CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212854Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
SUMMARY REVIEW
CLINICAL 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 Summary Review

Date	October 15, 2021
From	Jennifer Nadel, MD (Primary Clinical Reviewer) Celia Winchell, MD (Cross Discipline Team Leader) Rigoberto Roca, MD (Division Director)
Subject	Summary and Cross-Discipline Team Leader Review
NDA Number	212854
Applicant	Adamis Pharmaceuticals Corp
Date of Original Submission	December 31, 2018 Complete Response Letter issued November 22, 2019
Date of First Complete Response Submission	May 15, 2020 Complete Response Letter issued November 13, 2020
Date of Second Complete Response Submission	May 13, 2021
PDUFA Goal Date	November 13, 2021
Proprietary Name	ZIMHI
Established or Proper Name	Naloxone hydrochloride
Dosage Form(s)	Injection: 5 mg/0.5 mL naloxone hydrochloride (HCl) solution in a pre-filled syringe
Applicant Proposed Indication(s)/Population(s)	1. An opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. 2. Intended for immediate administration as emergency therapy in settings where opioids may be present. Not a substitute for emergency medical care.
Recommendation on Regulatory Action	*Approval*

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DMEPA 1 = Division of Medication Error Prevention and Analysis 1
DPV II = Division of Pharmacovigilance II
DPT-N = Division of Pharmacology/Toxicology for Neuroscience
DEPI II = Division of Epidemiology II
CDRH = Center for Devices and Radiological Health
OMEPRM = Office of Medication Error Prevention and Risk Management
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Opioid overdose is a major problem in the United States. It contributes to a significant number of accidental deaths. The Centers for Disease Control and Prevention (CDC) data indicated that in 2017, opioids were involved in 47,600 overdose deaths (67.8% of all drug overdose deaths). Overdose can occur in patients and household contacts of a patient prescribed opioids by accidental exposure or through intentional misuse and abuse. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that may lead to significant morbidity and mortality due to irreversible hypoxic injury. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. It is known to be an effective treatment for suspected opioid overdose if an adequate dose is administered in time. There is currently one FDA approved and available naloxone product for use in adults and pediatric patients in the community. Narcan nasal spray (naloxone hydrochloride; NDA 208411) was approved on November 18, 2015 and is approved in a single-dose 4 mg strength.

ZIMHI is a drug-device combination product designed to deliver 5 mg of naloxone in 0.5 mL in a single use pre-filled syringe. It is intended to be injected via intramuscular (IM) or Subcutaneous (SC) use via an injection at the anterolateral thigh for the treatment of opioid overdose. Adamis [Applicant], has submitted this New Drug Application (NDA) proposing to use the 505(b)(2) regulatory pathway. The indication sought for ZIMHI is emergency treatment for known or suspected opioid overdose in the community setting by untrained personnel, identical to that of Evzio and Narcan Nasal Spray (NNS) (the only approved naloxone products for community use). The carton/container contains two syringes with the second syringe serving as a second dose if needed. The original NDA 212854 received a complete response due to deficiencies in product quality, medical device, nonclinical, clinical pharmacology issues. The second cycle submission was a complete response due to medical device concerns. The resubmission includes further information from the Applicant regarding safety of their epinephrine product, Symjepi (which uses a very similar device as ZIMHI), as well as proposals to change the labeling on the device and for pharmacovigilance.

The Applicant states that ZIMHI was developed in response to increasing numbers of reports indicating that multiple doses of naloxone have been required in resuscitations (b) (4) Because of the established efficacy of naloxone and challenges with the feasibility of clinical trials, applicants have chosen to support efficacy by relying on the Agency's prior findings of efficacy and safety for approved naloxone products. To create a scientific bridge to rely on the previous safety and efficacy findings for the original Narcan (NDA 16636), the Applicant conducted a comparative bioavailability study. The PK data provided in the application established the scientific bridge between the proposed product ZIMHI and reference drug Narcan injection,

thus supporting the efficacy of the proposed product ZIMHI for the proposed indication. The PK data were reviewed during the second cycle and were not evaluated in this review.

The Applicant has previously submitted a literature review and safety data from two PK studies (APC6000-01 and APC6000-03) to support the safety of ZIMHI (naloxone injection, 5 mg / 0.5 mL). According to the prescribing information of Narcan Injection, up to 2 mg of Narcan may be administered intravenously initially and may be repeated at two-minute intervals up to a total dose of 10 mg. The Applicant has provided literature to support the safety of 5 mg and higher of naloxone injection in non-opioid dependent patients. The main risks of naloxone are severe precipitated opioid withdrawal and associated cardiovascular risks in opioid-dependent patient population. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis. In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema. Cardiac arrhythmias, cardiac arrest, and death have been reported in postoperative reversal of opioid depression and have primarily occurred in patients with pre-existing cardiovascular disorders.

The Applicant has not completely addressed all device-related safety concerns identified from the first and second review cycles. Specifically, the Applicant has not provided adequate data to demonstrate that the device performance of ZIMHI meet the current criteria for device reliability. The Applicant has not provided adequate data to support that their product has a device reliability of 99.999%. A device reliability of at least 99.999% is recommended by CDRH because of the life-or-death setting of use. Additionally, the medical device is designed with a manually activated needle safety guard to cover the exposed needle after the injection. The Applicant has not provided data to demonstrate the success rate of deployment of the needle guard among laypersons without medical training. An exposed needle will present a risk to the device user for transmission of blood borne pathogens such as HIV, Hepatitis B, and Hepatitis C.

There are several device concerns with this product which have been thoroughly outlined in the CDRH review and summarized in this review. However, the Agency feels that the importance of approval of more community-use naloxone products outweighs the potential device concerns. Additionally, a device that is very similar to the device that ZIMHI will use was already cleared by the Agency for the epinephrine product Symjepi years ago. Given the perceived need for this product, ZIMHI will be approved with the PMRs outlined in the Postmarking Recommendations section. These PMRs were developed with the CDRH team to evaluate the reliability of the device and also the risk of needlestick after device use. Based on the results of the required studies, the Applicant may be asked asked to incorporate additional strategies to mitigate risks of needlestick injury after the approval for the proposed product, including the possibility of redesign of the device.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• According to the CDC https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed September 20, 2019), o From 1999 to 2017, more than 700,000 people have died from a drug overdose. o Around 68% of the more than 70,200 drug overdose deaths in 2017 involved an opioid. o In 2017, the number of overdose deaths involving opioids (including prescription opioids and illegal opioids like heroin and illicitly manufactured fentanyl) was 6 times higher than in 1999. • On average, 130 Americans die every day from an opioid overdose.	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While naloxone is the treatment of choice to reverse the acute opioid intoxication of a patient, it is not a permanent solution for opioid abuse, misuse, and addiction.
Current Treatment Options	• There is currently one approved and available community-use naloxone product, Narcan Nasal Spray (NNS) 4 mg IN (intranasal). Evzio (both 0.4 mg and 2 mg intramuscular [IM]) is not currently marketed. The recently approved Kloxxado 8 mg IN is not currently marketed. • Some harm reduction organizations distribute unapproved kits comprising parenteral naloxone packaged with a syringe and nasal atomizer. • Anecdotally, some overdoses have required multiple administrations of standard doses of naloxone. However, it is not known whether these represent failures of the products approved for use in the community, or the injection solution administered with a nasal atomizer as part of a kit. The latter provides a lower concentration, higher volume dose that results in a lower systemic exposure.	There are FDA-approved treatment options for opioid overdose. There may be a role for products with a higher dose and for presentations that offer a second dose in a single package. There has been increasing concern in the community regarding overdoses with highly potent and synthetic opioids. This high-dose naloxone product may be more effective at reversing certain opioid overdoses although that is theoretical at this time. The Applicant has not investigated whether the proposed product offers any advantages compared to approved products and is not seeking an indication for high-potency opioid overdose reversal.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product and the reference product Narcan 2 mg injection through a pharmacokinetic (PK) study APC 6000-03. The pharmacokinetic data demonstrated that a single dose of 5 mg naloxone IM injection for the proposed product, ZIMHI, results in the same median Tmax (15 min), greater naloxone concentrations at all critical time points including earlier time points (e.g., 2.5, 5 min post-dose). • The efficacy of this product in the entire pediatric age range is supported by literature review. • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from high-potency synthetic opioids • There are no comparative efficacy data between this product and other approved naloxone products for community use.	The Applicant provided literature and PK data to support the effectiveness of ZIMHI for the proposed indication intended for community use. The target patient population will include adult and entire pediatric population. The application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids compared to other approved products.
Risk and Risk Management	• The safety profile of naloxone is well known. Previous reviews of this product have discussed the safety findings from the PK studies as well as the supporting nonclinical studies. • There is literature to support the safety of naloxone doses exceeding the proposed dose for this product in adults and in the entire pediatric age range • Recurrent respiratory and central nervous system depression if duration of action of certain opioids, such as extended-release opioids, exceeds duration of action of naloxone • Naloxone administration causes withdrawal symptoms in opioid dependent individuals. Although precipitated withdrawal may be severe and occasionally serious, the risks of precipitating withdrawal are outweighed by the benefits of reversing a potentially fatal overdose. • An association between pulmonary complications and higher naloxone doses has been reported in a recent publication • Proposed product labeling includes prominent language about the serious risks of precipitating acute opioid withdrawal in the neonate	The Applicant has not provided adequate data to demonstrate that the proposed medical device meets the more stringent criteria expected by CDRH. The device as designed requires the deployment of a needle-guard and risks needlestick injury. Additional measures to mitigate risk of needlestick injury include changes to labeling. A postmarket pharmacovigilance study may provide information about the types and circumstances of needlestick injury that could inform changes to product design. Approval of this product would provide an additional approved naloxone product. It would also be the only intramuscular naloxone

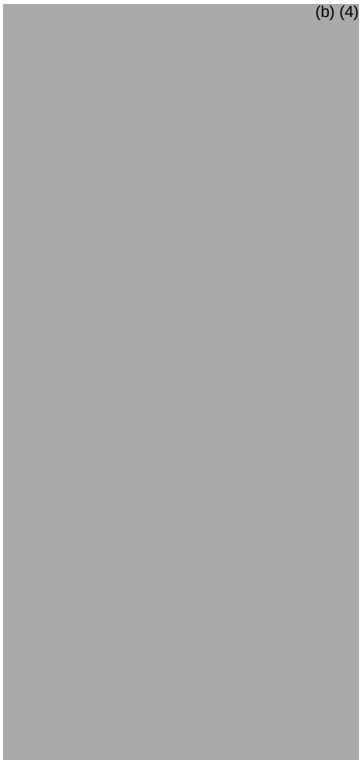
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to mitigate the risk of precipitated withdrawal in this population. • There are no comparative safety data between this product and other naloxone products to inform prescribing decisions when choosing product for opioid reversal	device product on the market (unless Evzio becomes marketed again). The more rapid uptake of intramuscular doses compared to intranasal doses may be advantageous in some situations.

2. Background

2.1 Product Information

This is the third review cycle for ZIMHI, a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. ZIMHI is a naloxone hydrochloride injection (NDA 212854) relying upon the agency's previous findings of safety and efficacy of Adapt Pharma's Narcan (NDA 16636).

The Applicant developed ZIMHI (Naloxone Hydrochloride) as a combination drug-device product and is submitting it under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act). ZIMHI is a single-use intramuscular (IM) device that delivers 5 mg of naloxone hydrochloride (HCl).



Source: From the CDRH review Section 2.2 page 6.

ZIMHI is intended for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is a drug-device combination product intended for use in the community. It is designed for use in non-healthcare settings by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under IND 136,148. The investigational new drug (IND) application was submitted by Adamis Pharmaceuticals Corporation (also referred to as the "Applicant" throughout this review), on November 21, 2017.

The Applicant submitted a request for a priority review with the New Drug Application (NDA) on December 31, 2018 (first NDA review cycle). The Applicant based their request on the recent rise in opioid-related deaths from potent synthetic opioids. (b) (4) the request for priority review was denied.

The Applicant is relying on the Agency's prior findings of efficacy and safety for the original Narcan (NDA 16636). The Narcan labeled dosing is an initial dose of 0.4 mg to 2 mg via the intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes, followed by additional doses up to 10 mg. The Applicant is also relying on published literature to support the safety of the 5 mg dose. The Applicant specifically cited an article from Bracken *et. al*[1] which describes a study that evaluated the effects of naloxone on acute spinal-cord injury. In this study, naloxone was given to 154 patients as a 5.4 mg/kg bolus (324 mg to 378 mg for an average 60 kg to 70 kg adult). The patients then received 4.0 mg/kg/hour for 23 hours. The mortality and major morbidity findings in the naloxone group were similar to that of the placebo group. In a study by Cohen *et al*[2]. healthy subjects received up to 4 mg/kg of naloxone without serious adverse effects reported.

The Division previously concluded that the action on the first submission would be a Complete Response (CR). The CR letter was sent to the Applicant on November 22, 2019. Please see Appendix A or DARRTS for the letter which has a full description of the deficiencies.

In the second cycle, Study APC 6000-03 was reviewed. The clinical pharmacology deficiencies were resolved during that cycle. The other deficiencies were related to photo-degradants and particulate matter, storage condition data, and extractables and leachables. These were discussed in the product quality and nonclinical sections of the first CR letter. There were also concerns regarding device reliability outlined in the device section of the letter. These concerns, other than those related to the device were all resolved during the second cycle.

The Division concluded that the action on the second submission would be a Complete Response. The CR letter was sent to the Applicant on November 13, 2020. Please see Appendix B: November 13, 2020, Complete Responseor DARRTS for the letter which has a full description of the deficiencies. The deficiency most pertinent to the clinical review, was deficiency number 1:

> "You have not provided adequate data to support the safe use of the proposed product ZIMHI (Naloxone HCl Injection, 5 mg/0.5 mL) pre-filled syringe for the emergency

[1] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury. New England Journal of Medicine. 1990;322(20):1405-11.
[2] Cohen M, Cohen R, Pickar D, Weingartner H, Murphy D, Bunney WJR. Behavioural effects after high dose naloxone administration to normal volunteers. The Lancet. 1981;318(8255):1110.

> treatment of opioid overdose in community settings. The product as currently designed raises safety concerns for intended users. Specifically, you haven't provided data to demonstrate that intended users are able to deploy the needle safety guard without difficulties with the current user interface in the intended use environments. Failure to deploy the needle safety guard will result in risk of needlestick injury after the injection. Additionally, patients who will be prescribed [this] may have [not] familiarity with your product. However, the intended users could include laypersons, who may administer this to patients. Your product, if approved, is anticipated to be widely used in community settings by laypersons who are not familiar with the use of the product at all. There is possibility that your product will be used on patients with an increased rate of bloodborne pathogens disease than the general public[3]. Potential risks of transmission of bloodborne pathogens from opioid-overdose patients to the intended users are high for your product. Your current user interface is not adequate to mitigate potential risks of needlestick injury and prevent risks of transmission of bloodborne pathogens from opioid-overdose patients to the intended users."

The other deficiencies were related to concerns about device design and reliability. These concerned are completely outlined in both the full CR letter as well as the review from CDRH.

2.2 Therapeutic Context: Opioid Overdose and Naloxone

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids although current data indicate that deaths associated with prescription opioid use are declining while those associated with illicit opioids continue to rise (CDC 2019). Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury.

As the opioid epidemic continues in the United States, as noted above, current data include reports/investigations showing increases in fentanyl-related overdose fatalities. Additionally, there have been reports of overdose patients requiring multiple doses of naloxone and also reports of naloxone being ineffective. Unfortunately, these reports do not usually describe if these events have occurred with the approved community-use naloxone products, Evzio and/or Narcan Nasal Spray. However, these recent reports and articles such as Somerville et al[4] suggest that there may be a need for higher doses of naloxone to counteract overdoses with fentanyl and other high-potency opioids. The Applicant has also cited other published literature to suggest that multiple doses of naloxone are required in an increasing number of opioid overdose cases. It is worth noting that the vast majority of out-of-hospital naloxone use consists of an improvised intranasal product using the naloxone solution for injection with a

[3] https://www.cdc.gov/pwid/index html

[4] Somerville NJ, O'Donnel J, Gladden RM, Zibbel JE, Green TC, Youngkin M, et al. Characteristics of Fentanyl Overdose - Massachusetts, 2014-2016. MMWR. 2017;66(14):382-6.

concentration of 1 mg/mL in a 2 mL vial (compared to 40 mg/mL in a 100-microliter volume for the approved intranasal naloxone product) administered using a mucosal atomizer device and these studies rarely distinguish between products. Therefore, it is unclear whether the apparent increased need for multiple doses of naloxone would have been observed had the higher concentration products been uniformly used. Recent data being developed by the Division of Applied Regulatory Science via modeling also appears to suggest that neither higher doses nor repeated doses would be helpful unless the initial dose is given nearly immediately (i.e., <2-3 minutes), which is rarely the case in the community setting.

Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor. If immediately administered, naloxone can reverse the life-threatening effects of an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone 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. Also, the duration of action of naloxone is shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

Naloxone has been approved for commercial use since 1971. The table below lists approved drug products containing the active ingredient naloxone in the United States.

Table 1 Current Approved Naloxone Treatment Options

Drug Product Name	NDA	Approval Date	Dose Form	Dose	Route[5]
Narcan	016636	4/13/1971	Solution for injection	0.2-2 mg	IV, IM, SC
Evzio	205787[6]	4/3/2014	Autoinjector	0.4 mg	IM, SC
Narcan Nasal Spray	208411	11/18/2015	Nasal Spray	4 mg	IN
EVZIO	209862[7]	10/19/2016	Autoinjector	2 mg	IM, SC
Narcan Nasal Spray	208411 S-001[8]	1/24/2017	Nasal Spray	2 mg	IN
Kloxxado	212045[9]	4/29/2021	Nasal Spray	8 mg	IN

Evzio, Narcan nasal spray, and Kloxxado are approved with the same indication as proposed for ZIMHI and are for community use. Naloxone is included as an active ingredient in several products in combination with opioid ingredients for the treatment of opioid dependence. It is generally included in these products to deter abuse of the opioid component.

