CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208411
Applicant Name	Adapt Pharma, Inc.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Established (USAN) Name	Narcan nasal spray / Naloxone hydrochloride
Dosage Forms / Strength	Intranasal spray / 40 mg/ml
Proposed Indication(s)	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression 2. Intended for immediate administration as emergency therapy in settings where opioids may be present 3. Not a substitute for emergency medical care
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Joshua Lloyd, MD
Pharmacology Toxicology Review	Newton Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Venkat Pavuluri, PhD, Christina Capacci-Daniel, PhD, Erika Pfeiler, PhD, Grace McNally, PhD, Edwin Jao, PhD, Steve Kinsley, Julia Pinto, PhD
CDRH Review CDRH OCP	Ryan McGowan, Rick Chapman Juandria Williams
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
OSI	Arindam Dasgupta, PhD, Yiyue Zhang, PhD, Melkamu Getie-Kebtie, PhD, RPh, Charles Bonapace, PharmD
OSE/DMEPA	Millie Shah, PharmD, BCPS; Vicky Borders-Hemphill, PharmD; Quynh Nhu Nguyen; MS, Irene Chan, PharmD, BCPS
OPDP/DCDP	L. Shenee Toombs
OMP/DMPP	Nathan Caulk, MS, BSN, RN; Barbara Fuller, RN, MSN, CWOCN; LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric Maternal Health Staff	Mona Khurana, MD: Hari Cheryl Sachs, MD; Linda Lewis, MD

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OPQ= Office of Pharmaceutical Quality
CDRH=Center for Device and Radiological Health
OCP = Office of Combination Products
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion, DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives, DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

The current application is a 505(b)(2) application for Narcan (naloxone hydrochloride) Nasal Spray which cross references the efficacy and safety information from Narcan, (NDA 016636). This application represents the first nasal naloxone spray to meet the criteria for novel naloxone products described by the Agency during the public meetings held in 2012 and in 2015. The application was accepted for rolling review and was granted priority review status upon submission of the final sections reflecting the importance this product from the public health perspective. The application relies on a relative bioavailability study in healthy volunteers. As the marketing of Narcan has been discontinued, the Applicant used a generic product, International Medicinal System's naloxone HCl injection USP pre-filled syringe (ANDA 072076) for the relative bioavailability study necessary to create a scientific bridge to the Agency's prior findings for Narcan. This review will focus on the pharmacokinetic parameters, local adverse events, and the potential for use in pediatric overdose situations.

2. Background

Naloxone HCl was first approved in 1971(Narcan, NDA 016636), for intravenous, intramuscular, and subcutaneous administration. The current labeling of Narcan recommends an initial dose of 0.4 mg to 2 mg, followed by repeated doses up to 10 mg in the setting of suspected opioid overdose. The off-label use of commercially available naloxone hydrochloride by the intranasal route of administration using a nasal atomizer is growing in popularity as many programs and communities seek to address the public health problem of prescription and illicit opioid abuse and the overdoses that occur in these settings. The need for a naloxone product for use outside of a controlled medical setting extends beyond the setting of abuse. As the management of chronic pain in the US relies heavily on the use of chronic opioid treatment, there is risk for overdose for patients and household contacts. The first product approved to address the risk of opioid overdose in all settings was Evzio (naloxone HCl injection), approved on April 3, 2014. Evzio is an autoinjector with audible and written instructions for use, and delivers 0.4 mg of naloxone in 0.4 mL to the subcutaneous or intramuscular space.

There is evidence that the off-label use of naloxone by the intranasal route has been effective in reversing opioid overdose in many cases. However, there are no data that specifically quantitate the success rate, leaving the question of whether there are situations that could have benefited from a higher dose of naloxone. Unpublished pharmacokinetic data suggest that naloxone levels following off-label use by the intranasal route are lower than by the approved routes of administration. The lowest effective dose of naloxone is unclear, and is likely dependent on a number of factors, including dose, route of administration, and the amount and

type of opioid involved in the overdose. In discussion with the Applicant during product development, it was determined that designing an efficacy study to define an effective range of naloxone use in the proposed setting would be difficult to justify as it would require administration of opioids to create an overdose, albeit in a controlled setting. The use of pharmacodynamic measurements such as pupil dilation or response to inhaled carbon dioxide may demonstrate an effect of naloxone, however, because the relationship between experimental opioid effects and reversal of a clinically meaningful overdose is not well defined, could not be relied upon for dose selection. Furthermore, there is an approved dosing regimen for naloxone. Therefore, the approach required by the division was to match the naloxone exposure achieved by administration of naloxone using an approved dose and route. This is done by conducting a relative bioavailability study that demonstrates the new product matches or exceeds the pharmacokinetic parameters of Cmax and Tmax for naloxone by an approved route, intramuscular, intravenous, or subcutaneous injection. The first few minutes are of particular importance, because if the overdose has led to apnea, time is of the essence if the brain is to be spared permanent hypoxic injury. Therefore, in addition to Cmax and Tmax, it is necessary to demonstrate that the naloxone levels are comparable to the approved route during the first minutes after dosing. Given the known safety profile of naloxone, the relative bioavailability study can be conducted in a normal healthy volunteer population without risk to the study participants. This approach has been discussed at two public meetings hosted by FDA.[1,2]

