

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217722Orig1s000

OTHER REVIEW(S)

Draft Labeling Review for RiVive (Naloxone Hydrochloride 3 mg) Nasal Spray

SUBMISSION DATES:	October 28, 2022; May 12, 2023, June 06, 2023, June 23, 2023, July 06, 2023, July 19, 2023
NDA:	217722 (Original NDA)
ACTIVE INGREDIENTS:	Naloxone hydrochloride 3 mg
DOSAGE FORM:	Nasal spray
APPLICANT:	Harm Reduction Therapeutics
REVIEWER:	Robert Bahde, PhD, DNPD I/ONPD
TEAM LEADER:	Kevin Lorick, PhD, RAC, DNPD I/ONPD
PROJECT MANAGER:	CDR Trang Tran, Pharm.D., MBA, BCPS DRO-NPD/ORO/OND

I. BACKGROUND

Harm Reduction Therapeutics submitted, on September 30, 2022 and October 28, 2022, an original new drug application (NDA), NDA 208411, for RiVive Nasal Spray (naloxone hydrochloride 3 mg). If approved, this drug product will be the second approved nonprescription nasal spray for the emergency treatment of opioid overdose. Applicant proposed new labeling that follows nonprescription labeling approved for Narcan Nasal Spray (naloxone hydrochloride 4 mg), which was approved early this year on March 29, 2023 (see NDA 208411).

Naloxone hydrochloride (“naloxone”) is a known opioid antagonist with a history of safe and effective use in prescription and emergency settings for reversing the effects of opioid overdoses. In response to the increasing number of opioid overdose deaths, the Agency has sought to increase access to naloxone drug products. These efforts include: 1.) increasing the shelf life of naloxone nasal spray drug products from 24 to 36 months, 2.) requiring recommendations about naloxone in the prescribing information of opioid drug products, 3.) approving more naloxone drug products (including naloxone products approved under ANDAs, i.e. “generics”) and 4.) issuing an immediately-in-effect guidance to industry clarifying the scope of the public health emergency exclusion and exemption under the Drug Supply Chain Security Act as they apply to the distribution of FDA-approved naloxone products (**87 FR 68702**, November 16, 2022). However, none of these previous actions address the stigma that is associated with purchasing naloxone drug products. By introducing more nonprescription drug products, in addition to Narcan Nasal Spray (see NDA 208411/S-006), more naloxone products will be placed on store shelves necessitating competitive pricing, thus increasing naloxone accessibility. OTC access of more naloxone products will also mitigate some stigma associated with naloxone use and the need to interact with a pharmacist when obtaining naloxone.

To encourage drug manufacturers to develop a nonprescription naloxone drug product, FDA developed and validated two model DFLs that differ by the route of administration (injection vs nasal spray). The validation studies of the model label (Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study) were announced in Federal Register (**87 FR 68702**, November 16, 2022) and published in The New England Journal of Medicine (NEJM 382(22) 2129–2136). When developing the model DFL, FDA considered, with input from addiction experts, what information in the Full Prescribing Information (Rx label) for prescription naloxone drug products was critical for proper consumer use during an emergency, for example indication, “**Directions**”, “**Warning**” and “Precautions.” This information was organized in the model DFL using an abundance of white space and “chunking” information (i.e., breaking up information into small units, or chunks, that make it easier to notice). The “**Warning**” heading, which usually is provided before telling a consumer how to use a product, were placed after the “**Directions**” heading. This re-ordering of headings was found to increase label comprehension during the testing of the model DFL. Pictograms, whose presence in the DFL would not be compatible with 21 CFR 201.66, were added adjacent to the DFL to improve the understanding of the DFL’s “**Directions**” section.

Applicant created their DFL by modifying the model DFL to provide device-specific instructions for their drug product. These changes were evaluated in a human factors validation study (HFVS) intended to demonstrate that users can safely and effectively use the drug product when following the modified DFL. In this case, Applicant modified steps 2, 3, and 4 of the “**Directions**” for their nasal spray device. Division of Medication Error Prevention and Analysis 2 (DMEPA 2) reviewed the results of the HFVS for RiVive Nasal Spray and made labeling recommendations aimed at addressing the use errors that occurred in the HFVS. These recommendations were aimed at 1.) modifying language in Steps 2, 3, and 4 of the “**Directions**,” 2.) adding statements to the outer carton, blister label, and quick start guide (QSG) (i.e., package insert), and 3.) adding an image of a hand properly holding the nasal spray device on the outer carton PDP and to the QSG. This image of a hand holding the nasal spray device included labels that point to the nozzle and plunger.

Five important statements were developed using DMEPA’s recommendations (see below). These statements should be included in labeling to ensure easy, consistent, safe, and effective use of this drug product.

- For use in the nose only
- Do not test nasal spray device before use
- 1 nasal spray device contains 1 dose of medicine
- Each device sprays 1 time only
- Read directions before use

14 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

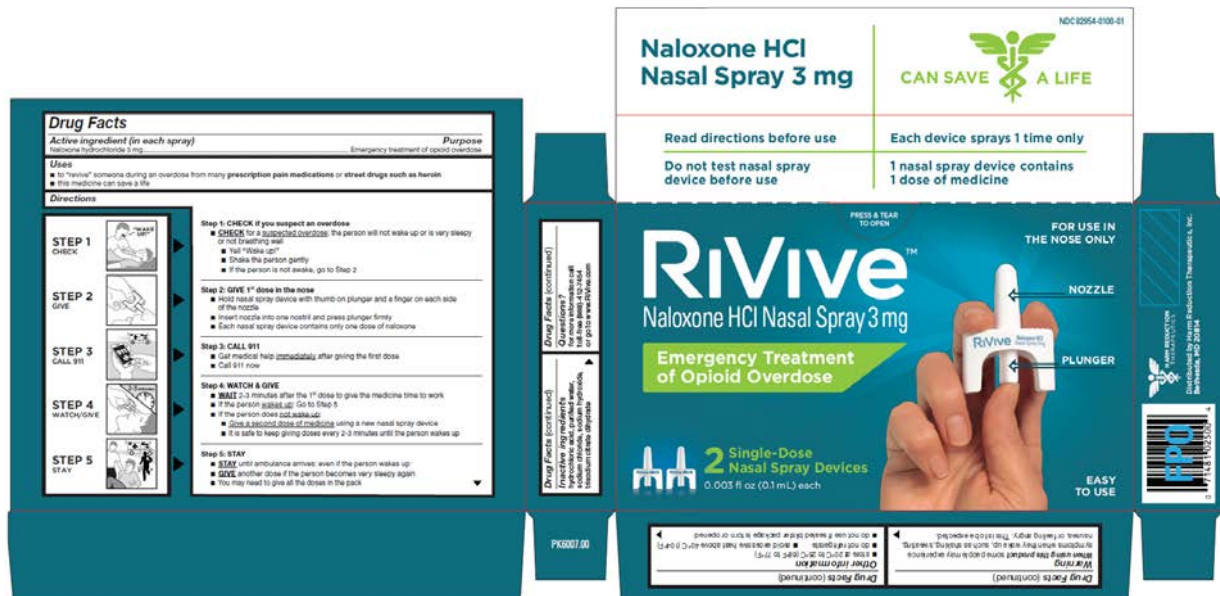
Submitted Labeling	Dates Submitted
2-Count Outer Carton	October 28, 2022; May 12, 2023, June 06, 2023, June 23, 2023, July 06, 2023
Package Insert (aka Quick Start Guide)	October 28, 2022; May 12, 2023, June 06, 2023; June 23, 2023
Immediate Container (Blister Package) Label	October 28, 2022; May 12, 2023, June 06, 2023
Drug-Delivery Device Label (Front & Back))	October 28, 2022
Drug-Delivery Device Label (Front)	May 12, 2023, June 06, 2023
Drug-Delivery Device Label (Back)	May 12, 2023, June 06, 2023

II. REVIEWER'S COMMENTS

A. Outer Carton Label

Applicant proposed secondary container labeling (i.e., outer carton) to hold blister packages (two in each outer carton), and each blister package will contain one nasal spray device. A labeling file for an outer carton presentation that will be used in retail settings and harm reduction centers (i.e., non-retail) was submitted for review.