Evzio was initially approved as a 0.4 mg dose, which was replaced following approval of a 2 mg IM dose of naloxone. Kaleo (the company who developed and owns Evzio) is not

[5] Currently available routes include intravenous (IV), intramuscular (IM), subcutaneous (SC), and intranasal (IN)
[6] This product was replaced by the Sponsor with a 2 mg product using the same device.
[7] This product is not currently marketed by the Sponsor and is listed as Discontinued in the Orange Book.
[8] This product was never marketed by the Sponsor and has never been available for sale since the approval date.
9 This product is not yet launched.

currently marketing either Evzio dose. Narcan Nasal Spray was initially approved as a 4 mg dose, followed by approval of a 2 mg dose. The 2 mg dose was never marketed. The 8 mg IN naloxone product Kloxxado was recently approved this year. It is not available for purchase at the time of this review. The Applicant's (Adamis) proposed product has a dose of 5 mg of naloxone for IM or subcutaneous injection and if approved, would have the highest dose of naloxone commercially available. Figure 2-1 shows a comparison of the pharmacokinetic (PK) profiles of ZIMHI, Kloxxado, and Narcan Nasal Spray. ZIMHI produces the highest levels naloxone measured in the blood stream during the PK studies used as part of the NDA submission. All products show very fast elevation to peak naloxone concentration level. The standard of approval for community-use naloxone products has been demonstration that the PK of a new product meets or exceeds that of 0.4 mg naloxone (usually intramuscularly). All of three of the products have PK levels that exceed that level.

Figure 2-1 Comparison of PK Profiles for ZIMHI (NDA 212854), Kloxxado (NDA 212045), and Narcan Nasal Spray (NDA 208411)

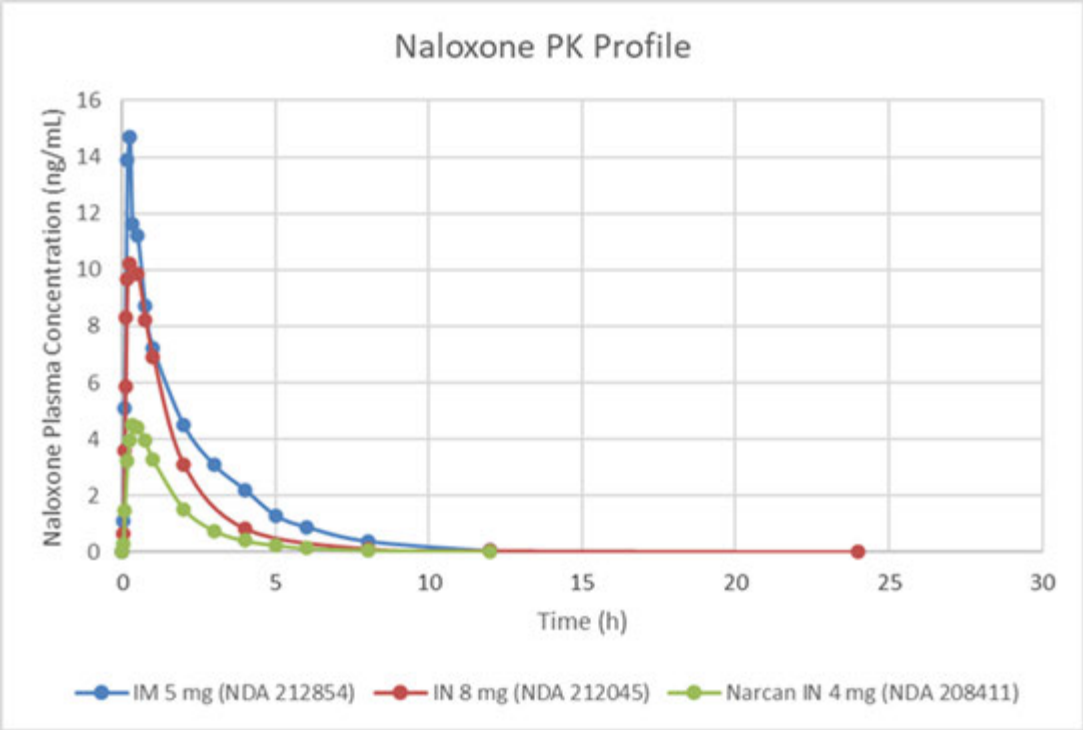


Figure created by Wei Qui, PhD from the clinical pharmacology team

An observational and retrospective article by Farkas et al[10]. in 2020 reported that higher doses of naloxone (defined as greater than 4.4 mg) in a pre-hospital environment were associated with a higher rate of pulmonary complications. While association does not equal causation and this was a retrospective trial, pulmonary edema is a labeled warning for naloxone. As

[10] Farkas, A., Lynch, M. J., Westover, R., Giles, J., Siripong, N., Nalatwad, A., . . . Martin-Gill, C. (2020). Pulmonary Complications of Opioid overdose Treated with Naloxone. *Ann Emerg Med, 75*(1), 39-48.

higher and higher doses of naloxone are used to treat opioid overdoses, we will need to keep this is mind as a possible complication.

Labeling for naloxone products contain warnings regarding acute opioid withdrawal. Naloxone may abruptly precipitate of opioid withdrawal in persons who are physically dependent on opioids. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis. The Vivitrol (naltrexone intramuscular) label precipitated opioid withdrawal with the following warning:

> The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Review of postmarketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit.

In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema.

Clinical efficacy trials present significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of opioid overdose, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it is not necessary to conduct clinical efficacy trials with novel naloxone products as effective doses have been established. The efficacy of a new formulation or route of administration of naloxone relies on a demonstration of adequate systemic naloxone levels in relative bioavailability studies which compare the systemic exposure of naloxone from the new product to an approved product.

For novel naloxone products intended to be used in the community, it is necessary to demonstrate comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration. This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose.

2.3 Summary of Regulatory Activity Since the 2nd Complete Response

A Type A End of Review meeting was held with the Applicant on April 8, 2021. The Applicant submitted six questions regarding the deficiencies from the CR letter. The Division provided answers to the Applicant prior to the meeting. The Applicant discussed their plans to mitigate the risk of transmission of blood-borne pathogens from needle-stick injuries. It was discussed with the Applicant their proposals would be a review issue during another NDA

review. A majority of the time of the meeting was focused on discussing the device deficiencies and what would be needed to resolve the deficiencies, with the CDRH team. Please see the meeting minutes in DARRTS for a full summary.

On May 13, 2021 the Applicant responded to the Complete Response. The Applicant did not submit new clinical information for review. The Applicant's responses will be the subject of this review.

3. Product Quality

The drug substance, drug product, process/facilities, and microbiology review teams all recommend approval. The Application included adequate information to address the product quality deficiencies identified during the first review cycle.

4. Center for Devices and Radiological Health (CDRH)

The CDRH team identified some unresolved concerns, but agrees these may be addressed post-marketing.

The CR letter issued after the first review cycle included the following Product Quality deficiencies outlined in Appendix B: November 13, 2020, Complete Response deficiencies 2-4. Please see the full CDRH review from the second cycle for a full discussion of these deficiencies. Please see the full CDRH review from the third cycle for a full discussion of the outstanding device concerns from this cycle.

The following is reproduced from the third cycle CDRH review, which outlines the remaining device related open issues:

> Several open issues remain in this file and, following discussion with CDER Clinical on 8/5/21 and 8/11/21, it was determined that outstanding issues related to the device could be sent as PMRs/PMCs. Three PMR/PMCs are recommended. See Section 4.4 for complete text and rationale[11].
>
> 1) Redesign of the needle safety device to be automatically deploying
> 2) Provide a Fault Tree Analysis which demonstrates dose delivered at 99.999% Reliability and 95% Accuracy.
> 3) Update QMS documents relating to complaint/CAPA documents

[11] Note that CDRH consult includes draft language for PMR templates. The final versions of these templates are prepared by LCDR Mark Liberatore, Deputy Director for Safety, DAAP, and the language does not entirely correspond to the drafts provided. In particular, there is no regulatory mechanism by which FDA can require Adamis to redesign the needle safety device post-approval. Therefore, they cannot be included as post-market requirements under FDAA.

In addition, because of the noted quality system issues and items noted as lacking data, a post-approval inspection is recommended at this time regarding the device related attributes of the system.

After discussion of the above recommendations, CDER determined that that DAAP lacks the regulatory authority to require a redesign of the needle safety device as a PMR.

5. Nonclinical Pharmacology/Toxicology

The nonclinical team recommends approval of this application. The Application included adequate information to address nonclinical deficiencies identified during the first review cycle.

6. Clinical Pharmacology

The clinical pharmacology team recommends approval of this application. The Application included adequate information to address the clinical pharmacology deficiency identified during the first review cycle.

7. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

8. Clinical/Statistical-Efficacy

No new clinical efficacy data were included in this submission. The Applicant plans to rely on the agency's prior findings of efficacy from the reference product, Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish the efficacy of the proposed product. The PK data provided in the application established the scientific bridge between the proposed product ZIMHI and reference drug Narcan injection, thus supporting the efficacy of the proposed product ZIMHI for the proposed indication.

9. Safety

9.1 Summary of Drug Safety

The Applicant has submitted a literature review and safety data from two PK studies to support the safety of ZIMHI (naloxone injection, 5 mg / 0.5 mL). The Applicant also submitted adequate animal data to characterize local injection reaction profile. This data was reviewed in the first and second review cycles (see reviews in DARRTS from 3/4/2019 and 11/13/2020).

The safety for this high-dose naloxone product is based primarily on the agency's prior findings for Narcan (naloxone hydrochloride) solution for injection. Given that PK data showed the systemic exposure level of ZIMHI (naloxone injection, 5 mg / 0.5 mL) is higher than the reference product, Narcan (naloxone hydrochloride, NDA 16636), the Applicant submitted literature review to support the safety of the systemic exposure observed with ZIMHI (naloxone injection, 5 mg / 0.5 mL). The Applicant has described several studies to support higher doses of naloxone in the submission. An example of an article that the Applicant specifically cited is from Bracken *et. al*[12] which describes a study that evaluated effects of naloxone on acute spinal-cord injury. In this study, naloxone was given to 154 patients as a 5.4 mg/kg bolus (324 mg to 378 mg for an average 60 kg to 70 kg adult). The patients then received 4.0 mg/kg/hour for the 23 hours. The mortality and major morbidity findings in the naloxone group were similar to that of the placebo group. Reversal of an opioid overdose in an individual not physically dependent on opioids would likely be safe. However, the safety when administered in persons who are physically dependent on opioids is less clear, as it may precipitate an acute withdrawal syndrome. The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Review of postmarketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit.[13] Acute opioid withdrawal syndrome (OWS) due to excessive or overly rapid reversal of opioid overdose includes vomiting, seizure, delirium, and agitation[14] (Kim and Nelson, 2015). Relative to the available doses of Evzio and Narcan Nasal Spray, it is likely that a precipitated withdrawal from a 5 mg IM dose would be more severe. However, these potential safety concerns are still outweighed by the benefit of reversing a life-threatening opioid overdose.

9.2 Device Related Safety Concerns and the Applicant's Proposals to Deal with Needle Safety

The device-related safety concerns regarding needle safety and reliability of the device were the reason for the complete response during the second cycle review for this product. The concerns are fully described in both the clinical review and CDRH review. They are also outlined in the Complete Response letter in Appendix B: November 13, 2020, Complete Response.

[12] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury. New England Journal of Medicine. 1990;322(20):1405-11.
[13] Vivitrol (depot naltrexone) label
[14] Kim HK, Nelson LS. Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review. Expert Opin Drug Saf. 2015;14(7):1137-46.

In the resubmission, the Applicant has proposed what they describe as, "additional safety measures to further mitigate the risks of accidental needlesticks and blood-born pathogen transmission for all intended users." Their proposal includes the following:

- Adding labeling on the ZIMHI device and outer plastic case that emphasizes deployment of the needle shield as an element of the safe use of ZIMHI
- Implementing a training program for use of ZIMHI that incorporates both a training video and use of a trainer device, both of which will emphasize deployment of the needle shield and placement of the used ZIMHI device back into its case
- A pharmacovigilance program that will seek out reports of accidental needle sticks and consider whether additional safety measures are necessary

It is difficult to predict what kind of safety impact to expect from the Applicant's proposals. The Applicant has not provided documentation of a study of laypeople using this device with the new labeling. It is unknown if laypeople will be able to read/comprehend the needle guard instructions in the event of an overdose. It is difficult to predict the impact of a training program, as until the overdose occurs, it is unknown who will be administering the product and who will be the overdose patient. Additionally, community-use naloxone products are intended to be used by untrained laypeople

The possibility of requiring (as a PMR) or requesting (as a PMC) the Applicant to make a device change post approval (e.g., improvements to the instructions for use and to the carton/container labeling to identify the needle guard more clearly and to ensure it is deployed properly, or redesign of the device, as recommended by CDRH) was discussed with staff from ONDP and ORP. The conclusion was that the Agency does not have the regulatory authority to require a future redesign in the approval letter for a drug product. Additionally, a PMC would not be appropriate because the product meets the standard for approval at this time. If specific new safety concerns are identified based on results of the post-marketing studies, such changes and improvements could then be considered.

9.3 Drug Utilization Review

To support the safety of the device used in ZIMHI, the Applicant cites previous experience with their approved epinephrine product Symjepi. To further analyze the adequacy of the Applicant's claim regarding the safety and experience with Symjepi, the Drug Utilization team within the Division of Epidemiology II (DEPI II) was consulted. The team reported that NDA 207534 (Symjepi) was approved in June of 2017 but was not introduced commercially until 2019. Initial distribution appears to have been to institutional settings (e.g., schools) where users were likely to be trained. The report from DEPI II focused on analyzing the distribution data from retail and mail-order pharmacies.

Table 2 below provides the nationally estimated number of injections for Symjepi sold from manufacturers to all settings of care.

Table 3 below provides the nationally estimated number of injections for Symjepi sold from retail and mail-order pharmacies.

Table 2 Nationally-Estimated Number of Symjepi Injections Sold Annually from Manufacturers to All U.S. Health Care Settings from January 2019 through June 2021

	2019 Injections	2020 Injections	Jan – Jun 2021 Injections	Total Injections Jan 2019 – Jun 2021
SYMJEPI	(b) (4)			

Source: (Table 3.2.1 from DEPI II review) IQVIA National Sales Perspectives™. Data time period: January 2019 – June 2021. Data extracted Aug 2021. File name: Symjepi - Sales (NSP)_1_Aug-03-2021.xlsx

Table 3 Nationally-Estimated Number of Symjepi Injections Dispensed from U.S. Outpatient Retail and Mail-Order Pharmacies from January 2019 through June 2021

	2019 Prescriptions	2020 Prescriptions	Jan – Jun 2021 Prescriptions	Total Prescriptions Jan 2019 – Jun 2021
SYMJEPI	(b) (4)			

Source: (Table 3.2.2 from DEPI II review) IQVIA National Prescription Audit™. Data time period: January 2019 – June 2021. Data extracted July 2021. File name: SYMJEPI - Rx (NPA)_1_Jul-29-2021.xlsx

The Drug Utilization team found that only (b) (4) total prescriptions for Symjepi have been distributed to consumers (i.e., via pharmacy). Emergency epinephrine products are prescribed to patients with life-threatening allergies to have on hand "in case of emergency." It is unknown how many of these (b) (4) products have actually been used by patients and family members. However, given the low numbers of products distributed, it is difficult to conclude any safety findings and leverage any safety assumptions from this data and the claims of no adverse events related to needle safety is not reassuring. Although there is room for improvement in the way the instructions are conveyed and the appearance of the device to ensure proper deployment of the needle guard, the product does meet the requirements for approval at this time. Based on the results of the post-marketing studies, such changes could be considered post-approval.

9.4 Human Factors Concerns

As mentioned in previously, the Applicant is relying on the previous Human Factors studies for the Symjepi product. In review of those studies, there were several concerning findings/reports from participants. Our concerns were shared with the Applicant in an Information Request dated July 22, 2021. Please see DARRTS for the full IR. Reproduced below are the most clinically relevant concerns:

- Your validation study included 12 subjects who had concerns regarding needle-stick injuries and the design attributes of the device being inadequate to mitigate these.
- Nine subjects in your validation left the needle exposed and two subjects conducted multiple injections.
- You did not evaluate needle guard function as a critical task.
- You under-report the severity of needle stick injury as a '2.' Needle stick injuries are likely to require clinical intervention. Community-use naloxone products have unclearly defined relationships between drug administrator and patient as they are intended to be used by bystanders/unknown laypeople. The likelihood of a layperson using this product on a stranger, whose status with respect to various bloodborne pathogens is not known, and unlikely to be able to be determined after-the-fact, is much higher for naloxone injectors than for epinephrine injections. It may not be predictable in advance who will administer the naloxone product and your indicated user and patient populations remain unclearly defined in your labeling/Indications for Use

As noted above, subjects had multiple concerns regarding using the epinephrine product safely. Another concern related to human factors related to the Symjepi product, was found on the Applicant's website https://www.symjepi.com/how_to_use_symjepi. The website shows a demonstration on using the product, and shows how to use the needle guard using a two-hand method. This method was not used in the Human Factors studies for approval and is not the method which ZIMHI is labeled for use.

Importantly, a device that is very similar to the device that ZIMHI will use was already cleared by the Agency for the epinephrine product Symjepi years ago. Although the Human Factors studies did identify a residual risk of needlestick, given the risk/benefit considerations, this risk is acceptable and the ZIMHI application has met the regulatory threshold for approval. Improvements in product appearance or design could be considered based on the results of post-marketing studies.

The DMEPA review team has explained that their own analysis did consider the needle guard to be a critical attribute, and that their review of the data on the Symjepi product did acknowledge the potential for needlestick injury and the less-than-optimal design of the product. However, like ZIMHI, the public health need for Symjepi was felt to outweigh the needlestick injury risk. The review team considered requiring an additional Human Factors study of the ZIMHI device, but was advised by DMEPA that no further information could be gained from such a study. The flaws in the product have been elucidated in prior studies of both ZIMHI and Symjepi. Adamis will be required to conduct a postmarketing study of the types and circumstances of needlestick injuries that could potentially be used to inform the need for future product redesign and improvement.

10. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held to discuss this product because there were no issues that required presentation or discussion at an advisory committee meeting.

11. Pediatrics

The safety and effectiveness of naloxone has already been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone in this population has already been supported by adult bioequivalence studies as well as evidence of safety and effectiveness in pediatrics in clinical practice.

During the first cycle for this NDA, the Division of Pediatric and Maternal Health (DPMH) was consulted to assist in the review of the submitted pediatric information, label, and approval recommendations including the Pregnancy and Lactation Labeling Rule (PLLR) language. After an internal meeting with DPMH and the wrap-up meeting for this NDA cycle, both Divisions agreed that this product is appropriate for pediatric use for all ages including down to birth. Please see the joint Summary and CDTL review (2019) in DARRTS for a full discussion.

