CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

SUMMARY REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave. Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	Refer to signature date at the end.
From	Silvana Borges, MD, Clinical Team Leader and Deputy Division Director Rigoberto Roca, MD, Division Director
NDA	208969
Applicant	Amphastar Pharmaceuticals, Inc.
Date of Original Submission	April 19, 2016 Complete Response letter issued February 17. 2017
Date of Complete Response Submission	September 7, 2022
PDUFA Goal Date	March 7, 2023
Proprietary Name	To be determined
Established or Proper Name	Naloxone Hydrochloride
Dosage Form	Nasal Spray; 4 mg of naloxone hydrochloride in 0.25 mL
Applicant Proposed Indication/Populations	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Applicant Proposed Dosing Regimen	• Seek emergency medical care immediately after use. • Administer a single spray of Naloxone Hydrochloride Nasal Spray to adults or pediatric patients intranasally into one nostril. • Administer additional doses of Naloxone Hydrochloride Nasal Spray using a new nasal spray device with each dose if the patient does not respond or responds and then relapses into respiratory depression. Additional doses of Naloxone Hydrochloride Nasal Spray may be given every 2 to 3 minutes until emergency medical assistance arrives. • Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
Regulatory Action	Approval

Review Team

Discipline	Primary/Secondary/Tertiary Assessment
Office of Pharmaceutical Quality	
Chemistry, Manufacturing, and Control (CMC)	Zhixing Shan/ Gaetan Ladouceur Mari Chelliah/ Valerie Amspacher Qiang Han/ Kamal Tiwari
Microbiology	George Arhin/ Elizabeth Bearr
Pharmacology/Toxicology	Carlic Huynh/Nikunj Patel/Newton Woo/Dan Mellon
Clinical Pharmacology	Srikanth Nallani/ Yun Xu
Clinical	Corinne Ahmar/Silvana Borges
ADL	Lisa Basham
PM	Namrata Thakkar/Matthew Sullivan
Consults	
DMEPA	Damon Birkemeier/ Oluwamurewa Oguntimein (Murewa)/Valerie Vaughn
OSE PM	Carol Corbie
OPDP	LaToya Shenee Toombs
DPV	Sarah Kang/ Mallika Mundkur
DPMH	Ndidi Nwokorie/Mona Khurana
CDRH	Kyran Gibson
Patient Labeling	Ruth Mayrosh/Barbara Fuller

1. Benefit-Risk Assessment

Opioid overdose is a major public health problem in the United States leading to tens of thousands of deaths every year. Naloxone is a nonselective opioid receptor antagonist with high affinity for the mu-opioid receptor developed to reverse life-threatening opioid overdose and prevent hypoxia associated with injury and death.

There are many FDA approved naloxone products for use in adults and pediatric patients in the community, of which the following are currently available in the market: Narcan (naloxone nasal spray 4 mg, NDA 208411) approved in 2015; Kloxxado **(**naloxone nasal spray 8 mg, NDA 212045) and Zimhi (naloxone 5 mg, pre-filled syringe for intramuscular or subcutaneous injection, NDA 212854), both approved in 2021. Several generic naloxone 4 mg nasal spray products are also available for use in the community.

The Applicant (Amphastar Pharmaceuticals, Inc.) resubmitted NDA 208969 on September 7, 2022, pursuing approval of naloxone hydrochloride nasal spray 4 mg in 0.25 ml for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients through the 505(b)(2) pathway. Naloxone nasal spray 4 mg/0.25ml is a drug-device combination intended for use in the community. In this resubmission, the Applicant relies on FDA's previous findings of efficacy and safety for Narcan injection (naloxone hydrochloride 0.4 mg, NDA 16636) and naloxone injection 2 mg (ANDA 072076).

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The efficacy of Naloxone NS 4 mg/0.25ml was evaluated in one PK study comparing the systemic exposure to naloxone following the administration of Naloxone NS 4 mg/0.25ml, naloxone 0.4mg IM, naloxone 2mg IV, and naloxone nasal spray 10 mg/0.25 ml. In this PK study, Naloxone NS 4 mg/0.25ml demonstrated higher concentrations and greater partial AUCs at the early absorption phase, greater C_{max}, greater AUC_{0-t} and AUC_{0-inf} than Narcan injection. The naloxone concentrations during the early absorption phase, and the C_{max}, AUC_{0-t} and AUC_{0-inf} values with Naloxone NS 4 mg/0.25ml were all lower than with naloxone 2 mg IV. Therefore, Naloxone NS 4 mg/0.25ml has demonstrated naloxone systemic exposure between that of Narcan injection 0.4 mg IM and naloxone injection 2 mg IV, supporting the Applicant's reliance on efficacy findings of Narcan injection and systemic safety findings of naloxone injection 2 mg IV.

The main risks of naloxone are severe precipitated opioid withdrawal and associated cardiovascular risks. Cardiac arrhythmias, cardiac arrest and death have been reported following the reversal of opioid-induced respiratory depression and have primarily occurred in patients with pre-existing opioid dependence and cardiovascular disorders. Despite these known risks, the Division have previously found the benefit-risk assessment to be favorable for naloxone products for intranasal administration of similar or higher strengths than Naloxone NS 4 mg/0.25ml (e.g., Narcan nasal spray 4 mg and Kloxxado nasal spray 8 mg). The extensive use of these products in the community has also shown that the benefit of reversing a life-threatening opioid overdose outweighs their risks.