In patients managed with opioid analgesics, an opioid overdose leading to death can occur in a variety of settings. Patients may inadvertently take too much trying to better manage pain, or through errors in dose or frequency. Initiating a new concomitant medication that inhibits the metabolic pathway of an opioid, or discontinuation of a concomitant medication that induces the metabolic pathway can result in overdose in a patient who has used their opioid analgesic according to instructions. Addition of a new medication with the adverse effect of central nervous system depression, or an error in judgment surrounding the use of alcohol can also create a situation of over sedation in a patient previously stable on an opioid. Overdose can occur in household contacts of a patient prescribed opioids by accidental exposure or through intentional misuse or abuse. Individuals abusing prescription opioid analgesics or illicit opioids can also inadvertently overdose. With the range of potency of available opioids, death from overdose can occur with the first attempt at abuse. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. However, there are limitations in the prevention of death in this setting. The effects of some opioids such as buprenorphine may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is no substitute for seeking emergency medical help.

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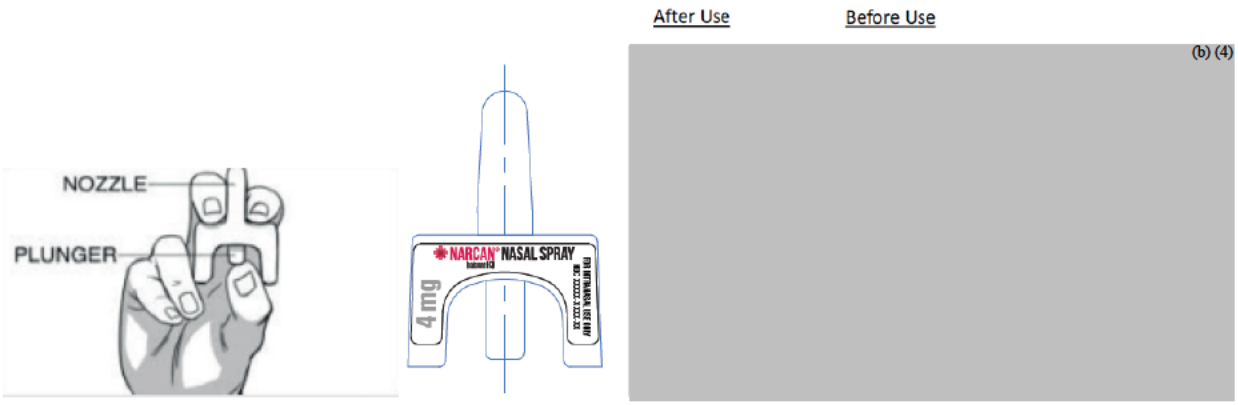
[1] Exploring Naloxone Uptake and Use – A Public Meeting, July 1 and 2, 2015. http://www fda.gov/Drugs/NewsEvents/ucm442236.htm

[2] Role of Naloxone in Opioid Overdose Fatality Prevention; Request for Comments; Public Workshop, April 12, 2012. http://www fda.gov/Drugs/NewsEvents/ucm277119.htm

3. OPQ/Device

Narcan Nasal Spray consists of the formulated drug product filled into a unit-dose vial which is stoppered and placed within a Unit-dose Delivery Device produced by (b) (4). This unit-dose device is then placed into a single blister pack. The container closure-spray device is a single-entity combination (drug/device) product. The device contains 100 microliters of a 40 mg/mL solution of naloxone hydrochloride, and is intended to deliver a dose of 4 mg with one spray. The device is displayed in the following figures:



From the Office of Pharmaceutical Quality review:

> The naloxone API is supplied by (b) (4) The drug product is formulated in (b) (4) comprising the following excipients: Sodium chloride, (b) (4) and benzalkonium chloride, in a concentration of 40mg/ml. The container closure system is a glass vial with a (b) (4) stopper which is then encased within a nasal actuator and container holder. The nasal spray device is by (b) (4), under DMF (b) (4), and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room temperature. Further, the Office of Process and Facilities, has made an overall recommendation of adequate for all facilities related to this application. Therefore, from a quality perspective, this NDA is recommended for approval.

Mr. McGowan performed an evaluation of the design of the device constituent parts of the combination product and covered the intended design and design control information for the subject device constituent part. From Mr. McGowan's review:

> The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, the consulting reviewer has determined that the device constituent parts of the

combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture.

The reviewer was not able to locate information which assures that the combination product is free from unacceptable risk with respect to the potential for under-dose or failure-to-dose events. Specifically, the sponsor has not demonstrated that a population of manufactured product is able to activate reliability after conditioning to applicable environmental or physical effects.