12. Other Relevant Regulatory Issues

Financial Disclosures
The Applicant submitted form FDA 3454 and certified that the Investigator did not have reportable financial disclosures during the first cycle for this NDA.

Compliance with Good Clinical Practices
During the first cycle for this NDA, the Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

Inspections
The Office of Study Integrity and Surveillance (OSIS) was requested to inspect the site for study APC 6000-3 during the second review cycle, but OSIS declined to conduct an on-site inspection for the clinical and analytical sites. The reason given for declining was that the sites had previously been inspected for other applications and they found that a repeat inspection was not warranted.

13. Labeling

During the previous review cycle Dr. Cameron Johnson and Dr. Otto Townsend from Division of Medication Error Prevention Analysis (DMEPA) provided a review of the proprietary name ZIMHI (naloxone hydrochloride) injection, 5 mg/0.5 ml and found it to be acceptable.

The following is a high-level list/description of modifications the Agency required prior to approval of ZIMHI:

- A warning for needle stick injuries was added to Section 5
- The labeling on diagrams of the device were modified
- The adverse events that took place in the Applicant's clinical studies was appropriately updated to include all adverse events that occurred in the studies
- To reflect the limitations of the human factors data and the challenges using the device, language was added to advise that Zimhi is intended to be administered by individuals twelve years of age or older, and that people with smaller hands or less hand strength could find the device difficult to use
- The diagrams in the instructions for use were revised to show proper positioning of the patient and proper location for injection

One of the concerns for the labeling of naloxone products with different doses and routes intended for use in the community is regarding differentiating those doses in labeling to inform prescribers, and even laypersons, of the clinical scenarios or dosing criteria to determine when one dose would be used over another in a community setting, which is a different setting than was intended for the reference product Narcan. The Applicant's submission did not include data to inform that decision. If approved, there is concern that the Applicant will attempt to promote ZIMHI for a wider spectrum of opioid overdoses than competitors. Because that concept is only theoretical, such language is not appropriate for labeling.

14. Postmarketing Recommendations

The following will be conveyed to the Applicant.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of needlestick injuries and known serious risk related to combination product reliability of successful injection of ZIMHI

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4153-1 Conduct a study to complete testing which evaluates the combination product reliability of successful injection of ZIMHI.

Draft Protocol Submission:	02/2022
Final Protocol Submission:	07/2022
Study Completion:	07/2023
Final Report Submission:	10/2023

Note the following considerations regarding the postmarketing requirement described above:

1. Testing must include a fault tree analysis to demonstrate your device will provide successful injection with at least 99.999% reliability at the 95% confidence interval.
    a. The fault tree analysis must include information from your combination product's design and manufacturing methods by identifying all basic failure modes anticipated
    b. The data supporting the fault tree analysis must be provided
2. Devices assessed within the reliability test should be preconditioned to reasonably foreseeable worst-case conditions. We recommend the following preconditioning activities, below. 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.
    a. Aging
    b. Storage orientation and conditions
    c. Vibration handling
    d. Shock handling (e.g., resistance to random impacts, such as being dropped)
3. Verification of product reliability must employ Corrective And Preventative Action Process (CAPA) standards, and Standard Operating Procedures, which at a minimum must include:
    a. Active searching of product field failures such as those reported by news outlets, or are otherwise publicly available on social media; or by contacting product users directly
    b. Statistical analyses to detect recurring quality problems
    c. Retesting and reevaluation of any non-conforming product (after rework), to ensure the product meets current approve specifications

d. Recording of changes in methods and procedures needed to correct and prevent identified quality problems

e. Dissemination of information related to quality problems and information on corrective action so as to assure the quality of the product or prevention of the identified problem

4153-2 Conduct a study of needlestick injuries associated with the use of ZIMHI. Provide a detailed analysis of incidents (including reported incidents that did, as well as did not, result in patient and/or provider harm), full event narratives of the incidents and any subsequent adverse events, and the results of root cause analysis performed for the reported event.

Draft Protocol Submission:	02/2022
Final Protocol Submission:	07/2022
Study Completion:	07/2025
Final Report Submission:	10/2025

15. Recommended Comments to the Applicant

Not applicable.

13 Pages containing excerpts from 2 Complete Response letters have been withheld as duplicative. To view these letters, see the posted reviews on Drugs@FDA.com

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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/

CELIA J WINCHELL on behalf of JENNIFER L NADEL
10/15/2021 04:24:17 PM

CELIA J WINCHELL
10/15/2021 04:24:28 PM

RIGOBERTO A ROCA
10/15/2021 04:26:39 PM

Clinical and Cross-Discipline Team Leader Review
Division Director Summary review

Date	11/13/2020
From	Jennifer L. Nadel, MD (Primary Clinical Reviewer) Emily Deng, MD, MPH (Cross-Discipline Team Leader Reviewer) Rigoberto Roca, MD (Division Director)
Subject	Clinical Review and Cross-Discipline Team Leader Review
NDA	212854
Applicant	Adamis Pharmaceuticals Corp
Date of Original Submission	December 31, 2018 Complete Response letter issued on November 22, 2019
Date of Complete Response Submission	May 15, 2020
PDUFA Goal Date	November 15, 2020
Proprietary Name	ZIMHI
Established or Proper Name	Naloxone hydrochloride
Dosage Form	Injection: 5 mg/0.5 mL naloxone hydrochloride (HCl) solution in a pre-filled syringe
Route of Administration	Intramuscular or subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	1. An opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. 2. Intended for immediate administration as emergency therapy in settings where opioids may be present. 3. Not a substitute for emergency medical care.
Regulatory Action	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Jennifer Nadel, MD; Emily Deng, MD
Pharmacology Toxicology Review	Carlic Huynh, PhD; Newton Woo, PhD; R Daniel Mellon PhD
OPQ Review	Valerie Amspacher, PharmD; Sam Bain, PhD; Donna Christner, PhD; Jizhou Wang, PhD; Julia Pinto, PhD; Tarun Mehta, PhD; Jonathan Swoboda, PhD
Microbiology Review	Jennifer Patro, PhD; Jesse Wells, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, PhD

OND=Office of New Drugs OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
DRISK=Division of Risk Management
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1 Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

ZIMHI is a drug-device combination product designed to deliver 5 mg of naloxone in 0.5 mL in a single use pre-filled syringe. It is intended to be injected via intramuscular (IM) or Subcutaneous (SC) use via an injection at the anterolateral thigh for the treatment of opioid overdose. Adamis [Applicant], has submitted this New Drug Application (NDA) proposing to use the 505(b)(2) regulatory pathway on 12/31/2018. The indication sought for ZIMHI is emergency treatment for known or suspected opioid overdose in the community setting by untrained personnel, identical to that of Evzio and Narcan Nasal Spray (NNS) (the only approved naloxone products for community use). The carton/container contains two syringes with the second syringe serving as a second dose if needed. The original NDA 212854 received a complete response due to deficiencies in product quality, medical device, nonclinical, clinical pharmacology issues. Adamis submitted their response on May 15, 2020. The resubmission includes adequate information to address the deficiencies in product quality, nonclinical, and clinical pharmacology issues. However, the Applicant has not provided adequate information to address the medical device deficiencies identified during the first review cycle. A Complete response is recommended for this Application.

Opioid overdose is a major problem in the United States. It contributes to a significant number of accidental deaths. The Centers for Disease Control and Prevention (CDC) data indicated that in 2017, opioids were involved in 47,600 overdose deaths (67.8% of all drug overdose deaths). Overdose can occur in patients and household contacts of a patient prescribed opioids by accidental exposure or through intentional misuse and abuse. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that may lead to significant morbidity and mortality due to irreversible hypoxic injury. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. It is known to be an effective treatment for suspected opioid overdose if an adequate dose is administered in time. There are currently two FDA approved naloxone products for use in adults and pediatric patients in the community. Evzio (naloxone hydrochloride injection; NDA 205787) was approved on April 3, 2014 and is a prefilled auto-injector for intramuscular and subcutaneous use that delivers a single 2 mg dose of naloxone hydrochloride per injection. Narcan nasal spray (naloxone hydrochloride; NDA 208411) was approved on November 18, 2015 and is approved in a single-dose 4 mg strength.

The Applicant states that ZIMHI was developed in response to increasing numbers of reports indicating that multiple doses of naloxone have been required in resuscitations (b) (4)

(b) (4) Because of the established efficacy of naloxone and challenges with the feasibility of clinical trials, applicants have chosen to support efficacy by relying on the Agency's prior findings of efficacy and safety for approved naloxone products. To create a scientific bridge to rely on the previous safety and efficacy findings for the original Narcan (NDA 16636), the Applicant conducted a comparative bioavailability study. Study APC 6000-03 compared the pharmacokinetic (PK) profile of ZIMHI to the listed drug product Narcan Injectable (NDA 016636), 2mg[1]. The pharmacokinetic study APC 6000-03 demonstrated that a single dose of 5 mg naloxone IM injection for the proposed product, ZIMHI, resulted in the same median Tmax (15 min), higher naloxone concentration at all critical time points including earlier time points (e.g., 2.5, 5 min post-dose), 2.6-fold greater AUC0-2.5min, 4.1-fold greater AUC0-5min, 4.9-fold greater Cmax, 2.8-fold greater AUClast, and 2.7-fold greater AUC0-inf values, than a single dose of 2 mg naloxone IM injection for the reference product, naloxone HCl injectable (1 mg/1 mL, International Medical Systems, ANDA 072076). The PK data provided in the application established the scientific bridge between the proposed product ZIMHI and reference drug Narcan injection, thus supporting the efficacy of the proposed product ZIMHI for the proposed indication.

The Applicant has submitted a literature review and safety data from two PK studies (APC6000-01 and APC6000-03) to support the safety of ZIMHI (naloxone injection, 5 mg / 0.5 mL). According to the prescribing information of Narcan Injection, up to 2 mg of Narcan may be administered intravenously initially and may be repeated at two-minute intervals up to a total dose of 10 mg. The Applicant has provided literature to support the safety of 5 mg and higher of naloxone injection in non-opioid dependent patients and opioid dependent patients. The main risks of naloxone are severe precipitated opioid withdrawal and associated cardiovascular risks in opioid-dependent patient population. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis. In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema. Cardiac arrhythmias, cardiac arrest, and death have been reported in postoperative reversal of opioid depression and have primarily occurred in patients with pre-existing cardiovascular disorders.

No new safety issues related to ZIMHI were identified in these two PK studies. Common adverse events from the pharmacokinetic studies in healthy volunteers were nausea and dizziness. Injection site reaction assessment in two PK studies do not raise any clinically significant safety concerns. The Applicant provided nonclinical toxicology data to support the safety of local injection reactions. This Application has been discussed in the pediatric research committee (PeRC) during the first review cycle. PeRC and the Division concluded that the proposed product ZIMHI is safe and effective for the pediatric population down to birth. As with other approved naloxone products, the risk of acute opioid withdrawal in opioid depend population is outweighed by the benefit of reversing a life-threatening overdose. Labeling for naloxone products contain warnings regarding acute opioid withdrawal.

[1] The comparator dose of 2 mg naloxone IM injection is within the approved initial dose range (i.e., 0.4 to 2 mg) for the listed drug product Narcan Injectable (NDA 016636). Note the original product Narcan Injectable (NDA 016636) was discontinued not because of safety or effectiveness reasons, so its generic product ANDA 072076 was used as the comparator in the comparative bioavailability study APC 6000-03.

However, the Applicant has not provided adequate information to address device related safety concerns identified from the first review cycle. Specifically, the Applicant has not provided adequate data to demonstrate that the device performance of ZIMHI meet the criteria for device reliability. Because of the life or death setting of use, device reliability is now required to be at least 99.999% per the Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features. Additionally, the medical device is designed with a manually activated needle safety guard to cover the exposed needle after the injection. The Applicant has not provided data to demonstrate the success rate of deployment of the needle guard among laypersons without medical training. An exposed needle will present a risk to the device user for transmission of blood borne pathogens such as HIV, Hepatitis B, and Hepatitis C. The Applicant has not provided adequate strategies to mitigate risks of needlestick injury after the injection for the proposed product. The Clinical team agrees with the CDRH reviewer that a Complete Response is recommended for this Application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• According to the CDC https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed September 20, 2019), o From 1999 to 2017, more than 700,000 people have died from a drug overdose. o Around 68% of the more than 70,200 drug overdose deaths in 2017 involved an opioid. o In 2017, the number of overdose deaths involving opioids (including prescription opioids and illegal opioids like heroin and illicitly manufactured fentanyl) was 6 times higher than in 1999. o On average, 130 Americans die every day from an opioid overdose.	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While naloxone is the treatment of choice to reverse the acute opioid intoxication of a patient, it is not a permanent solution for opioid abuse, misuse, and addiction.
Current Treatment Options	• There are currently two approved community-use naloxone products, Evzio 2 mg IM and Narcan Nasal Spray (NNS) 4 mg IN (intranasal) • Anecdotally, some overdoses have required multiple administrations of standard doses of naloxone. However, it is not known whether these represent failures of the products approved for use in the community,	There are FDA-approved treatment options for opioid overdose. There may be a role for products with a higher dose or longer duration of action (e.g. nalmefene) There has been increasing concern in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or the injection solution administered with a nasal atomizer as part of a kit. The latter provides a lower concertation, higher volume dose that results in a lower systemic exposure.	community regarding overdoses with highly potent and synthetic opioids. This high-dose naloxone product may be more effective at reversing certain opioid overdoses although that is theoretical. The Applicant has not investigated whether the proposed product offers any advantages compared to approved products and is not seeking an indication for high-potent opioid overdose reversal.
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product and the reference product Narcan 2 mg injection through a pharmacokinetic (PK) study APC 6000-03. The pharmacokinetic data demonstrated that a single dose of 5 mg naloxone IM injection for the proposed product, ZIMHI, results in the same median Tmax (15 min), greater naloxone concentrations at all critical time points including earlier time points (e.g., 2.5, 5 min post-dose). • The efficacy of this product in the entire pediatric age range is supported by literature review. • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from high potency synthetic opioids • There are no comparative efficacy data between this product and other approved naloxone products	The Application provided literature and PK data to support the effectiveness of ZIMHI for the proposed indication intended for community use. Target patient population will include adult and entire pediatric population. The application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids compared to available product Evzio or NNS.
Risk and Risk Management	• The most frequent adverse events with ZIMHI in 28 healthy volunteers from two PK trials (APC6000-01 and APC6000-03)were dizziness and nausea. • All adverse events were mild to moderate in severity.	The Applicant has not provided adequate data to demonstrate that the proposed medical device meet the criteria per the Guidance for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Injection site reaction assessments do not raise any clinically significant safety concerns. • There were no deaths or serious adverse events • There is literature support for the safety of the use doses exceeding the proposed dose for this product in adults and in the entire pediatric age range • There are nonclinical toxicology data to support the safety of local injection reactions • Recurrent respiratory and central nervous system depression with duration of action of opioid may exceed duration of action of naloxone • Naloxone could potentially cause withdrawal symptoms in opioid dependent individuals; however, these symptoms are generally not life-threatening in adults • An association between pulmonary complications and higher naloxone doses has been reported in a recent publication • Proposed product labeling includes prominent language about the serious risks of precipitating acute opioid withdrawal in the neonate to mitigate the risk of precipitated withdrawal in this population. • There are no comparative safety data between this product and other naloxone products to inform prescribing decisions when choosing product for opioid reversal	Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features. The Applicant has not provided a strategy to mitigate risks of needlestick injury. Additional measures to mitigate risk of needlestick injury will include medical device change and label change.

2 Background

2.1 Product Information

This is the second review cycle for ZIMHI, a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. ZIMHI is a naloxone hydrochloride injection (NDA 212854) relying upon the agency's previous findings of safety and efficacy of Adapt Pharma's Narcan (NDA 16636).

The Applicant developed ZIMHI (Naloxone Hydrochloride) as a combination drug-device product and is submitting it under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act). ZIMHI is a single-use intramuscular (IM) device that delivers 5 mg of naloxone hydrochloride (HCl). ZIMHI is intended for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is a drug-device combination product intended for use in the community. It is designed for use in non-healthcare settings by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under IND 136,148. The investigational new drug (IND) application was submitted by Adamis Pharmaceuticals Corporation (also referred to as the "Applicant" throughout this review), on November 21, 2017.

The Applicant submitted a request for a priority review with the New Drug Application (NDA) on December 31, 2018. The Applicant based their request on the recent rise in opioid-related deaths from potent synthetic opioids. (b) (4) the request for priority review was denied.

The Applicant initially planned to rely on the agency's prior findings of efficacy and safety for the original Narcan (NDA 16636) and Evzio (NDA 205787). During the NDA review, it was determined that the Applicant could not rely on Evzio due to existing patent protection. The Applicant decided to only rely on NDA 16636. The Narcan labeled dosing is an initial dose of 0.4 mg to 2 mg via the intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes, followed by additional doses up to 10 mg. The Applicant is also relying on published literature to support the safety of the 5 mg dose. The Applicant specifically cited an article from Bracken *et. al*[2] which describes a study that evaluated the effects of naloxone on acute spinal-cord injury. In this study, naloxone was given to 154 patients as a 5.4 mg/kg bolus (324 mg to 378 mg for an average 60 kg to 70 kg adult). The patients then received 4.0 mg/kg/hour for 23 hours. The mortality and major morbidity findings in the naloxone group were similar

[2] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury. New England Journal of Medicine. 1990;322(20):1405-11.

to that of the placebo group. In a study by Cohen *et al*[3]. healthy subjects received up to 4 mg/kg of naloxone without serious adverse effects reported.

The Division previously conclude that the first submission would be a Complete Response (CR). The CR letter was sent to the Applicant on November 22, 2019. Please see Appendix A: November 21, 2019, Complete Response Letter or DARRTS for the letter which has a full description of the deficiencies. The deficiency most pertinent to the clinical review, was deficiency number 8:

> "Although you submitted relative bioavailability Study APC 6000-03, this information was submitted too late in the review cycle to allow for a substantive review. Therefore, we have not determined whether you have established an acceptable scientific bridge between your proposed drug product and the referenced Narcan product to demonstrate that such reliance is scientifically justified. We are withholding any comments on the relative bioavailability study until after you submit a response to this Complete Response letter."

