patient the naloxone antidote and breathing again.

525. The below claim chart shows the relevant disclosures of each reference related to this element.

Claims 10–11	**Davies in view of Djupesland, HPE, Bahal, and Kushwaha**
"wherein the delivery time is less than about 25 seconds" (claim 10) "wherein the delivery time is less than about 20 seconds." (claim 11)	**DAVIES (Nalox1009)** "This invention relates to a composition for application by spray in the reversal of opioid depression. More particularly, compositions are provided for buccal or nasal administration for treatment of patients suffering from opioid over-dosage. Addicts of opioid drugs such as heroin sometimes suffer respiratory failure as a result of administration of an excessive dose of the opioid drug. While opioid antagonists may be given to reverse severe opioid respiratory depression, the standard method of administration is by intravenous injection, which is difficult for a medically unskilled person to carry out successfully, particularly in the stress of an emergency situation. The present invention seeks to provide systems of

Claims 10–11	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
	administering an opioid antagonist which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage. According to one aspect of the present invention there is provided a spray applicator having a solution of an opioid antagonist selected from naloxone and/or naltrexone contained in a reservoir therein, the applicator being capable of delivering single or multiple doses of an efficacious amount of said antagonist from the reservoir and the applicator comprising a projecting delivery portion shaped and dimensioned for introduction into the nose or mouth of a patient." (1:1–18). "A single dose of the antagonist can readily be sprayed into the nose or mouth of an addict who is having difficulty breathing, while undertaking standard resuscitation procedures." (5:28–30).

526. Accordingly, it is my opinion that the prior art suggests these limitations of these claims.

5. Claims 12–14

527. It is my opinion that claim 12 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies in view of Djupesland, HPE, Bahal, and Kushwaha.

528. Claim 12 depends from claim 7 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via

drainage into the nasopharynx or externally." '253 patent Nalox1001, claim 12. Claim 13 depends from claim 12 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." *Id.*, claim 13. Claim 14 depends from claim 13 and recites the limitation that "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." *Id.*, claim 14. The disclosures of the prior art in regard to the limitations of claim 7 are discussed above in section VII.H.3.

529. This limitation is met by Davies's and Djupesland's disclosure of administration of 100 µL sprays to a patient. *See* section VII.G.1(b), *supra*. 100 µL of liquid spray will not drip out or drain when placed on the surface of the nasal cavity. Several references show that this volume is small enough to be retained in the nasal cavities: for instance, Wermeling 2013 (Nalox1016) discloses that "[t]he nasal cavity can retain 100–150µL without causing immediate runoff out the front of the nose or down the nasopharynx." Nalox1016 at 65; *see also* Grassin-Delyle (Nalox1011) at 368 ("The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff."). Furthermore, other

intranasal products frequently use shot volumes of 100 µL. *See, e.g.*, PDR 2003 (Nalox1044); PDR 2010 (Nalox1045). Thus, Davies discloses this limitation to a Formulator POSA.

530. The below claim chart shows the relevant disclosures of Davies related to this element.

Claims 12–14	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
"wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." (claim 12) "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally." (claim 13) "wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical	**DAVIES (Nalox1009)** "For example, the shot volume could vary between 20µ1 and 100µ1…." (3:3–4). *See also* **WERMELING 2013 (Nalox1016)** "The dose must have sufficient solubility to be administered in approximately 100–200 µL (one spray per naris) of solution. The nasal cavity can retain 100–150 µL without causing immediate runoff out the front of the nose or down the nasopharynx []." (65). *See also* **GRASSIN-DELYLE (Nalox1011)** "The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff. For insulin preparations of between 80 and 160 µL in volume, it has been shown that the entire administered dose is deposited in the nasal cavities, with no passage to the lungs (Newman et al., 1994). The unit volume administered is also important because it appears that the administration of a single volume of 100 µL leads to deposition over a greater surface area than that obtained with the administration of two 50 µL volumes (Newman et al., 1994; Kundoor & Dalby 2011)." (368).

Claims 12–14	Davies in view of Djupesland, HPE, Bahal, and Kushwaha
composition leaves the nasal cavity via drainage into the nasopharynx or externally." (claim 14)	

531. Accordingly, it is my opinion that the prior art discloses these limitations of these claims.

I. A Formulator POSA reading Davies in view of Djupesland, HPE, Bahal, Kushwaha, and the '291 patent would have had ample reason and know-how to arrive at the subject matter of claims 8–9.

532. In my opinion, claims 8–9 of the '253 patent are unpatentable as obvious in view of the prior art as I explain below.

533. The claim charts and discussion below show where each and every limitation of claims 8–9 are disclosed in Davies (Nalox1009), Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), Kushwaha (Nalox1013), and the '291 patent (Nalox1015).

534. It is my opinion that claims 8–9 would have been obvious to a Formulator POSA as of at least March 16, 2015, over Davies (Nalox1009) in view of Djupesland (Nalox1010), HPE (Nalox1012), Bahal (Nalox1014), Kushwaha (Nalox1013), and the '291 patent (Nalox1015).

535. Claim 8 depends from claim 7 and recites the limitation that "the 90% confidence interval for dose delivered per actuation is ±about 2%." '253 patent

(Nalox1001), claim 8. Claim 9 depends from claim 7 and recites the limitation that "the 95% confidence interval for dose delivered per actuation is ±about 2.5%." *Id.*, claim 9.

536. The disclosures of Davies, Djupesland, HPE, Bahal, and Kushwaha, with regard to the limitations of claim 7, are discussed above in section VII.H.3.

537. A person of ordinary skill in the art would have combined the disclosure of the '291 patent disclosure with the disclosures of Davies, HPE, and Djupesland to arrive at the claimed invention with a reasonable expectation of success. Davies discloses placing the compositions disclosed therein in a single-use device. Nalox1009 at 2:1–3. Davies does not explicitly disclose the 90% or 95% confidence intervals of the dose delivered per actuation from such devices.

538. A Formulator POSA looking for information on the 90% or 95% confidence intervals of the dose delivered per actuation from single-use, pre-primed devices like the Aptar/Pfeiffer Unitdose device disclosed in Djupesland (*see* Nalox1010 at 49) would have looked to the '291 patent. The '291 patent also discloses intranasal opioid compositions that can be delivered with a Pfeiffer Unitdose Second Generation Spray Device, which is a single-use, pre-primed device like the Aptar/Pfeiffer Unitdose device disclosed in Djupesland. *See* Nalox1015 at 8:2–4, 8:30–9:19. The '291 patent discloses a study to compare bioavailability of a butorphanol formulation when administered using a unit-dose

or multi-dose delivery device. *Id.* at 7:60–63. The formulation contained 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0. *Id.* at 7:63–67. This composition was loaded into a Pfeiffer "Unitdose Second Generation" in quantities sufficient to deliver 0.1 mL (100 μL) of the butorphanol test formulation. *Id.* at 8:13–18. The applicators were weighed prior to and after delivery of one dose into a subject's nostril, with each patient receiving a total of two doses from two separate devices. *See id*. at 8:20–27. The weight of the pair of devices before and after delivery was compared and the difference was calculated to determine the dose delivered. *See id*. at 8:29–37.

539. For the 23 sets of two Pfeiffer Unitdose spray devices weighed before and after actuation, it was found that the two sprayers together had delivered a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams, (*id.* at 8:39–47), and a 95% confidence interval of (0.203 g, 0.209 g). This corresponds to a 95% CI for the dose delivered over two sprays of about ±1.5% and a 90% CI for dose delivered over the two sprays of about ±0.9%. This indicates that, for the Pfeiffer Unitdose Spray device in combination with the formulation disclosed in the '291 patent, the 90% confidence interval for dose delivered is within ±about 2%, and that the 95% confidence interval for dose

delivered is within ±about 2.5%. A Formulator POSA would have been motivated to achieve similar results through selection of an appropriate delivery device that reproducibly and consistently delivered the same dose upon each actuation, and the '291 patent evidences that such devices were available to a Formulator POSA prior to March 16, 2015. *See* paragraphs 87–88, *supra*.

540. A Formulator POSA would reasonably have expected the device to behave similarly when used in combination with the formulations suggested and disclosed by Davies, as the reliability and repeatability of dose delivery is a function of the device and the reproducibility of loading into the device. *See* '291 patent (Nalox1015) at 6:51–56 ("Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J.… These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition.").

541. The below claim chart shows the relevant disclosures of Davies in view of HPE, Djupesland, Bahal, Kushwaha, and the '291 patent related to this element.

Claims 8–9	**Davies in view of Djupesland, HPE, Bahal, Kushwaha and the '291 patent**
"wherein the 90% confidence interval for dose delivered per actuation is ±about 2%"	**DAVIES (Nalox1009)** "Suitable spray applicators are preferably single trip devices, and normally incorporate a pump or syringe action for forcing an amount of the solution of the

Claims 8–9	Davies in view of Djupesland, HPE, Bahal, Kushwaha and the '291 patent
(claim 8) "wherein the 95% confidence interval for dose delivered per actuation is ±about 2.5%" (claim 9)	opioid antagonist out of a nozzle." (2:1–3). **DJUPESLAND (Nalox1010)** "Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com)." (48). "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49).

Claims 8–9	Davies in view of Djupesland, HPE, Bahal, Kushwaha and the '291 patent
	'291 PATENT (Nalox1015) "In accordance with one embodiment of the present invention, it has now been surprisingly found that intranasal pharmaceutical compositions can be made having improved bioavailability in terms of plasma opioid levels…. Opioids as herein include any substance naturally or synthetically derived from opium. Suitable opioids for use in the present invention include, but are not limited to, morphine, apomorphine, hydromorphone, oxymorphone, dihydromorphine, levorphanol, levallorphan, levophenacylmorphan, norlevorphanol, nalorphine, nalbuphine, buprenorphine, butorphanol, naloxone, naltrexone, nalmexone, oxilorphan, cyclorphan, ketobemidone, fentanyl, sufentanil, alfentanyl, or combinations thereof." (3:51–4:6). "Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J. and Valois of America, Inc. of Greenwich, Conn. These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition. These devices are easily operable by the patient, leave virtually no opioid remaining in the device after use and can thereafter be discarded without concern that others may abuse the opioid or other controlled substance." (6:51–60). "This example compares bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. The formulation contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0….

Claims 8–9	Davies in view of Djupesland, HPE, Bahal, Kushwaha and the '291 patent
	The second delivery system employed to administer the butorphanol compositions was a unit-dose disposable intranasal applicator that is commercially available from Pfeiffer of America under the designation 'Unitdose Second Generation.' Each of the Pfeiffer spray applicators was charged with sufficient liquid to deliver a 0.1 mL dose of the butorphanol test formulation. The glass containers were filled using a pipette under clean conditions, sealed and assembled to the applicator. Each of the applicators was weighed prior to use and after use. Qualified medical personnel administered, one dose into each nostril, after which the applicator was recovered for weighing. In the case of the unit-dose applicators (test formulation), two devices were used for each patient, both of which were discarded following the post-use weighing. The results of these studies of the method and system of the invention and the comparative prior art method follow…. Unit-Dose: The statistical comparison of dose 1 and dose 2 for the test formulation unit dose delivery system was done using a paired t-test. Analysis of the data indicated that the difference between the mean, sprays of the two applications using the Pfeiffer device was not statistically significant (t=1.0; p=0.3). The sample of 23 sprayers (actually 23 sets of 2 sprayers, since they were single-dose) had a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams. … A t-test was used in each case to compare the observed sample mean to the desired weight of 0.2 grams. The unit-dose sprayer dispensed a mean total weight that

Claims 8–9	Davies in view of Djupesland, HPE, Bahal, Kushwaha and the '291 patent
	was significantly higher than the goal of 0.2 grams ($t=4.4$; $p<0.001$). A 95% confidence interval for the mean total weight dispensed by the unit-dose sprayer is (0.203, 0.209)." (7:60–9:11).

542. Accordingly, it is my opinion that the prior art discloses these limitations of these claims.

VIII. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

543. I have been informed by counsel that, during prosecution of a related patent, the patent applicants raised several secondary considerations of non-obviousness in asserting that the claims were patentable. In particular, the patent applicants asserted that the prior art as a whole taught away from the claimed invention. For reasons I will discuss below, a Formulator POSA would not have concluded that the prior art as a whole taught away from the claimed invention for the reasons the patent applicants raised in prosecution. Rather, a Formulator POSA would have concluded that the wealth of prior art as a whole taught directly towards the claimed invention.

544. I also understand that Patent Owner Opiant Pharmaceuticals, Inc. may raise the following secondary considerations of non-obviousness: commercial success, long-felt but unmet need, failure of others, and unexpected superior results.

A. No teaching away

545. From my review of the file history of related U.S. Patent No. 9,561,177 ("the '177 patent"), I understand that the applicants for that patent asserted, during prosecution, that the prior art as a whole taught away from the claimed invention. In particular, the applicants argued that Wyse taught away from combining benzalkonium chloride and b) that the prior art taught away from using a concentration of 4% (w/v) naloxone hydrochloride and doses of naloxone hydrochloride as high as 4 mg. I have addressed the first point in prior section IV.A.3(e)(iv). I disagree with and address this second point as follows.