The consulting reviewer discussed the lack of reliability information available within the submission record with CDER/OND/ODEII/DAAAP within a September 23, 2015 mid-cycle meeting and an October 22, 2015 wrap-up meeting. The review division agreed with the consulting reviewer's assessment that additional information is needed regarding combination product reliability, however given the benefits of the product; the review division determined that this information could be requested within a post-market commitment or post-market requirement. Please see the final section of this review memorandum for recommended post-market commitment/requirement language regarding combination product reliability.

Therefore, the consulting review finds this submission to be approvable for device constituent part design considerations and requests commitment from the sponsor to engage in post-market activities to verify combination product reliability.

As discussed by Dr. Lloyd in his review:

> Mr. McGowan determined that "the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture." However, Mr. McGowan notes that the application contains inadequate information to demonstrate that the manufactured product is able to activate reliably after exposure to a variety of real-world conditions. There is a potential for under-dose or failure-to-dose events leading to undertreated, life-threatening CNS and respiratory depression as a consequence of a device failure under these conditions.

Also noted by Dr. Lloyd in his review:

> Mr. McGowan found the device-related product specifications acceptable with the exception of dose content uniformity, which allowed for relatively wide batch release specifications. This specification requires that (b) (4) Given the relatively wide safety margin with naloxone, there is little concern for the upper limits of these release specifications, particularly since Narcan is labeled with dosing recommendations up to a total of 10 mg of naloxone. In general, the greatest concern would be for releasing a batch that might not deliver an adequate dose of naloxone in an immediately life-threatening situation. However, given the pharmacokinetic profile of this product (refer to Section 5 below), which achieves much higher systemic exposures to naloxone than the approved comparator dose of naloxone (i.e., 0.4 mg IM), the lower

limit of these specifications are also acceptable. Additionally, Narcan nasal spray should only be made available in a two-pack configuration, (b) (4) (refer to Section 12 below for additional discussion), ensuring that a second dose is available in the event of an inadequate response.

The postmarket requirement recommended by Mr. McGowan is as follows:

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:

    - Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as R(t) = x%, where t = time and x% = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

    - Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.

    - Perform a test to verify the reliability requirements specified in above.

    - Devices assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.
        - Shipping
        - Aging
        - Storage orientation and conditions
        - Vibration handling
        - Shock handling (e.g., resistance to random impacts, such as being dropped)

    - Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.
        - Activation orientation
        - Environmental temperature

2. Establish a post-market monitoring program for detection and evaluation of under-dose and failure-to-dose events, regardless of cause, and provide periodic reports to the Agency which contain descriptions of each reported event along with results of root-cause and contributing-cause analyses.

I concur with the conclusions reached by the OPQ review team and the CDRH reviewer regarding the acceptability of the manufacturing of the drug product, drug substance, and

device. While Mr. McGowan has found that the reliability has not been formally documented, leading to the PMR, there is considerable experience with the nasal spray device by (b) (4) leading to a low suspicion that there will be a problem with reliability. Further, Mr. McGowan noted wide batch release specifications for the dose content uniformity. As will be discussed in the Clinical Pharmacology Section, the amount of naloxone and resultant exposure in each dose of the Narcan Nasal Spray are large enough to assure that even at the low end of the specifications, a large enough dose of naloxone will be delivered to expect efficacy. Further, as noted by Dr. Lloyd, the product will be available only in two-pack configurations so that a second dose will be available if needed.

Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues that preclude approval. I concur with the recommended PMR.

4. Nonclinical Pharmacology/Toxicology

From Dr. Woo's review:

> The Applicant did not submit any new nonclinical studies to support this marketing NDA as none were required. Local tolerance studies would normally be required to support a reformulated drug product that employs an alternate route, however, the Division determined that nonclinical studies would not be required given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication.
>
> The Applicant has provided adequate data to support the safety of the drug substance, drug product, and drug product formulation. To support the safety of the container closure system, the Applicant has submitted extractables data under various extraction conditions. Under the most relevant solvent condition using water, no peaks were present indicating that there were no compounds that appeared after harsh extraction conditions. It is notable that a leachables assessment was not conducted but the Applicant has indicated that potential leachables will be evaluated in long-term stability samples. It is in the opinion of this Reviewer that the absence of leachables data does not preclude marketing approval for the following reasons: 1) the (b) (4) plungers is used in other FDA-approved aqueous based nasal and injectable drug products; 2) analysis of water extracts did not identify any substances; 3) the Applicant has committed to monitor for leachables during stability; 4) most importantly, this product is indicated for an acute, single-use indication; and 5) the drug product is a potentially life-saving therapy. The Applicant has committed to monitoring batches on stability for leachables. This should be solidified as a formal post-marketing commitment (PMC).

The PMC recommended by Dr. Woo is:

> As proposed, conduct and submit an adequate leachable safety assessment for your drug product and container closure system. This assessment must include leachable data from long-term stability studies taking into consideration the proposed shelf-life to determine if the specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the leachables taking into consideration the maximum daily dose of the identified materials for this drug product.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval and with the PMC described.