As mentioned in deficiency number 8, Study APC 6000-03 was not evaluated in that review cycle and so was not evaluated for safety findings either and will part of the review of the resubmission.

The other deficiencies were related to concerns photo-degradants and particulate matter, storage condition data, and extractables and leachables. This was discussed in the product quality and nonclinical sections of the CR letter. There were also concerns regarding device reliability outlined in the device section of the letter.

2.2 Therapeutic Context: Opioid Overdose and Naloxone

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids although current data indicate that deaths associated with prescription opioid use are declining while those associated with illicit opioids continue to rise (CDC 2019). Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury.

As the opioid epidemic continues in the United States, as noted above, current data include reports/investigations showing increases in fentanyl-related overdose fatalities. Additionally, there have been reports of overdose patients requiring multiple doses of naloxone and also reports of naloxone be ineffective. Unfortunately, these reports do not usually describe if these

[3] Cohen M, Cohen R, Pickar D, Weingartner H, Murphy D, Bunney WJR. Behavioural effects after high dose naloxone administration to normal volunteers. The Lancet. 1981;318(8255):1110.

events have occurred with the approved community-use naloxone products, Evzio and/or Narcan Nasal Spray. However, these recent reports and articles such as Somerville et al[4] suggest that there may be a need for higher doses of naloxone to counteract overdoses with fentanyl and other high potency opioids. The Applicant has also cited other published literature to suggest that multiple doses of naloxone are required in an increasing number of opioid overdose cases. It is worth noting that the vast majority of out-of-hospital naloxone use consists of an improvised intranasal product using the naloxone solution for injection with a concentration of 1 mg/mL in a 2 mL vial (compared to 40 mg/mL in a 100 microliter volume for the approved intranasal naloxone product) administered using a mucosal atomizer device and these studies rarely distinguish between products. Therefore, it is unclear whether the apparent increased need for multiple doses of naloxone would have been observed had the higher concentration products been uniformly used.

Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor. If immediately administered, naloxone can reverse the life-threatening effects of an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone 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. Also, the duration of action of naloxone is shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

Naloxone has been approved for commercial use since 1971. There are approved drug products containing the active ingredient naloxone in the United States (**Error! Reference source not found.**).

Table 1 Current Naloxone Treatment Options

Drug Product Name	NDA	Approval Date	Dose Form
Narcan	016636	4/13/1971	Solution for injection
EVZIO (Naloxone HCl)	209862	10/19/2016	Autoinjector
Narcan Nasal Spray	208411	11/18/2015	Nasal Spray

Evzio and Narcan nasal spray are approved with the same indication as proposed for ZIMHI and are for community use. Naloxone is included as an active ingredient in several products in combination with opioid ingredients for the treatment of opioid dependence. It is generally included in these products to deter abuse of the opioid component.

Evzio was initially approved as a 0.4 mg dose, which has been replaced following approval of a 2 mg IM dose of naloxone. Narcan Nasal Spray was initially approved as a 4 mg dose,

[4] Somerville NJ, O'Donnel J, Gladden RM, Zibbel JE, Green TC, Youngkin M, et al. Characteristics of Fentanyl Overdose - Massachusetts, 2014-2016. MMWR. 2017;66(14):382-6.

followed by approval of a 2 mg dose. The 2 mg dose is no longer marketed. The Applicant's proposed product has a dose of 5 mg of naloxone for IM or subcutaneous injection and if approved, would have the highest dose of naloxone commercially available. An observational and retrospective article by Farkas et al. in 2019 reported that higher doses of naloxone (defined as greater than 4.4 mg) in a pre-hospital environment were associated with a higher rate of pulmonary complications. While association does not equal causation and this was a retrospective trial, pulmonary edema is a labeled warning for naloxone. As higher and high doses of naloxone are used to treat opioid overdoses, we will need to keep this is mind as a possible complication.

Labeling for naloxone products contain warnings regarding acute opioid withdrawal. Naloxone may abruptly precipitate of opioid withdrawal in persons who are physically dependent on opioids. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis. In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema.

Clinical efficacy trials present significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of opioid overdose, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it is not necessary to conduct clinical efficacy trials with novel naloxone products as effective doses have been established. The efficacy of a new formulation or route of administration of naloxone relies on a demonstration of adequate systemic naloxone levels in relative bioavailability studies which compare the systemic exposure of naloxone from the new product to an approved product.

For novel naloxone products intended to be used in the community, it is necessary to demonstrate comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration. This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose.

2.3 Summary of Regulatory Activity Since the Complete Response

A Type A End of Review meeting was held with the Applicant on February 12, 2020. The Applicant submitted 14 questions regarding the deficiencies and answers were provided prior to the meeting. The bulk of the face-to-face meeting time was spent discussing the CMC and non-clinical deficiencies. Please see the meeting minutes in DARRTS for a full summary.

On June 3, 2020 the Applicant submitted an application for COVID-19 Emergency Use Authorization (EUA) for their product ZIMHI. The request was declined with the following language:

> "Under EUA 71, Adamis Pharmaceuticals Corporation requests that FDA authorize its ZIMHI autoinjector product (naloxone HCl) for emergency use. According to Adamis'

submission, the ZIMHI autoinjector is intended treat opioid overdose. While FDA acknowledges that opioid overdose is a serious or life-threatening disease or condition, the requestor has not provided sufficient information and/or data that opioid overdose is a serious and/or life-threatening disease or condition that is caused by COVID-19, the CBRN agent specified in the Secretary's declaration dated March 27, 2020."

3 Product Quality

The drug substance, drug product, process/facilities, and microbiology review teams all recommend approval. The Application included adequate information to address the product quality deficiencies identified during the first review cycle.

The drug product, Naloxone Hydrochloride injection, 5 mg / 0.5 mL is a clear, colorless, sterile solution packaged in a prefilled syringe for subcutaneous or intramuscular administration. The prefilled syringe for single use consists of a (b) (4) glass syringe barrel sealed with a rubber plunger on one side after filling and fitted with stainless-steel needle (25G 5/8" cannula) and a rigid needle shield on the other. (b) (4) . All excipients meet compendial requirements and are within the range used in approved products. The drug product specifications for naloxone and related impurities (b) (4) are all acceptable. The acceptance criteria for impurities are acceptable and the risk assessment of elemental impurities is adequate.

The following executive summary is reproduced verbatim from the Integrated Quality Review:

> CMC recommends approval of this application. Drug substance, drug product, process and facilities and microbiology all recommend approval. This is the second review of this application. See the original CMC IQA dated 8 Oct 19 in DARRTS. A shelf-life of (b) (4) months is acceptable when stored at 20°–25° (68°–77°F). Excursions between 15° and 30° (59° and 86° F) are allowed. Do not refrigerate. Protect from light, extreme heat and freezing.
>
> The drug product is a clear solution of naloxone hydrochloride for injection packaged in a single use prefilled syringe in a delivery device. The 5 mg per 0.5 ml of naloxone HCl injection pre-filled single dose syringe in its device is intended for immediate administration as emergency therapy in settings where opioids may be present. The drug product is a clear, colorless, sterile solution, free from particles.
>
> A shelf-life of (b) (4) months is acceptable when stored at 20°–25° (68°–77° F). Excursions between 15° and 30° (59° and 86° F) are allowed. Do not refrigerate. Protect from light, extreme heat and freezing.

Additionally the team felt that the assessments of drug substance, drug product, manufacturing, and microbiology were adequate. See the full review dated October 21, 2020 in DARRTS for further details.

The CR letter issued after the first review cycle included the following Product Quality deficiencies:

1. There is no correlation established between the extractable and leachable studies. The extractables studies failed to detect any extractables and specifically failed to detect the leachables observed in the leachable study.

   To address this deficiency:
   Perform a more vigorous extractables studies that can establish a good correlation with the leachable assessments. Use USP <1663> and <1664> as guides in conducting these studies.

2. We note inconsistency in the leachable data during stability testing. Additional data are required to justify these results:

   To address this deficiency:

   a. Provide the lapsed time between the sample's withdrawal and date of reanalysis of the 6-month time point.

   b. Justify the use of (b) (4) for the 6-month sample time point, analyzed at (b) (4) and not for the original data presented at other time points.

   c. Explain why the (b) (4)-related leachants have not been observed in the (b) (4) and have not been removed after (b) (4)

   d. Provide the background peaks from the (b) (4) to confirm that the extra peaks are from the (b) (4)

   e. Unambiguously establish the structures of the leachables at RRT (b) (4) and (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

   f. Repeat the leachable study at each time point of the stability study, using validated analytical methods. Run blanks to establish background. Provide all data in your resubmission.

3. The photo-degradants at RRT (b) (4) have not been identified.

   To address this deficiency:

Unequivocally establish the structures of the photo-degradants at RRT (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

4. Particulate matter is a critical attribute for injectables. We note an inconsistency in the data provided at the 6-month time point for particulate matter testing under the long-term condition for Batch 1838-022. These out of trend results may mean variation in the analytical methods used for determination of particulate matter.

   To address this deficiency:
   Re-evaluate the analytical method and revalidate if required.

5. As the naloxone product may be widely available in the community, it could be stored in other than controlled conditions (such as a vehicle in the summer or winter). Sufficient data to support these storage conditions were not provided.

   To address this deficiency:
   Provide additional accelerated stability data to demonstrate lack of degradation, color change, or particulate formations. Similarly test the product when frozen and thawed. Report any particulate formation, color change, degradation and time required to thaw.

4 Center for Devices and Radiological Health (CDRH)

The CDRH team recommends a Complete Response for this application.

The CR letter issued after the first review cycle included the following Product Quality deficiencies:

> We previously requested reliability testing and analysis to demonstrate that the reliability for drug delivery using a single device is 99.99% or greater. The provided results demonstrate that the reliability of a single device is 99.96%. Your analysis uses the availability of two devices to achieve 99.99%; however, this does not adequately mitigate the risk of a patient failing to receive the complete dose because they may need both doses. The expectation is that the reliability of an individual product dose delivery is not less than 99.99%.
>
> To address this deficiency:
> Implement appropriate modifications to the device control strategy and provide additional data demonstrating that the product has a reliability of at least 99.99% for a single device.

Please see the full review from CDRH for a full discussion of the deficiencies as well as the Recommended Comments to the Applicant section. Reproduced here are the CDRH recommendations to the Applicant:

It is our expectation that you demonstrate that your device functions safely at worst-case, reasonably conceivable conditions (i.e. sterile device, at expiry, following shipping challenge), with testing to verify your requirements are adequately met. We recommend you review the following guidance documents as you address this deficiency and consider the recommendations contained within:

• *Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submission* (https://www.fda.gov/media/113230/download) from December 2019.
• *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices* (https://www.fda.gov/media/71983/download) from September 2018

Provide data verifying and validating that your needle safety function effectively protects against accidental needlesticks per FDA Guidance Document "*Medical Devices with Sharps Injury Prevention Features.*"

5 Nonclinical Pharmacology/Toxicology

The nonclinical team recommends approval of this application. The Application included adequate information to address nonclinical deficiencies listed in the CR letter. The following is reproduced verbatim from the nonclinical pharm/tox review:

> This is a second cycle review. The NDA was originally submitted on December 31, 2018. The original NDA resulted in a Complete Response (see Complete Response Letter dated November 22, 2019). There were no new nonclinical studies submitted in support of the proposed drug product. The first cycle review concluded with a Complete Response with a deficiency aimed at the lack of adequate extractable and leachable studies to support the safety of the container closure system. Specifically, the extraction studies conducted should establish an acceptable extractables leachables correlation that will assure adequate monitoring of the potential leachable compounds from the container closure system was well as providing a toxicological risk assessment for any leachable compound detected above the 5 mcg/day threshold.
>
> The extractables study used 24-hour reflux in five solvents including a product simulation solvent (saline pH 4.0), isopropanol, hexane, and water at pH 2.0 and pH 11.0. These extraction solvents appear harsh (isopropanol and hexane) and cover physiologic conditions (water and saline). The Analytical Evaluation Threshold (AET) was based on a Safety Concern Threshold (SCT) of 5 mcg/day. The AET was (b) (4) mcg/g for the syringe and (b) (4) mcg/g for the stopper. The analytical methods used were able to detect a variety of compounds (volatile, non-volatile and semi-volatile). The reader is referred to the quality review for the adequacy of the extraction study and the extractable leachable correlation.

The leachable study was performed on 5 batches that were stored for up to 18 months under normal conditions (25^{O}C/60% RH). The only leachable that was detected above the 5 mcg/day threshold is (b) (4). The safety of (b) (4) was provided by the toxicological risk assessment from the original submission. The toxicological risk assessment of (b) (4) was not changed in this submission except for the levels of (b) (4) detected to date. The levels of (b) (4) in the stability batches increased slightly and as a result, the safety margin decreased slightly (from (b) (4) to (b) (4)). Thus, there were no safety concerns with (b) (4).

The drug product specifications were revised and these meet ICH Q3A(R2) qualification thresholds and as such, there are no safety concerns with the drug product specifications.

From a nonclinical pharmacology toxicology perspective, the NDA may be approved.

The safety for nonclinical local toxicity was reviewed during the first cycle and is discussed in the nonclinical and joint Clinical CDTL and Summary Reviews from that cycle. The following is excerpted from the Clinical CDTL and Summary Review:

To support the local safety of the higher concentration of the naloxone formulation, a local tolerance study in New Zealand White rabbits (previously reviewed by Dr. Newton Woo) was conducted. Minimal necrosis and regeneration along the needle tract were observed in the treatment group (10 mg/mL naloxone); however, the incidence and severity were not different when compared to a group that received the highest currently approved naloxone concentration of 5 mg/mL. Given the results from the local tolerance study, there are no safety concerns from a local perspective with the Applicant's 10 mg/mL naloxone formulation. In terms of systemic safety of the formulation, the Applicant was asked in the 74-day letter to justify the systemic safety of the new formulation with nonclinical data or with prior clinical experience. The Applicant replied and argued the systemic safety of the new formulation through a clinical literature-based justification (refer to the Medical Officer's review for the systemic safety of the formulation).

The CR letter issued after the first review cycle included the following nonclinical deficiencies:

You have not provided appropriate extractable/ leachables data to permit a substantive nonclinical toxicological risk assessment for the proposed container closure system.

<u>To address this deficiency:</u>

Submit a revised toxicological risk assessment based on adequate extractable leachable data. To inform the risk assessment, conduct adequate extractable leachable studies to support the safety of your proposed container closure system, taking into consideration the following:

a. Results of the extraction studies should establish an acceptable extractable leachables correlation that will assure adequate monitoring of the drug product stability samples for all potential leachables from the container closure system.

b. Provide a justification for the compounds targeted in the leachable study based on the extraction data. In general, all extractables exceeding 5 mcg/day should be targeted in the leachable study.

c. Based on the results of the leachable studies, identify all compounds in the drug product present at levels equal to or greater than 5 mcg/day taking into consideration the maximum daily dose of your drug product and submit a toxicological risk assessment for every leachable present in the drug product at or above the 5 mcg/day qualification threshold. The risk assessment must be based on the highest level of the leachable over the course of the proposed shelf-life.

d. Toxicology data from published literature or from the public domain that are used to support leachable qualifications must meet regulatory standards with adequate details to permit substantive independent review. Referencing databases, such as ECHA, with limited details regarding toxicity information is not acceptable. QSAR analysis and identification of a NOAEL (no observed adverse effect level) for structurally similar compounds to qualify leachables that have limited toxicity information is not acceptable unless it is accompanied with adequate justification via scientific data or literature that allows for such a bridge or extrapolation. These databases can be used to identify the pivotal studies used to support your toxicological risk assessment; however, the pivotal studies should be submitted with the NDA to permit independent review. Revise your toxicological risk assessment to employ permission daily exposure levels accordingly as per ICH Q3C(R5) principles. Submit copies of toxicology risk assessment reports and cited literature.

6 Clinical Pharmacology

The clinical pharmacology team recommends approval of this application. The Application included adequate information to address the clinical pharmacology deficiency listed in the CR letter. The following has been reproduced verbatim from the clinical pharmacology review:

> The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the NDA 212854 resubmission dated May 15, 2020 and finds it acceptable from clinical pharmacology perspective.
>
> **Key Clinical Pharmacology Findings:**

> In the comparative bioavailability study APC 6000-03, a single dose of 5 mg naloxone IM injection for the proposed product, ZIMHI (Naloxone HCl injection single-use prefilled syringe for IM or SC use 5 mg/0.5 mL), exhibited the same median Tmax (15 min), greater naloxone concentrations at all time points including earlier time points (e.g., 2.5, 5 min post-dose), 2.6-fold greater AUC0-2.5min, 4.1-fold greater AUC0-5min, 4.9-fold greater Cmax, 2.8-fold greater AUClast, and 2.7-fold greater AUC0-inf values, than a single dose of 2 mg naloxone IM injection for the reference product, naloxone HCl injectable (1 mg/1 mL, International Medical Systems, ANDA 072076). The comparator dose of 2 mg naloxone IM injection is within the approved initial dose range (i.e., 0.4 to 2 mg) for the listed drug product Narcan Injectable (NDA 016636). Note the original product Narcan Injectable (NDA 016636) was discontinued not because of safety or effectiveness reasons, so its generic product ANDA 072076 was used as the comparator in the comparative bioavailability study APC 6000-03.

The CR letter issued after the first review cycle included the following clinical pharmacology deficiency:

> Although you submitted relative bioavailability Study APC 6000-03, this information was submitted too late in the review cycle to allow for a substantive review. Therefore, we have not determined whether you have established an acceptable scientific bridge between your proposed drug product and the referenced Narcan product to demonstrate that such reliance is scientifically justified. We are withholding any comments on the relative bioavailability study until after you submit a response to this Complete Response letter.

7 Clinical Microbiology

Not applicable.

8 Clinical/Statistical- Efficacy

No new clinical efficacy data were included in this submission. The Applicant plans to rely on the agency's prior findings of efficacy from the reference product, Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish the efficacy of the proposed product. The PK data provided in the application established the scientific bridge between the proposed product ZIMHI and reference drug Narcan injection, thus supporting the efficacy of the proposed product ZIMHI for the proposed indication.

9 Safety

9.1 Summary of Drug Safety

The Applicant has submitted a literature review and safety data from two PK studies to support the safety of ZIMHI (naloxone injection, 5 mg / 0.5 mL). The Applicant also submitted adequate animal data to characterize local injection reaction profile.