546. A Formulator POSA would not consider the prior art as a whole to teach away from using a 4 mg dose of naloxone hydrochloride or a hydrate thereof. During prosecution of the related '177 patent, the applicants argued that the prior art as a whole taught away from using a 4 mg dose of naloxone. The applicants stated as follows:

> 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…. 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. Therefore, the art cannot be said to guide the ordinary artisan toward about 4 mg naloxone.

Oct. 21, 2016 Response to Office Action (Nalox1005) at 12. I disagree that the prior art taught away from this dose for the following reasons.

547. First, the Applicants incorrectly state that Wyse did not disclose a 4 mg dose. Rather, Wyse disclosed in one example administering a dose of 2 mg intranasally, followed by another 2 mg intranasally in five minutes. *See* Nalox1007, 23:40–55. Wyse specifically discloses a pharmacokinetic study of this dose that will "provide useful information since naloxone is a drug that is titrated to clinical effect if the initial dose is insufficient. Therefore, Treatment B, which includes redosing was added which will increase exposure after a short period, 5 minutes from initial dosing, and mirrors clinical practice with naloxone injection." *See id*., 24:1–6. One would have understood from this disclosure that a dose of 4 mg naloxone was not expected to trigger precipitous withdrawal symptoms in all patients.

548. Moreover, I note that the Examiner did not accept this argument from the Applicants in his reasons for allowance, and rather maintained that the "concentration range disclosed 5–50 mg/mL is considered to read on the instantly claimed amount." *See* Notice of Allowance (Nalox1006) at 7–8.

549. For the foregoing reasons, I disagree with the premise that the prior art as a whole taught away from using a 4 mg naloxone dose.

B. No commercial success

550. I understand that commercial success requires that the success of the claimed product must have resulted from the merits of the claimed invention as

opposed to the prior art or other extrinsic factors. In other words, the patent owner must "link" the commercial success with features of the invention not shown in the prior art. I also understand that commercial success must be demonstrated by sales in a relevant market.

551. I fail to see how the success of the claimed product must have resulted from the merits of the claimed invention as opposed to the prior art or other extrinsic factors. The formulations claimed in the '253 patent are so similar to those disclosed in Wyse, Wang, and Davies that I fail to see how the aspects of the formulation that differ from the formulations disclosed in those references contribute to its sales.

552. For at least these reasons, I do not see any evidence of commercial success that sufficiently alters my opinion that these claims are obvious.

C. No long-felt but unmet need or failure of others

553. I understand that a showing of a long-felt and unmet need requires three factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. Second, the long-felt need must not have been satisfied by another before the invention. Third, the invention must in fact satisfy the long-felt need. Furthermore, I understand that long-felt need should be a need created by inadequacies in the technical knowledge, not one due to business-driven market forces that are unrelated to technical considerations.

554. I understand that the Patent Owner may also argue that long-felt need is demonstrated because Narcan was approved by FDA while other naloxone nasal sprays were not. But even if there had been a need in the art for a single-use naloxone nasal spray formulated at an appropriate dose and concentration, there is insufficient evidence to suggest that this was outside of the skill of a Formulator POSA. The disclosures of Wyse, Wang, and Davies all indicate that others had formulated and developed intranasal formulations of naloxone and considered use of higher doses of naloxone than 1 mg or 2 mg intranasally, and it is unclear whether Wang or Davies ever attempted to obtain regulatory approval for, or to market, their intranasal formulations of naloxone.

555. Likewise, there was not a long-felt or unresolved need for an FDA-approved formulation with sufficient stability that provided equal or improved action compared to the approved injectable products. I note that the FDA first announced its requirements for making a naloxone nasal spray in April of 2012, (*see* Hertz Presentation (Nalox1032) and 2012 FDA Meeting (Nalox1049)), and the earliest application to which Wyse claims priority was filed in December of 2013, with six months of stability data, indicating that a formulation had been selected by no later than June of 2013. *See* '802 Appl. (Nalox 1055) at [00145]. Likewise, the earliest application to which the '253 patent claims priority was filed in March of 2014, with 12 months of stability data. *See* '379 provisional

(Nalox1058) at 41. This relatively short timeline does not indicate the existence of a "long-felt" need, but rather indicates that the claimed subject matter was arrived at with little more than the application of ordinary skill. I reiterate, for good measure, first responders had been administering the injectable formulation of naloxone intranasally via a syringe with a Luer-fitted tip and Mucosal Atomizer Device for years prior to FDA's 2012 meeting.

556. Similarly, Patent Owner cannot point to failure of others to arrive at the claimed naloxone nasal spray. During prosecution of the '177 patent, the applicants argued that "Applicant was the first to conceive of a formulation with the right dose of naloxone and the right concentration of excipients" to make a "stable, compatible, bioequivalent nasal formulation" of naloxone. Again, I note that the FDA first announced its requirements for making a naloxone nasal spray in April of 2012, and the earliest application to which Wyse claims priority was filed in December of 2013, with six months of stability data, indicating that a formulation had been selected by no later than June of 2013. *See* '802 Appl. (Nalox1055) at [00145]. Likewise, the earliest application to which the '253 patent claims priority was filed in March of 2014, with 12 months of stability data. *See* '379 provisional (Nalox1058) at 41. This hardly indicates that others "repeatedly tried and failed" to develop bioequivalent and stable naloxone nasal spray

formulations. Rather, these development timelines indicate that the claimed formulation is nothing more than the result of ordinary skill in drug development.

557. For at least these reasons, I do not see any evidence of commercial success that sufficiently alters my opinion that these claims are obvious.

D. No unexpected superior results

558. I understand that "unexpectedly superior results" can be evidence of non-obviousness if the patent owner shows that the results are unexpectedly greater than those that would have been expected from the closest prior art and that the results have a significant and practical advantage. It is also my understanding that unexpectedly superior results must be commensurate in scope with the claims.

559. I understand that the Patent Owner may allege that evidence of unexpected results is demonstrated by the fact that the subject matter claimed in the '253 patent demonstrate beneficial pharmacokinetic properties relative to those of Wyse.

560. I understand that Dr. Hochhaus, an expert in clinical pharmacology, has concluded a Pharmacologist POSA would have found the pharmacokinetic results claimed in the '253 patent to be entirely expected, and that he is not aware of any unexpected pharmacokinetic benefit or result that can be tied to any particular excipient contained in the intranasal formulation recited in the claims of

the ’253 patent. I adopt that conclusion herein, but otherwise render no opinion on the topic.

561. Furthermore, I am not aware of any unexpected benefit or result of relevance to a Formulator POSA that is tied to the claimed devices or the formulations in them. Rather, as discussed above, the claimed devices and formulations appear to combine known ingredients and devices according to their known functions and purposes.

IX. CONCLUSION

562. In conclusion, it is my opinion as an expert in the field of formulation of intranasal drugs that the subject matter recited in claims 1–14 and 16–24 of the ’253 patent are unpatentable because the differences between the claimed distribution systems and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a Formulator POSA.

563. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for

cross-examination within the United States during the time allotted for cross-examination.

564. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Dated: 2/13/2019

Maureen D. Donovan, Ph.D.

CLAIMS	WYSE
Claim 1 [Preamble]	**WYSE in view of HPE**
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	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris." (10:29–35). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products " (10:53–57).
Claim 1.1	**WYSE in view of HPE**
a pharmaceutical composition which is an aqueous solution of about 100 µL comprising	**WYSE (Nalox1007)** "In one aspect, the disclosed compositions may comprise from about 5 mg/mL to about 50 mg/mL . . . of an opioid antagonist. . . . The opioid antagonist may be naloxone or a pharmaceutically acceptable salt thereof. In one aspect, the opioid antagonist may be naloxone, naloxone HCl, or naloxone HCL dihydrate. Unless otherwise specified, the term 'naloxone,' as used herein, refers to naloxone, naloxone HCl, naloxone

CLAIMS	WYSE
	HCl dihydrate, any pharmaceutically acceptable salt of naloxone, or combinations thereof." (6:50–65). "The compositions are formulated with a suitable carrier to form a pharmaceutically acceptable nasal spray. In one aspect, the carrier may comprise water, saline, dextrose, or other suitable aqueous or non-aqueous carriers suitable for application to the nasal mucosa. In one aspect, the nasal spray is formed with an aqueous carrier, such as water or saline. Other suitable carriers will be readily understood by one of ordinary skill in the art." (8:25–32). "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 μL per spray. This delivery system is used in other approved nasal spray drug products . . . ." (10:53–57).
Claim 1.2	**WYSE in view of HPE**

CLAIMS	WYSE
about 4 mg naloxone hydrochloride or a hydrate thereof	**WYSE (Nalox1007)** "In one aspect, the disclosed compositions may comprise from about 5 mg/mL to about 50 mg/mL . . . of an opioid antagonist. . . . The opioid antagonist may be naloxone or a pharmaceutically acceptable salt thereof. In one aspect, the opioid antagonist may be naloxone, naloxone HCl, or naloxone HCL dihydrate. Unless otherwise specified, the term 'naloxone,' as used herein, refers to naloxone, naloxone HCl, naloxone HCl dihydrate, any pharmaceutically acceptable salt of naloxone, or combinations thereof." (6:50–65). "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products " (10:53–57).
Claim 1.3	**WYSE in view of HPE**
between about 0.2 mg and about 1.2 mg of an isotonicity agent	**WYSE (Nalox1007)**

CLAIMS	WYSE
	"In one aspect, the composition may comprise sodium chloride in an amount sufficient to adjust the osmolality of the compositions from about 300 to about 500, or from about 350 to about 450, or about 400." (7:64–67). Table 13 discloses use of a concentration of 6.4 mg/mL sodium chloride in various naloxone formulations. (*See* 26:23–27:17).
Claim 1.4	**WYSE in view of HPE**
between about 0.005 mg and about 0.015 mg of a preservative	**WYSE (Nalox1007)** "In certain aspect, the composition may further comprise from about 0.1 weight % to about 2 weight %, or about 0.2 weight % to about 1.0 weight %, or about 0.5 weight % of an antimicrobial agent. The antimicrobial agent may comprise an alcohol antimicrobial agent. In one aspect, the antimicrobial agent may comprise benzyl alcohol. Other suitable antimicrobial agents may be readily understood by one of ordinary skill in the art." (7:21–28). **HPE (Nalox1012)** "Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative . . . . In nasal, and otic formulations a concentration of 0.002–0.02% w/v is used . . . Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products." (56).

CLAIMS	WYSE
	Table II: Minimum inhibitory concentrations (MICs) of benzalkonium chloride. **Microorganism** / **MIC (μg/mL)** *Aerobacter aerogenes* 64 *Clostridium histolyticum* 5 *Clostridium oedematiens* 5 *Clostridium tetani* 5 *Clostridium welchii* 5 *Escherichia coli* 16 *Pneumococcus II* 5 *Proteus vulgaris* 64 *Pseudomonas aeruginosa* 30 *Salmonella enteritidis* 30 *Salmonella paratyphi* 16 *Salmonella typhosa* 4 *Shigella dysenteriae* 2 *Staphylococcus aureus* 1.25 *Streptococcus pyrogenes* 1.25 *Vibrio cholerae* 2 (57). "Benzethonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative. Typically, it is used for this purpose in injections, ophthalmic and otic preparations at concentrations 0.01–0.02% w/v." 59.

CLAIMS	WYSE

Table II: Minimum inhibitory concentration (MIC) for benzethonium chloride.

Microorganism	MIC (μg/mL)
Aspergillus niger	128
Candida albicans	64
Escherichia coli	32
Penicillium notatum	64
Proteus vulgaris	64
Pseudomonas aeruginosa	250
Pseudomonas cepacia	250
Pseudomonas fluorescens	250
Staphylococcus aureus	0.5
Streptococcus pyogenes	0.5

(*Id.*).

"Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations, including oral and parenteral preparations, at concentrations up to 2.0% v/v. The typical concentration used is 1% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006." (64).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.[44]

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

(*Id.*).

Table I: Uses of methylparaben.

Use	Concentration (%)
IM, IV, SC injections[a]	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18

[a] See Section 14.

(442).

CLAIMS	WYSE
	Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[14] **Microorganism** — **MIC (μg/mL)** *Aerobacter aerogenes* ATCC 8308 — 2000 *Aspergillus oryzae* — 600 *Aspergillus niger* ATCC 9642 — 1000 *Aspergillus niger* ATCC 10254 — 1000 *Bacillus cereus var. mycoides* ATCC 6462 — 2000 *Bacillus subtilis* ATCC 6633 — 2000 *Candida albicans* ATCC 10231 — 2000 *Enterobacter cloacae* ATCC 23355 — 1000 *Escherichia coli* ATCC 8739 — 1000 *Escherichia coli* ATCC 9637 — 1000 *Klebsiella pneumoniae* ATCC 8308 — 1000 *Penicillium chrysogenum* ATCC 9480 — 500 *Penicillium digitatum* ATCC 10030 — 500 *Proteus vulgaris* ATCC 8427 — 2000 *Proteus vulgaris* ATCC 13315 — 1000 *Pseudomonas aeruginosa* ATCC 9027 — 4000 *Pseudomonas aeruginosa* ATCC 15442 — 4000 *Pseudomonas stutzeri* — 2000 *Rhizopus nigricans* ATCC 6227A — 500 *Saccharomyces cerevisiae* ATCC 9763 — 1000 *Salmonella typhosa* ATCC 6539 — 1000 *Sarcina lutea* — 4000 *Serratia marcescens* ATCC 8100 — 1000 *Staphylococcus aureus* ATCC 6538P — 2000 *Staphylococcus epidermidis* ATCC 12228 — 2000 *Trichoderma lignorum* ATCC 8678 — 250 *Trichoderma mentagrophytes* — 250 (*Id.*).