The clinical data for Naloxone NS 4 mg/0.25ml has shown a similar safety profile for this product compared to other naloxone products in the adult population.

Regarding the pediatric population, naloxone products intended for use in the community are expected to be used in the entire pediatric age range. The dosing volume of 0.25 ml in Naloxone NS 4 mg/0.25ml is 2.5 times higher than the highest dosing volume in approved naloxone products for intranasal administration (i.e., 0.1 ml). Therefore, there were concerns about the safety and possible impact on efficacy of a dosing volume of 0.25 ml administered intranasally to pediatric patients. To address these concerns, the Applicant submitted 1) a retrospective observational safety study of different medications administered intranasally at dosing volumes >0.25 ml in pediatric patients 3 years of age and younger; and 2) modeling data estimating the nasal spray run-off following the administration of 0.25 ml intranasally in infants. The data from these pediatric studies, along with the efficacy and safety data from the studies in adults, addressed our efficacy and safety concerns related to the use of Naloxone NS 4 mg/0.25ml in the pediatric population of all ages down to birth.

The Applicant has demonstrated the safety and efficacy of Naloxone NS 4 mg/0.25ml for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients. The regulatory action for this application is Approval.

2. Background

The Applicant (Amphastar Pharmaceuticals, Inc.) developed Naloxone NS 4 mg in 0.25ml, referred as "Naloxone NS 4 mg/0.25ml" in this review, for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients. The product is a single-use, drug-device combination product intended to be used in the community by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention.

The Applicant's original formulation contained (b) (4) mg of naloxone hydrochloride in (b) (4) ml. Of note, the highest dosing volume in an approved naloxone product for intranasal administration is 0.1 ml. In interactions with the Applicant preceding the original NDA submission, the FDA expressed concerns about the safety and possible impact on efficacy of a dosing volume of (b) (4) ml administered intranasally to pediatric patients. The original NDA was submitted on April 19, 2016 and received a Complete Response (CR) on February 17, 2017, due to lack of support for the safety and efficacy of the (b) (4) ml dosing volume in pediatric patients, and deficiencies related to the human factors validation study (b) (4)) and CMC specifications. Following this CR action, two Type A meetings (on May 15 and November 28, 2017) and one Type C meeting (on March 18, 2020) were conducted between the Applicant and the FDA to discuss pathways to resolve the deficiencies of the original NDA. In these meetings, among other exchanges, the Applicant proposed or agreed to:

- Change the naloxone dose in their product from (b) (4) mg to 4 mg.
- Change their naloxone formulation from (b) (4) to 4 mg in 0.25 ml.
- Change the device to a pre-assembled device design, (b) (4)
- Conduct a comparative bioavailability study and a study of the effects on olfactory function with the new formulation (i.e., 4 mg/0.25 ml).
- Provide additional information to support the safety and efficacy of the new formulation in pediatric patients.

The Applicant resubmitted the NDA on September 7, 2022, pursuing approval of Naloxone NS 4 mg/0.25ml, through the 505(b)(2) pathway. The listed drug is Narcan injection (naloxone hydrochloride 0.4 mg, NDA 16636). In support of their 505(b)(2) application, the Applicant submitted bioavailability data comparing Naloxone NS 4 mg/0.25ml with naloxone 0.4mg IM, naloxone 2mg IV, and naloxone nasal spray 10 mg/0.25 ml, to establish a scientific bridge to the efficacy and safety findings of Narcan injection for the proposed indication. The Applicant also submitted safety data from a study evaluating the effects of Naloxone NS 4 mg/0.25ml on olfactory function. To address the concerns related to the use of a dosing volume of 0.25 ml in the pediatric population, the Applicant submitted 1) a retrospective observational safety study of different medications administered intranasally at dosing volumes >0.25 ml in pediatric patients 3 years of age and younger; 2) modeling data estimating the nasal spray run-off following the administration of 0.25 ml intranasally to infants.

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3. Product Quality

The CMC team conducted a full review of this resubmission as the Naloxone NS 4 mg/0.25ml product constitutes a new formulation and new device, compared to the product in the original NDA. According to the review by Valerie Amspacher, the CMS team leader, no deficiencies have been identified in the drug substance, drug product, manufacturing, or microbiology of the product. All CMC disciplines recommend approval of Naloxone NS 4 mg/0.25ml. Refer to the review by Valerie Amspacher dated February 16, 2023, for more details.

For Naloxone NS 4 mg/0.25ml, the Applicant redesigned the device developed for the original product, i.e., naloxone nasal spray (b) (4). The original device (b) (4) was deemed inadequate for the intended use. The redesigned device for Naloxone NS 4 mg/0.25ml comes preassembled and ready to be used. The Naloxone NS 4 mg/0.25ml device has been deemed acceptable for the intended use.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Carlic Huynh's review, no pharmacology/toxicology deficiencies were identified in the original submission of this NDA, as noted in the nonclinical review dated January 23, 2017. There were no new nonclinical studies submitted in this NDA. The formulation contains 4 mg of naloxone hydrochloride in 0.25 mL (16 mg/mL) with no novel excipients. The drug substance and drug product specifications, elemental impurities and (b) (4) assessments are acceptable. The extractable/leachables data supports the safety of the container closure system. Therefore, Dr. Huynh concludes that there are no nonclinical concerns with the Naloxone NS 4 mg/0.25ml product and recommends its approval.