The Applicant submitted safety data from two pharmacokinetic studies in a total of 28 healthy volunteers, APC6000-01 and APC6000-03 to support the Application. The Applicant initially performed one relative bioavailability study in healthy volunteers, Study APC6000-01 that was reviewed during the first cycle. There were no major safety findings and no new safety signals in the PK study. Please see the joint Summary and CDTL review in DARRTS for a full discussion. In this submission the Applicant performed a second bioavailability study in healthy volunteers Study APC6000-03. Both studies included routine clinical safety assessments (e.g. vital signs, EKG, physical exams, clinical Labs) and injection site reaction assessments. All assessments including injection site reactions were categorized according to DAIDS grading scale. Review of the safety data from pharmacokinetic studies APC6000-01and APC6000-03 revealed no new safety signals with use of ZIMHI. There were no deaths or serious adverse events in the healthy volunteers exposed to single dose injection of ZIMHI. Common adverse reactions were nausea and dizziness. No clinically significant change of vital signs, EKG were reported. One subject had an AE (blood bilirubin increased) related to clinically significant out-of-range laboratory values at the end of study, however, no other liver enzymes (AST, ALT or ALP[5]) were noted to be elevated before or after study drug or comparator.

The safety for this high-dose naloxone product is based primarily on the agency's prior findings for Narcan (naloxone hydrochloride) solution for injection. Given that PK data showed the systemic exposure level of ZIMHI(naloxone injection, 5 mg / 0.5 mL) is higher than the reference product, Narcan (naloxone hydrochloride, NDA 16636). The Applicant submitted literature review to support the safety of the systemic exposure observed with ZIMHI (naloxone injection, 5 mg / 0.5 mL). The Applicant has described several studies to support higher doses of naloxone in the submission. An example of an article that the Applicant specifically cited is from Bracken *et. al*[6] which describes a study that evaluated effects of naloxone on acute spinal-cord injury. In this study, naloxone was given to 154 patients as a 5.4 mg/kg bolus (324 mg to 378 mg for an average 60 kg to 70 kg adult). The patients then received 4.0 mg/kg/hour for the 23 hours. The mortality and major morbidity findings in the naloxone group were similar to that of the placebo group. Reversal of an opioid overdose in an individual not physically dependent on opioids would likely be safe. However, the safety when administered in persons who are physically dependent on opioids is less clear, as it may precipitate an acute withdrawal syndrome. Acute opioid withdrawal syndrome (OWS) due to Excessive or overlay rapid reversal of opioid overdose includes vomiting, seizure, delirium, and agitation[7] (Kim and Nelson, 2015). Relative to the available

[5] Aspartate aminotransferase, alanine transaminase, alkaline phosphatase
[6] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury. New England Journal of Medicine. 1990;322(20):1405-11.
[7] Kim HK, Nelson LS. Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review. Expert Opin Drug Saf. 2015;14(7):1137-46.

doses of Evzio and Narcan Nasal Spray, it is likely that a precipitated withdrawal from a 5 mg IM dose would be more severe. However, these potential safety concerns are still outweighed by the benefit of reversing a life-threatening opioid overdose.

9.2 Device related safety concerns

There are medical device related safety concerns that need to be addressed by the Applicant. Specifically, the medical device is designed with a manually activated needle safety guard (Appendix D: Applicant's Device Diagrams) to cover the exposed needle after the injection. The Sponsor has not provided data to demonstrate the success rate of deployment of the needle guard among laypersons without medical training. An exposed needle will present a risk to the device user for transmission of blood borne pathogens such as HIV, Hepatitis B, and Hepatitis C.

Note the proposed device for ZIMHI is also used in an approved epinephrine product, SYMJEPI (NDA 207534). The intended patient populations and intended users for these two products are quite different. Epinephrine is the treatment for anaphylaxis, a life-threatening condition. Patients who are prescribed SYMJEPI have a known serious allergy and are instructed to carry this product (SYMJEPI or other epinephrine products) with them at all times. When patients are prescribed SYMJEPI, they are instructed on its use and they have time to further learn about the product and completely familiarize themselves with the package insert. Patients who are prescribed the epinephrine product will be planning to use it on themselves (or for pediatrics, parents will plan to use it on their children) and should be aware of how to safely use and dispose of the used product. Therefore risk of blood borne pathogen transmission to someone else is extremely low for SYMJPEI.

In the clinical context of naloxone products for community-use, the intended patient population and intended users are two different populations. The naloxone product may be used on the patient for whom the naloxone was prescribed, *by someone other than the patient*, and so it is unknown who will administer the potentially life-saving treatment. Another possible scenario is that the patient (who was prescribed naloxone) may need to use it on a household contact who overdoses on opioids in the home. There are endless scenarios, but the main concern is that it is unknown who will be the administrator and who will be the receiver of the naloxone, and so straightforward needle safety is a requirement. Patients who will be prescribed ZIMHI are patients who are at high-risk of opioid overdose and they may be instructed on its use and familiarize themselves with the package insert. However, when patients overdose on opioids, they are unconscious and unable to self-administer anything. Any household contacts (or other bystanders) who are not familiar with the product may administer ZIMHI to reverse the overdose. The risks of needlestick injury for intended users and possibility of transmission of bloodborne pathogens from overdosed patients to the naloxone administer is concerning.

Evzio is a community-use naloxone product that also delivers naloxone by injection. It has a different device and is an autoinjector. Its device automatically retracts the needle after use

and so does not have this same inherent risk of needlestick injury and potential for disease transmission.

Given the device related safety concerns regarding needlestick injury, an information request (IR) was sent to the Applicant on September 23, 2020 (Appendix B). The Applicant was requested to provide data following all the recommendations in the Medical Device with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download) guidance document and provide strategies to mitigate potential risks of needlestick injury and prevent risks of transmission of blood borne pathogens from opioid-overdose patients to the intended users.

The response regarding the device concerns was reviewed by CDRH reviewer and they concluded that the Applicant has not provided adequate data to demonstrate the proposed medical device meets the recommendations in "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/media/71142/download) from August 2005. Please see the CDRH review for further details. Additionally, the Applicant has not provided any measure to mitigate potential risks of needlestick injury and prevent risks of transmission of blood borne pathogens from opioid-overdose patients to the intended users

Given the continued device safety concerns, several meetings were held with the DMEPA[8] and CDRH[9] teams. The CDRH concerns are briefly summarized in Section 4 of this review and fully outlined in the Recommended Comments to the Applicant section. DMEPA reported that the Applicant is relying on Human Factors data for this product from a previous NDA (SYMJEPI NDA 207534) using the same device. In communications with the DMEPA team they reported, "The Applicant conducted two human factors studies for SYMJEPI. For the first study, they included "deploy the needle guard" as a critical task and 23% out of all simulated injections resulted in successful deployment of the needle guard. There were several use errors involving multiple critical tasks that occurred during this first study. The NDA received a complete response for several deficiencies including human factors. As a result of the various use errors the Applicant made modifications (b) (4) The Applicant conducted a second human factors study (b) (4) however, the task of "deploy needle guard" was not considered a critical task in this study so data on rate of successful deployment of the needle guard was not assessed or provided in the study report. In the second study the Applicant considered deploying the needle guard as one of three options for protecting against needlesticks. The other two options included putting the used syringe back in the case and closing the case and, while not recommended, recapping with the needle cap. The SYMJEPI product that is currently marketed is the same design as the one that was evaluated in the second human factors study." Given the very high rate of failure of the critical task of deploying the needle guard in the only human factors study that assessed that issue, we remain very concerned about needle safety. The Applicant should modify their device to include an

[8] Division of Medication Error Prevention and Analysis
[9] Center for Devices and Radiological Health

automatically deploying needle safety element to decrease the risk of needlestick injury (to avoid transmission of blood borne pathogens).

10 Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held to discuss this product.

11 Pediatrics

The safety and effectiveness of naloxone has already been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone in this population has already been supported by adult bioequivalence studies as well as evidence of safety and effectiveness in pediatrics in clinical practice.

During the first cycle for this NDA, the Division of Pediatric and Maternal Health (DPMH) was consulted to assist in the review of the submitted pediatric information, label, and approval recommendations including the Pregnancy and Lactation Labeling Rule (PLLR) language. After an internal meeting with DPMH and the wrap-up meeting for this NDA cycle, both Division have agreed that this product is appropriate for pediatric use for all ages including down to birth. Please see the joint Summary and CDTL review in DARRTS for a full discussion.

12 Other Relevant Regulatory Issues

Financial Disclosures
The Applicant submitted form FDA 3454 and certified that the Investigator did not have reportable financial disclosures during the first cycle for this NDA.

Compliance with Good Clinical Practices
During the first cycle for this NDA, the Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

Inspections
The Office of Study Integrity and Surveillance (OSIS) was requested to inspect the site for study APC 6000-3, but OSIS declined to conduct an on-site inspection for the clinical and analytical sites. The reason given for declining was that the sites had previously been inspected for other applications and they found that a repeat inspection was not warranted.

The Applicant originally planned, during the first NDA cycle, to reference the agency's prior findings of efficacy and safety for Evzio (Kaleo, NDA 212854). This infringed upon existing patents for Evzio and a lawsuit was initiated against the Applicant. After the Applicant withdrew the Patent IV Certification for Evzio and planned to reference a different product as the listed drug, Kaléo agreed to withdraw the patent infringement suit. The two parties have each filed a copy of the settlement agreement along with a request of voluntary dismissal in the Delaware and Virginia courts.

13 Labeling

Dr. Cameron Johnson and Dr. Otto Townsend from Division of Medication Error Prevention Analysis (DMEPA) provided a review of the proprietary name, container label, carton labeling, and Instructions for Use. They concluded that the revised prescribing information, container labels and carton labeling are unacceptable from a medication error perspective. They also concluded that the proposed proprietary name ZIMHI (naloxone hydrochloride) injection, 5 mg/0.5ml was found to be acceptable.

Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed pregnancy, lactation, and pediatric sections of labeling. DPMH provided recommendations for the proposed labeling. Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review.

A labeling concern brought up by the 505(b)(2) Committee was from section 5.3 of the label. This information is not verbatim from the original Narcan NDA label that the Applicant is relying:

(b) (4)

After further internal discussions with DPMH, we have concluded that this language is non-product-specific information. The Division considers this language to be general safety related information for community-use naloxone products. Please see the review by DPMH in DAARTS for further discussion.

Labeling is ongoing but has not been completed as the product will be a Complete Response (CR). Should the Applicant adequately address the deficiencies identified in this review cycle, key issues in labeling include:

- One of the concerns for the labeling of naloxone products with different doses and routes intended for use in the community is regarding differentiating those doses in labeling to inform prescribers, and even laypersons, of the clinical scenarios or dosing criteria to determine when one dose would be used over another in a community setting, which is a different setting than was intended for the reference product Narcan. The Applicant's submission did not include data to inform that decision.
- If approved, there is concern that the Applicant will attempt to promote ZIMHI for a wider spectrum of opioid overdoses than competitors. Because that concept is only theoretical, such language is not appropriate for labeling.

14 Postmarketing Recommendations

Not applicable as this will be a CR.

15 Recommended Comments to the Applicant

Complete response is recommended for this Application.

CLINICAL

1. You have not provided adequate data to support the safe use of the proposed product ZIMHI (Naloxone HCl Injection, 5 mg/0.5 mL) pre-filled syringe for the emergency treatment of opioid overdose in community settings. The product as currently designed raises safety concerns for intended users. Specifically, you haven't provided data to demonstrate that intended users are able to deploy needle safety guard without difficulties with the current user interface in the intended use environments. Failure to deploy the needle safety guard will result in risk of needlestick injury after the injection. Additionally, patients who will be prescribed may have familiarity with your product. However, the intended users could include laypersons, who may administer this to patients. Your product, if approved, is anticipated to be widely used in community settings by laypersons who are not familiar with the use of the product at all. There is possibility that your product will be used on patients with an increased rate of bloodborne pathogens disease than the general public[10]. The possibility of transmission of bloodborne pathogens from opioid-overdose patients to the intended users is high for your product. Your current user interface is not adequate to mitigate potential risks of needlestick injury and prevent risks of transmission of bloodborne pathogens from opioid-overdose patients to the intended users.

[10] https://www.cdc.gov/pwid/index.html

To address this deficiency

Modify your device to include an automatically deploying needle safety element to decrease the risk of needlestick injury (to avoid transmission of bloodborne pathogens).

Please submit your updated comprehensive use-related risk analysis (URRA) taking into consideration the changes to the user interface. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

We recommend you submit your HF validation study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance titled Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications11 for the content of a human factors validation study protocol submission.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents12:

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[11] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[12] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling13:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

DEVICE

2. In response to our October 2, 2020, request for a fault tree analysis which provides pointers between Panels A-E to demonstrate your device's overall reliability of successful activation/dose delivery at 99.999% and 95% confidence, you state, (b) (4) [redacted] Your Fault Tree Analysis (Panels A-E) should consider all applicable basic failure modes of your device, grouped in a fashion to consider the logical relation (i.e., and/or) so that your device's overall reliability calculation is accurate and complete.

   To address this deficiency:

   Revise your Fault Tree Analysis to consider all the basic design and manufacturing failure modes.

[13] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3. In your revision to Panel A from SN0053 (August 17, 2020) and Panel E from SN0055 (September 10, 2020) you make consistent logical and scientific arguments which are unsubstantiated by your evidence or do not clearly support your claims. Without this information, you cannot support your overall claim of successful activation/dose delivery at 99.999% reliability and 95% confidence or 99.99% reliability and 95% confidence. This is not intended to be an exhaustive list due to the consistent errors identified.

To address this deficiency:

Revise your fault tree analysis and address the following:

a. (b) (4)

ii. You provide no explanation on how you link Cpk to failure rate.

Therefore, your claimed failure rate of (b) (4) is unsubstantiated by this evidence. This is similarly noted for items in SN0055. Provide a clear explanation linking of Cpk or other data sources (e.g., Monte Carlo Simulations, qualifications of go-no/go gauges) to your basic failure rates for items which you rely on statistical data.

b. In SN0055, Table 1 of 1.11.1, for the basic failure mode "unable to actuate due to part defects," you point to 3.2.P.7.8.1.2.4 Tables 18 and 20-23 and state the assessed failure rate is (b) (4) with "Reliability analysis of each manufactured part was found to be 99.999999%." However:

i. (b) (4)
There are three items connected to this basic failure event with an 'OR' gate (b) (4) Therefore, this appears to be combining data from several sources without explaining how you relate these to your stated failure rate. Provide an analysis that uses a single failure rate for each failure mode and clearly link these data with logical connectors (i.e. AND, OR) to arrive at failure rate.

ii. The critical dimension data in the referenced tables refers to several Cpk values, including (b) (4). You do not clearly relate these Cpk values to your stated failure rate of (b) (4) Provide the assessment described in 2.a: a linking of Cpk(s) to a failure rate.

iii. Under Table 23 you state, "Due to the high process capability for the manufacture of these parts, with a Cpk of (b) (4) the critical the failure probability of this basic failure mode was considered negligible but will be set at the (b) (4) for the purpose of the fault tree analysis quantification." Therefore, it is unclear why you do not use the lowest identified Cpk in your analysis or considering all the parts' failure rates. Provide failure rate data for the basic events in your analysis.

iv. You appear to use Cpk data in Table 18, 22, and 23 to arrive at a failure rate. You do not provide evidence that the data is normal. Cpk analyses are predicated on a normal data set. Provide a normality test to demonstrate your analysis is valid.

v. You appear to use Cpk data in Table 20 and 21 to arrive at a failure rate. You failed your normality test. Therefore, your Cpk analysis, as presented, is invalid. Provide an assessment of your non-normal data to determine why your data is non-normal and provide a statistical analysis which is valid for your data set.

c. You provide a failure rate based on your pFMEA for several items and justify these based on validated assembly figures and work instructions. You do not provide process validation references demonstrating your assembly line has been determined to be adequate. Therefore, your determined failure rates are unsubstantiated. Provide evidence that your assembly process and equipment are validated and can adequately identify parts as passing or failing. Ensure the evidence clearly supports your proposed failures rates.

d. In response to comment b in SN0055, you provide a statistical tolerance analysis. However, you do not provide the source of these data, the areas of your Fault Tree Analysis these data are supporting, or a normality assessment of these data. We are unable to determine if your statistical tolerance analysis is valid without knowing the source of the data, how you collected it, how you are using it to support your claims, and that your analysis techniques are valid. Provide a reference to the original location of these data, explain where these data are being used in your Fault Tree Analysis, and provide a normality test of these to determine the presented analysis is valid.

Also consider the Complete Response Deficiency 4 regarding your needle safety device as you revise your Fault Tree Analysis and consider that any changes to your device design should be considered as you address this comment.

4. You provide SN0057 (October 7, 2020), in response to our September 23, 2020, Information Request, Issue 1, which contains Table 1 and a discussion of how you meet the recommendations in "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/media/71142/download) from August 2005. However, the evidence you reference to support your claimed device malfunction mitigations in 3.2.P.2.4.4.2.4, 3.2.P.2.4.4.2.6, 3.2.P.2.4.4.2.7, 3.2.P.2.4.4.2.8 contain consistent scientific flaws:

    a. You do not detail your test methods or explain why the methods chosen are adequate in demonstrating your requirements are verified

    b. You do not state the number of samples used to verify each requirement

    c. You do not justify your sample size based on the risks present in your system

    d. You do not present a complete analysis of your data: You lack both a discussion of your approach (e.g., variable or attribute) and statistical analysis demonstrating adequacy of the data (e.g., data normality for variable data)

    e. Your samples are not representative of your use case. For example, in Section 3.2.P.2.4.4.2.6 you state:

        i. "Units were held at 55°C for the 5.5 weeks period to simulate a 12-month shelf and use life." We understand your device has a shelf-life of 18 months. Therefore, your data do not demonstrate your device functions at expiry.

        ii. "All samples subject to accelerated life testing were fabricated from alpha build components…" However, you present no discussion comparing the components from alpha builds to the to-be-marketed device or state there are no functional/design changes between these components and your to-be-marketed device. Therefore, the device used is not understood to be representative of your to-be-marketed device.

    f. While you state, "…after storage at 55 °C for simulated aging to 18 months, 576 devices were evaluated for needle guard function…The result was recorded as a Pass/Fail. The acceptance criteria was: (b) (4) failures are required to demonstrate a (b) (4)% confidence that the true failure rate is no higher than (b) (4)% and a (b) (4)% confidence that the true failure rate is no higher than (b) (4)%..." under Simulated Clinical Use Testing.