Outer Carton Label



i. Outer Carton Label Outside Drug Facts

Principal Display Panel

The principal display panel (PDP) is compliant with 21 CFR 201.60, 21 CFR 201.61, 21 CFR 201.62, and 21 CFR 299.4 as described below.

a. **Proprietary Name**

The proprietary name, RiVive, was reviewed by the Division of Medication Error Prevention and Analysis-2 (DMEPA 2), which found it to be acceptable (see the February 13, 2023, review completed by DMEPA 2). (b) (4)

RiVive is displayed on the outer carton PDP in white print that contrasts distinctly with a blue/green background. The proprietary name is the most prominent text on the PDP. Its letter height (about 0.8 in) appears three times larger than the letter height of the established name (about 0.24 in) and more than five times larger than the letter height of the pharmacological category (about 0.15 in).

Comment: This labeling is acceptable. The proprietary name is prominent and conspicuous on the PDP. DMEPA 2 also found it to be acceptable (see the February 13, 2023, review by DMEPA 2).

b. **Statement of Identity**



The proposed statement of identity (SOI) is immediately beneath the proprietary name. During this review, the SOI was revised from (b) (4)

to "Naloxone HCl Nasal Spray 3 mg Emergency Treatment of Opioid Overdose." The established name is displayed in white print against a blue/green background and the pharmacological category is displayed in white print against a green background.

Comment: This labeling statement is acceptable. The SOI now consists of an established name, "Naloxone HCl Nasal Spray 3 mg," and the pharmacological category, which matches the purpose found in the DFL, "Emergency Treatment of Opioid Overdose." The established name displays the active ingredient, dosage form, and strength, and it is immediately followed by the pharmacological category. This format follows decades of precedent for approved nonprescription NDA labeling. Overall, the SOI meets the requirements found in § 201.61 and § 299.4.

c. **Net Quantity**



The net quantity numerical count was revised from (b) (4) to "2 Single-Dose Nasal Spray Devices." It was revised so that it uses an informative and useful

measurement, “single-dose nasal spray device”. It is displayed in the lower left corner in green-color type against a blue background. Below the net quantity numerical count is the net content (fill) volume, “0.003 fl oz (0.1 mL) each.”

To the left side of the next quantity statement are graphic images of two nasal spray devices. Applicant was requested to provide accurate graphic image depiction of the nasal spray device (b) (4) to comply with FDA guidance and policy.

Comment: This labeling is acceptable. The net quantity is evident per § 201.62 and meets the type size requirements in § 201.62(h)(2). Per 21 CFR 201.62(a), the net quantity statement was augmented to inform that each nasal spray contains only 1 dose and is for single use. It was determined that “Single-Dose Nasal Spray Devices” is an informative and useful measurement for this nasal spray dosage form. Unlike all other nonprescription nasal spray devices, this naloxone nasal spray contains only a single dose. The net content (fill) volume was rephrased so that volume is first presented in fluid ounces (i.e., fl oz) first, followed by milliliters (i.e., mL) in parentheses (e.g., “0.003 fl oz (0.1 mL) each”).

Applicant included photographic imaging of the nasal spray devices. These images align with approved nonprescription labeling. Images of dosage forms and devices should be accurate to avoid confusion, per Guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).

d. **Image Depicting Correct Hand and Finger Position**



The above image was added to the PDP to address user errors identified in the HFVS. This image includes labels that point to the nozzle and plunger.

Comment: The image is acceptable. It was added to address the uniqueness of this drug product in the OTC market and to reduce user error (see DMEPA 2 review dated May 1, 2023). During the HFVS, four participants did not correctly hold the nasal spray device. DMEPA recommended a prominent depiction outside of the DFL of the correct hand and finger orientation when holding the nasal spray device.

e. For Use in nose only



At the Agency's request, Applicant added the statement "For use in the nose only" above the graphic image of the nasal spray device on the PDP.

Comment: This labeling is acceptable. Three HFVS participants administered the nasal spray to the mouth. This statement further promotes the correct route of administration.

f. Instructive Statements on Top Panel

Read directions before use	Each device sprays 1 time only
Do not test nasal spray device before use	1 nasal spray device contains 1 dose of medicine

Four important statements were added to the top panel to mitigate errors observed during the HFVS:

- Do not test nasal spray device before use
- 1 nasal spray device contains 1 dose of medicine
- Each device sprays 1 time only
- Read directions before use

Comment: This labeling is acceptable. The statements should be included in future labeling to ensure consistent, safe, and effective use of this drug product. Unlike other nonprescription nasal spray devices, the naloxone nasal spray devices contain only a single dose that will be wasted if the device is tested prior to use. Moreover, this drug product will be used in emergencies and consumers should read the "**Directions**" before use to familiarize themselves how to use this nasal spray device.

The Agency and Applicant agreed that these statements should be placed on the top panel after multiple correspondences. The Agency was concerned about ensuring that these statements are prominently displayed and initially requested that they were included in the "fifth panel" instead of the top panel. Data from other nonprescription NDA applications, which could not be shared, suggests that the fifth panel attracts consumers' attention. And applicants have successfully exploited this attention-grabbing feature to convey important messages, which were tested in labeling comprehension studies and actual use trials. However, the review team was later convinced that the top panel is an appropriate location for these statements because the top panel is free of clutter and competing messages. The Agency expressed the need for the top panel to remain exclusively reserved for these statements in the June 29, 2023, advice letter.

g. **Expiration Dating and Lot Number**



A placeholder for the expiration date, YYYY-MM, and lot number is indicated by a blue box on the side panel of the outer carton.

Comment: This labeling is acceptable. Applicant designated an area for expiration dating and lot numbers, per 21 CFR 201.17 and 21 CFR 211.37 (expiration dating) and 21 CFR 201.18 (control numbers).

h. **Place of Business of Distributor**

Distributed by Harm Reduction Therapeutics, Inc.
Bethesda, MD 20814

The place of business of distributor statement, “Distributed by Emergent Devices Inc. Plymouth Meeting, PA 19462 USA,” is contained on the side panel below the expiration dating area.

Comment: This labeling is acceptable per 21 CFR 201.1

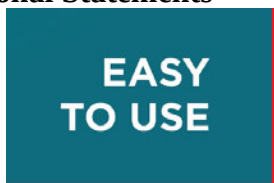
i. **Bar code**



Sponsor added a UPC bar code to the side panel at the Agency’s request.

Comment: This labeling is acceptable. Bar codes are required for nonprescription drug products under 21 CFR 201.25.

j. **Promotional Statements**



The PDP contains the promotional statement “Easy to Use” in the lower right corner of the PDP. The fifth panel contains the statement “Can Save a Life.”

Comment: These promotional statements are acceptable. They are truthful and nonmisleading. Both statements were also approved for the Narcan Nasal Spray labeling (NDA 208411/S-006).

The promotional statement “Can Save a Life” repeats the message under the “**Uses**” heading in the DFL, “this medicine can save a life.” This is a truthful statement that may encourage use of naloxone nasal spray drug product.