5. Clinical Pharmacology/Biopharmaceutics

The basis for efficacy for Narcan Nasal Spray cross reference to the efficacy and safety information from Narcan and the relative pharmacokinetic profile of naloxone from this new Nasal Spray. The key study as described by Dr. Lloyd:

> The Applicant conducted study Naloxone-Ph1a-002 (also referred to as study 002, in this review), a pivotal relative bioavailability study, in support of this application to establish a scientific bridge to their NDA for Narcan (NDA 16636) in order to establish the safety and efficacy of Narcan nasal spray.
>
> Study 002 was an open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study conducted in 30 adult male and female healthy volunteers in an inpatient setting to evaluate the pharmacokinetics of two doses of Narcan nasal spray (i.e., 4 mg [one spray in one nostril] and 8 mg [one spray in each nostril) in comparison to an approved generic version of naloxone given intramuscularly (i.e., 0.4 mg). Two doses of another formulation of intranasal naloxone that are not the to-be-marketed formulation were also evaluated in this study. Subjects were assigned to one of five sequences, with six subjects planned in each sequence. A four-day washout period separated the treatments. Narcan nasal spray was administered using an (b) (4) single-dose device (b) (4) with the subject in a fully supine position. The left nostril was used for the 4-mg dose, and one spray was administered into each nostril for the 8-mg dose. Subjects were instructed not to breathe through the nose during administration of Narcan nasal spray and remained fully supine for approximately one hour post-dose. Intramuscular (IM) naloxone was administered as a 1-ml (i.e., 0.4 mg/ml) single injection into the gluteus maximus muscle using a 23-gauge needle.

The following figure and two tables from Dr. Naraharisetti's review demonstrate the naloxone levels for one spray of Narcan Nasal Spray into one nostril, two sprays of Narcan Nasal Spray as one spray into each nostril, and an intramuscular injection of 0.4 mg of naloxone. The critical findings supporting the expected efficacy of Narcan Nasal Spray are best captured by the exposure in the first five minutes following dosing. The naloxone levels from one nasal spray rise as early as from the intramuscular injection and peak higher.

Figure Mean plasma concentration time profiles of naloxone from 0 to 4 hours following

intranasal and intramuscular naloxone administration to healthy subjects (N = 29)

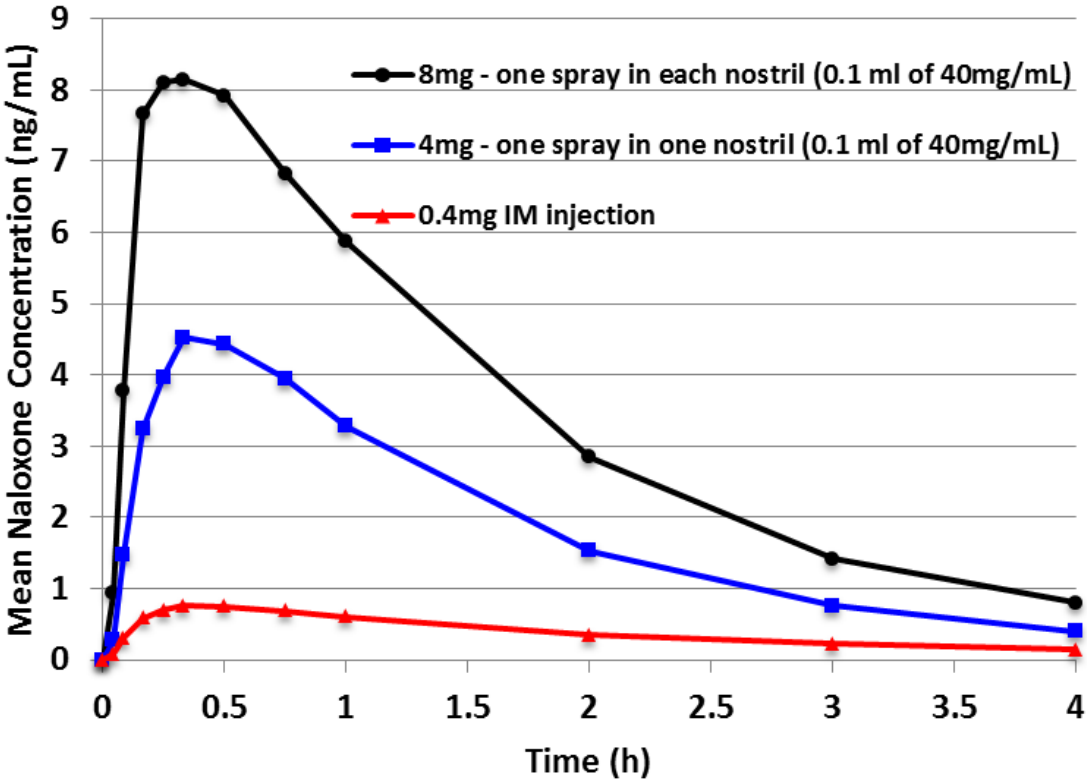


Table Geometric mean ratios and 90% CIs for plasma naloxone pharmacokinetic parameters following intranasal and intramuscular administration.

