Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208411/S-001
Applicant Name	Adapt Pharma, Inc.
Date of Submission	March 25, 2016
PDUFA Goal Date	January 25, 2017
Proprietary Name / Established (USAN) Name	Narcan nasal spray / Naloxone hydrochloride
Dosage Forms / Strength	Intranasal spray / 20 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	N/A
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Venkat Pavuluri, PhD, Julia Pinto, PhD
CDRH/GHDB/DAGRID Review	John McMichael, Alan Stevens, LCDR, USPHS
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
OSI	N/A
OSE/DMEPA	Millie Shah, PharmD, BCPS; Vicky Borders-Hemphill, PharmD; Quynh Nhu Nguyen; MS, Irene Chan, PharmD, BCPS
OPDP/DCDP	Koung Lee, Olga Salis, L. Shenee Toombs
OMP/DMPP	Morgan Walker, PharmD, MBA, CPH; Barbara Fuller, RN, MSN, CWOCN; LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric Maternal Health Staff	Mona Khurana, MD; Leyla Sahin, MD; Hari Cheryl Sachs, MD; Miriam Dinatale, DO, LCDR, USPHS, John Alexander, MD, MPH

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 supplemental NDA for Narcan (naloxone hydrochloride) Nasal Spray 2 mg. Narcan Nasal Spray 4 mg was approved on November 18, 2015, as a 505(b)(2) application, which cross referenced the efficacy and safety information from Narcan, (NDA 016636). The formulations for the approved 4 mg product and proposed 2 mg product (b) (4)

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 has been 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 U.S. relies heavily on the use of chronic opioid treatment, there is risk of 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 (NDA 205787) 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. A higher dose version, Evzio 2 mg (NDA 209862) was approved on October 19, 2016.

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. Highly potent opioids have been found mixed into heroin, in particular fentanyl and carfentanil, and this has led to a number of overdose deaths among those abusing heroin. Also, it is important to realize that the duration of antagonists such as naloxone is generally shorter than the duration of action of most opioids.

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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

Therefore, even when an antagonist is available, it is no substitute for seeking emergency medical help.

3. OPQ/Device

Narcan Nasal Spray 2 mg [redacted] (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 20 mg/mL solution of naloxone hydrochloride, and is intended to deliver a dose of 2 mg with one spray. The device is displayed in the following figures:

(b) (4) [redacted]

The drug substance, DMF (b) (4), remains acceptable to support the product. As noted in the OPQ review, page 3:

> The proposed drug product, intended for intranasal delivery of naloxone hydrochloride, 2 mg per spray, contains naloxone hydrochloride dihydrate as active ingredient (b) (4) in a (b) (4) aqueous solution along with disodium edetate as stabilizer and benzalkonium chloride as (b) (4) preservative. The composition of proposed drug product, (b) (4) is similar to the approved NARCAN® metered nasal spray, 4 mg / spray and thus there are no scientific or regulatory concerns on the components and composition.

From the OPQ review, page 22:

> Based on the data presented above for clinical and registration batches of naloxone formulations at concentration of 20 mg/mL, the worst case scenario for the formulation at the concentration of 10 mg/mL out to 24 months, and the 12 month stability data from the 40 mg/mL clinical and registration batches, sponsor proposed an expiration date of twenty four (24) months for the to be marketed 20 mg/mL Naloxone Nasal Spray concentration.
>
> ***3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment***
>
> Sponsor commits to place the first three production (validation) batches and at least one production batch each year thereafter on stability in the final container closure system according to the stability protocol described in section 3.2.P.8.1. Sponsor also commits to perform the microbiological contamination tests (TAMC, TYMC, E. coli, S. aureus, P. aeruginosa and B. cepacia) on an annual basis

for the first three (3) production batches [redacted].