The statement “easy to use” may benefit consumers who may be reluctant to purchase a complicated product necessary to save a life. “Easy to use” is not fully supported by the Applicant’s HFVS study, as some use errors occurred. However, as noted above, DNPDI and DMEPA have agreed that the four important statements currently located on the top

panel of the outer carton will mitigate these errors. The informative statements were added to the PDP, QSG, and blister package to mitigate future user error. If significant complaints come in from post-market studies of naloxone use, this claim may need to be reevaluated.

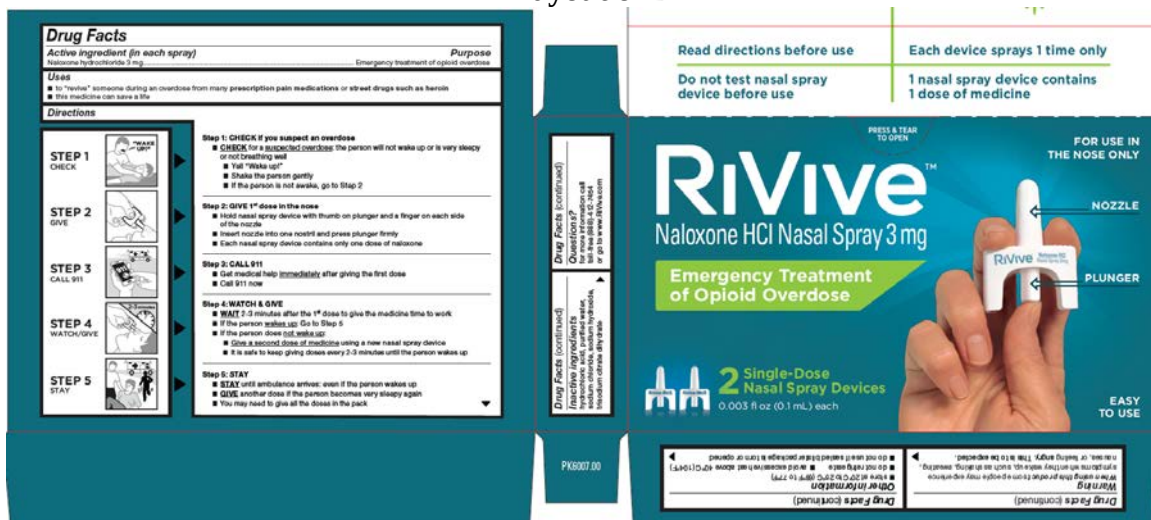
ii. Outer Carton Drug Facts Label

The outer carton Drug Facts label (DFL) is presented across three panels (see image below). The DFL begins on the back panel, with “**Active ingredient**,” “**Uses**,” and “**Directions**.” The DFL then continues to the bottom panel, which contains the “**Warning**” and “**Other information**” headings. Finally, the DFL ends on the panel to the right of the back panel.

This panel contains the “**Inactive ingredients**” and “**Questions?**” headings.

Comment: This labeling arrangement is acceptable. The DFL follows the order of the DFL headings tested in the Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study. Per 21 CFR 201.66(d)(5), a visual graphic (e.g., an arrow) was used to signal the continuation of the Drug Facts labeling to the next adjacent panel.

Layout of DFL



a. Drug Facts Title



The Drug Facts title, “**Drug Facts**,” appears at the top of the DFL in italicized, boldface 14-point type. “**Drug Facts (continued)**” appears in italicized, boldface 8-point type at the top of each subsequent panel.

Comment: This labeling is acceptable per § 201.66.

b. Active Ingredient/Purpose

The “**Active ingredient**” heading was changed from “(b) (4)” to “**Active ingredient (in each spray)**.”

“**Active ingredient (in each spray)** **Purpose**” now appears as the first headings in italicized, boldface 8-point print.

“Naloxone hydrochloride 3 mg..... Emergency treatment of opioid overdose” appears as the active ingredient and purpose in 6-point print.

Comment: This labeling is acceptable. The active ingredient, naloxone hydrochloride, matches the USP compendium nomenclature. It is followed by the strength, 3 mg, per § 201.66(c)(2). The active ingredient is separated from the purpose by a leader. The purpose matches the pharmacological category found in the SOI, per § 201.66(c)(3).

c. Uses

Uses

- to “revive” someone during an overdose from many **prescription pain medications** or **street drugs such as heroin**
- this medicine can save a life

The heading, *Uses*, appears below the active ingredient/purpose section in italicized 8-point boldface print. Two indications are listed below the *Uses* heading.

Comment: This labeling is acceptable. It follows the contents and formatting of the model DFL. The Agency requested two minor formatting changes to this section so that it meets regulation and matched the model DFL. 1.) To align with nonprescription labeling, the first word for each bulleted statement now begins with a lower-case letter. 2.) the phrases “prescription pain medications” and “street drugs such as heroin” are now presented in boldface type. This emphasis matches the labeling tested in the “Comprehension for OTC Naloxone” (CONFER) label comprehension study.

d. Directions

FDA Model DFL

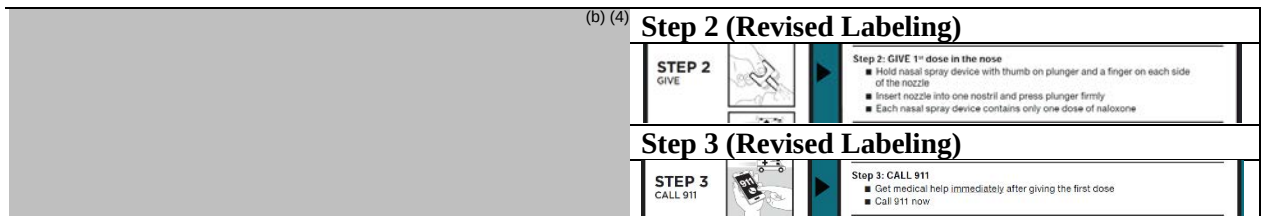
Directions	
	Step 1: CHECK if you suspect an overdose: ■ CHECK for a suspected overdose: the person will not wake up or is very sleepy or not breathing well ■ yell “Wake up!” ■ shake the person gently ■ If the person is not awake, go to Step 2
	Step 2: GIVE 1st dose ■ GIVE the 1st dose of this medicine ■ insert in NOSE and press
	Step 3: CALL ■ CALL 911 immediately after giving the 1st dose
	Step 4: WATCH & GIVE ■ WAIT 2-3 minutes after the 1st dose to give the medicine time to work ■ If the person wakes up: Go to Step 5 ■ If the person does not wake up: ■ CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up ■ It is safe to keep giving doses
	Step 5: STAY ■ STAY until ambulance arrives, even if the person wakes up ■ GIVE another dose if the person becomes very sleepy again ■ You may need to give all the doses in the pack

Proposed DFL for RiVive Nasal Spray

Directions	
STEP 1 CHECK 	Step 1: CHECK if you suspect an overdose ■ CHECK for a suspected overdose: the person will not wake up or is very sleepy or not breathing well ■ yell “Wake up!” ■ Shake the person gently ■ If the person is not awake, go to Step 2
STEP 2 GIVE 	Step 2: GIVE 1st dose in the nose ■ Hold nasal spray device with thumb on plunger and a finger on each side of the nozzle ■ Insert nozzle into one nostril and press plunger firmly ■ Each nasal spray device contains only one dose of naloxone
STEP 3 CALL 911 	Step 3: CALL 911 ■ Get medical help immediately after giving the first dose ■ Call 911 now
STEP 4 WATCH/GIVE 	Step 4: WATCH & GIVE ■ WAIT 2-3 minutes after the 1st dose to give the medicine time to work ■ If the person wakes up: Go to Step 5 ■ If the person does not wake up: ■ Give a second dose of medicine using a new nasal spray device ■ It is safe to keep giving doses every 2-3 minutes until the person wakes up
STEP 5 STAY 	Step 5: STAY ■ STAY until ambulance arrives: even if the person wakes up ■ GIVE another dose if the person becomes very sleepy again ■ You may need to give all the doses in the pack

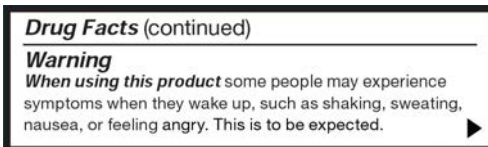
The only substantive difference in content between this “**Directions**” section and the “**Directions**” section from FDA’s model DFL are the instructions for use associated with a nasal spray drug delivery device (see steps 2 and 4) and step 3, “Call 911.”