I. Your referenced data in Section 3.2.P.2.4.4.2.6, which refers to devices aged only to12 months, contradicts this statement.

II. You provide no other data location to support this statement.

To address this deficiency:

You should demonstrate that your device functions safely at worst-case, reasonably conceivable conditions (i.e., sterile device, at expiry, following shipping challenge), with testing to verify your requirements are adequately met. We recommend you review the following guidance documents as you address this deficiency and consider the recommendations contained within:

- Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submission, available at https://www.fda.gov/media/113230/download

- Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices, available at https://www.fda.gov/media/71983/download

Provide data verifying and validating that your needle safety function effectively protects against accidental needle sticks per FDA Guidance Document “Medical Devices with Sharps Injury Prevention Features.”

Appendix A: November 21, 2019, Complete Response Letter

PRODUCT QUALITY

1. There is no correlation established between the extractable and leachable studies. The extractables studies failed to detect any extractables and specifically failed to detect the leachables observed in the leachable study.

   To address this deficiency:
   Perform a more vigorous extractables studies that can establish a good correlation with the leachable assessments. Use USP <1663> and <1664> as guides in conducting these studies.

2. We note inconsistency in the leachable data during stability testing. Additional data are required to justify these results:

   To address this deficiency:

   g. Provide the lapsed time between the sample's withdrawal and date of reanalysis of the 6-month time point.

   h. Justify the use of (b) (4) for the 6-month sample time point, analyzed at (b) (4) and not for the original data presented at other time points.

   i. Explain why the (b) (4)-related leachants have not been observed in the (b) (4) and have not been removed after (b) (4).

   j. Provide the background peaks from the (b) (4) to confirm that the extra peaks are from the (b) (4)

   k. Unambiguously establish the structures of the leachables at RRT (b) (4) and (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

   l. Repeat the leachable study at each time point of the stability study, using validated analytical methods. Run blanks to establish background. Provide all data in your resubmission.

3. The photo-degradants at RRT (b) (4) have not been identified.

   To address this deficiency:
   Unequivocally establish the structures of the photo-degradants at RRT (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

4. Particulate matter is a critical attribute for injectables. We note an inconsistency in the data provided at the 6-month time point for particulate matter testing under the long-term condition for Batch 1838-022. These out of trend results may mean variation in the analytical methods used for determination of particulate matter.

   To address this deficiency:
   Re-evaluate the analytical method and revalidate if required.

5. As the naloxone product may be widely available in the community, it could be stored in other than controlled conditions (such as a vehicle in the summer or winter). Sufficient data to support these storage conditions were not provided.

   To address this deficiency:
   Provide additional accelerated stability data to demonstrate lack of degradation, color change, or particulate formations. Similarly test the product when frozen and thawed. Report any particulate formation, color change, degradation and time required to thaw.

DEVICES

6. We previously requested reliability testing and analysis to demonstrate that the reliability for drug delivery using a single device is 99.99% or greater. The provided results demonstrate that the reliability of a single device is 99.96%. Your analysis uses the availability of two devices to achieve 99.99%; however, this does not adequately mitigate the risk of a patient failing to receive the complete dose because they may need both doses. The expectation is that the reliability of an individual product dose delivery is not less than 99.99%.

   To address this deficiency:
   Implement appropriate modifications to the device control strategy and provide additional data demonstrating that the product has a reliability of at least 99.99% for a single device.

NONCLINICAL

7. You have not provided appropriate extractable/ leachables data to permit a substantive nonclinical toxicological risk assessment for the proposed container closure system.

   To address this deficiency:

   Submit a revised toxicological risk assessment based on adequate extractable leachable data. To inform the risk assessment, conduct adequate extractable leachable studies to support the safety of your proposed container closure system, taking into consideration the following:

e. Results of the extraction studies should establish an acceptable extractable leachables correlation that will assure adequate monitoring of the drug product stability samples for all potential leachables from the container closure system.

f. Provide a justification for the compounds targeted in the leachable study based on the extraction data. In general, all extractables exceeding 5 mcg/day should be targeted in the leachable study.

g. Based on the results of the leachable studies, identify all compounds in the drug product present at levels equal to or greater than 5 mcg/day taking into consideration the maximum daily dose of your drug product and submit a toxicological risk assessment for every leachable present in the drug product at or above the 5 mcg/day qualification threshold. The risk assessment must be based on the highest level of the leachable over the course of the proposed shelf-life.

h. Toxicology data from published literature or from the public domain that are used to support leachable qualifications must meet regulatory standards with adequate details to permit substantive independent review. Referencing databases, such as ECHA, with limited details regarding toxicity information is not acceptable. QSAR analysis and identification of a NOAEL (no observed adverse effect level) for structurally similar compounds to qualify leachables that have limited toxicity information is not acceptable unless it is accompanied with adequate justification via scientific data or literature that allows for such a bridge or extrapolation. These databases can be used to identify the pivotal studies used to support your toxicological risk assessment; however, the pivotal studies should be submitted with the NDA to permit independent review. Revise your toxicological risk assessment to employ permission daily exposure levels accordingly as per ICH Q3C(R5) principles. Submit copies of toxicology risk assessment reports and cited literature.

CLINICAL PHARMACOLOGY

8. Although you submitted relative bioavailability Study APC 6000-03, this information was submitted too late in the review cycle to allow for a substantive review. Therefore, we have not determined whether you have established an acceptable scientific bridge between your proposed drug product and the referenced Narcan product to demonstrate that such reliance is scientifically justified. We are withholding any comments on the relative bioavailability study until after you submit a response to this Complete Response letter.

PRESCRIBING INFORMATION

9. During our review of your submitted labeling, we identified the following labeling issue that should be addressed in your resubmission:

Your annotated labeling submitted December 31, 2018, included (b) (4) [redacted]

The acceptability of the labeling will be a review issue.

We reserve remaining comments on the proposed labeling until the application is otherwise adequate.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[14]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

10. We acknowledge receipt of the revised draft carton and container labeling on September 30, 2019. We reserve our comments on the acceptability of the packaging labels for the next review cycle.

PROPRITERAY NAME

11. Please refer to correspondence dated, March 28, 2019, which addresses the proposed proprietary name, ZIMHI. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

Safety Update:

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and

[14] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   a. Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

   b. Present tabulations of the new safety data combined with the original application data.

   c. Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

   d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

Appendix B: September 23, 2020 Information Request (IR)

We are reviewing your NDA 212854 and have identified the following issues that you need to address:

Issue 1 The proposed device requires manual activation of the safety guard to cover the needle after the injection. Given that the intended users of your product are laypersons without medical training, there are potential risks of needlestick injury for the intended users. Exposed needles pose a risk for transmission of blood borne pathogens from opioid-overdose patients to the intended users. On July 23, 2020 FDA released a new Drug Safety Communication discussing this https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain. Because the FDA is committed to encouraging health care professionals to raise awareness of the availability of naloxone when they are prescribing and dispensing opioid pain relievers or medicines to treat opioid use disorder (OUD), we expect increases in prescriptions for naloxone products and an increase in availability of naloxone to more of the population. If approved, your naloxone product will be widely used, and the proposed device may pose an increased risk of needlestick injury.

Actions that may address this issue

- Provide data following all the recommendations in the Medical Device with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download) guidance document

- Provide strategies to mitigate potential risks of needlestick injury and prevent risks of transmission of blood borne pathogens from opioid-overdose patients to the intended users.

Issue 2 You have not provided adequate safety information regarding local injection site reactions.

Actions that may address this issue

Provide further clinical information to support the local safety for injection of this naloxone concentration.

Issue 3 You have not provided adequate safety information to support use of your product in the opioid-dependent population. While there appears to be adequate information to support your naloxone dose in healthy volunteers, you have not provided information (such as literature) to support your dose in the opioid-dependent population. We are concerned that higher doses of naloxone may precipitate severe and life-threatening adverse events in this population.

Actions that may address this issue

Provide further clinical information to support the safety of your product in this population. Potentially this can be conducted through a literatures review and summary.

Appendix C: Clinical Protocol and Safety Summary for Study APC6000-03

Objectives/Rationale

- To compare bioavailability of 5 mg/0.5 mL intramuscular naloxone hydrochloride to 2 mg/2 mL intramuscular naloxone hydrochloride injection in healthy subjects

Overall Design

This study was a randomized, open-label, 2-period, 2-treatment crossover PK study in 14 healthy volunteers aged 18 to 55 years old to evaluate the PK of ZIMHI vs. 2mg intramuscular (IM) naloxone. Subjects received intramuscular injections to anterolateral aspect of the thigh. The study consisted of a screening visit (up to 28 days prior to Study Visit 1) and two dosing visits (each separated by a minimum of 48 hours). Safety assessments were conducted throughout the study, including physical exams, routine laboratory tests, pregnancy tests, ECGs, adverse events assessments, vital sign assessments, and local skin monitoring.

Treatment

Each subject received both of the treatments. The injections were given in the anterolateral aspect of the thigh. There treatments were 5 mg/0.5 mL IM naloxone (ZIMHI) and 2 mg IM naloxone. The Applicant used the to-be-marketed formulation and device for the ZIMHI test product.

Population

The planned enrollment was for 14 healthy subjects.

Inclusion and Exclusion Criteria

The enrolled population was otherwise healthy, not pregnant, aged 18 to 55 years of age inclusive. Appropriate precautions were taken to screen for medical history, physical exam, and any medications. The population enrolled was appropriate for the study.

Table 2 Summary of Activities

Activity	Screening	For Periods 1 and 2			Period 2 only
	Days -28 to Day -1	Day - 1	Day 1 Pre-Dose Dosing	Day 2	End of Study/ Prior to discharge
			Pre-Dose / Dosing	REST OF DAY AT THE	
Informed Consent	X				
Medical History	X	X			
History of drug, alcohol and tobacco use	X				
Physical Examination		X			X
Body Weight	X				X

Height, BMI Calculation	X					
Safety Laboratory / Urinalysis	X					X
Serum Pregnancy Test (β-HCG)	X	X				X
Urine Drug Test	X	X				
Urine Alcohol Test	X	X				
12-lead ECG	X		X			X
Vital signs	X		X	X		X
Admission to the Clinical Research Unit		X				
Study Treatment Administration				X		
PK Blood Sampling			X	X		
Continuous cardiac monitoring			X			
Discharge from Clinic						X
Adverse Event Monitoring and injection site monitoring	X					X
Prior / Concomitant Medication	X					X

Source: Clinical Study Report pages 18-19

Discontinuation Criteria

- Withdrawal of consent
- Investigator feels it is unsafe for subject to continue
- Impossible to obtain laboratory specimens
- AE occurs for which the subject desires to discontinue treatment or investigator determines that is in subject's best interest to be discontinued
- Significant protocol deviation/violation or a trend in deviations/violations
- Concomitant therapy is reported or required which is likely to interfere with the results of the study or compromise subject safety
- Subject is lost to follow-up
- Pregnancy

Evaluations/Endpoints

The primary objective of this study was to establish PK and safety/tolerability profiles on the proposed intramuscular product. This was measured against IM naloxone. Subjects had scheduled PK assessments.

Primary Endpoint: Plasma pharmacokinetic parameters of naloxone hydrochloride

Safety Assessments

- Changes in vital signs[15]
- Changes in 12-lead ECG[16]
- Adverse drug events (ADEs)
- Laboratory screening[17]
- Physical exam

Results

Exposure

Fourteen subjects were included in the PK study. Because the Applicant is utilizing the 505(b)(2) pathway and relying on the Agency's previous findings of Narcan, this exposure is adequate for the purposes of this safety evaluation.

Demographics and Baseline Characteristics

Subjects ranged in age from 22 to 54 years. There were seven men and seven women. The population race was 42.9% black and 57.1% white. No subjects had a clinically significant medical history that would exclude them from participating in the study or were taking exclusionary medications prior to dosing.

Summary of Supportive Safety Findings

There were no major safety findings and no new safety signals in the PK study. There were no deaths or serious adverse events (SAE). There were no severe adverse events (AE) or any discontinuations due to an AE. There were no dropouts or discontinuations.

Injection site evaluation was a predefined safety outcome. Per the Applicant this information was to be collected at each adverse event collection time and categorized per the DAIDS ratings scale at least every eight hours per protocol. The Applicant reported that there were no injection site adverse events and no toxicity was noted at the injection sites during the study.

There were 13 treatment-emergent adverse events (TEAEs) reported by seven subjects. Three TEAEs were reported by two (14.3%) subjects following Treatment A (5 mg/0.5 mL) naloxone HCl IM injection and ten TEAEs reported by five (35.7%) subjects following Treatment B (2 mg/2 mL) IM naloxone HCl.

There were no clinically significant changes in ECGs, physical exams, or vital signs. Subject (b) (6) had a clinically significant laboratory finding which will be discussed further below.

Summary of Adverse Events (AEs)

The most frequently reported TEAEs were nausea (three subjects; one in Treatment A and two in Treatment B) and dizziness (two subjects; one in Treatment A and one in Treatment B). The Applicant classified a majority of the AEs as mild in severity.

Narrative for Subject (b) (6)

Subject (b) (6) was a 54-year old man with no reported past medical history and not taking concomitant medication. His screening (b) (6) bilirubin was elevated at 1.7 mg/dl, despite that, he was enrolled in the study. His end of study bilirubin was further elevated to 2.4 mg/dl. See **Error! Reference source not found.** for further laboratory values for this subject. The Applicant reports that the subject was requested to return for further laboratory testing but he was lost to follow up. The Investigator described this AE as moderate in severity and not related to the study treatment.

Table 3 Summary of Liver Enzymes Subject (b) (6)

Measurement	Screen – (b) (6)	Unscheduled Visit – (b) (6)	End of Study- (b) (6)
Bili (0.2-1.2 mg/dl)	1.7	1.0	2.4
Direct Bili (0-0.5 mg/dl)	0.7		0.6
Indirect Bili (0.0-0.7)	1		1.8
AST (5-34 u/l)	19		18
ALT (0-55 u/l)	17		11
AP (40-153 u/l)	63		51

Source: Summary of Clinical Safety page 4

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/

JENNIFER L NADEL
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11/13/2020 04:06:46 PM

RIGOBERTO A ROCA
11/13/2020 04:14:29 PM

Summary, Clinical, and Cross-Discipline Team Leader Review

Date	
From	Jennifer L. Nadel, MD and Joshua M. Lloyd, MD
Subject	Summary and Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	212854
Applicant	Adamis Pharmaceuticals Corp
Date of Submission	December 31, 2018
PDUFA Goal Date	October 31, 2019
Proprietary Name	Zimhi
Established or Proper Name	Naloxone hydrochloride
Dosage Form(s)	Intramuscular injection
Applicant Proposed Indication(s)/Population(s)	1. An opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. 2. Intended for immediate administration as emergency therapy in settings where opioids may be present. 3. Not a substitute for emergency medical care.
Recommendation on Regulatory Action	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Jennifer Nadel, MD; Josh Lloyd, MD
Pharmacology Toxicology Review	Carlic Huynh, PhD; Newton Woo, PhD; R Daniel Mellon PhD
OPQ Review	Paresma Patel, PhD; Donna Christner, PhD; Jizhou Wang, PhD; Julia Pinto, PhD; Tarun Mehta, PhD; Ubrani Venkataram, PhD (Process) / Jonathan Swoboda, PhD (Facilities),
Microbiology Review	Jennifer Patro, PhD; Jesse Wells, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, MD, PhD
OSI	Xiaohan Cai, PhD; Seongeun Cho, PhD
DPMH	Ethan D. Hausman, MD; Hari Cheryl Sachs, MD

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
DRISK=Division of Risk Management
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

- # Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
Zimhi is a combination product designed to deliver 5 mg of naloxone in 0.5 mL in a pre-filled syringe. Adamis [Applicant], has submitted this New Drug Application (NDA) proposing to use the 505(b)(2) regulatory pathway. The carton/container contains two syringes with the second syringe serving as a second dose if needed. The indication sought for Zimhi is emergency treatment for known or suspected opioid overdose in the community setting by untrained personnel, identical to that of Evzio and Narcan Nasal Spray (NNS). The Applicant states that Zimhi was developed in response to increasing numbers of reports indicating that multiple doses of naloxone have been required in resuscitations, presumably due to the increasing incidence of high-potency opioids in overdoses. To address this, the Applicant has increased the dose of naloxone to 5 mg to be delivered intramuscularly (IM). Evzio delivers 2 mg IM and Narcan Nasal Spray (NNS) delivers 4 mg intranasally (with a relative bioavailability of 50%). Thus, Zimhi is expected to result in higher exposures than the approved drugs. Because of the established efficacy of naloxone and challenges with the feasibility of clinical trials, applicants have chosen to support efficacy by relying on the agency's prior findings of efficacy and safety for approved naloxone products. To do create a scientific bridge to rely on the findings for another product, applicants must conduct a relative bioavailability study comparing the PK of the investigational drug product to a relevant approved product, along with human factors testing, reliability testing, and usability assessments for devices. The systemic safety is extrapolated from approved formulations of naloxone. For this particular product, which is dosed higher than the comparable products, the literature and dosing regimens from naloxone injection in the hospital setting also support systemic safety. As described above, the Division has made every effort to provide an efficient approach to the approval of novel formulations of naloxone to advance the goal of increasing the access to naloxone in the community. However, there are a number of deficiencies that preclude approval of this product. Because of the life or death setting of use, device reliability is required to be at least 99.99%. The calculated reliability for Zimhi was 99.96%. The other deficiencies leading to a Complete Response action an inadequate assessment of extractables and leachables in the drug product, and a failure to provide a scientific bridge to a reference product. The Applicant conducted one comparative pharmacokinetic (PK) study using Evzio (NDA 205787) as the reference drug. Adamis was not able to successfully negotiate right-of-reference from Kaleo, the NDA-holder and subsequently changed the reference product to Narcan NDA 16636 during the review cycle. Thus, Adamis will have to conduct and submit a new PK study using the new reference product.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• According to the CDC https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed September 20, 2019), o From 1999 to 2017, more than 700,000 people have died from a drug overdose. o Around 68% of the more than 70,200 drug overdose deaths in 2017 involved an opioid. o In 2017, the number of overdose deaths involving opioids (including prescription opioids and illegal opioids like heroin and illicitly manufactured fentanyl) was 6 times higher than in 1999. o On average, 130 Americans die every day from an opioid overdose. • Products that deliver naloxone rapidly and can be used by non-healthcare professionals have the potential to save lives by reversing an opioid overdose. Two such products are approved (Narcan Nasal Spray and Evzio). • (b) (4) according to the Applicant, Zimhi was developed to address that concern by increasing the delivered dose. However, there is no direct evidence that high-dose bolus offers any advantage over existing products with regard to overdose with high-potency opioids. • Anecdotally, some overdoses have required multiple administrations of standard doses of naloxone. However, it is not known whether these represent failures of the products approved for use in the community, or the injection solution administered with a nasal atomizer as part of a kit. The latter provides a lower concertation, higher volume dose that results in a lower systemic exposure. Theoretically, a product that delivers more naloxone may offer greater benefits in a subset of cases. The Applicant has not investigated whether the product offers any advantages	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While naloxone is the treatment of choice to reverse the acute opioid intoxication of a patient, it is not a permanent solution for opioid abuse, misuse, and addiction. There has been increasing concern in the community regarding overdoses with highly potent and synthetic opioids. This high-dose product may be more effective at reversing certain opioid overdoses although that is theoretical.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to approved products and is not seeking labeling to that effect.	
Current Treatment Options	• Evzio 2 mg IM • Narcan Nasal Spray (NNS) 4 mg IN	There are currently two approved community-use naloxone products, Evzio and Narcan Nasal Spray. They are administered via the IM and IN routes respectively.
Benefit	• Assuming that the Applicant can demonstrate systemic exposure that meets the criteria for approval and the other deficiencies are surmounted, this product has the potential to reverse opioid overdoses and can be used by non-medically trained persons. • Theoretically, this product may be able to reverse overdoses requiring multiple doses of other products.	Given that the Applicant has neither investigated nor demonstrated advantage related to the higher delivered dose of naloxone, this product would appear to offer benefit similar to Evzio or NNS.
Risk and Risk Management	• Theoretically, a larger bolus of naloxone has a greater risk of precipitating withdrawal in opioid-dependent patients. However, there is literature to support the safety of 5 mg and higher of naloxone in non-opioid dependent patients • The 5 mg dose is expected to generate much higher exposures in the pediatric population than in adults. One case series describing high bolus doses of naloxone in two pediatric patients reported no adverse events attributable to naloxone.	Internal vetting has resulted in the conclusion that no specific risk management is necessary.