From Mr. McMichael's CDRH review, p.4:

> The sprayer system is manufactured by a third part sponsor named [redacted] This third party sponsor has provided a number of non-clinical resources to support approval of NDA 208411. The specific sprayer devices used within the subject NDA is stated as also used spray products in the U.S. [redacted]

And from page 9 of the CDRH review:

> The Design Controls of the NARCAN Nasal Spray was reviewed and established to be adequate under the original approved NDA submission NDA 208411. This supplement includes no changes to the design controls of the device constituent parts of the combination product, however due to the newly proposed dosage of 2 mg Naloxone, performance testing and stability data was required to re-verify the essential performance requirements of the device with the lower dosage form. It should be noted that the deliverable volume of the nasal spray remains the same for both dosage forms.
>
> The Sponsor submitted updated stability testing for the 2 mg combination product that is adequate to the consultant reviewer.
>
> A post-market requirement for reliability of the NARCAN nasal spray was established for the original NDA submission [redacted]
> After discussion with the CDER review team the same rationale applies for this supplemental dose that applied for the original NDA dosage in that the safety and efficacy of the drug product dosage is not in question and the concerns regarding the reliability of the device constituent do not outweigh the potential benefit of the device reaching market. [redacted]

The postmarket requirement in place from the original application is as follows:

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability [redacted]:

   - 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. [redacted] (b) (4)

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.

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.

3. Nonclinical Pharmacology/Toxicology

From Dr. Huynh's review, page 4 review:

> There were no nonclinical studies submitted in this NDA. The current proposed 2 mg naloxone hydrochloride formulation has a lowered amount of naloxone hydrochloride from the approved 4 mg dosage strength formulation with all excipients within safe limits. [redacted] (b) (4) The container closure is identical to the approved 4 mg dosage strength product and as such, the extractable/leachable profile is not expected to be worse. Therefore, there are no additional nonclinical concerns with the 2 mg dosage strength for NARCAN Nasal Spray.

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.

4. Clinical Pharmacology

The basis for efficacy for Narcan Nasal Spray 2 mg is the same relative bioavailability study submitted in support of the 4 mg product. The Applicant conducted study Naloxone-Ph1a-002 (also referred to as Study 002, in this review). 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. The treatment arms were:

- Treatment A- 2 mg IN (one 0.1 mL spray of 20 mg/mL solution in one nostril)
- Treatment B- 4 mg IN (one 0.1 mL spray of 20 mg/mL solution in each nostril)
- Treatment C- 4 mg IN (one 0.1 mL spray of 40 mg/mL solution in one nostril)
- Treatment D- 8 mg IN (one 0.1 mL spray of 40 mg/mL solution in each nostril) and
- Treatment E- 0.4 mg IM (1 mL of 0.4 mg/mL commercial formulation)

The following two figures and table from Dr. Naraharisetti' s review (pages 5,6) demonstrate the naloxone levels for one spray of Narcan Nasal Spray 2 mg, one spray of Narcan Nasal Spray 4 mg, and a 0.4 mg intramuscular injection into one nostril.

Figure 1.3 Mean plasma concentration time profiles of naloxone from 0 to 1 h following intranasal (2 mg and 4 mg dose, 20 mg/mL) and intramuscular (0.4 mg) naloxone administration to healthy subjects (N = 29)