CLAIMS	WYSE

Table I: Uses of propylparaben in pharmaceutical preparations.

Use	Concentration (%)
IM, IV, SC injections	0.005–0.2
Inhalation solutions	0.015
Intradermal injections	0.02–0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005–0.01
Oral solutions and suspensions	0.01–0.02
Rectal preparations	0.02–0.01
Topical preparations	0.01–0.6
Vaginal preparations	0.02–0.1

(596).

Table III: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1000
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	125
Bacillus subtilis ATCC 6633	500
Candida albicans ATCC 10231	250
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	500
Escherichia coli ATCC 9637	100
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	125
Penicillium digitatum ATCC 10030	63
Proteus vulgaris ATCC 13315	250
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	125
Saccharomyces cerevisiae ATCC 9763	125
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	500
Staphylococcus epidermidis ATCC 12228	500
Trichophyton mentagraphytes	65

(597).

CLAIMS	**WYSE**
Claim 1.5	**WYSE in view of HPE**
about 0.2 mg of a stabilizing agent	**WYSE (Nalox1007)** "In one aspect, the composition may comprise from about 2 mM to about 20 mM, or from about 5 mM to about 15 mM, or from about 8 mM to about 12 mM, or about 10 mM disodium ethylene diamine tetraacetic acid (EDTA)." (7:17–20).
Claim 1.6	**WYSE in view of HPE**
an amount of an acid sufficient to achieve a pH of 3.5-5.5.	**WYSE (Nalox1007)** "The compositions may further comprise sodium hydroxide or hydrochloric acid in an amount sufficient to adjust the pH to from about 3 to about 5.5, or from about 3.5 to about 5, or about 4±0.5." (8:1–4). "5. Verify pH to 4.25 and adjust if necessary, with 1 N NaOH or 1 N HCl solutions. . . ." (14:51–52).
Claim 2.1	**WYSE in view of HPE**
The device as recited in claim 1 wherein: the isotonicity agent is NaCl;	*See* claim 1.3.
Claim 2.2	**WYSE in view of HPE**
the preservative is benzalkonium chloride;	*See* claim 1.4

CLAIMS	WYSE
Claim 2.3	**WYSE in view of HPE**
the stabilizing agent is disodium edetate;	*See* claim 1.5
Claim 2.4	**WYSE in view of HPE**
2.4 and the acid is hydrochloric acid.	*See* claim 1.6
Claim 3.1	**WYSE in view of HPE**
The device of claim 2, wherein the aqueous solution comprises: about 4.4 mg naloxone hydrochloride dihydrate;	*See* claims 1.2 and 2.
Claim 3.2	**WYSE in view of HPE**
about 0.74 mg NaCl;	*See* claims 1.3 and 2.
Claim 3.3	**WYSE in view of HPE**
about 0.01 mg benzalkonium chloride;	*See,* claims 1.4 and 2.
Claim 3.4	**WYSE in view of HPE**
about 0.2 mg disodium edetate;	*See* claims 1.5 and 2.
Claim 3.5	**WYSE in view of HPE**

CLAIMS	**WYSE**
3.5 and an amount of hydrochloric acid sufficient to achieve a pH or 3.5-5.5.	*See* claims 1.6 and 2.
Claim 4	**WYSE in view of Djupesland and HPE**
The device of claim 2, wherein said device is actuatable with one hand.	*See* claim 2. **WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers . . . ." (10:29–36). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products in the U.S. (Imitrex nasal spray NDA #20-626). The direct product contact components of the container closure may comprise a container (glass vial) . . . ." (10:53–59).

CLAIMS	WYSE
	DJUPESLAND (Nalox1010) "The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. ***These devices are held between the second and the third fingers with the thumb on the actuator.*** A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49) (emphasis added).
Claim 5	**WYSE in view of Djupesland and HPE**
The device of claim 4, wherein the volume of said reservoir is not more than about 140 µL.	*See* claim 4. **WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per

CLAIMS	WYSE
	naris. The device may comprise one or more unit dose containers . . . .” (10:29–36). “In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds).” (10:45–48). “In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products in the U.S. (Imitrex nasal spray NDA #20-626). The direct product contact components of the container closure may comprise a container (glass vial) . . . .” (10:53–59). **DJUPESLAND (Nalox1010)** “The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. ***These devices are held between the second and the third fingers with the thumb on the actuator.*** A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu-Mist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but

CLAIMS	WYSE
	overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design." (49) (emphasis added).
Claim 6	**WYSE in view of Djupesland and HPE**
The device of claim 5, wherein about 100 µL of said aqueous solution in said reservoir is delivered to said patient in one actuation.	*See* claims 1.1 and 5. **WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris." (10:29–35). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products " (10:53–57).
Claim 7	**WYSE in view of Djupesland and HPE**

CLAIMS	**WYSE**
The device of claim 6, wherein the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate.	*See* claims 1.2 and 6.
Claim 8	**WYSE in view of Djupesland, HPE, and the '291 Patent**
The device of claim 7, wherein the 90% confidence interval for dose delivered per actuation is ±about 2%.	*See* claim 7. **WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers . . . ." (10:29–36). "In one aspect, the nasal spray device is an Aptar/Pfeiffer Unitdose device (available from Aptar Pharma, Congers, N.Y., http://www.aptar.com/pharma/prescription-division/products/uds)." (10:45–48). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products in the U.S. (Imitrex

CLAIMS	WYSE
	nasal spray NDA #20-626). The direct product contact components of the container closure may comprise a container (glass vial) . . . .” (10:53–59). **THE ’291 PATENT (Nalox1015)** “In accordance with one embodiment of the present invention, it has now been surprisingly found that intranasal pharmaceutical compositions can be made having improved bioavailability in terms of plasma opioid levels. . . . Opioids as herein include any substance naturally or synthetically derived from opium. Suitable opioids for use in the present invention include, but are not limited to, morphine, apomorphine, hydromorphone, oxymorphone, dihydromorphine, levorphanol, levallorphan, levophenacylmorphan, norlevorphanol, nalorphine, nalbuphine, buprenorphine, butorphanol, naloxone, naltrexone, nalmexone, oxilorphan, cyclorphan, ketobemidone, fentanyl, sufentanil, alfentanyl, or combinations thereof.” (3:51–4:6) “Preferred devices for intranasal delivery of pharmaceutical compositions of the present invention are available from, for example, Pfeiffer of America of Princeton, N.J. and Valois of America, Inc. of Greenwich, Conn. These devices are preferred because they have the capability of consistently delivering the pharmaceutical composition. These devices are easily operable by the patient, leave virtually no opioid remaining in the device after use and can thereafter be discarded without concern that others may abuse the opioid or other controlled substance.” (6:51–60).

CLAIMS	WYSE
	"This example compares bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. The formulation contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0. . . . The second delivery system employed to administer the butorphanol compositions was a unit-dose disposable intranasal applicator that is commercially available from Pfeiffer of America under the designation 'Unitdose Second Generation.' Each of the Pfeiffer spray applicators was charged with sufficient liquid to deliver a 0.1 mL dose of the butorphanol test formulation. The glass containers were filled using a pipette under clean conditions, sealed and assembled to the applicator. Each of the applicators was weighed prior to use and after use. Qualified medical personnel administered, one dose into each nostril, after which the applicator was recovered for weighing. In the case of the unit-dose applicators (test formulation), two devices were used for each patient, both of which were discarded following the post-use weighing. The results of these studies of the method and system of the invention and the comparative prior art method follow. . . . Unit-Dose: The statistical comparison of dose 1 and dose 2 for the test formulation unit dose delivery system was done using a paired t-test. Analysis of the data indicated that the difference between the mean, sprays of the two

CLAIMS	WYSE
	applications using the Pfeiffer device was not statistically significant (t=1.0; p=0.3). The sample of 23 sprayers (actually 23 sets of 2 sprayers, since they were single-dose) had a mean total dose for two sprays of 0.206 grams with a standard deviation of 0.00660 grams. . . . A t-test was used in each case to compare the observed sample mean to the desired weight of 0.2 grams. The unit-dose sprayer dispensed a mean total weight that was significantly higher than the goal of 0.2 grams (t=4.4; p<0.001). A 95% confidence interval for the mean total weight dispensed by the unit-dose sprayer is (0.203, 0.209).” (7:60–9:11)
Claim 9	**WYSE in view of Djupesland, HPE, and the ’291 Patent**
The device of claim 7, wherein the 95% confidence interval for dose delivered per actuation is ±about 2.5%.	*See* claims 7 and 8.
Claim 10	**WYSE in view of Djupesland and HPE**
The device of claim 7, wherein the delivery time is less than about 25 seconds.	*See* claim 7. **WYSE (Nalox1007)** “[T]here is a need for integrating compositions, methods, and devices that can allow for an effective reversal of opioid overdose, but which eliminates or minimizes the use of needles. There is further a need for effective formulations and methods of providing such compositions to an

CLAIMS	WYSE
	individual, for rapid absorption into the nasal mucosa and for reversing opioid overdose, that can be quickly and easily used, but which minimize sudden and severe side effects of rapid reversal of opioid overdose." (2:67–3:8). "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof." (10:29–33). "Naloxone HCl dihydrate nasal spray, 10 mg/mL, 100 µL/spray, assembled into the Aptar/Pfeiffer Unitdose delivery device or in vials (not assembled into the delivery device) may be stored protected from light. Bulk vials and assembled Unitdose delivery device units of drug product may be stored in bulk sealed containers pending further processing. The disclosed compositions may be assembled in the Unitdose delivery devices and packaged in 4"x4" foil pouches, one device/pouch, heat-sealed and labeled as appropriate." (10:65–11:6).
Claim 11	**WYSE in view of Djupesland and HPE**
The device of claim 7, wherein the delivery time is less than about 20 seconds.	*See* claims 7 and 10.
Claim 12	**WYSE in view of Djupesland and HPE**
The device of claim 7, wherein upon nasal delivery of said pharmaceutical	*See* claim 7.

CLAIMS	WYSE
composition to said patient, less than about 20% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.	**WYSE (Nalox1007)** "The disclosed nasal spray device, as set forth above, is intended for use by both medical and non-medical personnel. In particular, the device may have one or more features selected from being single-use, needle-free, ready-to-use, disposable, and combinations thereof. The device may be configured to administer the disclosed compositions as a single spray per naris. The device may comprise one or more unit dose containers, each container delivering about one 100 µL spray containing about 1 mg naloxone HCl dihydrate (a 10 mg/mL solution) or a 2 mg naloxone hydrochloride dihydrate in 100 µL." (10:29–39). "In one aspect, the Aptar/Pfeiffer Unitdose delivery device may be used to deliver the disclosed compositions. In one aspect, the nasal spray device delivers a volume of about 100 µL per spray. This delivery system is used in other approved nasal spray drug products . . . ." (10:53–57). *See also* **WERMELING 2013 (Nalox1016)** "The dose must have sufficient solubility to be administered in approximately 100–200 µL (one spray per naris) of solution. The nasal cavity can retain 100–150 µL without causing immediate runoff out the front of the nose or down the nasopharynx []." (65). *See also* **GRASSIN-DELYLE (Nalox1011)** "The nasal mucosa's low surface area limits the administration of active principles to volumes below 200 µL, in order to avoid direct loss of the drug via anterior or posterior runoff. For insulin preparations of between 80 and 160 µL in volume, it has been shown that the entire administered

CLAIMS	WYSE
	dose is deposited in the nasal cavities, with no passage to the lungs (Newman et al., 1994). The unit volume administered is also important because it appears that the administration of a single volume of 100 µL leads to deposition over a greater surface area than that obtained with the administration of two 50 µL volumes (Newman et al., 1994; Kundoor & Dalby 2011).” (368).
Claim 13	**WYSE in view of Djupesland and HPE**
The device of claim 12, wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 10% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.	*See* claim 12.
Claim 14	**WYSE in view of Djupesland and HPE**
The device of claim 13, wherein upon nasal delivery of said pharmaceutical composition to said patient, less than about 5% of said pharmaceutical composition leaves the nasal cavity via drainage into the nasopharynx or externally.	*See* claims 12 and 13.
Claim 15	**WYSE in view of Djupesland and HPE**