- **Background**

This is a 505(b)(2) application for Naloxone Hydrochloride injection (NDA 212854) relying upon the agency's previous findings of safety and efficacy of Adapt Pharma's Narcan (NDA 16636).

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids although current data indicate that deaths associated with prescription opioid use are declining while those associated with illicit opioids continue to rise (CDC 2019). Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury.

As the opioid epidemic continues in the United States, as noted above, current data include reports/investigations showing increases in fentanyl-related overdose fatalities. Additionally, there have been reports of overdose patients requiring multiple doses of naloxone and also reports of naloxone be ineffective. Unfortunately, these reports do not usually describe if these events have occurred with the approved community-use naloxone products, Evzio and/or Narcan Nasal Spray. However, these recent reports and articles such as Somerville et al[1] suggest that there may be a need for higher doses of naloxone to counteract overdoses with fentanyl and other high potency opioids. The Applicant has also cited other published literature to suggest that multiple doses of naloxone are required in an increasing number of opioid overdose cases. It is worth noting that the vast majority of out-of-hospital naloxone use consists of an improvised intranasal product using the naloxone solution for injection with a concentration of 1 mg/mL in a 2 mL vial (compared to 40 mg/mL in a 100 microliter volume for the approved intranasal naloxone product) administered using a mucosal atomizer device and these studies rarely distinguish between products. Therefore, it is unclear whether the apparent increased need for multiple doses of naloxone would have been observed had the higher concentration products been uniformly used.

Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor. If immediately administered, naloxone can reverse the life-threatening effects of an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone 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. Also, the duration of action of naloxone is shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

[1] Somerville NJ, O'Donnel J, Gladden RM, Zibbel JE, Green TC, Youngkin M, et al. Characteristics of Fentanyl Overdose - Massachusetts, 2014-2016. MMWR. 2017;66(14):382-6.

Naloxone has been approved for commercial use since 1971. There are approved drug products containing the active ingredient naloxone in the United States (**Error! Reference source not found.**).

Table 1 Current Naloxone Treatment Options

Drug Product Name	NDA	Approval Date	Dose Form
Narcan	016636	4/13/1971	Solution for injection
EVZIO (Naloxone HCl)	209862	10/19/2016	Autoinjector
Narcan Nasal Spray	208411	11/18/2015	Nasal Spray

Evzio and Narcan nasal spray are approved with the same indication as proposed for Zimhi and are for community use. Naloxone is included as an active ingredient in several products in combination with opioid ingredients for the treatment of opioid dependence. It is generally included in these products to deter abuse of the opioid component.

Labeling for naloxone products contain warnings regarding acute opioid withdrawal. Naloxone may abruptly precipitate of opioid withdrawal in persons who are physically dependent on opioids. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis. In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema.

Clinical efficacy trials present significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of opioid overdose, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it is not necessary to conduct clinical efficacy trials with novel naloxone products as effective doses have been established. The efficacy of a new formulation or route of administration of naloxone relies on a demonstration of adequate systemic naloxone levels in relative bioavailability studies which compare the systemic exposure of naloxone from the new product to an approved product.

For novel naloxone products intended to be used in the community, it is necessary to demonstrate comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration. This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose.

The Applicant developed Zimhi (Naloxone Hydrochloride) as a combination drug-device product and is submitting it under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act). Zimhi is a single-use intramuscular (IM) device that delivers 5 mg of naloxone hydrochloride (HCl). Zimhi is intended for the emergency treatment of known or suspected

opioid overdose, as manifested by respiratory and/or central nervous system depression. It is a drug-device combination product intended for use in the community. It is designed for use in non-healthcare settings by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under IND 136,148. The investigational new drug (IND) application was submitted by Adamis Pharmaceuticals Corporation (also referred to as the "Applicant" throughout this review), on November 21, 2017.

The Applicant submitted a request for a priority review with the New Drug Application (NDA) on December 31, 2018. (b) (4) the request for priority review was denied.

The Applicant initially planned to rely on the agency's prior findings of efficacy and safety for the original Narcan (NDA 16636) and Evzio (NDA 205787). During the NDA review, it was determined that the Applicant could not rely on Evzio due to existing patent protection. The Applicant decided to only rely on NDA 16636. The Narcan labeled dosing is an initial dose of 0.4 mg to 2 mg via the intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes, followed by additional doses up to 10 mg. The Applicant is also relying on published literature to support the safety of the 5 mg dose. The Applicant specifically cited an article from Bracken *et. al*[2] which describes a study that evaluated the effects of naloxone on acute spinal-cord injury. In this study, naloxone was given to 154 patients as a 5.4 mg/kg bolus (324 mg to 378 mg for an average 60 kg to 70 kg adult). The patients then received 4.0 mg/kg/hour for 23 hours. The mortality and major morbidity findings in the naloxone group were similar to that of the placebo group. In a study by Cohen *et al*[3]. healthy subjects received up to 4 mg/kg of naloxone without serious adverse effects reported.

Evzio was initially approved as a 0.4 mg dose, which has been replaced following approval of a 2 mg IM dose of naloxone. Narcan Nasal Spray was initially approved as a 4 mg dose, followed by approval of a 2 mg dose. The 2 mg dose is no longer marketed. The Applicant's proposed product has a dose of 5 mg of naloxone for IM or subcutaneous injection and if approved, would have the highest dose of naloxone commercially available. An observational and retrospective article by Farkas et al. in 2019 reported that higher doses of naloxone (defined as greater than 4.4 mg) in a pre-hospital environment were associated with a higher rate of pulmonary complications. While association does not equal causation and this was a retrospective trial, pulmonary edema is a labeled warning for naloxone. As higher and high

[2] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury. New England Journal of Medicine. 1990;322(20):1405-11.
[3] Cohen M, Cohen R, Pickar D, Weingartner H, Murphy D, Bunney WJR. Behavioural effects after high dose naloxone administration to normal volunteers. The Lancet. 1981;318(8255):1110.

doses of naloxone are used to treat opioid overdoses, we will need to keep this is mind as a possible complication.

Summary of Presubmission Regulatory Activity

There were no meetings with the Applicant prior to submission of this NDA.

Date	Meeting/Submission Type	Key Comments
1/10/2018	Initial IND (IND 136148) placed on full clinical hold	• (b) (4) • Sponsor also advised to use planned NDA device in pivotal PK study
4/10/2018	Full clinical hold removed	• Concentration lowered to 10 mg/mL • Nonclinical data submitted to support
12/27/2018	Fast Track Designation denied	
3/11/2019	Fast Track Designation denied after reconsideration	

- **Product Quality**

The drug product, Naloxone Hydrochloride injection, 5 mg / 0.5 mL is a clear, colorless, sterile solution packaged in a prefilled syringe for subcutaneous or intramuscular administration. The prefilled syringe for single use consists of a (b) (4) glass syringe barrel sealed with a rubber plunger on one side after filling, and fitted with stainless-steel needle (25G 5/8" cannula) and a rigid needle shield on the other. (b) (4) All excipients meet compendial requirements and are within the range used in approved products. The drug product specifications for naloxone and related impurities (b) (4) are all acceptable. The acceptance criteria for impurities are acceptable and the risk assessment of elemental impurities is adequate.

The microbiology review notes the following, reproduced verbatim:

Drug product is a sterile solution [redacted] (b) (4)

[redacted] (b) (4)

The following executive summary is reproduced verbatim from the Integrated Quality Assessment:

> The NDA 212854 for **Naloxone Hydrochloride injection, 5 mg / 0.5 mL** is **not approvable** from drug product quality perspective as well as device constituent of this combination product. Drug substance, manufacturing (process and facilities) and microbiology reviews recommend for approval. However, per the drug product review, extractables studies on primary container closure did not predict any leachables observed in the drug product. Primary batches of drug product also have out of trend results (OOT) related to [redacted] (b) (4) particulate matter and leachables reported in stability testing. Sponsor is unable to justify the root cause for the three OOT test results. Sponsor's root cause investigation outcome and reasoning for revision of problematic leachable data, [redacted] (b) (4) is not convincing. No data from [redacted] (b) (4) provided to support their explanation for the OOT". Thus, drug product reviewer recommended sponsor to perform more vigorous extractables studies to generate extractables profile that can predict the leachables.
>
> Drug product reviewer also recommend inspection (PAI) of the leachables testing facilities [redacted] (b) (4) in the next review cycle.
>
> CDRH is also recommending that the device constituent of the combination product is **not approvable** for the proposed indication, due to unacceptable product reliability test results using a single device.

- ## Nonclinical Pharmacology/Toxicology

The following is reproduced verbatim from the nonclinical pharm/tox review:

> No nonclinical studies were submitted in this NDA. There were no safety issues with the formulation as there are no novel excipients, with the drug substance and drug product specifications as the specifications did not exceed ICH Q3A(R2) and Q3B(R2)

qualification thresholds, and with the elemental impurities assessment as all levels of the elemental impurities were below ICH Q3D limits.

To support the local safety of the higher concentration of the naloxone formulation, a local tolerance study in New Zealand White rabbits (previously reviewed by Dr. Newton Woo) was conducted. Minimal necrosis and regeneration along the needle tract were observed in the treatment group (10 mg/mL naloxone); however, the incidence and severity were not different when compared to a group that received the highest currently approved naloxone concentration of 5 mg/mL. Given the results from the local tolerance study, there are no safety concerns from a local perspective with the Applicant's 10 mg/mL naloxone formulation. In terms of systemic safety of the formulation, the Applicant was asked in the 74-day letter to justify the systemic safety of the new formulation with nonclinical data or with prior clinical experience. The Applicant replied and argued the systemic safety of the new formulation through a clinical literature-based justification (refer to the Medical Officer's review for the systemic safety of the formulation).

The Applicant submitted an extractables/leachables evaluation to support the safety of the container closure system. However, the extractables/leachables assessment was deemed inadequate as the Chemistry, Manufacturing, and Controls (CMC) review team identified a number of deficiencies. Briefly, there was not an acceptable extractable leachable correlation as the extractables studies failed to detect several compounds observed in the leachable study. Given this lack of correlation, this Reviewer does not have confidence that the leachables assessment evaluated for all potential leachables. Further, there were several compounds that exceeded the qualification threshold of 5 mcg/day and there were several inconsistencies in the leachable data. As such, following consultation with the CMC review team, we agree that more robust extraction studies are needed to inform what compounds should be monitored for in the leachables evaluation and more robust leachables data will be required along with a risk assessment for all compounds that exceed the qualification threshold of 5 mcg/day.

- ## Clinical Pharmacology

The following has been reproduced verbatim from the clinical pharmacology review:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA 212854 submission dated 12/31/18. Since the Sponsor did not establish adequate scientific bridge to the listed drug, NDA 016636, for this 505(b)(2) application, the application is not acceptable from clinical pharmacology perspective. To solve this issue, the sponsor needs to provide adequate data to establish the scientific bridge.

In the NDA submission, the sponsor submitted a comparative bioavailability study APC 6000-01 using Evzio 2 mg auto-injector (NDA 209862) as the comparator but

identified Narcan injectable (NDA 016636) and Evzio 0.4 mg auto-injector (NDA 205787) as the listed drug products. In the Day 74 filling letter issued on 3/13/19, clinical pharmacology Information Request regarding the listed drug products and appropriate PK bridging were conveyed to the sponsor. In the response to the Day 74 letter, the sponsor stated that they reference Evzio 2 mg auto-injector (NDA 209862), the comparator used in Study APC 6000-01, as the listed drug. However, in a teleconference held on 6/3/19, the sponsor proposed to remove Evzio 2 mg auto-injector as the listed drug and identify Narcan injectable (NDA 016636) as the listed drug. The sponsor proposed to conduct a new comparative bioavailability study APC 6000-03 using Naloxone Hydrochloride injectable (ANDA 072076) as the comparator. When the Sponsor submitted the protocol on 7/3/19, it was decided then that study APC 6000-03 may be reviewed in this cycle if there is no other approvability issue. As of today (9/19/19), the final study report and data have not been submitted to the agency for review.

During the wrap-up meeting held on 9/18/19, it was mentioned that there are deficiencies from other disciplines to prevent approval of this NDA in this review cycle. Considering the PDUFA date is Oct 31, 2019, it was decided that the results of study APC 6000-03 will not be reviewed in this cycle, if the Sponsor is able to submit the study report before the PDUFA date. Therefore, the NDA submission does not provide adequate data to establish a PK bridging between the proposed product and the listed drug product, Narcan injectable (NDA 016636). To resolve the deficiency in establishing a sufficient PK bridging for this 505(b)(2) NDA, the sponsor must submit the comparative bioavailability APC 6000-03 to the agency for review.

- ## Clinical Microbiology

Not applicable.

- ## Clinical/Statistical- Efficacy

No new clinical efficacy data were included in this submission. The Applicant plans to rely on the agency's prior findings of efficacy from the reference product, Narcan. The Applicant's bioavailability study comparing their product to the reference product was not submitted with their NDA submission and so has not been reviewed.

- ## Safety

There were no safety studies submitted in support of this application. The Applicant originally stated they would be relying on the NDA for the original Narcan (NDA 16636) and Evzio (NDA 205787) to establish safety and efficacy of the proposed product.

The Applicant performed one relative bioavailability study in healthy volunteers, Study APC6000-01.

Study APC6000-01

"An Open-label Randomized, Single-dose, 2-period, 2-treatment Crossover Bioavailability Study Comparing 5 mg/0.5 mL of Intramuscular Naloxone Hydrochloride to 2 mg/0.4 mL Intramuscular Naloxone Hydrochloride Auto-injector (Evzio) in Healthy Subjects"

Study period April 16, 2018 to April 28, 2018

One clinical site in Dallas, Texas

Protocol

Objectives/Rationale

- To compare bioavailability of 5 mg/0.5 mL intramuscular naloxone hydrochloride to 2 mg/0.4 mL intramuscular naloxone hydrochloride auto-injector (Evzio) in healthy subjects

Overall Design

This study was a randomized, open-label, 2-period, 2-treatment crossover PK study in 14 healthy volunteers aged 18 to 55 years old to evaluate the PK of Zimhi vs. Evzio 2 mg. Subjects received intramuscular injections to anterolateral aspect of the thigh.
The study consisted of a screening visit (up to 28 days prior to Study Visit 1) and two dosing visits (each separated by a minimum of 48 hours). Safety assessments were conducted throughout the study, including physical exams, routine laboratory tests, pregnancy tests, ECGs, adverse events assessments, vital sign assessments, and local skin monitoring.

Treatment

Each subject received both of the treatments. The injections were given in the anterolateral aspect of the thigh. There treatments were 5 mg/0.5 mL IM naloxone (Zimhi) and 2 mg/0.4 mL IM naloxone (Evzio). The Applicant used the to-be-marketed formulation and device for the Zimhi test product.

Population

The planned enrollment was for 14 healthy subjects.

Inclusion and Exclusion Criteria

The enrolled population was otherwise healthy, not pregnant, aged 18 to 55 years of age inclusive. Appropriate precautions were taken to screen for medical history, physical exam, and any medications. The population enrolled was appropriate for the study.

Table 2 Summary of Activities

Activity	Screening	For Periods 1 and 2		Period 2 only

	Days -28 to Day -1	Day - 1	Day 1 Pre-Dose	Day 1 Dosing	Day 2	End of Study/ Prior to discharge
			Pre-Dose	Dosing		
Informed Consent	X					
Medical History	X	X				
History of drug, alcohol and tobacco use	X					
Physical Examination		X				X
Body Weight	X					X
Height, BMI Calculation	X					
Safety Laboratory / Urinalysis	X					X
Serum Pregnancy Test (β-HCG)	X	X				X
Urine Drug Test	X	X				
Urine Alcohol Test	X	X				
12-lead ECG	X		X			X
Vital signs	X		X	X		X
Admission to the Clinical Research Unit		X				
Study Treatment Administration				X		
PK Blood Sampling			X	X		
Continuous cardiac monitoring			X			
Discharge from Clinic						X
Adverse Event Monitoring	X					X
Prior / Concomitant Medication	X					X

REST AT THE CLINIC DAY E

Source: Study protocol pages 12-13

Discontinuation Criteria

- Withdrawal of consent
- Investigator feels it is unsafe for subject to continue
- Impossible to obtain laboratory specimens
- AE occurs for which the subject desires to discontinue treatment or investigator determines that is in subject's best interest to be discontinued
- Significant protocol deviation/violation or a trend in deviations/violations
- Concomitant therapy is reported or required which is likely to interfere with the results of the study or compromise subject safety
- Subject is lost to follow-up
- Pregnancy

Evaluations/Endpoints

The primary objective of this study was to establish PK and safety/tolerability profiles on the proposed intramuscular product. This was measured against IM naloxone. Subjects had scheduled PK assessments.