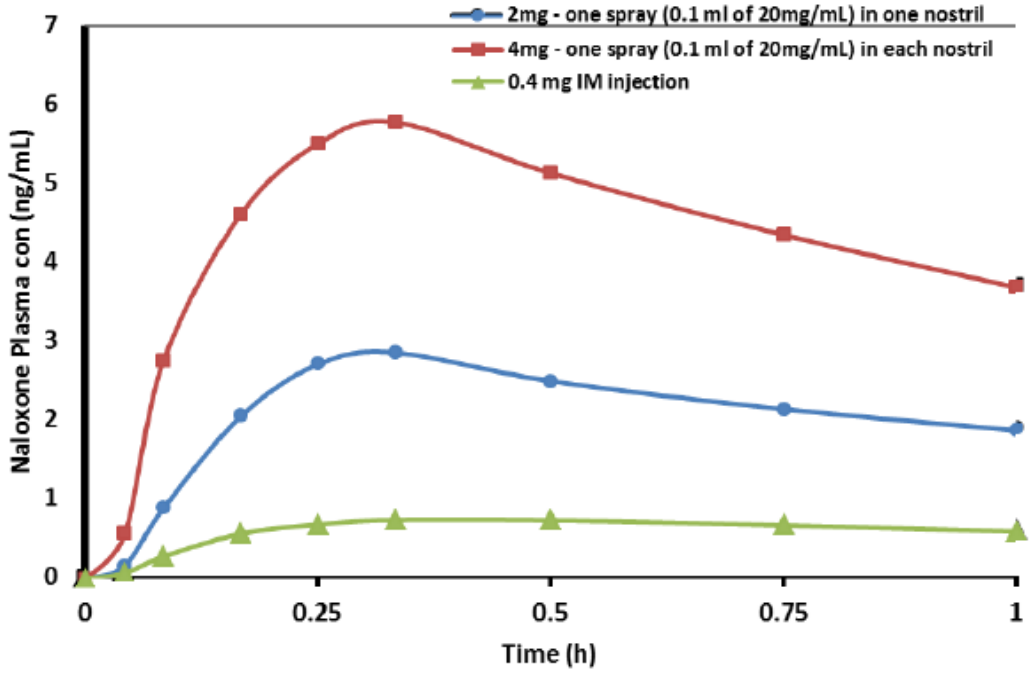

Figure 1.3a Mean plasma concentration time profiles of naloxone from 0 to 6 hours following intranasal (2 mg and 4 mg dose, 20 mg/mL) and intramuscular (0.4 mg) naloxone administration to healthy subjects (N = 29)

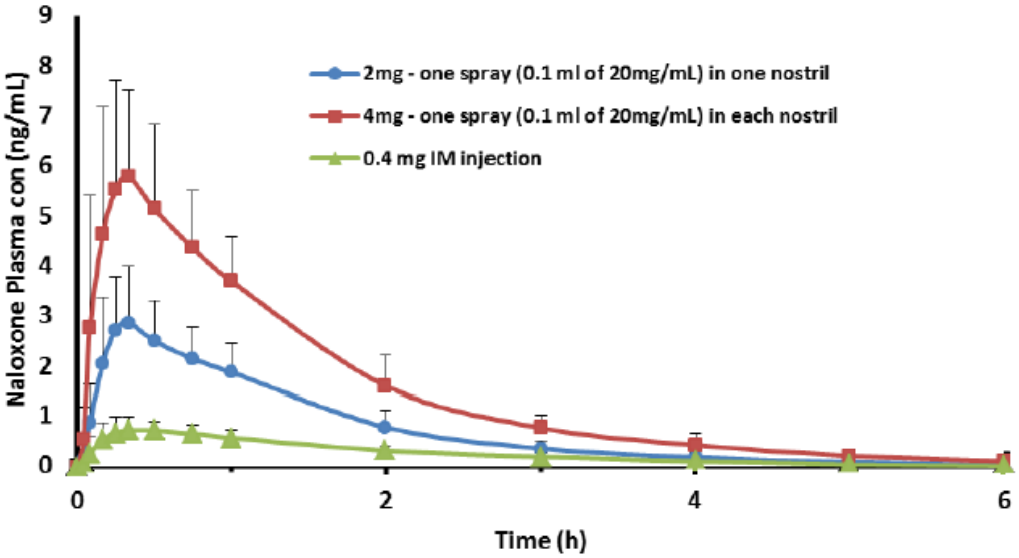

Table: 1.3a. Geometric mean ratios (90% CIs) for plasma naloxone pharmacokinetic parameters following intranasal and intramuscular administration.

Parameter	Test Vs Reference	Ratio %[Test/Reference] (lower , upper 90% CI of ratio)
Cmax (ng/mL)	2 mg dose (20mg/mL)- one IN Spray in one nostril (Test) Vs 0.4 mg IM (Reference)	333 (297, 373)
AUC0-t (h*ng/mL)		266 (247, 286)
AUC0-inf (h*ng/mL)		262 (244, 282)
Cmax (ng/mL)	4 mg dose (20mg/mL) – one Spray in each nostril (Test) Vs 0.4 mg IM (Reference)	714 (637, 801)
AUC0-t (h*ng/mL)		549 (511, 591)
AUC0-inf (h*ng/mL)		541 (503, 582)

The findings show that there is dose proportionality with the 2 mg and 4 mg Narcan Nasal Spray doses, and that the 2 mg Narcan Nasal Spray dose exceeds the exposure of the 0.4 mg IM injection, including during the first five minutes following dosing.