Refer to Dr. Carlic Huynh's review dated March 1, 2023, for more details.

5. Clinical Pharmacology

According to the review by Dr. Srikanth Nallani dated February 9, 2023, the Applicant conducted Study API-N002-CL-A3 (Study A3) comparing the systemic exposure to naloxone following the administration of Naloxone NS 4 mg/0.25ml, naloxone 0.4 mg IM, naloxone 2 mg IV, and naloxone 10 mg/0.25 ml IN, in support of this application. Although included in Study A3, the Applicant is not seeking approval of the 10 mg/0.25 ml intranasal naloxone product. Given that Narcan injection is not currently marketed, the Applicant utilized two generic products to evaluate the efficacy and safety of Naloxone NS 4 mg/0.25ml in Study A3: naloxone injection 0.4 mg (Hospira, ANDA 070256) administered IM and naloxone injection 2 mg (Amphastar/IMS, ANDA 072076) administered through IV infusion. The Applicant confirmed that the final to-be-marketed product (formulation and device) for Naloxone NS 4 mg/0.25ml was used in the comparative bioavailability Study A3.

The Applicant's strategy appeared to be one of demonstrating that the plasma naloxone concentrations with Naloxone NS 4 mg/0.25ml fall between the plasma concentrations achieved with the approved doses of naloxone 0.4 mg IM injection and naloxone 2 mg IV injection. In Study A3, the mean $AUC_{0\text{-}2min}$, $AUC_{0\text{-}3min}$, $AUC_{0\text{-}5min}$, and $AUC_{0\text{-}10min}$ for a single

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dose of Naloxone NS 4 mg/0.25ml were 117.5%, 159%, 208%, and 292%, respectively, of that for a single dose of 0.4 mg of naloxone IM. The lower limits of the 90% CIs for the partial $AUC_{0\text{-}30min}$ were all greater than 80%, with the exception of $AUC_{0\text{-}2min}$, for which the lower 90% CI was lower than 80%. Dr. Nallani interpreted that this result is likely due to the sample size not being sufficiently large and pointed to the data providing further evidence that Naloxone NS 4 mg/0.25ml leads to higher systemic exposure than the IM comparator during the early absorption phase (e.g., 1, 2, 3, 5, 10 min post-dose). The early partial AUC at 5 minutes was also higher with Naloxone NS 4 mg/0.25ml than with the intramuscular naloxone injection. Taken together, Dr. Nallani concluded that these observations support that Naloxone NS 4 mg/0.25ml is expected to deliver effective levels of naloxone for the proposed indication. The naloxone concentrations during the early absorption phase, and the C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ values with a single dose of Naloxone NS 4 mg/0.25ml were all lower than with a single 2 mg dose of naloxone IV.

The Office of Study Integrity and Surveillance (OSIS) determined that inspections in the clinical site and the analytical site for Study A3 were not needed at this time since inspections recently conducted at these sites fall within the surveillance interval.

Based on all these considerations, Dr. Nallani concluded that the Applicant has established a scientific bridge between Naloxone NS 4 mg/0.25ml and the listed drug (Narcan injection, naloxone hydrochloride 0.4 mg, NDA 16636) and recommended approval of this application.

Refer to Dr. Nallani's review for more details.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy of Naloxone NS 4 mg/0.25ml is supported by a scientific bridge to the listed drug Narcan injection (naloxone hydrochloride 0.4 mg) through one bioavailability pharmacokinetic study (Study A3) comparing Naloxone NS 4 mg/0.25ml and Narcan injection. Naloxone NS 4 mg/0.25ml demonstrated higher concentrations and greater partial AUCs at the early absorption phase, greater C_{max}, greater $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ than Narcan injection. These findings support the Applicant's reliance on FDA's previous findings of efficacy for Narcan injection in adults.

However, the higher dosing volume of Naloxone NS 4 mg/0.25ml (i.e., 0.25 ml) compared to the highest dosing volume in other approved naloxone nasal spray products (i.e., 0.1 ml), raised concerns about the potential run-off of the Naloxone NS 4 mg/0.25ml dose when administered to pediatric patients, particularly in the 0-3 years age range. The run-off of the Naloxone NS 4 mg/0.25ml dose could potentially decrease the efficacy of the product by the partial loss of the administered dose. The Applicant submitted data to address this concern. Refer to Section 10 of this review for a detailed discussion of such data.

8. Safety

According to Dr. Corinne Ahmar's clinical review, the Applicant provided new clinical safety data from Study A3. In this study, there were no clinically significant adverse events and no new safety signals with Naloxone NS 4 mg/0.25ml were identified.