Revisions were made to the Steps 2 and 3 (see images below for comparison). The title for Step 2 was modified from “(b) (4)” to “**Step 2: GIVE 1st dose in the nose.**” The first bulleted statement in Step 2 was revised from “(b) (4)” to “Hold nasal spray device with thumb on plunger and a finger on each side of the nozzle.” Finally, the second bulleted statement of Step 3 was changed from “(b) (4)” to “Call 911 now.”



Comment: This labeling is acceptable. The proposed “**Directions**” mostly follows the “**Directions**” in the model DFL. Step 2 was adapted to provide instructions specific to the RiVive nasal spray device. The proposed “**Directions**” section matches the formatting requirements in 21 CFR 201.66. However, the model DFL organized information using an abundance of white space. The abundance of white space in the proposed directions is less than the model DFL, but still greater than a typical nonprescription drug label. Likewise, the images adjacent to the model DFL were larger than the proposed labeling. There are no exact size requirements for the images and Applicant provided a human factors validation study (HFVS) that demonstrated their nasal spray can be used safely and effectively by consumers with the proposed labeling, with the caveat that some minor labeling revisions were identified by this review team and completed by Applicant.

e. Warning



The heading, “**Warning**,” appears below the “**Directions**” section in italicized 8-point boldface print. It contains a single warning in 6-point boldface print. This order of headings does not follow the order required in 21 CFR 201.66. However, this re-ordering of headings was found to increase label comprehension during the testing of the model DFL.

This warning section contains a single warning, “**When using this product** some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.”

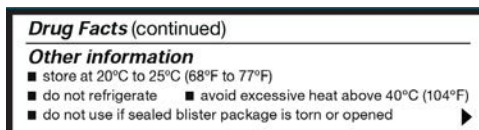
Comment: This labeling is acceptable. The “**Warning**” heading is singular. Even though FDA’s model DFL uses a plural heading, it must be singular because there is only one warning, per 21 CFR 201.66(c)(5).

f. Keep out of reach of children

The “**Keep out of reach of children**” warning was not included in the proposed labeling.

Comment: This absence is acceptable. Children may need to administer this drug product, therefore, nullifying the requirements in § 330.1(g) and § 201.66(c)(5)(x), while maintaining an appropriate risk-benefit (i.e., relatively non-toxic and affording the possibility to administer lifesaving drug product).

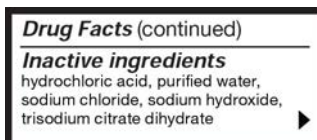
g. Other information



This section contains the proper storage conditions and the tamper evident statement.

Comment: This labeling is acceptable. It follows compendial temperature and storage definitions. The tamper evident statement clearly identifies the tamper evident features of the blister package and is prominently placed, meeting labeling requirement set forth in 21 CFR 211.132(c). As suggested by *Guidance for Industry Labeling OTC Human Drug Products* (May 2009), placing the tamper evident statement in the “**Other information**” section meets the prominence requirements of § 211.132(c).

h. Inactive ingredients



This section lists the inactive ingredients in alphabetical order, per 21 CFR 201.66(c)(8), which include hydrochloric acid, purified water, sodium chloride, sodium hydroxide, trisodium citrate dihydrate.

Comment: This labeling is acceptable and compliant with § 201.66(c)(8). Compounds such as trisodium citrate dihydrate have multiple synonyms. The nomenclature for these ingredients was confirmed by the OPQ review team members.

i. Questions or comments?



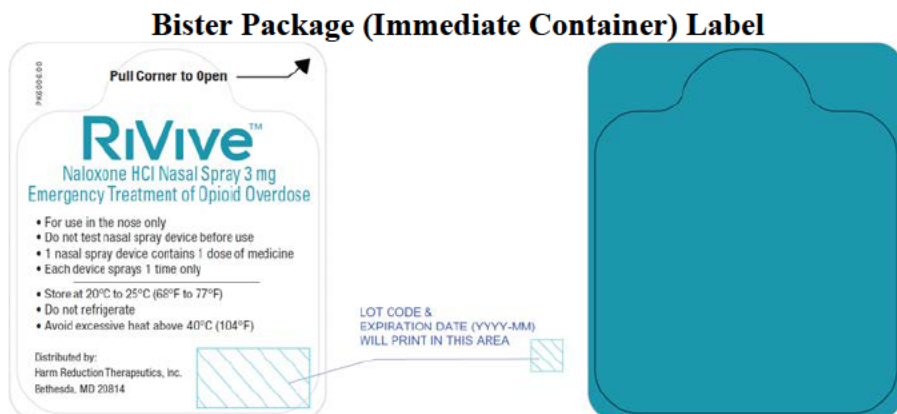
This section includes the telephone number of a source to answer questions about the product.

Comment: This labeling is acceptable and compliant with 21 CFR 201.66(c)(9). The Agency recommended listing the toll-free number first for consistency with other nonprescription DFLs. The purpose of this section is to provide a source that can answer questions about the drug product and to receive reports of adverse events associated with

the use of the drug product. The latter purpose is better fulfilled by listing the tollfree number first.

B. Immediate Container Label

Immediate container labeling was provided for a blister package that will house a drug-delivery nasal spray device (see image below).



Immediate Container Label

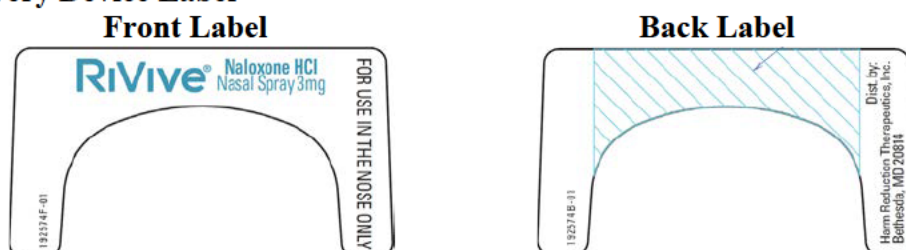
The first proposed blister label offered

(b) (4)

The Agency recommended labeling revisions that would revise the labeling to include a compliant SOI, four important instruction statements, storage conditions, and lot codes and expiration dating.

Comment: This labeling is acceptable. The SOI is now properly constructed with the established name and pharmacological category. The first four bulleted statement address user error concerns from the HFVS. The last three statements state the proper storage conditions. Expiration dating is present per 21 CFR 211.137.