Parameter	Test Vs Reference	Adjusted Geometric LS mean		Ratio %[Test/Reference] (lower , upper 90% CI of ratio)
		Test (n=29)	Reference (n=29)	
Cmax (ng/mL)	4 mg -one IN Spray in one nostril (Test) Vs 0.4 mg IM (Reference)	4.83	0.870	555 (464, 665)
AUC0-t (h*ng/mL)		7.90	1.68	469 (418, 527)
AUC0-inf (h*ng/mL)		7.99	1.73	462 (412, 519)
Cmax (ng/mL)	8 mg -one IN Spray in each nostril (Test) Vs 0.4 mg IM (Reference)	9.62	0.870	1110 (925, 1320)
AUC0-t (h*ng/mL)		15.0	1.68	890 (793, 999)
AUC0-inf (h*ng/mL)		15.2	1.73	878 (783, 985)

Table Comparison of mean naloxone concentrations between IM injection and NARCAN one spray in one nostril or one spray in each nostril from 2.5 to 60 minutes post dose.

Time post-dose after naloxone drug product administration (minutes)	Mean Concentration (ng/mL) (% CV) N=29			Fold higher naloxone concentration:	Fold higher naloxone concentration:
	Reference IM injection (0.4 mg)	Test One IN spray in one nostril (4mg)	Test One IN spray in each nostril (8mg)	One IN spray (4mg) Vs. IM injection (0.4 mg)	One IN spray in each nostril (8mg) Vs. IM injection (0.4mg)
2.5	0.079 (168)	0.28 (151)	0.93(131)	3.5	11.8
5	0.306 (108)	1.48 (117)	3.78 (105)	4.8	12.3
10	0.578 (55)	3.24 (67)	7.66 (68)	5.6	13.3
15	0.696 (46)	3.97 (56)	8.10 (44)	5.7	11.6
20	0.754 (36)	4.53 (50)	8.14 (31)	6.0	10.8
30	0.749 (25)	4.43 (43)	7.92 (25)	5.9	10.6
45	0.684 (25)	3.95 (41)	6.83 (24)	5.8	10.0
60	0.604 (24)	3.28 (37)	5.87 (23)	5.4	9.7

This pharmacokinetic profile from Narcan Nasal Spray demonstrates that a nasal spray can be formulated to result in efficacy comparable to the use of naloxone by intramuscular injection. In this case, the 4 mg dose of Narcan Nasal Spray provides naloxone concentrations ranging from 3.5-fold to 6-fold higher than a 0.4 mg intramuscular injection.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is relying on cross reference to the efficacy and safety information from Narcan (naloxone hydrochloride), NDA 016636.

8. Safety

There were no new safety studies submitted in support of this application. Two relative bioavailability studies were conducted in normal volunteers, but as only Study 002 used the final to-be-marketed formulation, the safety data from this study will be used for product labeling along with information from the referenced drug.

As described by Dr. Lloyd:

> In study 002, there were a total of 87 single exposures of Narcan nasal spray to a nostril (Table 3). Thirty unique subjects received Narcan nasal spray, including 28 subjects who received both 4 mg in one nostril and 4 mg in each nostril (8 mg total dose), 1 subject who received 4 mg in one nostril only (subject was discontinued due to an adverse event), and 1 subject who received 4 mg in each nostril (8 mg total dose) but not 4 mg in one nostril (discontinued at the subject's request), as summarized in Table 4. The extent of exposure and nasal irritation monitoring are adequate to evaluate the potential for local toxicity.

There were no deaths or serious adverse events during the clinical pharmacology studies. One subject was discontinued for because of elevated blood pressure measurements on the day prior to dosing of the second treatment period.

From Dr. Lloyd's review:

> There were 27 adverse events (AEs) reported by 17 subjects. All AEs were considered mild in severity except for the one subject who experienced a moderate increase in blood pressure that lead to discontinuation. Table 6**Error! Reference source not found.** lists all AEs that occurred in study 002. The list of AEs for a particular treatment includes all AEs recorded beginning with the administration of that treatment until the next treatment administration in the sequence. The Narcan nasal spray groups (40 mg/ml formulation) are highlighted in yellow in the table. AEs reported for subjects in the Narcan nasal spray groups included increased blood pressure, musculoskeletal pain, headache, and xeroderma, in addition to AEs indicative of local nasal irritation, including nasal dryness, nasal edema, nasal congestion, and nasal inflammation. The IM naloxone comparator arm reported nausea, dizziness, and headache.

These safety findings are acceptably balanced by the potential benefit of Narcan Nasal Spray.

Naloxone is generally not administered outside of the setting of a suspected opioid overdose. Based on the adverse events reported in the labeling for Narcan, in the setting of an opioid-tolerant patient, administration of naloxone can result in precipitation of an acute withdrawal syndrome characterized by body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, and hyperactive reflexes.