It is of note that naloxone injection 2 mg (Amphastar/IMS, ANDA 072076) is an approved product whose benefit-risk assessment has been deemed favorable. The Applicant has shown that the systemic exposure for Naloxone NS 4 mg/0.25ml is lower than for naloxone injection 2 mg. These pharmacokinetic data, along with the clinical data from Study A3 supports the systemic safety of Naloxone NS 4 mg/0.25ml.

Regarding local toxicity, the clinical evaluation of the nasal cavity in participants of Study A3 did not raise any safety concerns. The Applicant also conducted Study API-N002-CL-A4 (Study A4) to evaluate the effects of Naloxone NS 4 mg/0.25ml on olfactory function. This was a randomized, double-blinded, crossover study that evaluated the effects on olfactory function of a single dose of Naloxone 10 mg/0.25ml or placebo administered intranasally to 28 healthy volunteers. It is of note that this study utilized a 10 mg/0.25 ml naloxone formulation with a concentration of 40mg/ml, while the to-be-marketed drug product contains 4 mg of naloxone with a lower concentration of 16 mg/ml.

The olfactory function of study subjects was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). Two subjects who had received placebo and one subject who had received Naloxone NS 10 mg/0.25ml had a decrease in their olfactory performance observed from normosmia to mild microsmia (olfactory performance score change from 5 to 4). Dr. Ahmar concluded that no significant change in olfactory function was observed following administration of a single dose of Naloxone NS 10 mg/0.25ml with a concentration of 40 mg/ml. Given that this naloxone dose and concentration exceeds that of Naloxone NS 4 mg/0.25ml, these findings support the local safety of this product.

As mentioned before, the 0.25 ml dosing volume of Naloxone NS 4 mg/0.25ml raised concerns about the potential run-off of the Naloxone NS 4 mg/0.25ml dose when administered to pediatric patients. The run-off of the Naloxone NS 4 mg/0.25ml dose could have adverse consequences (e.g., aspiration), particularly in infants. The Applicant submitted data to address this concern. Refer to Section 10 of this review for a detailed discussion of such data.

9. Advisory Committee Meeting

No advisory committee meeting was held because there were no issues identified that required input from an advisory committee.

10. Pediatrics

The device used for Naloxone NS 4 mg/0.25ml was redesigned following FDA's recommendations as a pre-assembled device and deemed adequate for use in pediatric patients of all ages down to birth.

Naloxone products intended for use in the community (e.g., Narcan NS 4 mg) are approved for use in the entire pediatric age range. The safety and effectiveness of naloxone for the emergency treatment of known or suspected opioid overdose in pediatric patients of all ages has been previously established based on pharmacokinetic evaluations and extrapolation of efficacy and safety data from the adult population.

The efficacy of Naloxone NS 4 mg/0.25ml in the pediatric population is extrapolated from Study A3 in adults which demonstrated that the systemic exposure of Naloxone NS 4 mg/0.25ml is higher than that of Narcan injection (naloxone 0.4 mg IM). However, the dosing volume of 0.25 ml in the proposed product is 2.5 times higher than the highest dosing volume in approved naloxone products for intranasal administration (i.e., 0.1 ml). The Applicant evaluated the extent of run-off when administering a 0.25 ml dose intranasally to pediatric patients using CT scan data of the pediatric nasal airway anatomy from 6 children (5 of them younger than 1 year) and computational simulation using age-dependent nose-throat airway models. These simulations were conducted to estimate the run-off fractions from different nasal spray volumes and predicted that a minimal (~1%) run-off would occur with a spray volume of 0.25 ml, even when this spray volume is administered to neonates. However, the review team identified possible shortcomings in the Applicant's model: 1) the Applicant's predicted run-off fraction for the 0.5 ml volume was ~30% different from the run-off fraction for 0.5 ml found in the literature; 2) the Applicant's model used an airflow of 1.72 L/min (20% of estimated normal rate), which may not reflect the airflow during an opioid overdose, including a possible airflow of near zero in apneic patients.

Following our request, the Applicant incorporated the parameters from the literature into their model and demonstrated that their results were similar to the published data, therefore increasing the credibility of their model. They also estimated the run-off fractions using a range of airflow rates (0%, 10%, 30%, and 40% of estimated normal rate). This sensitivity analysis showed little impact from these airflow rates on the predicted run-off fraction. The highest predicted run-off fraction was 3.9% of the 0.25 ml volume administered intranasally in the 10-day old model. If this run-off is considered as a naloxone dose loss, the actual naloxone dose delivered when administering Naloxone NS 4 mg/0.25ml to a newborn (the worst-case scenario) would be 3.84 mg (i.e., 96.1 % of the dose) which is still higher than the approved 2-mg naloxone NS dose (NDA 208411) previously deemed effective for the intended indication. All these data support the efficacy of Naloxone NS 4 mg/0.25ml in the pediatric population of all ages down to birth.

The systemic safety of Naloxone NS 4 mg/0.25ml in the pediatric population is extrapolated from Study A3 in adults which demonstrated that the systemic exposure of Naloxone NS 4 mg/0.25ml was lower than that single 2 mg dose of naloxone IV. However, there were safety concerns related to the use of a dosing volume of 0.25 ml by the intranasal route in children, particularly in those 3 years of age and younger.