C. Drug-Delivery Device Label



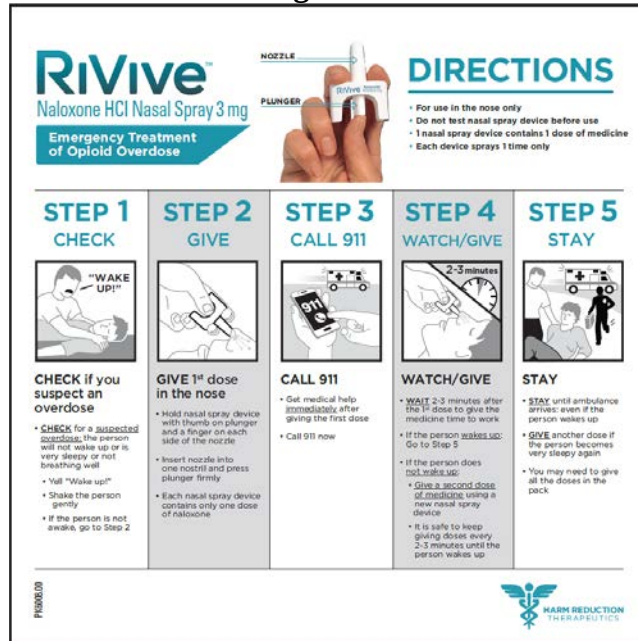
Applicant proposed a simplistic label for the nasal spray device. It contains five labeling elements (see below). These elements are repeated from the outer carton and blister labels. See Review Comments for outer carton and blister labeling for each element below.

1. The proprietary name, RiVive
2. The established name, Naloxone HCl Nasal Spray 3 mg
3. Statement, "FOR USE IN THE NOSE ONLY"
4. Distributor address, Dist. by Harm Reduction Therapeutics, Inc. Bethesda, MD 20814
5. Expiration Dating and Lot Number (to be printed on back label with blue slant lines)

D. Package Insert Label

In the event that a consumer does not transport the blister package with the outer carton, a package insert is included inside each blister package (see package insert label below).

Package Insert Label



This single-page insert repeats Steps 1 through 5 of the DFL “**Directions**” using identical text and figures from the DFL. It follows the recommendations of the advisory committee, DNPD 1, and DMEPA 2.

At the Agency’s request, Applicant made the following modifications.

- Retitled the top of the insert as “**DIRECTIONS**” to help users quickly identify that this piece of paper contains directions that are identical to the DFL “**Directions**.”
- Added the statement, “Unfold for Directions” so that it appears on both sides of the folded package insert.
- Added a labeled figure that shows the correct hand and finger position on the nasal spray device.
- Added the bulleted statements: “• For use in the nose only,” “• Do not test nasal spray device before use,” “• 1 nasal spray device contains 1 dose of medicine,” “• Each device sprays 1 time only.”

Comment: This labeling is acceptable. The package insert repeats critical information from the DFL in the likely event that this drug product is needed without an outer carton nearby. Key information includes 1.) the “**Directions**” from the DFL (with the steps listed horizontally, left to right), 2.) the image to show proper finger position on the nasal spray device, and 3.) important statements that inform consumers not to test the nasal spray because it contains only one dose and to spray in the nose.

III. RECOMMENDATIONS

An APPROVAL letter may be issued to Applicant for the submitted RiVive Nasal Spray (naloxone hydrochloride 3 mg) labeling submitted in NDA 217722 and request final printed labeling with the following reminder.

Request that the applicant submit final printed labeling (FPL) identical to the labels submitted On June 06, 2023, June 23, 2023, and July 06, 2023, as outlined in the table below.

Submitted Labeling	Date Submitted
Drug-Delivery Device Label (Front)	June 06, 2023
Drug-Delivery Device Label (Back)	June 06, 2023
Immediate Container (Blister Package) Label	June 06, 2023
Package Insert	June 23, 2023
2-Count Outer Carton	July 06, 2023

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

ROBERT J BAHDE
07/20/2023 04:51:34 PM

KEVIN L LORICK
07/20/2023 05:11:03 PM
I concur with the review and recommendations.

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 10, 2023
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 217722
Product Name, Dosage Form, and Strength:	RiVive (naloxone HCl) nasal spray, 3 mg per spray
Applicant Name:	Harm Reduction Therapeutics, Inc. (HRT)
TTT ID #:	2022-2691-3
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator: (Provided Nonprescription Labeling Review)	Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Deputy Division Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Directions leaflet and carton labeling received on June 23, 2023 and on July 6, 2023 for RiVive. The Division of Nonprescription Drugs I (DNPDI) requested that we review the revised labeling for RiVive (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that

we made during a previous label and labeling review and as communicated in the June 29, 2023 General Advice Letter.^{a b}

2 DISCUSSION AND CONCLUSION

The Applicant implemented our recommendation to improve the image of the arrows that point to the nozzle and plunger on the device image on the principal display panel by improving the contrast of the arrows on the background. However, the Applicant did not implement our recommendation to relocate the following statements to the fifth panel:

- o “Read directions before use”
- o “Do not test nasal spray device before use”
- o “Each device sprays 1 time only”
- o “1 nasal spray device contains 1 dose of medicine”

The Applicant enhanced the prominence of the statements above by enlarging the font and using boldface type. Additionally, the Applicant provided their rationale for keeping the statements on the top panel. We find the Applicant’s rationale acceptable and have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^a Shah, M. Memorandum Review of Revised Label and Labeling for RiVive (NDA 217722). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUN 14. TTT ID No.: 2022-2691-2.

^b Trang, T. General Advice Letter for RiVive (NDA 217722). Silver Spring (MD): FDA, CDER, OND, ONPD, DNPD1 (US); 2023 JUN 29.

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/

MILLIE B SHAH
07/10/2023 07:18:03 AM

GRACE JONES
07/10/2023 09:44:05 AM

COLLEEN L LITTLE
07/10/2023 09:53:13 AM

LOLITA G STERRETT
07/10/2023 10:23:42 AM

CHI-MING TU
07/10/2023 11:24:22 AM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	6/6/2023		
To:	Teshara Bouie		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Choose an item.
From	Dunya Karimi OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 217722, RiVive (Naloxone Hydrochloride) ICC 2200927 Case 00879292		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 6/6/2023 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Dunya Karimi -S Digitally signed by Dunya Karimi -S Date: 2023.06.29 15:43:50 -04'00'		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 217722
Sponsor	Harm Reduction Therapeutics, Inc.
Drug/Biologic	RiVive (Naloxone Hydrochloride)
Indications for Use	Emergency treatment of opioid overdose
Device Constituent	Nasal Spray
Related Files	

Review Team	
Lead Device Reviewer	<i>Dunya Karimi</i>

Important Dates	
Discipline-Specific Review Memos Due	6/9/2023
Final Lead Device Review Memo Due	6/9/2023
Interim Due Dates	Meeting/Due Date
Filing	12/27/2022
74-Day Letter	1/10/2023
Mid-Cycle	2/21/2023

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☐ Approvable with PMC or PMR, [See Section 2.3](#)
 - ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	Defer to DMEPA
Facilities & Quality Systems	X			

2.1. **Comments to the Review Team**

- ☐ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

Comment #1:

Please note that for FEI 1000110912, a post-approval inspection is required because the firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and a recent medical device inspection of the firm has not been performed.

2.2. **Complete Response Deficiencies**

- ☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☐

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3. PURPOSE/BACKGROUND

3.1. Scope

Harm Reduction Therapeutics, Inc. is requesting approval of RiVive (Naloxone Hydrochloride). The device constituent of the combination product is a Nasal Spray.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

RiVive (naloxone hydrochloride) 3 mg nasal spray is designed to be an over-the-counter (OTC) naloxone product for emergency treatment of opioid overdose. OPQ requests CDRH determine whether the proposed device is GMP exempt or not. Please assess the following facilities:

- Catalent Pharma Solutions, LLC (FEI: 1000110912) • The combination drug product Assembly • Profile: DKA, Device Kit Assembler; MSO, Metered Spray Other; and LIQ, non sterile liquid.