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

5. Clinical Microbiology

Not Applicable.

6. 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.

7. 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.

The following has been excerpted from my prior memo from the original application:

> 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.

While the adverse events described previously were observed in the 4 mg treatment group, the 2 mg groups had some of these too but additionally had constipation, toothache, muscle spasms, and rhinalgia. These additional terms will be included in the label.

8. Advisory Committee Meeting

This application was not taken to an advisory committee meeting. However, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee was convened on October 5, 2016, to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting. The committees were also asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

The following are the meeting minutes from this joint meeting:[3]

1. **DISCUSS:** The current pharmacokinetic standard for approval of naloxone products for use in the community requires demonstration of naloxone levels comparable to or greater than the levels achieved with the approved starting dose of 0.4 mg of naloxone injection administered by one of the approved, labeled routes of administration in adults [intravenous (IV), intramuscular (IM), or subcutaneous injection (SQ)], with a minimum of two doses packaged together.

a. Discuss whether matching or exceeding the naloxone exposure from a 0.4 mg injection of naloxone represents a high enough naloxone exposure to remain the basis for approval of novel products. Please take into consideration the variety of opioids that may be involved in an overdose in the community including: prescribed opioids vs. illicit opioids (heroin, heroin laced with fentanyl or carfentanil); partial agonists vs. full agonists.

[3] See http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM527701.pdf

b. If you think a higher minimum naloxone level is more appropriate as the basis for approval of new products intended for use in the community, describe the target naloxone level and the rationale for this approach.

c. In controlled settings with trained health care providers and adequate ventilatory support, naloxone can be titrated to reverse an opioid overdose and minimize the risk for precipitating an acute withdrawal syndrome in an opioid-tolerant individual. In the community, trained health care providers and adequate ventilatory support may not be available, and naloxone may be administered by a layperson relying solely on the instructions for use that accompanies the naloxone product. In this latter setting, there is a 5- to 10-minute window before hypoxic injury becomes irreversible. Discuss how to balance the need for rapid reversal of an opioid overdose with the risk for precipitating an acute opioid withdrawal syndrome when selecting the minimum naloxone exposure that forms the basis for approval of novel products.

Committee Discussion: *The committee members did not come to a consensus on the appropriateness of a higher starting dose of naloxone versus the current dose. The committee members discussed that it is unclear what should be the basis to choose an absolute correct dose; however, the committee noted that the risk of not having a high enough dose is much greater than not having enough. Some committee members stated that there is concern that lower doses of naloxone might require rescuers to titrate, taking time, and risking further hypoxic injury to the patient. Many committee members stated that the risk of acute withdrawal is acceptable for the benefit of saving a patient. Please see the transcript for details of the committee discussion.*

2. **DISCUSS:** The approved dosing for known or suspected opioid overdose in adults is as follows: 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 opioid induced or partial opioid induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

The approved dosing for known or suspected overdose in the pediatric population is as follows: The usual initial dose in pediatric patients 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.

The past AAP recommendations for naloxone dosing in infants and children are as follows: 0.1 mg/kg for infants and children from birth to 5 years of age or 20 kg of body weight. Children older than 5 years of age or weighing more than 20 kg may be given 2.0 mg. These doses may be repeated as needed to maintain opiate reversal.

a. Discuss whether the minimum exposure criterion (naloxone levels comparable to or greater than the levels achieved with 0.4 mg of naloxone injection) is appropriate for managing opioid overdose in children. If you do not think the standard is appropriate for children, discuss the criteria that should be used for naloxone products intended for use in children. Discuss whether the recommended criteria are suitable for use in adults.

b. If different standards and resultant naloxone products are recommended for adults and children, one concern is that the presence of more than one naloxone product in a home may

result in confusion about which product to administer in an emergency setting. Discuss how the risk of medication errors can be reduced in this setting.

c. Discuss the need (if any) for PK and safety information in pediatric patients, depending on the route of administration and inactive ingredients, and any recommendations for how these data can be obtained.