To support the safety of Naloxone NS 4 mg/0.25ml dosing volume, the Applicant conducted Study API-N002-CL-C, a retrospective observational pediatric study using electronic medical records (EMRs) from 4 US hospitals (Study C). This retrospective analysis included EMRs of 562 children aged 0-3 years who received medications through the intranasal (IN) route at volumes ranging from 0.25 ml to 3.90 ml. Of note, 37 out of the 562 patients (6.6%) were ≤1 year of age. The IN-administered medications were midazolam, fentanyl, ketamine, dexmedetomidine and/or additional sedative and analgesics. The study endpoint was adverse drug events (ADE) related to IN dosing, particularly any ADE defined as respiratory compromise (e.g., aspiration). No ADE related to the IN dosing volume were identified. These findings are supportive of the safety of the 0.25 ml IN spray volume in the youngest patients.

All these considerations led to the conclusion that the Applicant has addressed our efficacy and safety concerns related to the use of Naloxone NS 4 mg/0.25ml in the pediatric population of all ages down to birth.

Refer to Dr. Ahmar's clinical review and consult reviews by the Division of Pediatrics and Maternal Health (dated February 7, 2023) and the Division of Applied Regulatory Science (attached to Dr. Ahmar's review) for more details on these pediatric data.

Based on her review of the totality of the safety and efficacy data submitted in this NDA resubmission, Dr. Corinne Ahmar recommended approval of this application. We agree with her recommendation.

11. Other Relevant Regulatory Issues

In the original NDA submission, the Division of Medication Error Prevention and Analysis (DMEPA) had identified deficiencies in the two human factors validation studies submitted in support of the application. Following the 2017 CR, DMEPA provided advice to the Applicant on several aspects of the use of their device, including the review of a new human factors validation study, which was submitted to support the NDA resubmission subject of this review. Upon review of this new human factor validation study report in this review cycle, DMEPA concluded that the study did not demonstrate use errors, use difficulties, or close calls with any tasks, except for Step 7 in the instruction for use (IFU). However, DMEPA determined that the IFU Step 7 language could be improved to avoid misinterpretation and additional human factor data would not be necessary. The Applicant implemented DMEPA's labeling recommendations. DMEPA recommended approval of this application.

Please refer to the review from DMEPA (dated February 9, 2023) for details.

12. Labeling

The proposed prescribing information for Naloxone Hydrochloride Nasal Spray is based on the approved labeling for the listed drug Narcan injection (NDA 016636). The Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP) and the Division of Pediatric and Maternal Health (DPMH) were consulted regarding the proposed labeling. Dr. Ahmar, the clinical reviewer, identified necessary

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revisions throughout the label to reflect the adverse events findings with Naloxone NS 4 mg/0.25ml and also to make this product labeling consistent with most recently approved naloxone nasal spray products. CMC, DMEPA, clinical pharmacology, and pharmacology toxicology also requested labeling revisions from the Applicant. The Applicant agreed to our labeling revisions or provided adequate justification for their labeling language and agreement was reached with the Applicant on labeling for Naloxone NS 4 mg/0.25ml.

13. Postmarketing Requirements

No postmarketing study is required for this application at this time. All the information necessary for the safe and effective use of Naloxone NS 4 mg/0.25ml for the intended indication has been provided in this NDA resubmission.

14. Comments to the Applicant

No comments to the Applicant are necessary.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SILVANA BORGES
03/07/2023 02:16:12 PM

RIGOBERTO A ROCA
03/07/2023 02:32:56 PM

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208969
Applicant Name	Amphastar Pharmaceuticals, Inc.
Date of Submission	April 20, 2016
PDUFA Goal Date	February 19, 2017
Proprietary Name / Established (USAN) Name	Naloxone Hydrochloride Nasal Spray
Dosage Forms / Strength	Intranasal spray (b) (4)
Proposed Indication(s)	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression (b) (4)
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Clinical Review	Jennifer Nadel, MD, Josh Lloyd, MD
CDTL	N/A
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Joseph Leginus, PhD, Valerie Amspacher, PhD, Edwin Jao, PhD, Nutan Mytle, PhD, Christina Capacci-Daniel, PhD, Steven Kinsley, PhD, Ciby Abraham, PhD, Julia Pinto, PhD
CDRH/GHDB/DAGRID Review	Robert Meyer, Alan Stevens, LCDR, USPHS
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD
OSI	Yiyue Ahzng, PhD, Stanley Au, PharmD, BCPS, Charles Bonapace, PharmD, Xingfang Li, MD, RAC, Elise A. Murphy
CDRH/Office Of Compliance	Katelyn R. Bittleman, Vesa Vuniqi
OSE/DMEPA	James Schlick, RPh, MBA, Vicky Borders-Hemphill, PharmD; Quynh Nhu Nguyen; MS, Irene Z. Chan, PharmD, BCPS
Division of Pediatric and Maternal Health	Mona Khurana, MD, John J. Alexander, MD, MPH

OND=Office of New Drugs
OPQ= Office of Pharmaceutical Quality
OCP = Office of Combination Products
DMEPA=Division of Medication Errors Prevention
CDTL=Cross-Discipline Team Leader
CDRH=Center for Device and Radiological Health
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations

Reference ID: 4058322

Signatory Authority Review Template

1. Introduction

The current application is a 505(b)(2) application for Naloxone Hydrochloride Nasal Spray (b) (4) mg which relies on the Agency's previous findings of safety and efficacy for Narcan, (NDA 016636). 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, the potential for use in pediatric overdose situations, the review of the device, and the human factors testing.