CLAIMS	WYSE
The device of claim 7, wherein the plasma concentration versus time curve of said naloxone hydrochloride in said patient has a T_{max} of between about 20 and about 30 minutes.	*See,* claim 7. *See* Declaration of Gunther Hochhaus, Ph.D. (Ex. 1003), ¶¶87-90.
Claim 16	**WYSE in view of HPE**
The device of claim 1, wherein said patient is an opioid overdose patient or a suspected opioid overdose patient.	*See* claim 1. **WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21).
Claim 17	**WYSE in view of HPE**
The device of claim 16, wherein the patient exhibits one or more symptoms chosen from: respiratory depression, central nervous system depression, cardiovascular depression, altered level	*See* claim 16. **WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered

CLAIMS	WYSE
consciousness, miotic pupils, hypoxemia, acute lung injury, aspiration pneumonia, sedation, hypotension, unresponsiveness to stimulus, unconsciousness, stopped breathing; erratic or stopped pulse, choking or gurgling sounds, blue or purple fingernails or lips, slack or limp muscle tone, contracted pupils, and vomiting.	intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression." (9:33–35). "In one aspect, the known or suspected opioid overdose may be manifested by respiratory and/or central nervous system depression." (10:1–3).
Claim 18	**WYSE in view of HPE**
The device of claim 17, wherein the patient exhibits respiratory depression.	*See* claim 17.
Claim 19	**WYSE in view of HPE**
The device of claim 18, wherein said respiratory depression is caused by the illicit use of opioids, or by an accidental misuse of opioids during medical opioid therapy.	*See* claim 18. **WYSE (Nalox1007)** "In 2008, poisoning surpassed motor vehicle accidents as the leading cause of 'injury deaths' in the United States (Warner 2011). Nearly 90% of poisoning deaths are caused by drugs. During the past 3 decades, the number of drug poisoning deaths increased six-fold from about 6,100 in

CLAIMS	WYSE
	1980 to 36,500 in 2008. Of the 36,500 drug poisoning deaths in 2008, 14,800 involved prescription opioid analgesics. Approximately 3,000 deaths also involved heroin overdose (Warner 2011).” (1:36–44). “In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject.” (9:17–21). “In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression.” (9:33–35). “In one aspect, the known or suspected opioid overdose may be manifested by respiratory and/or central nervous system depression.” (10:1–3).
Claim 20	**WYSE in view of HPE**
The device of claim 19, wherein said patient is free from respiratory depression for at least about 1 hour following treatment comprising	*See* Claim 19. **WYSE (Nalox1007)**

CLAIMS	WYSE
essentially of delivery of said therapeutically effective amount of said opioid antagonist.	"In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the known or suspected opioid overdose is manifested by respiratory and/or central nervous system depression. The phrase 'treating an opioid overdose' includes 'reversing the effects of an opioid overdose'." (9:33–37). "In one aspect, a method for reversing the effects of an opioid overdose in an individual in need thereof is disclosed, which may comprise the step of administering intranasally a dose of a naloxone composition, wherein the naloxone composition may comprise about 10 mg/mL naloxone HCl dihydrate, about 25 mM citric acid, about 10 mM EDTA, and about 0.5% benzyl alcohol; wherein said dose comprises about 200 µL of said naloxone composition; and wherein said dose is divided into two half doses; wherein each said half dose comprises about 100 µL of said composition; and wherein each said half dose may be administered intranasally to a subject in need thereof." (10:13–24). **WERMELING 2013 (Nalox1016)**

CLAIMS	WYSE
	"Due to naloxone's high metabolic clearance and the fact that most opioids have a longer persistence in the blood stream, the symptoms of withdrawal dissipate, and in about 15–20 % of cases, administration of a repeat dose of naloxone may become necessary if overt toxicity such as central nervous system and respiratory depression recur." (71).
Claim 21	**WYSE in view of HPE**
The device of claim 20, wherein said patient is free from respiratory depression for at least about 2 hours following treatment comprising essentially of delivery of said thera-peutically effective amount of said opioid antagonist.	*See* claim 20.
Claim 22	**WYSE in view of HPE**
The device of claim 21, wherein said patient is free from respiratory depression for at least about 4 hours following treatment comprising essentially of delivery of said thera-peutically effective amount of said opioid antagonist.	*See* claims 20 and 21.
Claim 23	**WYSE in view of HPE**
The device of claim 22, wherein said patient is free from respiratory	*See* claims 20 and 22.

CLAIMS	WYSE
depression for at least about 6 hours following treatment comprising essentially of delivery of said therapeutically effective amount of said opioid antagonist.	
Claim 24	**WYSE in view of HPE**
The device of claim 16, wherein said patient is in a lying, supine, or recovery position.	*See* Claim 16. **WYSE (Nalox1007)** "In one aspect, disclosed are methods of treating a known or suspected opioid overdose in a subject in need thereof, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject. In one aspect, disclosed are methods for the complete or partial reversal of opioid intoxication, comprising administering a composition as disclosed herein, wherein the composition is administered intranasally via the nasal membranes to the subject." (9:17–21). "In one aspect, the kit may comprise a device as disclosed herein, and may further comprise instructions for use. In one aspect, the instructions may comprise visual aid/pictorial and/or written directions to an administrator of the device. The directions may include the steps of a) ***placing the individual on their back;*** b) inserting a first sprayer into the individual's nostril;

CLAIMS	WYSE
	c) aiming the nozzle towards the side of the individual's nose and away from the center of the nose; d) pressing a plunger of the device firmly with the thumb of the administrator; e) repeating steps b through d with a second sprayer in the second nostril of the individual's nose; f) monitoring the individual and the breaths of the individual, wherein if the individual does not improve or if signs of opioid overdose reappear 3-5 minutes after administering the composition, the administrator repeats the steps of b through e with a second device. The term 'does not improve' means wherein the individual does not exhibit increased breathing rates, for example, wherein an individual does not achieve 10 to 12 breaths per minute within about 3 to about 5 minutes after administration." (12:12–33) (emphasis added).
Claim 25	**WYSE in view of Djupesland and HPE**
The device of claim 7, wherein said single actuation yields a plasma concentration of ≥0.2 ng/mL within 2.5 minutes in said patient.	*See* claim 7. *See* Declaration of Gunther Hochhaus, Ph.D. (Ex. 1003),¶¶99-105.
Claim 26	**WYSE in view of Djupesland and HPE**

CLAIMS	WYSE
The device of claim 7, wherein said single actuation yields a plasma concentration of ≥1 ng/mL within 5 minutes in said patient.	*See* claim 7. *See* Declaration of Gunther Hochhaus, Ph.D. (Ex. 1003),¶¶106-112.
Claim 27	**WYSE in view of Djupesland and HPE**
The device of claim 7, wherein said single actuation yields a plasma concentration of ≥3 ng/mL within 10 minutes in said patient.	*See* claim 7. *See* Declaration of Gunther Hochhaus, Ph.D. (Ex. 1003),¶¶113-119.
Claim 28	**WYSE in view of Djupesland and HPE**
The device of claim 3, wherein said single actuation yields a plasma concentration of ≥0.2 ng/mL within 2.5 minutes in said patient.	*See* claim 3. *See* Declaration of Gunther Hochhaus, Ph.D. (Ex. 1003),¶¶99-105.
Claim 29	**WYSE in view of Djupesland and HPE**
The device of claim 3, wherein said single actuation yields a plasma concentration of ≥1 ng/mL within 5 minutes in said patient.	*See* claim 3. *See* Declaration of Gunther Hochhaus, Ph.D. (Ex. 1003),¶¶106-112.

Exhibit A

Curriculum Vitae

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PROFESSIONAL EXPERIENCE

2013-present **Associate Dean for Undergraduate Programs**
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2008-2013 **Division Head**
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1989-1996 **Assistant Professor**
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1991 **Visiting Scholar**
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1986-88 **Staff Pharmacist**
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ADDITIONAL POSITIONS AND MEMBERSHIPS

2011-present Visiting Professor, Tongji School of Pharmacy, Tongji Medical University, Wuhan, China

2010-present Member, Environmental Health Sciences Research Center, University of Iowa

2009-10 Member, Nanoscience and Nanotechnology Institute at the University of Iowa.

PUBLICATIONS

Thesis

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"Distribution of Antihistamines into the CSF following Intranasal Delivery" Kang-Jye Chou and Maureen D. Donovan. American Association of Pharmaceutical Scientists 8th Annual Meeting Orlando, FL November, 1993. *Pharm. Res*. 10, S196, 1993.

"Drug Interaction with and Permeation through Mucus" Pavan G. Bhat, Douglas R. Flanagan, Maureen D. Donovan. American Association of Pharmaceutical Scientists 8th Annual Meeting Orlando, FL November, 1993. *Pharm. Res*. 10, S259, 1993.

"Bradykinin Degradation in Rat Nasal Secretions and Plasma" Francis Y. Chung and Maureen D. Donovan. American Association of Pharmaceutical Scientists Midwest Regional Meeting Chicago, IL May, 1994.

"Comparison of Drug Permeation Rates through the Nasal Mucosa of Three Animal Species" Hsiao-Hui Wu, Peichung Kuo, and Maureen D. Donovan. American Association of Pharmaceutical Scientists Midwest Regional Meeting Chicago, IL May, 1994.

"Pre-Systemic Metabolism of Bradykinin and Substance P in the Nasal Mucosa" Francis Y. Chung and Maureen D. Donovan. American Association of Pharmaceutical Scientists 9th Annual Meeting San Diego, CA November, 1994. *Pharm. Res*. 11, S205, 1994.

"The Influence of Formulation Viscosity on Intranasal Clearance" Mengping Zhou and Maureen D. Donovan. American Association of Pharmaceutical Scientists 9th Annual Meeting San Diego, CA November, 1994. *Pharm. Res*. 11, S205, 1994.

"Selecting Nonabsorbable Markers to Study Water Flux During In Situ Nasal Perfusions" Pei-Fen Chou and Maureen D. Donovan. American Association of Pharmaceutical Scientists 9th Annual Meeting San Diego, CA November, 1994. *Pharm. Res*. 11, S206, 1994.

"In Vitro and In Vivo Correlations of Drug Permeability through the Nasal Mucosa" Benjamin P. Kuo, Hsiao-Hui Wu, and Maureen D. Donovan American Association of Pharmaceutical Scientists 9th Annual Meeting San Diego, CA November, 1994. *Pharm. Res*. 11, S206, 1994.

"Rheological Characteristics and Intestinal Bioadhesion of Polymer Gels" Mengping Zhou, Diane Venice, Douglas R. Flanagan, and Maureen D. Donovan 22nd International Symposium on Controlled Release of Bioactive Materials. Seattle, WA July, 1995. *Proc. Int. Symp. Control. Rel. Bioactiv. Mat*. 22, 310-11, 1995.

"Microsphere Transport Pathways in the Rabbit Nasal Mucosa" Ye Huang and Maureen D. Donovan 22nd International Symposium on Controlled Release of Bioactive Materials. Seattle, WA July, 1995. *Proc. Int. Symp. Control. Rel. Bioactiv. Mat*. 22, 622-3, 1995,

"Effects of Bioadhesive Polymer Gels on Nasal Mucociliary Clearance" Mengping Zhou and Maureen D. Donovan American Association of Pharmaceutical Scientists 10th Annual Meeting Miami, FL November, 1995. *Pharm. Res*. 12, S290, 1995.

"Characterization of Lipid-DNA Complexes Formed between Lipofectin® and Calf Thymus DNA" Alan M. Goldberg, Douglas R. Flanagan, and Maureen D. Donovan American Association of Pharmaceutical Scientists 10th Annual Meeting Miami, FL November, 1995. *Pharm. Res*. 12, S267, 1995.

"Effect of Osmolarity on Plasma Secretion into the Nasal Cavity" Pei-Fen Chou and Maureen D. Donovan American Assocaition of Pharmaceutical Scientists 10th Annual Meeting Miami, FL November, 1995. *Pharm. Res*. 12, S316, 1995.

"Drug Permeation through Cystic Fibrosis Mucus Solution" Pavan G. Bhat, Douglas R. Flanagan, and Maureen D. Donovan American Association of Pharmaceutical Scientists 10th Annual Meeting Miami, FL November, 1995. *Pharm. Res*. 12, S244, 1995.

"Correlation between Drug Diffusion through Cystic Fibrotic Mucus and Rheological Properties and Glycoprotein Morphology" Pavan G. Bhat, Douglas R. Flanagan, and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Seattle, WA October, 1996. *Pharm. Res*. 13, S170, 1996.

"Determination of Diffusion Coefficients of Sodium p-Aminosalicylate in Sheep Nasal Mucosae and Dialysis Membranes Using FT-IR-H-ATR Spectroscopy" Nahathai Nardviryakul, Dale Eric Wurster, and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Seattle, WA October, 1996. *Pharm. Res*. 13, S170, 1996.

"Modification of the Sol-Gel Transition Temperature and Gelling Time of Pluronic F127 Using Ionic and Non-Ionic Additives" Ye Huang and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Seattle, WA October, 1996. *Pharm. Res.* 13, S212, 1996.

"Intranasal Delivery of Local Anesthetics into the Central Nervous System" Kang Jye Chou and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Seattle, WA October, 1996.