Committee Discussion: *There was much discussion amongst the committee members concerning the need for trials to determine PK and PD data in children. The committee members stated that single products and simpler administration is important as is dosing information that can be used by those at reduced cognitive levels. The committee members stated that different standards do not seem to be necessary based on the limited data presented, and that the safety profile of naloxone is excellent based on forty years of history of safe use in even the tiniest infants. Some committee members discussed that PK and safety information in pediatric patients is not necessarily needed at this time. The committee members stated that if studies were done, they would most likely need to be done on postoperative patients receiving intravenous opioids and naloxone on an inpatient basis. The committee members also discussed some models of waiver of consent that could be possible and that the emergency waiver of consent model may also represent a design possibility but almost all studies would be inpatient because of the ethical concerns of studying children in extremis. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Is the pharmacokinetic standard based on 0.4 mg of naloxone given by an approved route (IV, IM, SQ) appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?

a. Continue with the current minimum standard of comparable or greater exposure compared to 0.4 mg of naloxone injection

b. Increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection

Vote Result: A: 13 B: 15

Committee Discussion: *A slight majority of the committee voted for "B", in favor of increasing the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection. The committee members who voted to continue with the current minimum standard dose of naloxone stated that, as previously discussed, there was no indication that the current standard was failing the Agency or industry. Those voting for an increase opined that the current standard was set in 1971 and reflected inpatient use rather than use in the community where time to resuscitate may be minimal. These committee members also stated that given the wide availability of potent opioids in the community requiring multiple doses of naloxone, an increase in the minimum standard dose of naloxone seemed appropriate. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Should there be different minimum standards used to support the approval of products intended for use in adults and in children?

Vote Result: Yes: 7 No: 21 Abstain: 0

Committee Discussion: *The majority of the committee members voted "No", indicating that there should not be different minimum standards used to support the approval of products intended for use in adults and in children. Please see the transcript for details of the committee discussion.*

5. **DISCUSS:** Some Sponsors have proposed marketing more than one dose strength for their naloxone products intended for use in the community. When these strengths all meet or exceed the minimum naloxone exposure level set forth by the Agency, it is unclear what factors to describe in labeling to assist health care providers in making a decision to prescribe one dose strength over another.

Discuss what, if any, data Sponsors should provide to support the approval of more than one dose strength for any one naloxone product, and that can provide guidance to assist clinicians in dose selection.

Committee Discussion: *There was limited discussion due to time constraints, but a few committee members stated that there did not seem to be any support to encourage multiple dosage forms. Simplicity was the major reason given. Please see the transcript for details of the committee discussion.*

6. **DISCUSS:** As part of the standard for approval, naloxone products intended for use in the community have Instructions for Use (IFU) suitable for use by laypersons as supported by human factors studies and additional training is not required.

a. Discuss whether there is a role for new naloxone products intended for use in the community that requires training beyond the IFU.

b. Discuss the characteristics that should be considered for the study population enrolled in human factor studies of novel naloxone products. In particular, discuss the appropriate age range of study participants and whether the studies should specifically enroll adolescents, and if so, down to what minimum age. Also discuss whether these studies should specifically enroll caregivers of infants and children.

Committee Discussion: *Question 6 was not discussed due to time constraints.*

9. 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
> 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
> 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 in 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. Khurana's review, pages 2-3:

The sNDA is supported by a pivotal relative bioavailability study in 29 healthy adults to establish a scientific bridge to Narcan NDA 016636. The study compared 4 intranasal naloxone doses (2 mg, 4 mg [2 nostrils], 4 mg [1 nostril], and 8 mg [2 nostrils] to a 0.4 mg intramuscularly administered naloxone dose. These data were previously submitted to and reviewed by FDA as part of the original NDA submission for the 4 mg product.

If the 2 mg product meets DAAAP's current pharmacokinetic standard for adult approval of naloxone drug products, then DPMH recommends approval of the 2 mg product in all pediatric ages. DPMH review of the pediatric assessment in the sNDA found no new pediatric-specific efficacy and safety data compared to the pediatric assessment previously reviewed by DPMH for the original NDA submission for the 4 mg product.