Throughout the individual reviews, the product has been referred to as Naloxone Hydrochloride Nasal Spray (b) (4), (b) (4), two proposed trade names, and as N002 and N002 (b) (4).

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. Narcan nasal spray 4 mg (NDA 208411), the first intranasal naloxone product, was approved on November 18, 2015 and a 2 mg version was approved on January 24, 2017.

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. 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. 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

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It is necessary that a naloxone product intended for use in the community be easy to use by a lay person. (b) (4)

(b) (4)

3. OPQ/Device

The proposed drug product, Naloxone Intranasal Spray (N002) is provided as a (b) (4) . N002 will be manufactured at International Medication Systems, Limited (IMS), a wholly owned subsidiary of Amphastar Pharmaceuticals Inc. (Amphastar). Below is a photograph and schematic of the product.

Figure 1

(b) (4)

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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The drug substance, Naloxone HCl is manufactured by (b) (4) and is referenced in DMF# (b) (4) which was found to be adequate upon last review, August 9, 2016.

The drug component of the product consists of naloxone hydrochloride solution, (b) (4) with no novel excipients. The results of microbiology studies were acceptable.

From the OPQ review, page 27:

(b) (4)

The Applicant conducted extractable and leachable studies. The results were acceptable, however, there were two outstanding issues. However, there were no concerns based on the pharmacology/toxicology review described below. The issues will be conveyed to the Applicant for response:

1. The description of the non-volatile leachables testing in the extractables and leachables report is inadequate to assure accurate monitoring of non-volatile extractables/leachables. Clarify which extractables/leachables standards were used when running the (b) (4) samples. Provide validation information on the (b) (4) method showing it is capable of detecting the likely extractables/leachables present.

2. There is an unexplained inconsistency in the results of the extractions studies using similar conditions in the assessment of extractables and leachables. (b) (4)

I concur with the conclusions reached by the OPQ review team regarding the acceptability of the manufacturing of the drug substance and drug component of the drug product. I concur with the CDRH review team that the overall drug product should not be approved due to the device deficiencies noted above.

4. Nonclinical Pharmacology/Toxicology

From Dr. Huynh's review, pages 6 and 7:

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There were no required nonclinical studies submitted in this NDA. The formulation is a (b) (4) mg/mL concentration of naloxone hydrochloride in (b) (4) mL (final dose of (b) (4) mg in (b) (4) mL) that contains no novel excipients. There are no nonclinical safety concerns with the drug substance and drug product specifications. There are no nonclinical safety concerns with the container closure (b) (4) . To support the container closure system, the Applicant submitted the results of the delay-typed hypersensitivity in guinea pigs testing extracts from a component of the container closure system as well as an intracutaneous reactivity test in rabbits, both of which did not demonstrate any skin sensitization or skin irritation of container closure system extractable compounds.

As part of the preNDA advice to the Sponsor, the Agency indicated that the Applicant should submit a review of the literature to determine if there were any findings since the approval of the referenced drug product that would impact labeling. The Applicant did not conduct a literature review or summarize any nonclinical data in the submission. Nonetheless, the Agency has conducted a literature review. Although there have been numerous articles describing the effects on naloxone on reproduction and developmental endpoints which suggest naloxone can potentially impact neuronal development, these findings would not negate the potential benefit of a life-saving therapeutic.

Therefore, there are no additional nonclinical concerns with the proposed naloxone hydrochloride drug product.

In addition, Dr. Huynh addressed the following (page 23):

(b) (4) Given the life-saving potential of this drug product, further evaluation does not appear warranted.