(b) (4)

(FEI: (b) (4)) •

(b) (4)

(b) (4)

Please let OPQ know if a PAI will occur by 1/13/2023.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device description, labeling, design controls, risk analysis, design verification, facilities and quality systems

This review will not cover the following review areas:

Human factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
RiVive (Naloxone Hydrochloride)	Emergency treatment of opioid overdose
Nasal Spray	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0002	
0017 (IR Response)	

4. DEVICE DESCRIPTION

4.1. Device Description

The combination product employs the (b) (4) (b) (4) drug delivery device designed and manufactured by (b) (4) (reference is made to to Letter of Authorization to DMF # (b) (4) (b) (4))

(b) (4) This delivery device is a single use, disposable device intended to administer a single, fixed dose of naloxone to the intranasal cavity of a patient to temporarily reverse a known or suspected opioid overdose.

The finished product consists of a cardstock product carton containing two blister packaged combination products. Each blister pack contains one combination product and a copy of the quick start guide (QSG) including the instructions for use. The product carton design includes a viewing window so that one combination product, sealed in its blister pack, is visible to the end user. Each blister pack consists of two components (a molded (b) (4) blister and paperboard backing) that are heat sealed to create the blister pack. (b) (4)

A representative photo of the finished product configuration is shown in Figure 1. A cutaway diagram of the assembled combination product is shown in Figure 2, and a component summary is shown in Figure 3. High level details on individual components are given in Table 1.

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Figure 3: Naloxone HCl Nasal Spray 3mg Component Summary

(b) (4)



Table 1: Naloxone HCl Nasal Spray 3mg Combination Product Components

(b) (4)

The combination product will leverage the (b) (4) (b) (4) drug delivery device designed and manufactured by (b) (4) (Refer to Letter of Authorization, to DMF # (b) (4) [Module 1, Section 1.4.2](#)). (b) (4)

The combination product is comprised of a filled vial, a plunger/stopper, a container holder, and the actuator subassembly. The injection-molded plastic and metal parts comprising the actuator subassembly supplied by (b) (4) are shown in [Table 3](#). Refer to [Figure 2](#) and [Figure 3](#) for a representative image of the device with each component and the combination product assembly, respectively.

4.2. Steps for Using the Device

(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A
Reviewer Comments								
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No								

5. FILING REVIEW

CDRH performed Filing Review ☐ Finalize Filing Review Section	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X – defer to DMEPA
	Shelf Life, Aging and Transportation	X		
	Clinical Validation			X
	Human Factors Validation			X – defer to DMEPA
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

5.2. Facilities Information

Firm Name:	Catalent Pharma Solutions LLC
Address:	160 Pharma Drive Morrisville NC 27560 US
FEI:	1000110912
Responsibilities:	Drug product manufacture, including preparation of solution and filling into vials. Assembly and labelling of the combination product containing the autoclaved vials. Quality control, including testing of the drug/device combination product. Stability testing of the combination product.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:

☐ Inspection was conducted (b) (4). The inspection covered both drug CGMPs and medical device QS and was classified OAI. A prior inspection of the firm was a preapproval inspection for a New Drug Application (NDA) (b) (4) submitted for (b) (4) which occurred (b) (4) and was classified as No Action Indicated.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Add Additional Facility

5.3. Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☐ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK

Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☐ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment

The proposed combination product is a Naloxone Nasal Spray intended to be administered to people who are suffering from a suspected and/or confirmed overdose of opioids. The final combination product is considered emergency use and has the possibility to be used for a vulnerable population. Additionally, if the product is not delivered correctly, the person suffering from an overdose may expire. Based on these, there is a high risk of cGMP issues.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing inspection: Catalent Phara Solutions (FEI: 1000110912)	
Reviewer Comments	
Refuse to File Deficiencies: ☐ Yes ☐ No ☐ N/A	
74-Day Letter Deficiencies: ☐ Yes ☐ No ☐ N/A	

Add Additional Information Request

6. LABELING

(b) (4)



6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		

Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			Defer to DMEPA
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Established name of the drug product	X		
Amounts of the drug substance delivered from the pump nasal actuator or mouthpiece	X		
Number of medication sprays per container	X		
Net content (fill) weight	X		
Usual dosage	X		
Route of administration	X		
Recommended storage conditions including any warning statements regarding temperature or light exposure	X		
Manufacturer's and/or distributor's name and address	X		
Use period once drug product is removed from protective packaging (if applicable)			X
Instructions regarding shaking of suspension drug products			X
NDC number (recommended)			X

Reviewer Comments

All required information per FDA Guidance "Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing, and Control Documentation" is included.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by
☐ Insert Consultant Name ; The full memo is located in [Appendix B](#).
☐ The Lead Reviewer
 Below is a summary of the review & [recommendation](#):
 See above

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A

Reviewer Comments

CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments

7.2. Design Inputs and Outputs

Essential Performance Requirements

<u>Design Inputs</u> (Essential Performance Requirement)	<u>Design Outputs</u> (Specification)
Pump Delivery (Spray Weight)	(b) (4)
Spray Pattern & Plume Geometry	
Droplet Size Distribution	

Spray Content Uniformity	(b) (4)
Actuation Force (Break/Glide Force)	

Reviewer Comments

The Essential Performance Requirements (EPRs) outlined for the Naloxone Nasal Spray combination product are aligned with EPRs typically assessed for nasal spray devices. The appropriateness and adequacy of the device to meet these specifications will be assessed in the performance testing. The specifications provided are aligned with the FDA guidance titled “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation” (<https://www.fda.gov/media/70857/download>) which state the following:

- In general, pump spray weight delivery acceptance criteria should control the weight of individual sprays to within “15 percent of the target weight and their mean weight to within “10 percent of the target weight. However, for small dosage pumps other acceptance criteria may be justified.*
- The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of relative uniform density) as well as the size of the pattern (e.g., no axis greater than x millimeters and the ratio of the longest to shortest axes should lie in a specified range).*
- There is no acceptance criteria recommendations outlined in the guidance for plume geometry and droplet size distribution.*
- The following acceptance criteria for spray content uniformity are recommended. However, alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of SCU.*
 - For acceptance of a batch (1) the amount of API per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations (10 from beginning and 10 from end) from 10 containers, (2) none of the determinations is outside of 75 to 125 percent of the label claim, and (3) the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim. If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim, but non are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim, and additional 20 containers should be sampled for second-tier testing.*

For the second tier of testing of a batch, the acceptance criteria are met if (1) the amount of API per determination is not outside of 80 to 120 percent of the label claim for more than 6 of all 60 determinations, (2) none of the 60 determinations is outside of 75 to 125 percent of label claim, and (3) the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	n/a
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	n/a

Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	n/a
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Defer to DMEPA

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

The purpose of this report is to summarize the risks identified as a result of a Technical Risk Assessment (TRA) conducted on March 06, 10, 18, April 22, and May 20, 26 and 27, 2020 for Naloxone Hydrochloride Nasal Spray 3 mg (b) (4)

8.2. Hazard Analysis and Risk Summary Report

Evaluation of Risk Documents

Document	Comments
----------	----------

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #		

	(b) (4)
Sponsor Response	
Reviewer Comments	All requested reports were provided. Please see table above for details on each individual report. This is acceptable.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	(b) (4)	
Sponsor Response		
Reviewer Comments	The reports included in the IR response include the requested information. See above for more details. This is acceptable.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Pump Delivery (Spray Weight)		(b) (4)	Spec adheres to FDA guidance doc	Unclear methods (sample size, results, how many batches used, etc) Shelf-life noted to be 36m, results only provided up to 24m (results unclear if from a single sample or an average from a larger sample size) See IRs below. RESOLVED	
Spray Pattern & Plume Geometry			Spec adheres to FDA guidance doc	Unclear methods (sample size, results, how many batches used, etc)	

v05.02.2019

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Conclusions/ Reviewer Comments:	Stability testing demonstrates adequate performance at the end of shelf-life with adequate test methods. This is acceptable.
Acceptable:	☒ Yes ☐ No

Reviewer Comment

Title:	Transportation Testing
Scope/Objective & Acceptance Criteria:	
Methods	(b) (4)

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Results:	It is noted that after the distribution and handling conditioning, samples were placed on stability (real time and accelerated). As such, all stability results above encompass devices subject to shipping simulation. See above for results.
Conclusions/ Reviewer Comments:	See stability results above.
Acceptable:	☒ Yes ☐ No

Reviewer Comment

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #3	(b) (4)	
Sponsor Response		
Reviewer Comments	The sponsor clarifies where stability results can be located. This IR is adequate addressed.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.