When compared to parenteral naloxone doses recommended by the American Academy of Pediatrics (AAP), a 2 mg intranasal dose would provide a 2 to 8 fold higher weight-based dose in neonates depending on body weight but would provide a lower fixed dose to pediatric patients greater than 5 years of age or weighing 20 kilograms or more. The AAP recommends a 2 mg parenteral dose in the latter pediatric sub-group, but a 2 mg intranasal naloxone dose would provide the equivalent of a 1 mg parenteral naloxone dose. DPMH recommends that this discrepancy should not preclude approval of the 2 mg product since the basis for the recommendations endorsed by the AAP for higher naloxone dosing in older pediatric patients are unclear. DPMH was unable to determine the basis for these recommendations, and could not find clinical data supporting higher naloxone doses for pediatric patients. We speculate that the AAP's recommendation was made on a theoretical basis that higher doses are unlikely to be harmful in the absence of opioid tolerance, which is expected in most cases of pediatric accidental ingestion.

Since information for both the 2 mg and 4 mg drug products will be included in a single labeling, DPMH recommends pediatric use information in the combined labeling clearly state the 2 mg drug product is preferred in clinical situations where dose-titration of naloxone is desirable to avoid precipitating acute withdrawal symptoms in opioid-tolerant individuals. Outside of the neonatal setting, there are no clear situations in the community setting where dose titration with the 2 mg product would be desirable in pediatric patients in whom accidental exposure to a single, large opioid dose is likely to be the most commonly encountered scenario for which naloxone would be needed. Neonates who have had chronic opioid exposure in utero represent a unique pediatric sub-population in whom dose titration with the 2 mg dose may be beneficial to avoid precipitating potentially life-threatening acute opioid withdrawal.

In the sNDA, the applicant clearly states the intent of the 2 mg product is to allow caregivers to titrate the dose to an appropriate effect and acknowledged that repeat dosing may be more frequently required with the 2 mg product to achieve an adequate response. Given the likelihood that the 2 mg product may need to be more frequently

re-dosed, DPMH agrees with DAAAP that the 2 mg product be co-packaged with four doses to allow provision of up to 8 mg intranasal naloxone (equivalent of 4 mg parenteral naloxone) if needed in community settings pending arrival of emergency medical personnel.

I concur with Dr. Khurana's assessment with one exception. There is no role for titration of a dose of naloxone in the outpatient setting when the patient is not provided with adequate ventilatory support. The 2 mg dose is only intended for situations where the prescriber believes the patient is at risk for precipitation of an acute withdrawal syndrome, such that the lower dose may be more prudent. In settings with a risk of accidental opioid overdose by children or others in the household, the labeling will recommend that the 4 mg dose be prescribed.

As noted at the advisory committee meeting, there was little support for a higher standard for dosing children than for adults, but general support that there should not be multiple strengths available to avoid confusion in the community.

The pediatric labeling will remain the same following approval of the 2 mg dose of Narcan Nasal Spray.

10. Other Relevant Regulatory Issues

Because the dosing instructions and instructions for use were not changed, no new human factors evaluation was necessary.

As no new studies were performed in support of this application, no new inspections were conducted.

There are no other unresolved relevant regulatory issues

11. Labeling

Recommendations from DMEPA regarding the label and labeling were conveyed to the Applicant. In particular, the Applicant improved the color of the new product to adequately differentiate the strengths in order to prevent product selection errors.

Subsequent to the DMEPA review, the Applicant has changed the packaging configuration to a four blister packages of the single-dose, 2 mg product. The value of this configuration is that if the individual experiencing the overdose does not respond to the lower dose of naloxone, the total amount on hand will be the same as with the 4 mg product which is packaged with two blister packages in a carton.

