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

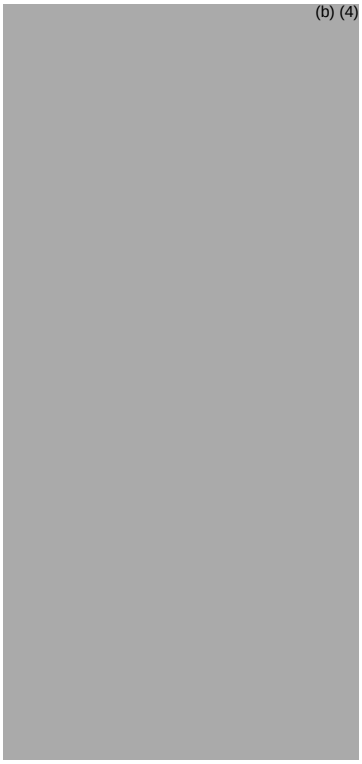
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to mitigate the risk of precipitated withdrawal in this population. • There are no comparative safety data between this product and other naloxone products to inform prescribing decisions when choosing product for opioid reversal	device product 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)

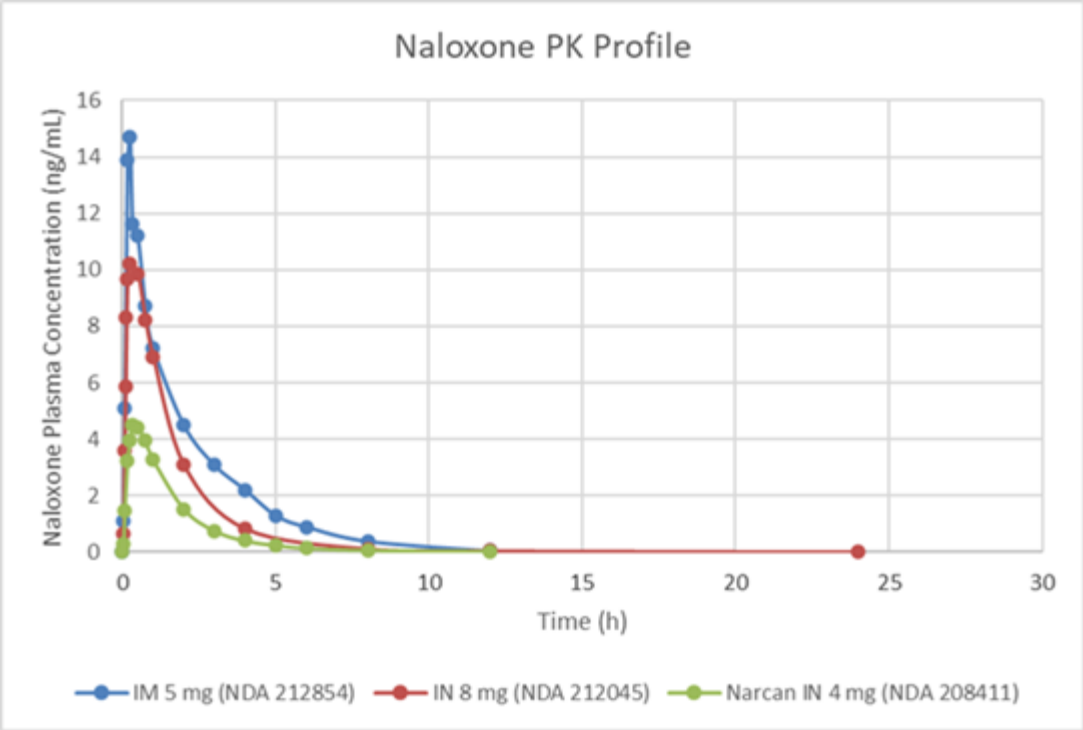


Figure created by Wei Qui, PhD from the clinical pharmacology team

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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/s/

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