"The Role of Water Flux in Altering Nasal Bioavailability" Pei-Fen Chou and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting San Francisco, CA November, 1998. *PharmSci* 1, S388, 1998

"An In Vitro Testing System for Assessing Performance of Vaginal Suppositories" V. Mark Kothapali, Nahathai Nardviriyakul, Eric R. Butikofer, Michelle L. Maynard, Dale Eric Wurster, and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting San Francisco, CA November, 1998. *PharmSci* 1, S494, 1998.

"Effect of Processing Variables on Adenoviral Vector Infectivity" Jeffrey J. Scott and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Indianapolis, IN October, 2000. *PharmSci* 4, S2285, 2000.

"Drug Permeation through Excised Bovine Olfactory Mucosa" Karunya Kandimalla and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Indianapolis, IN October, 2000. *PharmSci* 4, S3270, 2000

"Differential Transport Properties of Antihistamines across Olfactory and Respiratory Mucosae" Karunya Kandimalla and Maureen D. Donovan American Association of Pharmaceutical Scientists Annual Meeting Denver, CO October, 2001. *AAPS PharmSci* 3(3), 2001

"Influence of Emitted Spray Angle on Nasal Deposition Efficiency" Mow Yee Foo and Maureen D. Donovan. American Association of Pharmaceutical Scientists Annual Meeting. Toronto, Canada November 11, 2002. *AAPS PharmSci* 4(4), M1326.

"Dopamine Transport and Metabolism across the Nasal Mucosa" Nagendra Chemuturi and Maureen D. Donovan. American Association of Pharmaceutical Scientists Annual Meeting. Toronto, Canada November 14, 2002. *AAPS PharmSci* 4(4), R6127.

"Carrier Mediated Transport of Small Molecules across Bovine Olfactory Mucosa: Implications In Nose To Brain Transport" Karunya Kandimalla and Maureen D. Donovan. American Association of Pharmaceutical Scientists Annual Meeting, Salt Lake City UT October, 2003. *AAPS PharmSci* 5(4), T3140 (2003)

"Characterization Of Viscoelastic Properties Of Formulations Resistant To Mucociliary Clearance" Ankur J. Shah and Maureen D. Donovan. American Association of Pharmaceutical Scientists Annual Meeting, Salt Lake City, UT *AAPS PharmSci* 5(4), R6144 (2003)

"Drug Permeability Across Bovine Respiratory Tissues Compared To A Human Tracheobronchial Cell Culture (Epiairway™)" Nagendra Venkata Chemuturi, Maureen D Donovan, Patrick J Hayden, Mitchell Klausner AAPS Annual Meeting, Salt Lake City, UT October, 2003 *AAPS PharmSci* 5(4), T3102 (2003)

"Dopamine Transport And Metabolism across Nasal Mucosa" Nagendra Chemuturi and Maureen D. Donovan. AAPS Annual Meeting, Salt Lake City UT October, 2003. *AAPS PharmSci*, 5(4), T3103 (2003)

"Dopamine Transport across Respiratory Epithelium" Nagendra Venkata Chemuturi, Patrick J Hayden, Mitchell Klausner, Maureen D. Donovan AAPS Annual Meeting, Salt Lake City UT October, 2003. *AAPS PharmSci* 5(4), T3104 (2003)

"Formulation of Adenoviral Vectors with Inhibitors of Mucociliary Clearance Enhances Gene Transfer to Airway Epithelia In Vivo" Patrick L. Sinn, Ankur Shah, Maureen D. Donovan, Paul B. McCray, Jr. American Society of Gene Therapy Annual Meeting, Minneapolis MN June, 2004. Mol Therapy, 9, Suppl. 1, S191, 2004.

"Reducing mucociliary clearance rates through rheological property optimization" Ankur J Shah and Maureen D. Donovan. AAPS Annual Meeting, Baltimore MD November, 2004. AAPS J, 6(Suppl), 2004

"Nose to brain dopamine delivery: Targeting dopamine transporter and organic cation transporter-2 for improved CNS bioavailability and therapeutic effect" Nagendra V. Chemuturi and Maureen D. Donovan. AAPS Annual Meeting, Baltimore MD November, 2004. AAPS J, 6(Suppl),W4290, 2004.

"Localization of p-glycoprotein in human tracheal/bronchial epithelial cell culture (EpiAirway) system" Nagendra V. Chemuturi NV and Maureen D. Donovan. AAPS Annual Meeting, Baltimore MD November, 2004. AAPS J, 6 (Suppl), W4289, 2004

"Influence of viscosity and surface tension on nasal spray characteristics" Mow Yee Foo and Maureen D. Donovan. AAPS Annual Meeting, Baltimore MD November, 2004. AAPS J, 6 (Suppl), M1137, 2004

"Nose to brain delivery – Characterization of biomolecular processes controlling dopamine transport across the nasal mucosa" Nagendra V. Chemuturi and Maureen D. Donovan. AAPS Annual Meeting, Nashville, TN. November, 2005

"Rheological characterization of bioadhesive polymer gels with reduced mucociliary transit rates" Ankur J. Shah and Maureen D. Donovan. AAPS Annual Meeting, Nashville, TN. November, 2005

"Optimization of bioadhesive gels for extending intranasal residence time" Ankur J. Shah and Maureen D. Donovan. AAPS Annual Meeting, Nashville, TN. November, 2005

"Spray characteristics for optimal deposition beyond the nasal valve" Mow Yee Foo and Maureen D. Donovan AAPS Annual Meeting, Nashville, TN November, 2005

"Permeation and metabolism of cocaine in the nasal mucosa" Hefei Zhang and Maureen D. Donovan. AAPS Annual Meeting, San Antonio, TX, October, 2006

"Deposition of nasal sprays in an MRI-derived human nasal airway cast" Mow Yee Foo, YS Cheng, WC Su, and Maureen D. Donovan. AAPS Annual Meeting, San Antonio, TX, October, 2006.

"Nanoparticulate movement through viscoelastic barriers" Chen Ming Lee and Maureen D. Donovan. AAPS Annual Meeting, San Antonio, TX, October, 2006.

"Permeation of L-Phenylalanine across the Nasal Mucosa" Hefei Zhang and Maureen D. Donovan. AAPS Annual Meeting, San Diego, CA. AAPS Journal, Vol. 9, No. S2, Abstract T2023 (2007).

"A Geometric Approach to Simulating Nasal Spray Deposition Efficiency" Mow Yee Foo, YS Cheng, WC Su, and Maureen D. Donovan. AAPS Annual Meeting, San Diego, CA, November, 2007, AAPS Journal Vol. 9, No. S2, Abstract W5254 (2007).

"Nanoparticulate Movement in Concentrated Polymer Solutions" Chen Ming Lee and Maureen D. Donovan. AAPS Annual Meeting, San Diego, CA. AAPS Journal, Vol 9, No. S2, Abstract W4198 (2007).

"Measurement of Drug Transport in the Mammary Epithelium Using Cytometric Methods". Joanne E. Reiland and Maureen D. Donovan. AAPS Annual Meeting, San Diego, CA. AAPS Journal Vol. 9, No. S2, Abstract T2021 (2007).

"A Novel Biotinylated Chitosan Polymer for Applications in Tissue Engineering and Gene Delivery" Aiman Abbas, Maureen Donovan,Aliasger Salem. AAPS Annual Meeting, San Diego, CA. AAPS Journal, Vol 9, No. S2, Abstract T3044 (2007)

"Analysis of Mitoxantrone Uptake and Efflux in Mammary Epithelial Cells Using Flow Cytometry". JE Reiland and MD Donovan, AAPS Annual Meeting, Atlanta, GA, AAPS Journal 10(S2), 2524, (2008)

"Development of a Predictive Relationship between Nasal Membrane Permeability and Nasal Absorption Rate Constant". H Zhang and MD Donovan, AAPS Annual Meeting, Atlanta, GA. AAPS Journal 10(S2), 2916, (2008).

"Chitosan-Dextran Sulfate as Vaccine Delivery Systems "AO Abbas, MD Donovan, AK Salem. AAPS Annual Meeting, Los Angeles, CA. AAPS Journal 11(S2), 3849, 2009. www.aapsj.org/abstracts/AM_2009/AAPS2009-003849.pdf.

"Biotinylated Chitosan Applications in Enzyme Immobilization." AO Abbas , MD Donovan, AK Salem, AAPS Annual Meeting, Los Angeles, CA. AAPS Journal 11(S2), 3727, 2009. www.aapsj.org/abstracts/AM_2009/AAPS2009-003727.pdf.

"Expression of Drug Transporters in the Mammary Epithelium". JE Reiland and MD Donovan, , AAPS Annual Meeting, Los Angeles, CA. AAPS Journal 11(S2), 3760, 2009. www.aapsj.org/abstracts/AM_2009/AAPS2009-003760.pdf.

"PEPT1 and PEPT2 Activity in Human Mammary Epithelial Cells." JE Reiland, MD Donovan**,** , AAPS Annual Meeting, Los Angeles, CA. AAPS Journal 11(S2), 3553, 2009. www.aapsj.org/abstracts/AM_2009/AAPS2009-003553.pdf.

"Localization of Cytochrome P450 (CYP450) Enzymes in Bovine Olfactory and Respiratory Mucosa." VS Dhamankar , KS Walters, MD Donovan, , AAPS Annual Meeting, Los Angeles, CA. AAPS Journal 11(S2), 1421, 2009, www.aapsj.org/abstracts/AM_2009/AAPS2009-001421.pdf.

"Size and Surface Properties Determining Nanoparticle Uptake in the Nasal Mucosa". N Chen, DE Wurster, MD Donovan, , AAPS Annual Meeting, Los Angeles, CA. AAPS Journal 11(S2), 2528, 2009. www.aapsj.org/abstracts/AM_2009/AAPS2009-002528.pdf.

"The Presence of Multiple Nucleoside Transporters in the Nasal Mucosa". Manar Al-Ghabeish, K. Walters, M. Donovan AAPS Annual Meeting, New Orleans, LA AAPS Journal 12(S1), 1180, 2010.

"The Role of OCT-2 and OCTN-2 in the Transport of Amantadine Across the Nasal Mucosa". Maya George and M Donovan, AAPS Annual Meeting, New Orleans, LA AAPS Journal 12(S1), 1195, 2010.

"Characterization of CYP450 Drug Metabolizing Activities in the Nasal Mucosa". Varsha Dhamankar and M Donovan, AAPS Annual Meeting, New Orleans, LA AAPS Journal 12(S1), 4276, 2010.

"Surface Modification and Size Dependence of Nanoparticle Translocation in the Nasal Cavity." Nan Chen, Dale E. Wurster, M. Donovan, AAPS Annual Meeting, New Orleans, LA AAPS Journal 12(S1), 6110, 2010.

Role of OCT2 and OCTN2 in Nose to Brain Distribution of Amantadine". Jiangeng Huang, Maya George, Rakesh Awasthi, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26805)

"Identification of Multiple Nucleoside Transporters to Facilitate Intranasal Drug Delivery" Manar Al-Ghabeish, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=27021)

"Nose to Brain Delivery of Cimetidine in Rats" Maya George, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=27252)

"CYP1A2 Mediated Metabolism of Melatonin by the Nasal Mucosa" Varsha Dhamankar, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26519)

"Pharmacoimaging of Drug Disposition after Intranasal Administration" Laura B. Ponto, Susan Walsh, Jiangeng Huang, Christine Mundt, John Sunderland, Maureen Donovan. AAPS Annual

Meeting, Washington DC. 2011.
(http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26420)

"Surface Modification and Size Dependence of Nanoparticle Translocation in the Nasal Mucosa" Nan Chen, Maureen Donovan. AAPS Annual Meeting, Washington DC. 2011.
(http://abstracts.aaps.org/published/ContentInfo.aspx?conID=26234)

"Permeability Characteristics of Non-Functionalized Cellulose Membranes Prepared From Dimethyl Sulfoxide Paraformaldehyde Solvent System- Influence of Degree of Polymerization of Cellulose" Bhavik Bhatt, Maureen Donovan, Douglas Flanagan, Vijay Kumar. AAPS Annual Meeting, Washington DC. 2011.
(http://abstracts.aaps.org/published/ContentInfo.aspx?conID=27142)

"Expression of Drug Transporters in Animal Models Used for Nasal Absorption Characterization" Manar Al-Ghabeish, Todd Scheetz, Mahfoud Assem, Maureen Donovan. AAPS Annual Meeting, Chicago, IL 2012. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=1838)

"A Mass Transport Model for Concurrent Diffusion and Metabolism of Drugs across the Nasal Mucosa" Varsha Dhamankar, Stephen Stamatis, Maureen Donovan. AAPS Annual Meeting, Chicago IL 2012. (http://abstracts.aaps.org/published/ContentInfo.aspx?conID=893)

"Use of PET Imaging to Measure Nucleoside Transporter-Mediated Distribution from the Nasal Mucosa" Laura Ponto, Jiangeng Huang, Susan Walsh, Michael Acevedo, Christine Mundt, John Sunderland, Maureen Donovan. AAPS Annual Meeting, Chicago, IL 2012.
(http://abstracts.aaps.org/published/ContentInfo.aspx?conID=1329)

"Effect of Marijuana Smoking on Global Cerebral Blood Flow in Chronic and Occasional Users." Rakesh Awasthi, Daniel O'Leary, Jonathan Koeppel, R Nguyen, Maureen Donovan, Laura Ponto. AAPS Annual Meeting & Exposition, San Antonio TX, November, 2013.