DMEPA and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed labels and labeling. The patient labeling team reviewed the patient package insert, instructions for use, and quick start guide and found them acceptable with their recommended changes. The pertinent changes to the package insert are as follows:

Original Package Insert	New Package Insert
Section 1 INDICATIONS AND USAGE – new limitation of use	
NARCAN Nasal Spray is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. NARCAN Nasal Spray is not a substitute for emergency medical care.	NARCAN Nasal Spray is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. NARCAN Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. NARCAN Nasal Spray is not a substitute for emergency medical care. <u>Limitations of Use:</u> Restrict prescription of NARCAN Nasal Spray 2 mg to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.
Section 3 DOSAGE FORMS AND STRENGTHS - reference to new product	
NARCAN Nasal Spray is supplied as a single-dose intranasal spray containing 4 mg of naloxone hydrochloride in 0.1 mL.	NARCAN Nasal Spray is supplied as a single-dose intranasal spray containing 2 mg or 4 mg of naloxone hydrochloride in 0.1 mL.
Section 11 DESCRIPTION – reference to new product	
Each NARCAN Nasal Spray contains a 4 mg single dose	Each NARCAN Nasal Spray contains a 2 mg or 4 mg

of naloxone hydrochloride in a 0.1 mL (100 microliter) aqueous solution.	single dose of naloxone hydrochloride in a 0.1 mL (100 microliter) aqueous solution.
Section 12.3 Pharmacokinetics	
In a pharmacokinetic study in 30 healthy adult subjects, the relative bioavailability (BA) of one nasal spray in one nostril (4 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) and two nasal sprays administered as one nasal spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution in each nostril) was compared to a single dose of 0.4 mg naloxone hydrochloride intramuscular injection. For intranasal administration, the subjects were instructed not to breathe through the nose during administration of the nasal spray, and remained fully supine for approximately one hour post-dose. For intramuscular administration, naloxone was administered as a single injection in the gluteus maximus muscle. The pharmacokinetic parameters obtained in the study are shown in **Error! Reference source not found.**.	In a pharmacokinetic study in 30 healthy adult subjects, the relative bioavailability (BA) of one nasal spray in one nostril, consisting of a 2 mg total dose (0.1 mL of 20 mg/mL naloxone hydrochloride solution) and a 4 mg total dose (0.1 mL of 40 mg/mL naloxone hydrochloride solution), and two nasal sprays administered as one nasal spray in each nostril, consisting of a 4 mg total dose (0.1 mL of 20 mg/mL naloxone hydrochloride solution in each nostril) and an 8 mg total dose (0.1 mL of 40 mg/mL naloxone hydrochloride solution in each nostril), were compared to a single dose of 0.4 mg naloxone hydrochloride intramuscular injection. For intranasal administration, the subjects were instructed not to breathe through the nose during administration of the nasal spray, and remained fully supine for approximately one hour post-dose. For intramuscular administration, naloxone was administered as a single injection in the gluteus maximus muscle. The pharmacokinetic parameters obtained in the study are shown in **Error! Reference source not found.**.
Section 16 HOW SUPPLIED	
NARCAN Nasal Spray 4 mg is supplied as Carton containing two blister packages (NDC 69547-353-02) each with a single spray device.	NARCAN Nasal Spray 2 mg is supplied as a carton containing four blister packages (NDC 69547-212-04) each with a single spray device and as a carton containing 24 blister packages (NDC 69547-212-24) each with a single spray device. NARCAN Nasal Spray 4 mg is supplied as Carton containing two blister packages (NDC 69547-353-02) each with a single spray device.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

The pharmacokinetic profile from Narcan Nasal Spray 2 mg demonstrates dose proportional exposure to naloxone relative to the 4 mg product and provides acceptable exposure based on the current standards for approval of products intended for use in the community. As discussed at the October 5, 2016, advisory committee meeting, it is difficult to determine what is the most appropriate dose and naloxone exposure for use in the community. The myriad ways in which an opioid overdose can occur require a product be available that can reverse an overdose resulting from the worst case scenario of either a large amount of opioid or from exposure to a highly potent opioid. While it is possible to precipitate an acute withdrawal syndrome in patients who are physically tolerant to an opioid, there is no way to safely titrate a dose of naloxone to a patient who overdoses in settings where adequate ventilatory support cannot be assured. Rather the availability of more than one dose, in this case 4 doses of Narcan Nasal Spray 2 mg, is for situations in which it will take a large amount of naloxone to reverse the opioid.

- Recommendation for Postmarketing Requirements

The existing postmarketing requirements from the original application approval will address the outstanding concerns for this formulation. No new requirements are necessary at this time.

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/s/

SHARON H HERTZ
01/24/2017