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

5. Clinical Pharmacology

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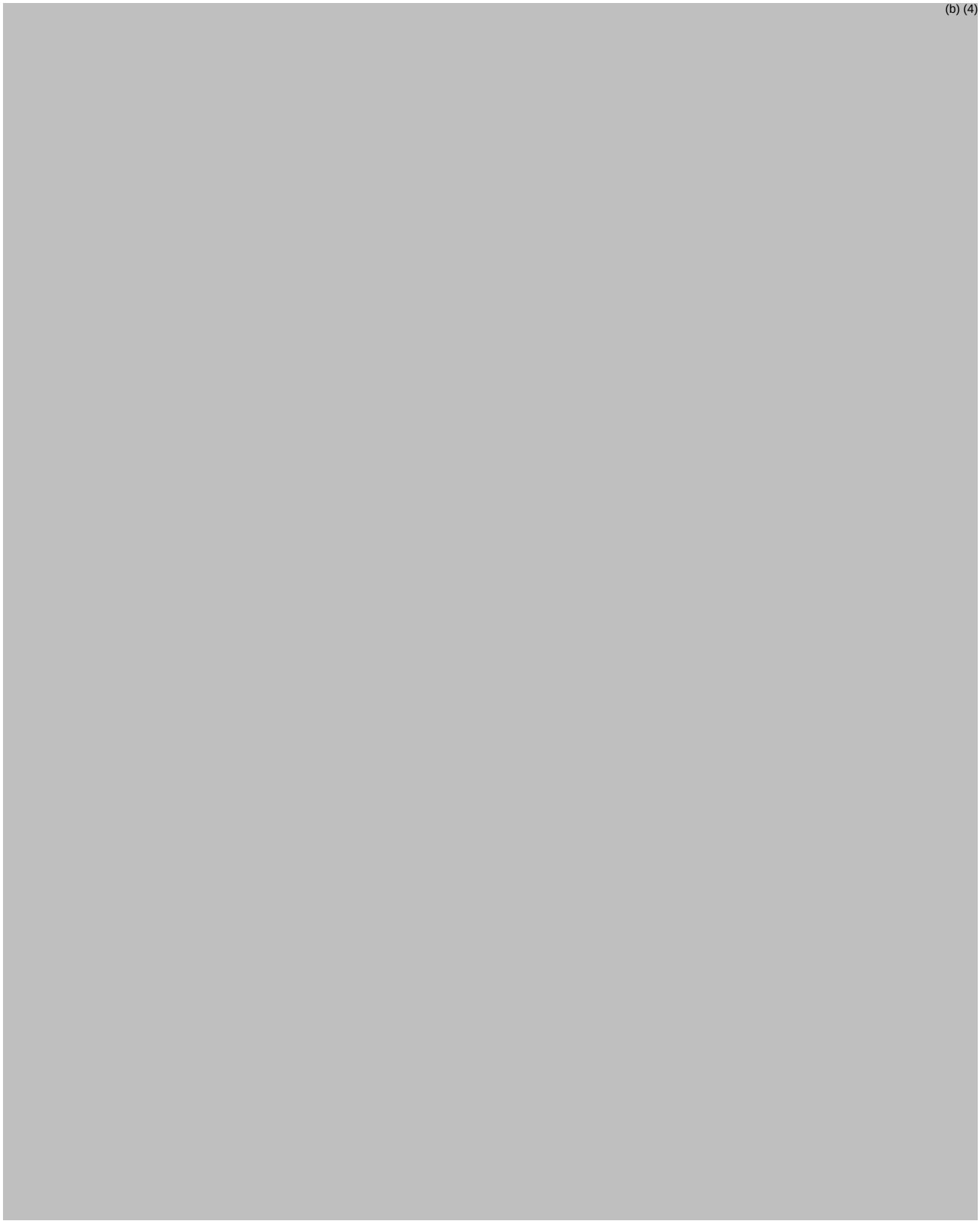
The basis for efficacy for Naloxone Hydrochloride Nasal Spray is a scientific bridge to the Agency's previous findings of safety and effectiveness for Narcan (NDA 016636). The scientific bridge was created by two pharmacokinetic studies.

(b) (4)



I concur with the conclusions reached by the clinical pharmacology 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. (b) (4)

(b) (4)

The safety of naloxone is generally well characterized. 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 (b) (4) mg of intranasal naloxone to a person who has not had an opioid overdose if the person is not opioi -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. 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]

[3] See

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.

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

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http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM527701.pdf

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.*

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.

(b) (4) makes it poorly suited for use in pediatric patients. As noted in the review by DPMH, page 5:

(b) (4)

The conclusions are reproduced below, pages 7 and 8:

III. Conclusions

Failures by untrained laypersons to use (b) (4) correctly in the Human Factors Validation Study raise concerns that (b) (4) may result in treatment failure in pediatric patients due to inadequate delivery of the full intended IN dose. (b) (4) The pediatric assessment does not adequately address the potential safety concerns associated (b) (4) to support use down to birth.

IV. Recommendations

DPMH recommends against approval of (b) (4) for the proposed indication in the pediatric population. Since pediatric studies to assess the safety (b) (4) for the proposed indication are challenging to conduct from both an ethical and feasibility perspective, the applicant should consider re-formulating their product

[4] Grassin-Delyle, Buenestado A, Naline E, et al. Intranasal Drug Delivery: An Efficient and Non-Invasive Route for Systemic Administration. Focus on Opioids. Pharmacology & Therapeutics 134: 366-379, 2012.

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(b) (4) consistent with that of currently approved IN drug products to ensure the product can be safely used in adults and pediatric patients down to birth.

(b) (4)

11. Other Relevant Regulatory Issues

Inspections

As the two pharmacokinetic studies form the scientific bridge to the listed drug, in lieu of efficacy and safety studies, inspections of the Clinical and Bioanalytical sites were conducted by OSIS. After reviewing the Establishment Inspection Report, inspection findings, and firm's response to Form FDA 483, the analytical data from the audited studies were found to be reliable by OSIS reviewers and the data were accepted for further review.