Primary Endpoint: Plasma pharmacokinetic parameters of naloxone hydrochloride

Safety Assessments

- Changes in vital signs[4]
- Changes in 12-lead ECG[5]
- Adverse drug events (ADEs)
- Laboratory screening[6]
- Physical exam

Results

Exposure

Fourteen subjects were included in the PK study. Because the Applicant is utilizing the 505(b)(2) pathway and relying on the Agency's previous findings of Narcan and Evzio, this exposure is adequate for the purposes of this safety evaluation.

Demographics and Baseline Characteristics

Subjects ranged in age from 31 to 53 years, and the study populations was predominantly male. The population was half White and half African-American (

Table 3).

Table 3 All Subjects in Study Population

Subject	Sex	Ethnicity Hispanic or Latino?	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
(b) (6)	Male	No	White	41	167.0	82.1	29.4
	Male	No	White	37	177.0	92.6	29.6
	Male	Yes	White	42	178.0	77.2	24.4
	Female	No	White	36	160.0	81.7	31.9
	Female	No	Black or African American	39	166.0	78.7	28.6
	Female	No	Black or African American	28	165.0	71.9	26.4

[4]Heart rate, systolic blood pressure/diastolic blood pressure, respiratory rate, body temperature measured at screening, pre-dose, 6 and 12 hours post-dose, Day 2, end of period 2 or early termination
[5]ECGs at screening, pre-dose (at period 1 and 2) and at period 2, prior to discharge
[6]CBC with differential, serum comprehensive metabolic panel, urinalysis

(b) (6)							
	Male	No	White	47	175.0	74.2	24.2
	Female	No	Black or African American	33	170.0	78.3	27.1
	Male	No	White	53	176.0	79.7	25.7
	Male	No	Black or African American	41	181.0	88.8	27.1
	Male	Yes	White	27	172.0	81.0	27.4
	Male	No	Black or African American	31	182.0	87.0	26.3
	Male	No	Black or African American	35	171.0	77.4	26.5
	Male	No	Black or African American	49	193.0	78.0	20.9

Source: Clinical Study Report Demographic Data Page 3

There were no major safety findings and no new safety signals in the PK study. There were no deaths or serious adverse events (SAE). There were no severe adverse events (AE) or any discontinuations due to an AE. No AEs were reported at all. There were no dropouts or discontinuations.

Summary of Safety

The safety for this high-dose naloxone product is based primarily on the agency's prior findings for Narcan (naloxone hydrochloride) solution for injection. As mentioned in the background section, there is literature to support the safety of doses of naloxone higher than 5 mg. The Applicant has described several of these studies in the submission. An example of an article that the Applicant specifically cited is from Bracken *et. al*[7] which describes a study that evaluated effects of naloxone on acute spinal-cord injury. In this study, naloxone was given to 154 patients as a 5.4 mg/kg bolus (324 mg to 378 mg for an average 60 kg to 70 kg adult). The patients then received 4.0 mg/kg/hour for the 23 hours. The mortality and major morbidity findings in the naloxone group were similar to that of the placebo group. Reversal of an opioid overdose in an individual not physically dependent on opioids would likely be safe. However, the safety when administered in persons who are physically dependent on opioids is less clear, as it may precipitate an acute withdrawal syndrome. Relative to the available doses of Evzio and Narcan Nasal Spray, it is likely that a precipitated withdrawal from a 5 mg IM dose would be more severe.

• Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held to discuss this product.

• Pediatrics

The safety and effectiveness of naloxone has already been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone

[7] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury. New England Journal of Medicine. 1990;322(20):1405-11.

in this population has already been supported by adult bioequivalence studies as well as evidence of safety and effectiveness in pediatrics in clinical practice.

This product represents a new dosing regimen and thus triggers the Pediatric Research Equity Act (PREA) (21 U.S.C 355c), and the Applicant is required to provide an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients. No pediatric clinical studies are proposed because pharmacokinetic (PK) studies in healthy, pediatric patients would involve more than minimal risk without the prospect of direct benefit to the population. Furthermore, PK studies cannot be conducted in a pediatric opioid overdose population because it is an immediately life-threatening condition and PK samples cannot be collected in the context of emergency treatment of the overdose, in addition to other ethical considerations that preclude conducting
studies.

The Applicant did not submit a Pediatric Study Plan (PSP) to the IND; therefore, no agreed PSP exists. The Applicant also did not submit a Pediatric Assessment with the NDA submission. The Applicant did submit a pediatric assessment, on May 20, 2019, in response to the 74-day letter sent after the Division Filing Meeting. The pediatric plan relies on the safety and effectiveness of other naloxone hydrochloride products in the post-marketing setting as well as data available in the medical literature, clinical practice guidelines, and approved labeling for the 0.4 mg auto-injector to support the pediatric labeling.

The Applicant is seeking approval of its 5 mg device for the treatment of all pediatric populations as an initial dose in cases of known or suspected opioid overdose. The 5 mg dose would represent a new and higher dose then the already approved community-use products. Evzio which is similar to this product in that it is intended for the intramuscular (IM) route uses a 2 mg dose. Narcan Nasal Spray is a 4 mg product that uses the intranasal (IN) route and shows a PK profile similar to a 2 mg IM dose of naloxone. The original Narcan product is labeled for dosing of 0.4 to 2 mg per dose via the IM, IV, or subcutaneous (SC) routes. The Applicant's proposed product would represent 2.5 times increase in the maximum approved community-use product. Please see the background section of this review for adult studies evaluating high dose naloxone.

The literature to support the safe and effective use of 5 mg naloxone of naloxone in the pediatric population is lacking and the Applicant has summarized only a small number of case reports. While there is not a particular concern regarding efficacy of this dose in children, there is a concern for safety given that the risks are unknown. To support use of this product in pediatrics, the Applicant has submitted articles discussing case reports of pediatric patients receiving high dose naloxone.

- Gourley and Coulthard[8] describe a case where a 2-year-old boy received naloxone boluses followed by an infusion of naloxone at a rate of 0.3 mg/hour (hr) in treatment of a nor-methadone overdose. The total naloxone dose received was 7 mg

[8] Gourlay GK and Coulthard K. The role of naloxone Infusions in the treatment of overdoses of long half-life narcotic agonists: Application to nor-methadone. British J of Clin Pharmacol. 1983;15: 269-72.

administered over 28 hours. The article reported that the patient recovered without any apparent sequalae and was discharged home.

- Lewis et al[9] described a case of a 31-month-old girl who required a naloxone infusion to treat codeine-induced respiratory and CN depression. She received naloxone at 0.4 mg/hr over 9 hours. Her total naloxone dose was 4.1 mg. She did not have any report of side effects or toxic effects from this infusion.
- Tenenbein[10] described two cases of high naloxone infusion in pediatric patients. The first case involved an accidental ingestion of 100 mg normethadone by a 1-year-old 11.3 kg). The patient was initially treated with multiple bolus doses of naloxone, but when respiratory depression recurred, an infusion of 0.04 mg/kg/hr was started. The infusion was continued for 2.5 days. The second infant, a 3-day-old (2.44 kg), received an inadvertent morphine overdose of 5 mg due to a dosing error while hospitalized. This patient was given 4 naloxone boluses, followed by an infusion of 0.16 mg/kg/hr. The infusion was continued for 5 days, during which repeated attempts to wean the infusion resulted in further worsening of respiratory function. In both cases, the patients were discharged without sequelae reported.
- Greenberg[11] reported two cases of ultra-rapid detoxification in infants, ages 9 and 18 months, who had developed physiologic dependence after receiving prolonged, high-dose opioid therapy following surgery for congenital heart disease. After administering propofol and clonidine, both patients were given naloxone by IV bolus (10 mg/kg) followed by an infusion of 10 µg/kg/hour in an intensive care unit. Naloxone was continued until the patients were extubated and free of withdrawal symptoms. Specific toxicity to naloxone was not mentioned in this article. Both patients were critically ill at baseline and had congenital heart disease among other medical problems.

Precipitation of acute opioid withdrawal is unlikely to occur with use of 5 mg of naloxone in the majority of the intended pediatric population since the most likely cause of opioid exposure in younger pediatric patients, particularly those less than 6 years of age, is acute accidental opioid ingestion. There are some pediatric patients who may be opioid dependent, particularly those with neonatal opioid withdrawal syndrome and administration of naloxone in patients being managed with an opioid taper could result in an acute withdrawal syndrome. Should this occur, the patient would require immediate medical care, but an acute withdrawal syndrome would be manageable with appropriate care and is outweighed by the need to avoid risk of death from an overdose.

The needle for the proposed product is a 25-guage needle with a length of 5/8 inches. This needle was specifically discussed with the DPMH team and DAAAP and the Divisions agree that it is acceptable. The needle length is within the CDC recommendations[12] for intramuscular injection in the anterolateral thigh muscle of pediatric patients down to the

[9] Lewis JM, Klein-Schwartz W, Benson BE, et al. Continuous naloxone infusion in pediatric narcotic overdose. Am J Dis Child. 1984;138(10):944-6.
[10] Tenenbein M. Continuous naloxone infusion for opiate poisoning in infancy. J Pediatr. 1984;105(4):645-8.
[11] Greenberg M. Ultrarapid opioid detoxification of two children with congenital heart disease. J Addict Dis. 2000;19:53-8.
[12] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration html#fig_2

neonatal age group. Additionally, to further diminish concerns regarding needle length, the instructions for use of the product in patients less than one year of age, include instructions to pinch the thigh muscle while administering the product.

Applicant's proposed labeling:

> Section 8.4 of the Prescribing Information:
>
> The safety and effectiveness of PRODUCT™ (for intramuscular and subcutaneous use) have been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone hydrochloride in all pediatric patients is supported by adult bioequivalence studies coupled with evidence from the safe and effective use of another naloxone hydrochloride injectable product. No pediatric studies were conducted for PRODUCT™.
>
> Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.
>
> In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect. [see Warnings and Precautions (5.3)].
>
> In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering PRODUCT™. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [see Dosing Information (2.2)].

Evzio, mentioned earlier in the review, is an auto-injector naloxone product with the same indication as the proposed product. As part of its approval, its Applicant was required to show safety of the needle length in neonates. This was required because of the auto-injector component and the concern that the force from that could cause the needle to hit the femur. The further concern was that this could cause device malfunction and that naloxone would not be delivered, or that the needle could break off the device and be left in the leg. Zimhi is not an autoinjector and so does not provide the same force or same concerns.

The Division of Pediatric and Maternal Health (DPMH) has been consulted to assist in the review of the submitted pediatric information, label, and approval recommendations including the Pregnancy and Lactation Labeling Rule (PLLR) language. After an internal meeting with DPMH and the wrap-up meeting for this NDA cycle, both Division have agreed that this product is appropriate for pediatric use for all ages including down to birth.

- **Other Relevant Regulatory Issues**

Financial Disclosures
The Applicant submitted form FDA 3454 and certified that the Investigator did not have reportable financial disclosures. There was one investigator listed, (b) (6)

Compliance with Good Clinical Practices
The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

Inspections
The site for study APC 6000-1 was inspected by the Office of Study Integrity and Surveillance (OSIS). The final inspection classification is Voluntary Action Indicated (VAI). OSIS did find an objectional condition during the inspection, however, the finding was determined to not impact the reliability of the clinical data from the study. Inspection for the new bioavailability study using a different naloxone product will be considered in a future review cycle.

505(b)(2)
The Applicant originally planned to reference the agency's priof findings of efficacy and safety for Evzio (Kaleo, NDA 212854). This infringed upon existing patents for Evzio and the a lawsuit was initiated against the Applicant. After the Applicant withdrew the Patent IV Certification for Evzio and planned to reference a different product as the listed drug, Kaléo agreed to withdraw the patent infringement suit. The two parties have each filed a copy of the settlement agreement along with a request of voluntary dismissal in the Delaware and Virginia courts.

- **Labeling**

Should the Applicant adequately address the deficiencies identified in this review cycle, key issues in labeling include:

- One of the concerns for the labeling of naloxone products with different doses and routes intended for use in the community is regarding differentiating those doses in labeling to inform prescribers, and even laypersons, of the clinical scenarios or dosing criteria to determine when one dose would be used over another in a community setting, which is a different setting than was intended for the reference product Narcan. The Applicant's submission did not include data to inform that decision.

- If approved, there is concern that the Applicant will attempt to promote Zimhi for a wider spectrum of opioid overdoses than competitors. Because that concept is only theoretical, such language is not appropriate for labeling.

• Postmarketing Recommendations

This section is not applicable as this will be a complete response.

• Recommended Comments to the Applicant

PRODUCT QUALITY

1. There is no correlation established between the extractable and leachable studies. The extractables studies failed to detect any extractables and specifically failed to detect the leachables observed in the leachable study.

   To address this deficiency:
   Perform a more vigorous extractables studies that can establish a good correlation with the leachable assessments. Use USP <1663> and <1664> as guides in conducting these studies.

2. We note inconsistency in the leachable data during stability testing. Additional data are required to justify these results:

To address this deficiency:

a. Provide the lapsed time between the sample's withdrawal and date of reanalysis of the 6-month time point.

b. Justify the use of (b) (4) for the 6-month sample time point, analyzed at (b) (4) and not for the original data presented at other time points.

c. Explain why the (b) (4)-related leachants have not been observed in the (b) (4) and have not been removed after (b) (4).

d. Provide the background peaks from the (b) (4) to confirm that the extra peaks are from the (b) (4)

e. Unambiguously establish the structures of the leachables at RRT (b) (4) and (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

f. Repeat the leachable study at each time point of the stability study, using validated analytical methods. Run blanks to establish background. Provide all data in your resubmission.

3. The photo-degradants at RRT (b) (4) have not been identified.

To address this deficiency:
Unequivocally establish the structures of the photo-degradants at RRT (b) (4) by comparison with reference standards if available, or spectroscopic techniques such as Mass spectra, UV, IR and NMR.

4. Particulate matter is a critical attribute for injectables. We note an inconsistency in the data provided at the 6-month time point for particulate matter testing under the long-term condition for Batch 1838-022. These out of trend results may mean variation in the analytical methods used for determination of particulate matter.

To address this deficiency:
Re-evaluate the analytical method and revalidate if required.

5. As the naloxone product may be widely available in the community, it could be stored in other than controlled conditions (such as a vehicle in the summer or winter). Sufficient data to support these storage conditions were not provided.

To address this deficiency:

Provide additional accelerated stability data to demonstrate lack of degradation, color change, or particulate formations. Similarly test the product when frozen and thawed. Report any particulate formation, color change, degradation and time required to thaw.

DEVICES

6. We previously requested reliability testing and analysis to demonstrate that the reliability for drug delivery using a single device is 99.99% or greater. The provided results demonstrate that the reliability of a single device is 99.96%. Your analysis uses the availability of two devices to achieve 99.99%; however, this does not adequately mitigate the risk of a patient failing to receive the complete dose because they may need both doses. The expectation is that the reliability of an individual product dose delivery is not less than 99.99%.

   To address this deficiency:
   Implement appropriate modifications to the device control strategy and provide additional data demonstrating that the product has a reliability of at least 99.99% for a single device.

NONCLINICAL

7. You have not provided appropriate extractable/ leachables data to permit a substantive nonclinical toxicological risk assessment for the proposed container closure system.

   To address this deficiency:

   Submit a revised toxicological risk assessment based on adequate extractable leachable data. To inform the risk assessment, conduct adequate extractable leachable studies to support the safety of your proposed container closure system, taking into consideration the following:

   a. Results of the extraction studies should establish an acceptable extractable leachables correlation that will assure adequate monitoring of the drug product stability samples for all potential leachables from the container closure system.

   b. Provide a justification for the compounds targeted in the leachable study based on the extraction data. In general, all extractables exceeding 5 mcg/day should be targeted in the leachable study.

   c. Based on the results of the leachable studies, identify all compounds in the drug product present at levels equal to or greater than 5 mcg/day taking into consideration the maximum daily dose of your drug product and submit a toxicological risk assessment for every leachable present in the drug product at or above the 5 mcg/day qualification threshold. The risk assessment must be based on the highest level of the leachable over the course of the proposed shelf-life.

d. Toxicology data from published literature or from the public domain that are used to support leachable qualifications must meet regulatory standards with adequate details to permit substantive independent review. Referencing databases, such as ECHA, with limited details regarding toxicity information is not acceptable. QSAR analysis and identification of a NOAEL (no observed adverse effect level) for structurally similar compounds to qualify leachables that have limited toxicity information is not acceptable unless it is accompanied with adequate justification via scientific data or literature that allows for such a bridge or extrapolation. These databases can be used to identify the pivotal studies used to support your toxicological risk assessment; however, the pivotal studies should be submitted with the NDA to permit independent review. Revise your toxicological risk assessment to employ permission daily exposure levels accordingly as per ICH Q3C(R5) principles. Submit copies of toxicology risk assessment reports and cited literature.

CLINICAL PHARMACOLOGY

Although you submitted relative bioavailability Study APC 6000-03, this information was submitted too late in the review cycle to allow for a substantive review. Therefore, we have not determined whether you have established an acceptable scientific bridge between your proposed drug product and the referenced Narcan product to demonstrate that such reliance is scientifically justified. We are withholding any comments on the relative bioavailability study until after you submit a response to this Complete Response letter.

- **Appendix**

Clinical Investigator Financial Disclosure
Review Template

Application Number: 212854

Submission Date(s): December 31, 2018

Applicant: Adamis Pharmaceuticals Corporation

Product: Zimhi

Reviewer: Jennifer Nadel, MD

Covered Clinical Study (Name and/or Number): (b) (6)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None identified		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator," and stated a total of 1 investigator was listed and the study was performed through the contract research organization, (b) (6) *The form certified that they had no financial interests or arrangements to disclose.*

Given no investigator had financial interests or arrangements to disclose, the possibility of bias in the results based on financial interests is unlikely.

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/

SWATI A PATWARDHAN
11/22/2019 03:09:13 PM

JENNIFER L NADEL
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SHARON H HERTZ
11/22/2019 03:32:00 PM