Also as noted in the labelling for Narcan, in the postoperative setting, there have been post-marketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation.

There is minimal to no risk from administration of a dose of 4 mg of intranasal naloxone to a person who has not had an opioid overdose if the person is not opioid-tolerant. In the setting of a patient who is obtunded with respiratory depression, if the cause is not opioid overdose, no ill effect is expected, the instructions to seek emergency medical care are appropriate, and use of Narcan nasal spray should not result in substantial delay in seeking that emergency care.

9. Advisory Committee Meeting

This application was not taken to an advisory committee meeting. There were no issues that arose during the review period requiring external advice.

10. Pediatrics

Pediatric patients and children may be at risk for an opioid overdose in the community as a result of several scenarios. Similar to adults, pediatric patients may receive an inadvertent overdose based on an error in dosing (too soon, too much), initiation of a concomitant drug that inhibits metabolism of the opioid, or cessation of a concomitant drug that had induced the metabolism of the opioid. In addition, children in a home where opioids are in use may come in contact with an opioid through improper storage or disposal with the risk of resultant overdose. Older children may experiment with opioid analgesics in an attempt to get high and inadvertently overdose. Therefore, pediatricians caring for pediatric patients prescribed opioids or caring for children who are otherwise well, but may be at risk for coming in contact with an opioid, may find it appropriate to prescribe naloxone to be kept in the home as a safety precaution.

The package insert for Narcan includes pediatric labeling as follows:

> USAGE IN CHILDREN
> o Narcotic Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, naloxone may be administered I.M. or S.C. in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

This is in contrast to the following dosing regimen in adults:

> USAGE IN ADULTS
> o Narcotic Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial

> narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The efficacy of Narcan Nasal Spray in pediatric patients is based on cross reference to the efficacy findings for naloxone as described in the labeling for Narcan for injection. Narcan Nasal Spray can be expected to be effective, settings where a child has signs of an opioid overdose requiring emergency treatment.

There is, however, a narrow set of situations in which a naloxone product that can be titrated to effect and/or is administered by a route other than the nasal route may be better suited. Neonates born to born to mothers using prescription opioids to manage pain or to treat opioid dependence or using illicit opioids may require an opioid antagonist to reverse respiratory depression immediately after birth. Rather than risking an abrupt precipitation of withdrawal symptoms with a large dose of naloxone, it would better serve the infant to use naloxone for injection dosed according to standard protocols and titrated to effect. Furthermore, infants under two months of age are obligate nose breathers and there is a small risk that use of a nasal spray in these infants could result in apnea. Some of these infants may be managed with a slow opioid taper once they are discharged to go home. In this setting, it is important to consider having a naloxone product available in case a problem with opioid overdose arises, and other products, such as the approved naloxone autoinjector may be more appropriate than a nasal spray.

As the first nasal spray formulation of naloxone, Narcan Nasal Spray triggers the requirements for pediatric studies under the Pediatric Research Equity Act. This raises a number of regulatory challenges. In contrast to adults, pharmacokinetic studies cannot be conducted in healthy children, while as with adults, efficacy studies are not possible either.

The following is from Dr. Lloyd's review:

> Therefore, the Applicant was required to support the safety and efficacy of Narcan nasal spray in pediatrics, based on a review of available information, including the published literature, clinical practice guidelines, and the approved labeling for Narcan. This pediatric assessment was required to have addressed the following issues:
>
> - The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates
> - Justification for the proposed dosing volume in all pediatric patients, including neonates
> - Justification for why the absorption of drugs through the nasal mucosa will not be different in pediatric patients, including neonates, compared to adults
> - A device (e.g., nasal tip) that can appropriately deliver the correct volume to all pediatric patients, including neonates
>
> The Applicant received an agreed upon pediatric study plan (PSP) on June 22, 2015, which included a plan to submit the required pediatric assessment with the NDA. The Division of Pediatric and Maternal Health (DPMH) was consulted to evaluate the

adequacy of the pediatric assessment to support approval in the full pediatric age range and the proposed labeling.

Dr. Lloyd goes on to summarize the consultative input from the Division of Maternal and Pediatric Health and the discussion at the Pediatric Research Committee:

> DPMH recommended "approval for the proposed indication for pediatric patients from birth to under age 17 years for emergency treatment of known or suspected opioid overdose until emergency medical services can be provided by trained professionals," provided that "DAAAP is satisfied that IN delivery with the proposed unit dose device will result in absorption of a minimally effective dose in pediatric patients of all ages."
>
> DPMH raised concerns in their review about the safety of the proposed product as it relates to IN drug delivery. Specifically, DPMH requested DAAAP to confirm that the actuator tip may be properly positioned and, based on concerns of differences in nasal morphology, can deliver a minimally effective dose in pediatric patients under five years of age. Further, given the fixed dose, DPMH raised concerns that the 4-mg dose could deliver a dose approximately 100-fold higher than what is recommended in Narcan labeling if the full dose is systemically absorbed. DPMH raised additional concerns for the potential to induce respiratory distress with intranasal instrumentation in the youngest patients because of obligate nasal breathing.
>
> Therefore, DPMH recommended a postmarketing requirement (PMR) and a postmarketing commitment (PMC) to, respectively, capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age and evaluate the pharmacokinetic profile of this product in patients under five years of age.
>
> This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on November 4, 2015, where the above PMC and PMR were initially discussed.