The CDRH Office of Compliance (OC) inspected International Medication Systems, Ltd, the site responsible for manufacturing, packaging, labeling and control operations, distribution, as well as release and stability testing of drug product (b) (4)

The following is from the CDRH/OC review, page 12:

RECOMMENDATION

The approvability of application for Naloxone HCl Nasal Spray – NDA 208969 should be delayed for the following reasons:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

(b) (4)

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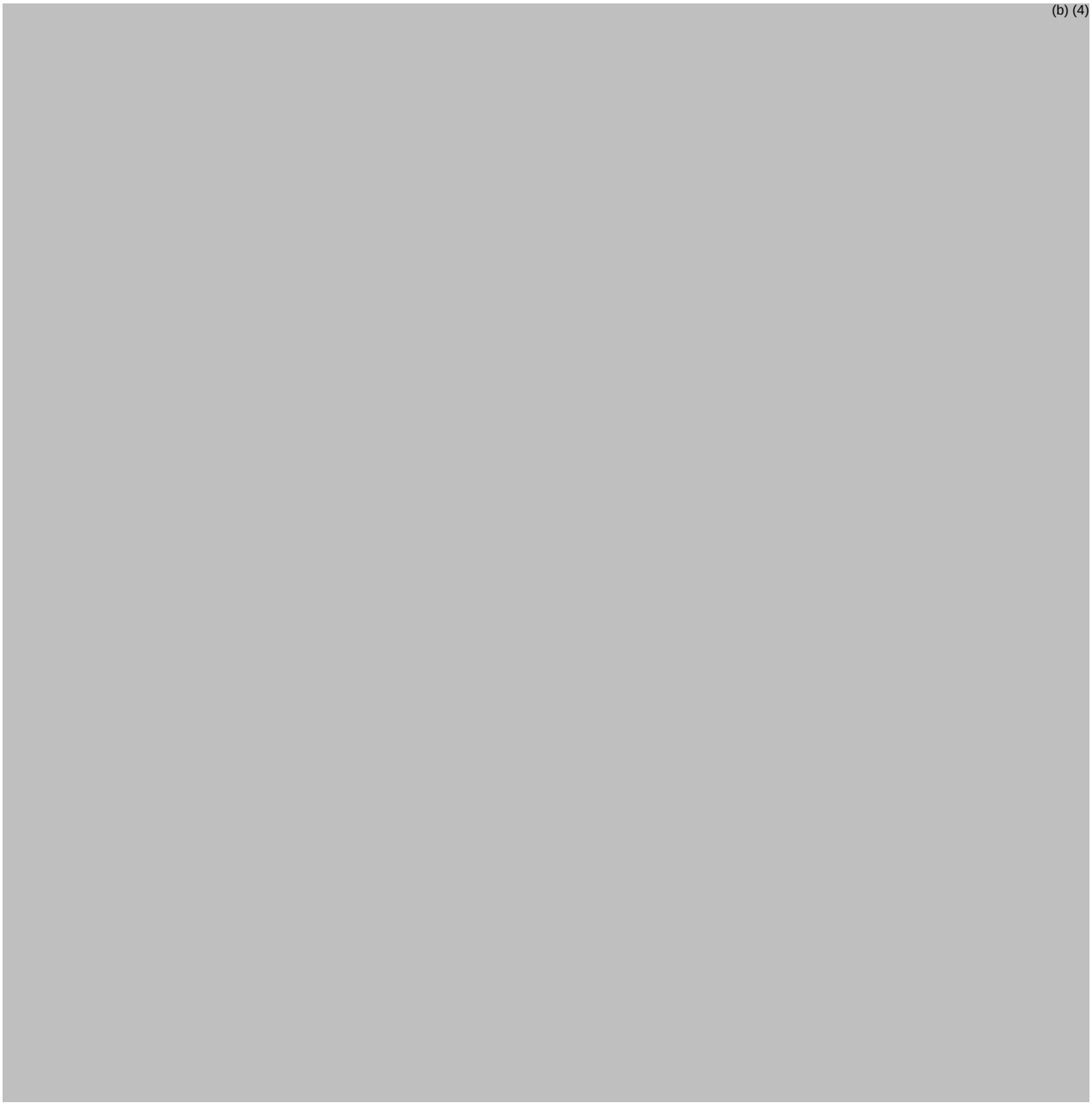
(2) A pre-approval inspection is recommended for the following facility:

a. International Medication Systems, Ltd.

Note that the CDRH/OC final recommendation is “DELAY”. However, that is not an option for an action on an NDA. This will be one of the deficiencies conveyed to the Applicant in the Complete Response Letter.

Human Factors Studies

In contrast to the currently approved and marketed Narcan Nasal Spray (NDA The Division of Medication Error Prevention and Analysis conducted a review of the human factors validation study results. From page 2 of the DMEPA review:



DMEPA has the following conclusions (page 7 or review):

> Based on the results of the HF validation study, we conclude that the product user interface does not support a conclusion that all intended users can use this product safely and effectively. (b) (4)

12. Labeling

Because of the numerous deficiencies that preclude approval, the product labeling was not reviewed during this review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response
- Risk Benefit Assessment

Although the pharmacokinetic profile of Naloxone Hydrochloride Nasal Spray (b) (4) mg meets the criteria set for this type of product, the overall risk outweighs the potential benefits. This is a result of numerous problems with the device. (b) (4)

6 (b) (4)

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[redacted] (b) (4)

The Applicant should redesign the product to address the stated concerns.

- Recommendation for Postmarketing Requirements

None at this time.

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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
02/17/2017