9.3. Discipline Specific Sub-Consulted Review Summary

- ☐ No Additional Discipline Specific Sub-Consults were requested
- ☐ The following additional Discipline Specific Sub-Consults were requested:

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
- ☐ There are clinical studies for review

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☐

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☐

Reviewer Comments

See above.

Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☐ No
--	------------------------------	-----------------------------

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

(b) (4)

		(b) (4)

Reviewer Comments

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒ Yes	☐ No

12.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

- ☐ [Device](#) QSR-based
- ☐ Drug cGMP-Based Streamline –
- ☐ Stream-line Both ([no streamlined approach](#))

21 CFR 820.20 Summary of Management Responsibility	Firm(s):	(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s):	
21 CFR 820.50 Summary of Purchasing Controls	Firm(s):	
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	
Subpart G – Production and Process Controls	Firm(s):	

[Reviewer Comments](#)

The information above was found in section 3.2.R, Regional Information Section 5.1. This is adequate.

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☐ No
---	------------------------------	-----------------------------

12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

(b) (4)

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Y
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	Y
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	Y
Investigations into the cause of nonconformities relating to product, processes, and the quality system	Y

Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Y
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Y
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	Y
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Y
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Y
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	Y
Requires documentation of all CAPA activities	Y

Reviewer Comments

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

☐ Yes

☐ No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing</u> activities:	Acceptable (Y/N/NA)
<u>EPR #1</u>	Droplet size distribution	Y
EPR #2	Spray pattern	Y
EPR #3	Plume geometry	Y
EPR #4	Pump delivery	Y
EPR #5	Spray content uniformity	Y
EPR #6	Actuation force	Y

Reviewer Comments

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☐ Yes

☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	(b) (4)	

<<END OF REVIEW>>

13.APPENDIX A ([INFORMATION REQUESTS](#))

13.1. Filing/74-Day Information Requests

13.2. Mid-Cycle Information Requests

13.3. Interactive Information Requests

13.3.1. Interactive Information Requests sent on [Click or tap to enter a date.](#)

14.APPENDIX B ([CONSULTANT MEMOS](#))

14.1. Human Factors Review Memo – Insert Consultant Name

14.2. Clinical Review Memo – Insert Consultant Name

14.3. Insert Discipline Review Memo – Insert Consultant Name

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/s/

TESHARA G BOUIE

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T. Bouie uploading CDRH review on behalf of Dunya Karimi, CDRH/OPEQ/OHT3/DHT3C

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 14, 2023
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 217722
Product Name, Dosage Form, and Strength:	RiVive (naloxone HCl) nasal spray, 3 mg per spray
Applicant Name:	Harm Reduction Therapeutics, Inc. (HRT)
TTT ID #:	2022-2691-2
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator: (Provided Nonprescription Labeling Review)	Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Deputy Division Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container/device label, blister labeling, carton labeling, and Directions leaflet received on June 6, 2023 for RiVive. The Division of Nonprescription Drugs I (DNPDI) requested that we review the revised labels and labeling for RiVive (Appendix A) to

determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 DISCUSSION AND CONCLUSION

The revised carton labeling includes a new carton opening feature with a semi-circle perforation to “Press & Tear to Open” on the principal display panel (PDP) that was not present on the carton evaluated in the human factors (HF) validation study. We do not anticipate that this new carton opening feature will negatively impact the readability of important information or performance of the open carton task based on the location of the semi-circle perforation. Additionally, we are aware of other nonprescription products that use this “press and tear to open” feature. Thus, in this instance, we find the change to add a new carton opening feature does not require submission of additional HF data.

The revised container/device label, blister labeling, and Directions leaflet are acceptable from a medication error perspective. However, the carton labeling is unacceptable from a medication error perspective due to the following issues:

- The prominence of the following statements can be improved because they appear on the top panel of the carton labeling instead of the fifth panel:
 - o “Read directions before use”
 - o “Do not test nasal spray device before use”
 - o “Each device sprays 1 time only”
 - o “1 nasal spray device contains 1 dose of medicine”
- The color of the arrows pointing to the nozzle and plunger on the device image on the principal display panel can be improved to increase clarity .

3 RECOMMENDATIONS FOR HARM REDUCTION THERAPEUTICS, INC. (HRT)

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling

1. We refer to our recommendation #A-3 in the General Advice letter dated May 31, 2023 to move the following statements from the top panel to the fifth panel to increase their prominence:

- “Do not test nasal spray device before use”
- “Each device sprays 1 time only”
- “1 nasal spray device contains 1 dose of medicine”

Additionally, we refer to our recommendation #A-4 in General Advice letter dated May 31, 2023 and continue to recommend you relocate the statement, “Read directions before use” to the fifth panel below the statements above.

We acknowledge your statements in the June 6, 2023 response that the above statements are prominent on the top panel. However, the fifth panel will be readily visible when the product is positioned on store shelves with the principal

^a Shah, M. Memorandum Review of Revised Label and Labeling for RiVive (NDA 217722). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 25. TTT ID No.: 2022-2691-1.

display panel shown, whereas the top panel will not be readily visible. Thus, we maintain our recommendation to relocate the above statements to the fifth panel.

2. The image of the arrows that point to the nozzle and plunger on the device image on the principal display panel can be improved for visibility to minimize confusion on what aspect of the device the arrows point to. We recommend improving the contrast of the arrows on the dark background.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 25, 2023
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 217722
Product Name, Dosage Form, and Strength:	RiVive (naloxone HCl) nasal spray, 3 mg per spray
Applicant Name:	Harm Reduction Therapeutics, Inc. (HRT)
TTT ID #:	2022-2691-1
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator: (Provided Nonprescription Labeling Review)	Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Deputy Division Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container/device label, blister labeling, carton labeling, and Directions leaflet received on May 12, 2023 for RiVive. The Division of Nonprescription Drugs I (DNPDI) requested that we review the revised labels and labeling for RiVive (Appendix A) to

determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container/device label, blister labeling, carton labeling, and Directions leaflet are unacceptable from a medication error perspective due to the following issues:

- The expiration date format is not defined on the device label, blister labeling, or carton labeling.
- The prominence of the statement, “For use in the nose only” may be further improved because it appears on the top panel of the carton labeling instead of the principal display panel (PDP).
- The presentation of the statement, “1 nasal spray device contains 1 dose of medicine” may be further improved on the top panel of the carton labeling because it’s split across 2 lines instead of all on the same line.
- The presentation of the storage statement on the blister labeling and carton labeling can be improved.
- The image of the nasal spray device on the Directions leaflet and carton labeling can be improved to be consistent with the container/device label.
- The image of the hand which is holding the nasal spray device on the Directions leaflet can be improved.