This will be conveyed in the package insert in Sections 5.3 and 8.4 as follows:

5.3 Precipitation of Severe Opioid Withdrawal
The last paragraph of this section:

There may be clinical settings, particularly the immediate postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, consider use of an alternative, naloxone-containing product that can be titrated to effect and, where applicable, dosed according to the infant's weight. *[see Use in Specific Populations (8.4)]*.

8.4 Pediatric Use
The final two paragraphs:

In settings such as in neonates with known or suspected exposure to maternal opioid use, where it may be preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be dosed according to weight and titrated to effect.

Also, in situations where the primary concern is for infants at risk for opioid overdose, consider whether the availability of alternate naloxone-containing products may be better suited than NARCAN Nasal Spray.

Regarding postmarket study requirements, the ability to study Narcan Nasal Spray in infants is fraught with ethical and technical challenges. It is not acceptable to study the pharmacokinetics of Narcan Nasal Spray in normal children. Naloxone is used in an emergency setting and its use cannot be predicted. As there is already approved therapy with naloxone for injection, and treatment cannot be delayed to discuss the study or obtain parental consent, there is no practical way to design a study to be conducted in the delivery room or an emergency room. The Applicant has agreed to provide the following enhanced pharmacovigilance:

- Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following:
    - All reports in patients less than one year of age
- Include a summary evaluation of each of these reports requested in the submission of the periodic reports for each reporting period, with an analysis of treatment failures and adverse events of airway obstruction, respiratory distress, or respiratory arrest; in addition to a summary of these events in the context of all similar events reported for Narcan Nasal Spray.

11. Other Relevant Regulatory Issues

From Dr. Lloyd's review:

> Vicky Borders-Hemphill, PharmD, conducted the Division of Medication Error Prevention and Analysis (DMEPA) summative human factors study review. The human factors study was conducted in 53 participants who were representative of the intended user group, which consists of the general population of individuals 12 years and older and low literacy layusers who were untrained on the use of the device. Dr. Borders-Hemphill notes that "[o]f the 53 participants, 5 participants did not successfully complete one of the two critical tasks of inserting the nozzle into the nostril and pressing the plunger to release the dose in the nose:
>
> - Two of the five participants administered the dose into the mouth of the overdose victim (mannequin). The Applicant's root cause analysis indicated that one of the participants used common sense rather than reading the IFU, and the other

participant thought that they only saw one opening on the mannequin, which was the mouth. None of the root causes were attributed to the product design or labeling.

- Two of the five participants did not press the plunger completely to release the dose. The Applicant's root cause analysis showed that these participants were confused by the setting of simulation, and attributed these failures to study artifacts.
- One of the five participants expelled the product into the air prior to inserting it into the nasal opening. The participant indicated that he was trying to test how hard to push the plunger prior to administering to the mannequin.

Dr. Borders-Hemphill concluded that "the human factors validation study report provides sufficient data to conclude that the product can be used safely and effectively by intended users for intended uses and environments" and recommended revised labeling based on this study.

Inspections of the clinical and analytical portions of the relative bioavailability study

Because the application is based on the results of the relative bioavailability study, a consult was issued to the Office of Study Integrity and Surveillance (OSIS) for inspection of the analytical portion of the pivotal relative bioavailability study (study 002) and the clinical portion of the study, arranged by OSIS with the Office of Regulatory Affairs (ORA). OSIS recommended that "the clinical and analytical data from study Naloxone-Phla-002 be accepted for Agency review." The final classification for both the clinical portion (Vince & Associates Clinical Research) and the analytical portion (b) (4) was VAI (voluntary action indicated).

The OSIS review noted two observations at the clinical site (Vince & Associates Clinical Research) and a Form FDA 483 was issued.

1. Observation: "An investigation was not conducted in accordance with the investigational plan."

2. Observation: "Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation."

Dr. Lloyd discusses these findings in detail in his review. For the first observation, there was failure to report a respiratory rate greater than 24 as an adverse event. Dr. Lloyd concurred with the OSIS conclusion that this was unlikely to have an impact on data reliability. It was also found that numerous pharmacokinetic samples that not placed in the freezer within the specified (b) (4) window. The analytical site, (b) (4) was requested to evaluate the stability of naloxone over conditions that mimicked the worst-case scenario for the samples at the clinical site. The results of this study were made available to the investigators over the course of this inspection, which demonstrated the stability of the samples. OSIS concluded that this issue "is unlikely to impact the integrity of the naloxone

concentration data." The clinical pharmacology review team concurred with OSIS's conclusion.