"Expression and Activity of LAT-2: An L-Type Amino-Acid Transporter in the Olfactory and Respiratory Nasal Mucosa". Ana Ferreira, Maureen Donovan. AAPS Annual Meeting & Exposition, San Antonio TX, November, 2013.

"Uptake of Quantum Dots Across the Nasal Mucosa". Bhanu Bejgum, Maureen Donovan. AAPS Annual Meeting & Exposition, San Antonio TX, November, 2013.

"Expression of the LAT-2 Transporter in the Nasal Mucosa and Its Role in the Uptake of Gabapentin." Nan Ferreira and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014.

"Uptake and Transport Pathways for Ultrafine Nanoparticles (Quantum Dots) in the Nasal Mucosa." Bhanu Bejgum and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014

"PBPK Simulation of Brain Tetrahydrocannabinol (THC) and Metabolites Based on Fitting to Plasma Concentrations following IV Administration of a Surfactant/Ethanolic Solution." Rakesh Awasthi, Michael Bolger, Maureen Donovan, and Laura Boles Ponto. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014

"Characterization of Atrazine Transport across Nasal Respiratory and Olfactory Mucosa". Wisam Al Bakri and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA November, 2014

"Assessment of Deposition Patterns of Nasal Sprays in Children Using an In Vitro MRI-Based Nasal Cast Model" Namita Sawant and Maureen Donovan. AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"An Effect-Compartment Modeling Approach to Relate the Plasma Concentrations of Δ^9-tetrahydrocannibinol (THC) and Active Metabolite to the Observed Psychoactive Effects". Rakesh Awasthi, Guohua An, Maureen Donovan, Laura Ponto. . AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"Atrazine Permeation across the Nasal Mucosa: Formulation Effects of Commercial Herbicide Products". Wisam Al Bakri and Maureen Donovan. . AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"Synergistic Behavior of LAT-2 and other Amino Acid or Cation Transporters in the Nasal Uptake of Gabapentin" Ana Ferreira and Maureen Donovan. . AAPS Annual Meeting and Exposition, Orlando, FL, October, 2015

"Enhancing Midazolam Permeability Across the Buccal Mucosa for Rapid Seizure Treatment". Laxmi Shanthi Chede, Max Baker and Maureen Donovan. AAPS Annual Meeting and Exposition, Denver, CO, November, 2016.

"Nasal Spray Deposition in Children-In Vitro Investigation of the Effect of Plume Angle and the Role of Surface Mucus". Namita Sawant and Maureen Donovan. . AAPS Annual Meeting and Exposition, Denver, CO, November, 2016

"Permeation of Herbicides Across the Nasal Mucosa: An Overlooked Route with Potential Toxicological Implications". Wisam Al Bakri and Maureen Donovan . AAPS Annual Meeting and Exposition, Denver, CO, November, 2016

"The Role of Efflux Transporters in the Direct Nose-to-Brain Transport of Atrazine and 2,4-D following Nasal Inhalation." Wisam Al Bakri and Maureen Donovan. AAPS Annual Meeting and Exposition, San Diego, CA, November, 2017.

"Mechanisms of Uptake of Polystyrene Nanoparticles by the Nasal Mucosa". Ammar Alkhafaji and Maureen Donovan. .. AAPS Annual Meeting and Exposition, San Diego, CA, November, 2017.

"Enhancing Midazolam Permeability across the Buccal Mucosa for Rapid Seizure Treatment". Laxmi Shanthi-Chede, Max Baker, and Maureen Donovan. .. AAPS Annual Meeting and Exposition, San Diego, CA, November, 2017.

"Preparation of Poly D, L Lactic Co-Glycolic Acid (PLGA) Nanoparticles and Evaluation of Uptake Pathways across the Nasal Mucosa. Mohammed Albarki and Maureen Donovan. .. AAPS Annual Meeting and Exposition, San Diego, CA, November, 2017."

"In Vitro Assessment of the Effect of Surface Mucus on Deposition Patterns of Nasal Sprays in Children." Namita Sawant and Maureen Donovan. .. AAPS Annual Meeting and Exposition, San Diego, CA, November, 2017.

INVITED PRESENTATIONS

"The Molecular Weight Dependence of Gastrointestinal and Nasal Absorption" Ciba-Geigy Corp. Ardsley, NY May 1, 1989.

"Nasal Drug Delivery: Molecular Weight and Formulation Effects" SmithKline Beecham Pharmaceuticals, Upper Merion, PA March 15, 1991.

"Drug Absorption into CSF and Plasma following Intranasal Administration" Glaxo Inc., Research Triangle Park, NC March 28, 1993.

"Presystemic Metabolism following Intranasal Delivery" First International Conference on Pharmaceutical and Food Sciences and Technology - Symposium on Drug Delivery Systems Chicago, IL August 26, 1993.

"Nasal Drug Delivery: Local vs. Systemic Effects" University of Connecticut School of Pharmacy Storrs, CT October 28, 1993.

"Local Effects following Intranasal Drug Administration" Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT October 29, 1993.

"Evaluation of Intranasal Dosage Forms Using *In Vitro* Systems" Miles Laboratories, Inc., Elkhart, IN November 8, 1993.

"Predicting Nasal Bioavailability and Toxicity Using *In Vitro* and *In Vivo* Animal Models" Syntex, Inc. Palo Alto, CA June 9, 1994.

“Career Opportunities in Pharmaceutics” 12th Annual Sumposium on Pharmaceutical Sciences Graduate Programs, Merrillville, IN October 15, 1994.

"Nasal Drug Delivery: Mucosal and Formulation Effects on Systemic Distribution and Bioavailability" Parke-Davis/Warner Lambert Pharmaceutical Research Division Ann Arbor, MI October 17, 1994.

"Nasal Drug Delivery: Local vs. Systemic Effects" Alza, Inc. Palo Alto, CA November 4, 1994.

“Limitations to Drug Permeability Due to Mucus Layers” Eli Lilly & Co. Indianapolis, IN April 10, 1996

“Metabolism and Residence Time Effects on Nasal Drug Delivery” Indianapolis/Cincinatti Pharmaceutical Discussion Group Indianapolis, IN April 10, 1996

“Drug Delivery to a Virtual Space: Development of Vaginal Formulations” Gilead Sciences, Inc. Foster City, CA September 6, 1996

“Drug Disposition into the CNS following Nasal Delivery” Nastech Pharmaceutical Company Hauppauge, NY October 4, 1996

“Preferential Drug Delivery to the CNS: Myth or Fact?” American Association of Pharmaceutical Scientists October 29, 1996

“Nasal Drug Delivery” American Association of Pharmaceutical Scientists October 31, 1996.

“Nasal Drug Delivery: Mucosal and Formulation Effects on Nasal Bioavailability” The West Company, January 6, 1997.

“Drug Delivery to a Ciliated Mucosal Surface: Trying to Trick Mother Nature” Aguoron Pharmaceuticals, Inc. March 28, 1997.

"Non-immunologic Complications of Nasal Drug Delivery" Nasal and Pulmonary Drug Delivery, Conference V, Stockholm, Sweden, September 30, 1997

"Nasal Drug Delivery: Formulation and Mucosal Surface Effects" Unigene, Inc. August, 1998

"Evaluation of Vaginal Drug Delivery System Efficacy", Women's Health Symposium, University of Iowa, March, 1999.

"Drug Disposition into the CNS Following Nasal Delivery" West Pharmaceutical Services, Inc. August, 2000

"Nasal Drug Delivery: Mucosal and Formulation Effects on Nasal Bioavailability" Bristol Myers Squibb, May, 2001

"Nasal Drug Delivery: Mucosal and Formulation Effects on Systemic Distribution and Bioavailability" Pharmacia Corporation, 2001

"Biopharmaceutics Curriculum at the University of Iowa: What to Include and Why" AACP Teachers of Pharmaceutics Seminar. American Association of Pharmaceutical Scientists Annual Meeting. Toronto, CA November 10, 2002.

"Carrier Mediated Processes as an Explanation for Selective Nose to Brain Transport" Uppsala University, Uppsala Sweden. March, 2003.

"Intranasal Deposition: Effect of Particle Size, Velocity, and Nasal Anatomy" AAPS Workshop on Particle Size Analysis. Alexandria, VA May 2, 2003

"Gender Differences in Medication Response: Drugs and Delivery Systems" 11th Annual Congress on Women's Health, Hilton Head, SC June 2, 2003.

"The Pharmaceutics Curriculum: Integrating Physical Concepts with Clinical Practice" AACP Annual Meeting, July 20, 2003.

"Gender and Racial Differences in Pharmacologic Response: Drug Delivery Systems" Expert Meeting on Improving the Use and Safety of Medications in Women Through Gender and Race Analysis. Sponsored by the Agency for Healthcare Research and Quality, April 19, 2004.

"Nose to Brain Delivery: An Optimistic Pessimist's Analysis" Respiratory Drug Delivery X Conference, Boca Raton, FL, May, 2006

"Nasal Drug Delivery: Passing the Sniff Test" Affymax, Inc. Palo Alto, CA September 22, 2006

"Using Biological Properties and Permeability to Select Routes of Administration" University of Michigan, October, 2006.

"Drug Delivery: Utilizing Chemistry, Biology and Materials Science to Improve Human Health" Department of Biomedical Engineering, University of Iowa, April, 2007

"Nasal Drug Delivery: Passing the Sniff Test" Pallatin, Inc.Cranbury, NJ April, 2007

"Some Do and Others Don't: Understanding Nose to Brain Delivery of Therapeutic Agents" University of Oklahoma College of Pharmacy, May, 2007.

"Prolonging Nasal Residence Time: Bioadhesive Polymers and Their Interactions with the Nasal Mucosa" NovaBay Pharmaceuticals, Inc. Emeryville, CA, April, 2008.

"Nasal Drug Delivery: Passing the Sniff Test" Centocor Pharmaceuticals, Palo Alto, CA February, 2009

"Alternative Routes of Delivery: Significance, Selection and Success" Glaxo SmithKline Consumer Products, Parsipanny, NJ March, 2009.

"Drug Transport Processes and Limitations in the Olfactory Mucosa" University of Michigan College of Pharmacy Science Symposium : Physical Chemistry in the Age of Molecular and Cellular Biology. October 15, 2010

"Size and Surface Characteristics Influencing Nanoparticle Uptake and Transport through the Olfactory Mucosa. Environmental Health Sciences Research Center, University of Iowa October 22, 2010.

"Size and Surface Properties Determining Nanoparticulate Uptake in the Nasal Mucosa" University of Iowa Environmental Health Sciences Research Center Retreat. January 10, 2011.

"Alternative Routes of Delivery: Significance, Selection and Success" Tongji Medical College School of Pharmacy, Huazhong University of Science and Technology, Wuhan, China. November 19, 2011.

"Materials and Methods for the Controlled Release of Ophthalmic Medications" Department of Ophthalmology Fourth Military Medical University, Xi'an, China. November 21, 2011.

"Some Do and Others Don't. Understanding Nose to Brain Transport of Therapeutic Agents" University of Iowa Department of Chemical and Biochemical Engineering. February 23, 2012.

"Career and Life Lessons Learned" University of Iowa Chapter of Women in Science and Engineering. February 26, 2012.

"The Nose to Brain Transport Pathway: Navigating the Entrance and Exit Ramps" Duquesne University College of Pharmacy. March 29, 2012.

"The Olfactory Neuroepithelial Barrier as a Delivery Pathway to the CNS" Gordon Research Conference on the Barrier Function of Mammalian Skin. August 21, 2013.

Using the Olfactory Neuroepithelium as a Delivery Pathway to the CNS. China Pharmaceutical Association, Wuhan, China, October 25, 2013.

Using the Olfactory Neuroepithelium as a Delivery Pathway to the CNS. Shiyan, China. October 28, 2013.

Abuse Deterrent Drug Products: Formulations and Drug Product Equivalence. University of Iowa College of Pharmacy. Cold Night, Hot Topics Symposium January 23, 2014.

Translational Medicine and Drug Development. University of Iowa Institute for Clinical and Translational Science. October, 2014.

In Vitro Assessment of Nasal Deposition Patterns in the Pediatric Population. NIPTE/FDA Science Meeting, Shady Grove, MD. April, 2015.

The Promise of Nose to Brain Transport: It's Not Nice (or Easy) to Fool Mother Nature. Eli Lilly & Co. May, 2015

Molecules and Macromolecules, Nano and Microparticles: Does the Olfactory System Provide a Drug Delivery Pathway to the Brain? Iowa State University Nanovaccine Initiative Annual Meeting. May, 2015

The Importance of Mentorship in Leadership Development. Zada M. Cooper Leadership Symposium. College of Pharmacy University of Iowa April 30, 2016

The Olfactory Access Pathway to the Brain: Potential Risks and Promising Rewards. Human Toxicology and Environmental Health Science Research Seminar Series. December 2, 2016.

Modeling Deposition in the Respiratory Tract: What Can We Learn That Impactors Don't Tell Us. 3rd FDA/PQRI Conference on Advancing Product Quality. Rockville, MD March 23, 2017.