For the second observation, discrepancies were found between the reported protocol deviations and the source documents, specifically, post-dose discrepancies in the actual sampling times in the pharmacokinetic analysis for three subjects, at one post-dose time point each. Two of these subjects received a different formulation and the remaining had a one-minute deviation that Dr. Lloyd and Dr. Naraharisetti concluded would not affect the calculated pharmacokinetic parameters. In addition, there were discrepancies in some of the adverse event reporting, particularly, two subjects with adverse events related to nasal irritation (i.e., nasal edema and left nostril dryness with occasional bleeding) had nasal examinations recorded as normal, and two subjects with adverse events of nasal irritation had the nasal examination scores changed from normal to inflamed mucosa, no bleeding after the subjects had completed the study. It is possible that in the first two cases there were normal nasal examinations and it is unclear why the changes were made for the second two cases. Regardless, the overall risk associated with opioid overdose and the importance of the use of Narcan Nasal Spray in these settings outweighs the risk for nasal irritation.

There are no other unresolved relevant regulatory issues

12. Labeling

As noted in Dr. Lloyd's review:

> The proprietary name, Narcan nasal spray, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed labels and labeling. DMEPA noted that their proposed changes do not require an additional human factors validation study. The patient labeling team reviewed the patient package insert, instructions for use, and quick start guide and found them acceptable with their recommended changes. Refer to the individual reviews for more details.
>
> Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed labeling (i.e., pregnancy and lactation labeling rule [PLLR]). DPMH provided recommendations for the proposed labeling, based on their review.
>
> Labeling is ongoing at the time of this writing, and specific recommendations have made in the relevant sections of this review. However, two additional aspects of the proposed labeling warrant further discussion here:
>
> 1. The Applicant proposed (b) (4)

The Applicant's proposal [redacted (b) (4)].

2. Additionally, the Applicant proposes [redacted (b) (4)]

I concur with Dr. Lloyd's analysis of the proposed labeling. Conceptually, all patients prescribed an opioid analgesic should have naloxone available to manage an opioid overdose. Also, I concur with the importance of having a second dose available in case of an error with the first dose or a failure to respond to the first dose.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

The pharmacokinetic profile from Narcan Nasal Spray demonstrates that a nasal spray can be formulated to result in efficacy comparable to the use of naloxone by intramuscular injection. In this case, the 4 mg dose of Narcan Nasal Spray provides naloxone concentrations ranging from 3.5-fold to 6-fold higher than a 0.4 mg intramuscular injection of 0.4 mg/mL naloxone solution. The 0.4 mg dose for the approved parental product represents a starting dose and is intended to be repeated up to a maximum of 10 mg if needed when attempting to reverse an known or suspected naloxone overdose. The benefit of using an incremental approach is that it may be possible to avoid precipitating an acute withdrawal syndrome in an opioid-tolerant patient, although this risk is outweighed if it means lessening the likelihood of reversing the overdose and reestablishing spontaneous respirations capable of providing adequate ventilation and oxygenation. Also, it is important to have at least one additional dose available for use in patients who fail to respond to the first dose.

- Recommendation for Postmarketing Risk Management Activities

The Applicant has agreed to the following request for special reporting of adverse events from use in pediatric patients less than one year of age. If any reports raise concerns about the safety, additional evaluation of the use in this age group will be considered.

- Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following:
    - All reports in patients less than one year of age

- Include a summary evaluation of each of these reports requested in the submission of the periodic reports for each reporting period, with an analysis of treatment failures and adverse events of airway obstruction, respiratory distress, or respiratory arrest; in addition to a summary of these events in the context of all similar events reported for Narcan Nasal Spray.

    - Recommendation for other Postmarketing Study Commitments

The following studies have been agreed to by the Applicant.

2990-1 Establish reliability requirements for the combination product Narcan Nasal Spray (naloxone hydrochloride), and complete testing which verifies the combination product reliability.

2990-2 Establish procedures for monitoring reports of failure of the combination product Narcan Nasal Spray (naloxone hydrochloride) to activate or failure of the combination product to deliver the full-labeled dose. Provide interim and final reports to the NDA, which contain a detailed analysis of reported device failures (including reported malfunctions that did, as well as did not result in patient harm), full event narratives of the failure and any subsequent adverse events, and the results of root cause analysis performed for the reported failure.

2990-3 Conduct an adequate leachable safety assessment for the (b) (4) plunger used in your container closure system. This assessment must include leachable data from long-term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples.

2990-4 Conduct a long-term stability evaluation placing at least three (3) manufactured lots of NARCAN Nasal Spray, 40 mg/mL, on long-term stability evaluation at the following temperatures:

a. 2 to 8°C
b. 40°C/75% RH - to extend the time points out to 24 months

APPEARS THIS WAY ON ORIGINAL

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

/s/

SHARON H HERTZ
11/18/2015