Cells vs. Nanoparticles: How to Let Them In and How to Keep Them Out. Boehringer Ingelheim, Ridgefield, CT. July 11, 2018.

CE Presentations

"Drug Delivery Systems: An Application of Technology"
Trends in Health Care CE Conference Iowa City, IA October 8, 1989.

GRADUATE STUDENTS

Ph.D. Degree Conferred

Yu-Min (Francis) Chung *The Limiting Effects of Mucosal Metabolism on Systemic Bioavailability from the Nasal Cavity,* May, 1995

Pavan G. Bhat *Drug Binding and Permeation in Normal and Cystic Fibrosis Mucus Solutions,* May, 1996

Mengping Zhou *Drug and Formulation Induced Toxicity and Clearance Alterations in the Nasal Cavity,* August, 1996

Kang-Jye Chou *Physicochemical Properties Controlling Transport into the CSF following Intranasal Drug Administration,* August, 1997

Ye (Bill) Huang *Characterization of the Rheological Properties of In Situ Gelling Systems and Their Potential Use in Nasal Drug Delivery*, August, 1997.

Pei Fen Chou Roghair *The Influence of Formulation Osmotic Pressure on Nasal Bioavailability,* July, 2001

Karunya Kandimalla *Carrier Mediated Transport of Small Molecules across Bovine Olfactory Mucosa: Implications in Nose to Brain Drug Delivery*, May, 2004

Ankur Shah *Viscoelastic Gels Resistant to Mucociliary Clearance: Rheological and Chemical Optimization for Prolonged Mucosal Contact,* July, 2005

Nagendra V. Chemuturi *The Characterization of Biomolecular Processes Controlling Dopamine Transport Across the Nasal Mucosa,* December, 2005

Mow Yee Foo *Deposition Patterns of Sprays in the Human Nasal Airway: Interactions Among Formulation, Device, Anatomy, and Administration Techniques*. Dec. 2007.

Chen-Ming Lee *Nanoparticle Mobility in Viscoelastic Media*. July, 2008

Hefei Zhang *Identification of Membrane Transporters to Facilitate Intranasal Drug Delivery Using Tissue-based and Pharmacokinetic Approaches.* July, 2009

Joanne Reiland *Analysis of Cell Culture Models of Mammary Transport*, July, 2009.

Varsha Dhamankar – *Role of Concurrent Metabolism and Saturable Uptake on Distribution Following Nasal Administration.* May, 2013

Maya George – The *Role of Organic Cation Transporters in the Nasal Uptake and Brain Distribution of Organic Cation Substrates.* May, 2013

Nan Chen – *Size and Surface Properties Determining Nanoparticle Uptake and Transport in the Nasal Mucosa.* July, 2013.

Manar Al-Ghabeish – *Drug Transports in the Nasal Epithelia and Their Contributions in Drug Delivery*. December, 2013.

Rakesh Awasthi – *Application of Modeling-based Approaches to Study the Pharmacokinetics and Pharmacodynamics of Δ^9-Tetrahydrocannabinol (THC) and Its Active Metabolite* May, 2017

Bhanu Bejgum – *Ultrafine Nanoparticle Uptake and Transport in the Nasal Mucosa* May, 2017

Master's Degree Conferred

Hsiao-Hui (Daisy) Wu *Comparison of Drug Permeation Rates through the Nasal Mucosae of Three Animal Species,* August, 1994.

Diane Venice *Factors Influencing the Viscoelastic Behavior of a (Poly)Acrylic Acid Gel System*, December, 1995.

Daniel Cullinan (non-thesis) August, 1997

Jeffrey Scott (non-thesis) July, 2000

Kavita Khanvilkhar (non-thesis) December, 2001

Saroj Vangani (non-thesis) December, 2003

Saurabh Agarwal (non-thesis) August, 2004

Anita Gondi (non-thesis) December, 2005

Salem Elghami (non-thesis) May, 2011

Juan Carlos Soza Rios (non-thesis) May, 2012

Wided Najahi-Missaoui (non-thesis) December, 2013

Krupal Robeshkumar Maity - *Targeting the Trigeminal Nerve System for Orofacial Pain Treatment* May, 2013

Wisam Al Bakri – *Characterization of Atrazine Transport Across Nasal Respiratory and Olfactory Mucosae*, May, 2014

Mohammed Albarki – *In Vitro Assessment of the Transport of Poly D, L Lactic-co-Glycolic Acid (PLGA) Nanoparticles Across the Nasal Mucosa*. July, 2016.

Ammar Al-Khafaji - *Nanoparticle Uptake Mechanisms in the Nasal Respiratory and Olfactory Mucosae.* December, 2016.

Zainab Bakri *The Effect of Nucleoside Transporters and P-glycoprotein on the Nasal Uptake of Ribavirin*. July, 2018.

Current Students (and tentative Ph.D. dissertation title)

Anna Ferreira – *Identification and Function of Amino Acid Transporters in the Nasal Mucosa (expected completion: Fall, 2018)*

Wisam Al-Bakri – *Enhanced CNS Distribution of Pesticides following Inhalation Exposure (expected completion: Fall, 2018)*

Namita Sawant – *Nasal Deposition Patterns in Pediatric Nasal Airways (expected completion: Fall, 2018)*

Mohammed Al Barki – *Endocytic Uptake Mechanisms Regulating Nanoparticle Uptake in Nasal Cell Cultures and the Nasal Mucosa (expected completion: December, 2018)*

Ammar Al Khafaji -*Targeting Epithelial vs NALT uptake of nanoparticles following Nasal Administration (expected completion June, 2019)*

Laxmishanthi Chede –*Solubility and Permeation Enhancement of Low Solubility Drugs Using Buccal Thin Films (expected completion, June, 2019)*

Saikishore Meruva – In Vitro Methods to Predict Nasal Abuse Potential of Abuse-Deterrent Dosage Forms *(Fall, 2019)*

Lindsey Floryence – PET-Enhanced Drug Disposition Modeling (pre-comp)

Post-Doctoral Fellows

Jiangeng Huang, Ph.D. – Pharmacokinetic Evaluation of Nose to Brain Transport (2010-12)

Visiting Scholars

Bjorn Jansson, Uppsala University, October – December, 2001

Jon Haraldsson, Uppsala University, January – May, 2004

Juan Pablo Cerasano, Neurosurgeon, Argentina, June – October, 2011

Bryan Gonzalez, University of Puerto Rico. SROP Scholars Program – June – August, 2012

Jiaqiang Xu, Tongji Medical College, Hubei University of Science and Technology– Dec 2011-March 2012; Sept 2012-Sept 2014.

Johnny Xu, Tongji Medical College, Hubei University of Science and Technology – March, 2014-June 2104.

Pharm.D. Student Trainees

Michael Arndorfer, (1990-1992)
Kristen Swantz, (1992-94)
Kelsey Mohs (P4 Research Rotation), September, 2013
Ashley Beckman, (2014-2015)
Amanda Rixen, (2014-2015)
Shanrae'L Vinel (2016)
Ellen Overholzer (2016-present)
Mitchell Roback (2016-present)
Connor Hunter (Spring, 2017)

Undergraduate Student Research Trainees

Kevin Tobin (January 2018-present)
Effect of User-Related Factors and Droplet Properties on Nasal Spray Deposition Patterns in the Nasal Cavity of a 12-Year-Old Child Using Computational Fluid Dynamics. Senior Honors Thesis, Department of Chemical and Biochemical Engineering.

GRANTS AND AWARDS

Investigation of the Limiting Role of Mucus in the Diffusion of Drug Molecules in the Lower Respiratory Tract The University of Iowa College of Pharmacy BRSG Seed Grant $6000, 1989.

Research gift from the Proctor and Gamble Co. $5000, 1989.

Molecular Weight Dependent Absorption following Intraperitoneal, Intramuscular, and Subcutaneous Administration Parenteral Drug Association Faculty Development Grant Program $15,000, 1990-91.

The Limiting Effects of Mucosal Metabolism on Systemic Bioavailability from the Nasal Cavity The University of Iowa College of Pharmacy BRSG Seed Grant $5000, 1990.

Research gift from SmithKline Beecham Pharmaceuticals $5000, 1990.

CSF vs. Plasma Drug Concentration following Intranasal Administration American Association of Colleges of Pharmacy Grant Program for Young Investigators $5000, 1991.

The Use of a PABA-Peptide (Bentiromide) as a Nasal Absorption Marker Pharmaceutical Manufacturers Association Undergraduate Research Fellowships Program $5000, 1991.

Research gift from SmithKline Beecham Pharmaceuticals $5000, 1991.

Physicochemical Properties Controlling Transport into the CSF Following Intranasal Administration Glaxo, Inc. $15,000, 1991.

Investigation of Epithelial Damage and Repair in the Nasal Mucosa Rugby Darby Group Companies, Inc. $30,000, 1991.

Eli Lilly & Co. Young Investigator Award $20,000, 1992-93.

National Institutes of Health, National Institute of Allergy and Infectious Disease, DAIDS NO1-AI-95040. T.F. Chin (principal investigator). M.D. Donovan and D. R. Flanagan, co-investigators Funds available $210,000 (January, 1994 - September 1995).

Abbott Laboratories, *Development of an Otic Formulation*, March - November, 1997, $25,000

Mimetix, Inc. *Development of Sustained Release Vaginal Formulations* M.D. Donovan and D.E. Wurster, co-investigators, $13,000, 1997.

Battelle, Inc. *Formulation Development of Solutions for Inhalation* M.D. Donovan and D.R. Flanagan, co-investigators, $120,000, 1997-1999.

Pharmacia & Upjohn *Preformulation and Formulation of a Veterinary Injectable Dosage Form*. $64,500, 1998 - 1999.

Aguoron Pharmaceuticals *Dissolution Characterization of Poorly Soluble Drugs*. D.E. Wurster (PI) and MD Donovan (co-investigator) $75,000, 1998-2000

Meyer Nutraceuticals *Dissolution Characterization of a Targeted Release Oral Dosage Form* $50,000, 1999-2000.

Pharmaceutical Research & Manufacturers of America Foundation. *Improved In Vitro Drug Release Testing Methods for Dosage Forms Administered to Limited Volume Sites*. $5000, 2001.

Pinney & Associates *Formulation and Evaluation of Nasal Dosage Forms*, $113,000, 2001

Bristol Myers Squibb *Bioavailability and Toxicologic Evaluation of Nasal Dosage Forms*. $108,750, 2002

Ross Products *Development of Gel Formulations*. $ 310,600, 2002-2006.

The University of Iowa Collaborative Interdisciplinary Projects *Cell Culture Models for Drug Transport across Mammary Epithelium.* co-investigator: Sarah England, Ph.D. $24,975, 2004

National Cancer Institute, Division of Cancer Treatment and Diagnosis, Developmental Therapeutics Program *Manufacturing of Oral and Topical Dosage Forms*
PI: Rolland Poust, Ph.D. (task order contract), $250,000 (annual) 2005-2011 ((MDD, 5% effort)

Abbott Laboratories *Investigation of Mucosal Transport* $60,000, 2005

Abbott Laboratories *Bioavailability of Sustained Release Injectables* $20,000, DR Flanagan (PI), 2006

NIH/NIDCD R01 DC008374 *Bypassing the Blood Brain Barrier: Modulation of Transporters in the Nasal Mucosa*, $1,500,000, (Donovan, PI), 2007-2012. ARRA Supplement $127,500 (2009)

Glaxo Smith Kline Consumer Products *In Vitro Formulation Evaluation*, $85,000, 2009-11.

Novartis Pharmaceuticals Corporation "*Novartis Pharmaceuticals Student Internships*". $108,318, 2010.

Acquisition of a Dispersive Raman Spectrometer with Confocal Microscope. Roy J. Carver Charitable Trust. $125,000, 2010

Novartis Pharmaceuticals Corporation "*Novartis Pharmaceuticals Student Internships*". $123,000 2011.

Nanoparticle Distribution from the Olfactory Epithelium to the Brain Institute for Clinical Translational Science – University of Iowa $50,000 2012-13

Enhanced CNS Exposure to Glyphosate following Inhalation Resulting from Olfactory Uptake Center for Health Effects of Environmental Contamination- University of Iowa $30,000 2013

Pediatric Nasal Dosage Forms: In Vitro Characterization of Intranasal Deposition Patterns in Children for Optimal Delivery and Performance. NIPTE/US FDA U01 $84,500 2013-2015.

Exposure Characterization following Nasal Inhalation of Narcotic-Containing Drug Products. Mallinckrodt Pharmaceuticals $65,000 2013-15.

Development of Alternative Dosage Forms of Vanoxerine. Clipse Therapeutics. $76,250 2015.

Enhanced CNS Exposure to Herbicides Following Inhalation Resulting from Olfactory Uptake. University of Iowa Environmental Health Sciences Research Center $40,000 2016-2017.

TEACHING RESPONSIBILITIES

Pharmacy Orientation, Pharmacy 46:014 (2 s.h.)
Spring 1990 - 1993

Drug Delivery Systems: Principles and Applications,
Pharmacy 46:202/46:232/46:110,111/46:238/239 (3 s.h.)
Fall 1990, 1992, 1994; 2009, 2011 ,2013
Spring, 1997, 1999, 2001, 2005, 2007, 2009, 2011, 2012, 2014, 2016

Introduction to Pharmaceutical Care 46:049
Fall 1993 - 1996 lecture on Dosage Forms for Colds and Allergies

Introduction to Pharmaceutical Sciences 46:050
Spring 1994, 1995 (15 lectures; course coordinator)

Therapeutic and Diagnostic Systems 46:145 (2 s.h.)
Fall 1995 – Fall, 2002

Principles of Equilibrium Processes 46:050
Spring 1996 (15 lectures; course coordinator))

Pharmaceutics Seminar 46:231 (2 s.h.)
1997-2003 (co-coordinator)
2012-2015 (coordinator)

Professional Practice 46:143
Fall 1997- 2000 8 lectures on Parenteral Dosage Forms

Pharmacy Projects (Calculations) 46:050 (2 s.h.)
Spring 1997

Pharmacy Honors Seminar 46:102 (1 s.h.)
1998-2001 (coordinator)

Pharmaceutics I: Solutions 46:123
Fall 2001-2004 (20 lectures)

Pharmaceutics II: Solids and Semi-solids 46:124
Spring 2002-2009 (30 lectures); 2010 (8 lectures), 2011 (15 lectures), 2012 (10 lectures), 2014 (8 lectures); 2015 (6 lectures)

Pharmaceutics III: Pharmacokinetics and Biopharmaceutics 46:138
Spring 2002, Fall 2002, 2003 (15 lectures); Fall 2009-2016 (25 lectures)

Foundations of Pharmaceutical Science II (46:8137)
Laboratory Instructor – 20 contact hrs 2016

Parenteral Products and Technology 46:173
Fall 2002 (6 lectures)

Pharmacy Practice Laboratory I
Fall 2004-2014 (25 - 35 contact hours)

Pharmacy Practice Laboratory II
Spring 2005-2009 (10 contact hours)

Pharmacy Practice Laboratory III
Fall 2004, 2005 (24 contact hours), 2007 (8 contact hours)

Pharmacy Practice Laboratory IV
Spring 2004-11 (7 contact hours)

Pharmacy Practice Laboratory V
Fall 2004, 2006, 2007 (8 contact hours)

Introductory Practice Experience I (preceptor)
2007-2009

First Year Seminar: Health in a Bottle – Drug Development in the 21st Century (1 sh)
Fall 2009-13

First Year Seminar: Apothecary 101 (1 sh) 46:1000
Fall 2015, 2016

Introduction to Pharmaceutical Sciences: Drug Development PHAR:1100 (1 sh)
Fall 2015, 2016, 2017
Spring 2016

New Drugs for New Therapies (2 sh) PHAR:8811
Spring 2016-17

Need A New Drug? (1 sh) PHAR:1111 (online)
Spring 2017, Summer 2017, Fall 2017

Foundations of Pharmaceutical Science II PHAR:8137 (6 contact hours)
Fall 2016 -17

Medicines That Changed the World (1 sh) PHAR:1200
Fall, 2016-17 (course coordinator)

Integrated Pharmacotherapy Courses (2016-17)
Dermatologics (3 hr lecture/6 hr lab)
Musculoskeletal (1 hr)
Genitourinary (2 hr)
Neurology and Psychiatric Therapies (3 hr)

Introduction to Basic Pharmaceutical Sciences PHAR:8791 (Spring, 2017)
Deposition Patterns of Nasal Sprays in Pediatric Patients – What Could Go Wrong?? (2hr)

Pharmacy Projects
Fall 2014, Spring 2015 – Ashley Beckman
Fall 2014, Spring 2015 – Amanda Rixen

EDITORIAL ADVISORY BOARD MEMBERSHIPS

Molecular Pharmaceutics (American Chemical Society), 2013-present

Journal of Pharmaceutical Innovation (Springer), 2010.

REVIEW AND ADVISORY PANEL MEMBERSHIPS

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) March, June (Chair), November (Chair), 2017; March (Chair), June (Chair) 2018.

FDA Anesthetic and Analgesic Drug Products Advisory Committee - Ad hoc member (May 2016)

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) February, June, October 2016

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) February, July, October 2015.

NIH/CSR – Small Business: Drug Discovery for Aging, Neuropsychiatric and Neurologic Disorders. ZRG1-ETTN-M(11) February, June, October, 2014.

NIH/NIDCD – Chemosensory Fellowship Application Review. ZDC1 SRB-Y (68) February, 2014.

NIH/NIDCD – Chemosensory Fellowship Application Review. ZDC1 SRB-Y (52) June, 2013.

NIH/NCI – Special Emphasis Panel – Development of Radiation Modulators for Radiotherapy. ZCA1 SRLB-V (C1) March 21, 2013.

NIH/NCI – Special Emphasis Panel – Development of Radiation Modulators for Use During Radiotherapy. ZCA1-SRLB-V (C2) March 27-28, 2012.

NIH/NIAID – Special Emphasis Panel – Therapeutics for Neurotropic Biodefense Toxins and Pathogens. February 3, 2012.

NIH/CSR – Special Emphasis Panel – Translational Research in Aging. ZAG1 ZIJ M1 February, 2012.

FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee – Ad hoc member (2012)

NIH/NCI – Special Emphasis Panel – Cancer Targeted Discovery and Development (CTDD) Network. November 14-15, 2011.

NIH/NCRR Special Emphasis Panel – Centers for Biomedical Research Excellence (COBRE), June 22-23, 2011.

NIH/NCI – Special Emphasis Panel – Preclinical Pharmacokinetic and Pharmacologic Studies. ZCA1 SRLB-V(C1)S September 30, 2010.

NIH/NIEHS – Special Emphasis Panel – Engineered Nanomaterials: Linking Physical and Chemical Properties to Biology. ZES1-SET-V 03 June 8-9, 2010.

NIH/CSR – Special Emphasis Panel – Emerging Technologies and Training in Neurosciences/ Neuropharmacology SBIR ZRG1 ETTN C-11, 2008, Chair 2009-2011

Society for Women's Health Research, Board of Directors, 2007-2009.

Invited reviewer, Leaders Opportunity Fund, Canada Foundation for Innovation, April, 2007

NIH/CSR –Special Emphasis Panel – Brain Disorders and Clinical Neurosciences/ Neuropharmacology SBIR ZRG1 BDCN A(11); 2006-2007

NIH/CSR Special Emphasis Panel (SBIR) – Pharmacology and Diagnostics for Neuropsychiatric Disorders, BDCN F(11); 2005-2006

NSF Scientific Review Panel (SBIR) - 2004

PROFESSIONAL SERVICE ACTIVITIES

American Association of Pharmaceutical Scientists

Program Review Team – Distance Learning, 2004-2005
Program Review Team – Students, 2003
Program Review Team – Books, 2003
AAPS Treasurer (1998-2000)
AAPS Publications Board Member (1998-2000)
AAPS Diversity Task Force-Mentoring Subcommittee Chair (1994-1995)
PDD Section Secretary-Treasurer (1993-1995)

AAPS Finance Committee (1991-95)
PPDM Travelships-Graduate Student Committee (1993)
Poster Session Moderator Las Vegas, NV (1991)
Pharmaceutics and Drug Delivery Section Nominations Committee (1990-91)
Pharmaceutics and Drug Delivery Section Paper Screening Committee (1990,1992)
Representative to AACP sponsored "Pharmacy in the 21st Century Conference" (1989)
Pharmaceutics and Drug Delivery Section Membership Committee (1989, 1990, chair 1991, 1992)
AAPS Long Range Planning Committee (1987,1988)
University of Iowa AAPS Student Chapter Adviser (1995-present)

American Association of Colleges of Pharmacy

Pharmaceutics Section Strategic Planning Initiative – Concepts Committee (2015)
Review Panel Member (Teachers of Pharmaceutics) 2006
Annual Meeting Program Committee (2005-06)
Academic Leadership Fellow (2004-05)
Review Panel Chair (Pharmaceutics – Biological) New Investigators Program (2003)
Chair, Section of Teachers of Pharmaceutics, 1998-99
Vice Chair, Section of Teachers of Pharmaceutics, 1997-98

American Pharmaceutical Association

APS Poster Session Committee (1984-85)
Student American Pharmaceutical Association 1980-83
SAPhA Special Grant Chairman (1982)

Society for Women's Health Research

Board of Directors (2007-2009)

Kappa Epsilon Pharmaceutical Fraternity

Alpha chapter pledge trainer 1982
Province E co-director 1982
Alpha chapter president 1983
Gamma Chapter Advisor 1990-1998

Rho Chi Pharmaceutical Honor Society

University of Iowa, chapter advisor (2005 2009)
Chapter secretary/treasurer (1982-83)

Crohn's and Colitis Foundation of America - Eastern Iowa Chapter

Board of Trustee's member 1992-95

Mortar Board Honor Society

Iowa Alumnae Chapter Treasurer 1994-96
Vice-president 1996-97
President 1997-98

Phi Kappa Phi Honor Society

ADMINISTRATIVE ACTIVITIES

University of Iowa Assignments

Online and Distance Education Strategic Planning Committee (2017)
Graduate College Post-Doc Professional Development Program – Grant Reviews and Study Sections Panelist (2014)

Graduate College Post-Doc Professional Development Program – Insights from Faculty Search Committees Panelis (2013)
Task Force on Graduate Education (2009-10).
Women Faculty Development Conference, Planning Committee Member (2009-17)
Advisory Board Member, Nanoscience and Nanotechnology Institute at the University of Iowa (2006-2010)
University of Iowa Animal Care and Use Committee (2006-09)
Faculty Senate (2006-09)
Gender Equity Task Force (2005)
James F. Jakobsen Graduate Forum Faculty Judge (2004, 2006, 2007)
University of Iowa Presidential Search Committee (2002)
Task Force on Post-doctoral Scholars – Graduate College (2001-2003)
University of Iowa Strategic Planning Committee (1998-2000)
University of Iowa Animal Care and Use Committee (1997-2003)
Graduate Council (University of Iowa Graduate College) (1996-99)
Advisory Committee in the Biological Sciences (University of Iowa) (1996-97)

College of Pharmacy Assignments

Accreditation Steering Committee (2014-2016)
Administration sub-committee chair
PSET Faculty Search Committee (pharmacogenomics) Chair 2016
Curriculum Committee (ad hoc) (2014-present)
College Council (2010-present)
Pharmaceutical Sciences Department Chair Search Committee (2010-12)
Executive Committee (2008-present)
Accreditation Steering Committee (2008-2010)
Facilities and Budget sub-committee chair
College of Pharmacy Dean Search Committee (2006-07)
Admissions Committee Chair (2006-08)
Rho Chi Honor Society Faculty Advisor (2005-present)
College of Pharmacy Accreditation Steering Committee
Students sub-committee chair (2002-2004)
Division of Pharmaceutics Search Committee (2001)
Pharmaceutics Vice-Chair for Professional and Undergraduate Curriculum (2000-2003)
Ad Hoc Task Force for Clinical Track Appointments (College of Pharmacy) (1999-2000)
Task Force for Development of B.S. in Pharmaceutical Sciences Program (1999-2001)
Ad Hoc Pharmaceutics Curriculum Review Committee (1999)
Advisor, College of Pharmacy Honors Program (1998-2001)
Task Force on the Development of Educational Outcomes (1997)
Graduate Studies Committee (College of Pharmacy) (1996 - 1999)
Division of Medicinal and Natural Products Chemistry Search Committee (1996)
Division of Pharmaceutics Faculty Search Committees (2) (1993-95)
College of Pharmacy Dean Search Committee (1991)
Faculty Secretary (College of Pharmacy) (1990-93)
Pharmaceutical Service Director Search Committee (1990-91)
Undergraduate Career Opportunities and Placement (1990 (chair), 1991-92)
Building and Space Utilization Committee (1989-91)
Safety Committee (1989, 1992)

HONORS AND AWARDS

Teacher of the Year, University of Iowa College of Pharmacy, 2005

American Association of Colleges of Pharmacy Academic Leadership Fellow (2004-05)

Treasurer, American Association of Pharmaceutical Scientists 1998-2000

Pharmaceutics and Drug Delivery Section Section Secretary-Treasurer, AAPS, 1993-1995

American Association of Colleges of Pharmacy, Chair, Section of Teachers of Pharmaceutics, 1998-99

Eli Lilly Young Investigator Award in Pharmaceutics, 1992-93

Fellowships (Graduate)
Horace H. Rackham Predoctoral Fellow 1987-88
American Foundation for Pharmaceutical Education Fellow 1985-88
1987 Abbott Pharmaceutics Fellow
Nellie Wakeman Fellowship (Kappa Epsilon) 1985

Nominations
National Dean's List 1980-81
Who's Who Among Students in American Universities and Colleges
Outstanding Young Women of America
Who's Who in Science and Engineering
Outstanding Mentor, University of Iowa Graduate College, 2003

MEMBERSHIPS
American Association of Pharmaceutical Scientists
American Association of Colleges of Pharmacy
American Chemical Society
American Society for Pharmacology and Experimental Therapeutics