3 RECOMMENDATIONS FOR HARM REDUCTION THERAPEUTICS, INC. (HRT)

We recommend the following be implemented prior to approval of this NDA:

A. Container/Device Label, Blister Labeling, and Carton Labeling

1. We acknowledge your revised label and labeling provide the location of the expiration date; however, as currently presented, the format for the expiration date is not defined. Therefore, we are unable to assess the proposed expiration date format from a medication safety perspective. Provide the expiration date format. To reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.^b

^a Shah, M. Human Factors Study Report and Label and Labeling Review for RiVive (NDA 217722). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 01. TTT ID No.: 2022-2109; 2022-2691.

^b Guidance for industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). Available at: <https://www.fda.gov/media/158522/download>.

B. Carton Labeling

1. We acknowledge you added the statement, “For use in the nose only” on the top panel of the carton labeling; however, as currently presented, the prominence of the statement may be further improved. We recommend adding the statement, “For use in the nose only” to the principal display panel under the statement, “Emergency Treatment of Opioid Overdose” to further improve the prominence of this important statement.
2. We acknowledge you added the statement, “1 nasal spray device contains 1 dose of medicine” on the top panel of the carton labeling; however, it is split across 2 lines instead of on a single line. Additionally, the top panel appears to have space for presenting this statement in a single line. We recommend revising the presentation of the statement to appear on a single line.

C. Carton Labeling and Blister Labeling

1. The storage statement, “ (b) (4)).” presents the temperature in Fahrenheit followed by Celsius , which is inconsistent with the order the temperature is presented in the statement, “Avoid excessive heat above 40° C (104° F)”. We recommend presenting the order of the temperature for all storage statements in a consistent manner to minimize the risk for confusion.

D. Carton Labeling and Directions Leaflet

1. We acknowledge you added the container/device label to the graphic image of the nasal spray device on the carton labeling and in the Directions leaflet; however, the container/device label in the image is inconsistent with the container/device label submitted. Therefore, we recommend revising the container/device label in the graphic image so it is consistent with the submitted container/device label.

E. Directions Leaflet

1. We acknowledge you added an image of a hand which is holding the nasal spray device; however, (b) (4) . Therefore, we recommend revising the image of the hand to be consistent with the image of the hand on the carton labeling such that all fingers are visible and the hand is in color.

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HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 1, 2023
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 217722
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength:	RiVive (naloxone HCl) nasal spray, 3 mg per spray
Device Constituent:	Nasal Spray
Rx or Nonprescription:	Nonprescription
Applicant/Sponsor Name:	Harm Reduction Therapeutics, Inc. (HRT)
FDA Received Date:	September 30, 2022, October 28, 2022, February 1, 2023
OSE RCM #:	2022-2109, 2022-2691
DMEPA 2 Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator: (Provided Nonprescription Labeling Review)	Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Deputy Division Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1. REASON FOR REVIEW

This review evaluates the human factors validation study (HFVS) report and labels and labeling submitted under NDA 217722 for RiVive (naloxone HCl) nasal spray.

1.1 BACKGROUND, PRODUCT INFORMATION, AND HUMAN FACTORS DEVELOPMENT PROGRAM

1.1.1 Background

RiVive (naloxone HCl) is a combination product with a proposed nasal spray device constituent part that is intended for nonprescription use to “revive” someone during an overdose from many prescription pain medications or street drugs such as heroin. RiVive (naloxone HCl) is being developed by HRT as a nonprescription product (no previous prescription marketing).

As communicated in a 2019 Federal Register Notice 984 (FR 8728), FDA developed two versions of a model naloxone Drug Facts Label (DFL) (one for nasal spray and one for injector) supported by a Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study to encourage naloxone Sponsors to enter the OTC market and increase access to naloxone.^a The FDA model DFL directions include placeholders that will need to be replaced with device-specific information (see Figure 1). If an Applicant elects to use the model DFL, the device-specific instructions may be added and evaluated in a simulated HFVS designed to evaluate whether the user interface can be used safely and effectively by intended users for the intended use under the expected environment(s) of use.^b

Figure 1. FDA Model DFL for Naloxone Nasal Spray Evaluated in CONFER

^a Information can be found at the following link to the Federal Register notice 84 FR 8728: <https://www.federalregister.gov/documents/2019/03/11/2019-04357/nonprescription-naloxone-labeling-resources-availability>.

^b Information can be found at the following link to the Federal Register notice 87 FR 68702: <https://www.federalregister.gov/documents/2022/11/16/2022-24874/safety-and-effectiveness-of-certain-naloxone-hydrochloride-drug-products-for-nonprescription-use>

Drug Facts

Active ingredient (in each XX)

Naloxone hydrochloride X mg.....

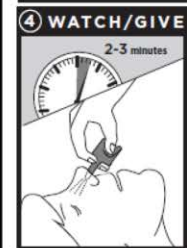
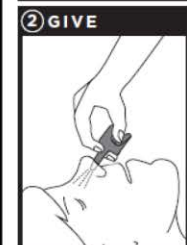
Purpose

Emergency treatment of opioid overdose

Uses

- To "revive" someone during an overdose from many **prescription pain medications** or **street drugs such as heroin**
- this medicine can save a life

Directions



Step 1: CHECK if you suspect an overdose:

- CHECK** for a suspected overdose: the person will not wake up or is very sleepy or not breathing well
 - yell "Wake up!"
 - shake the person gently
 - if the person is not awake, go to Step 2

Step 2: GIVE 1st dose

- GIVE** the 1st dose of this medicine
- insert in NOSE and press

Step 3: CALL

- CALL 911** immediately after giving the 1st dose

Step 4: WATCH & GIVE

- WAIT** 2-3 minutes after the 1st dose to give the medicine time to work
- if the person wakes up: Go to Step 5
- if the person does not wake up:
 - CONTINUE TO GIVE** doses every 2-3 minutes until the person wakes up
 - it is safe to keep giving doses

Step 5: STAY

- STAY** until ambulance arrives: even if the person wakes up
- GIVE** another dose if the person becomes very sleepy again
- You may need to give all the doses in the pack

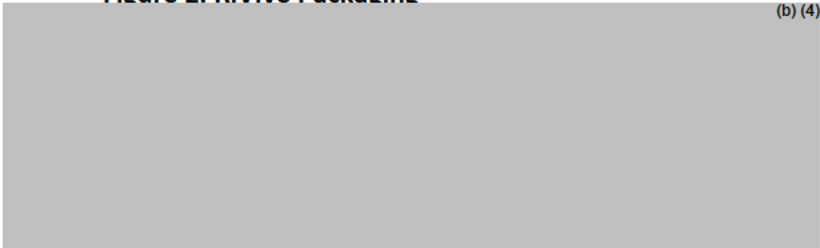
1.1.2 Product Information

On September 30, 2022, the Applicant submitted NDA 217722 for RiVive (naloxone HCl) nasal spray, 3 mg. To support nonprescription use, the Applicant used the model DFL to develop the proposed nonprescription labeling.

Steps 1 and 5 of the proposed RiVive nasal spray DFL are identical to the model DFL evaluated in CONFER in terms of both pictogram and text (see Figure 1 and Figure 4). Steps 2 and 4 of the proposed RiVive nasal spray DFL include different product-specific pictograms and text compared to the model DFL evaluated in CONFER. Step 3 includes different text compared to the model DFL evaluated in CONFER; however, the pictogram is the same.

Table 1 presents relevant product information for the proposed RiVive (naloxone HCl) nasal spray that Harm Reduction Therapeutics, Inc. (HRT) submitted on September 30, 2022 and October 28, 2022.

Table 1. Relevant Product Information for RiVive (naloxone HCl) nasal spray

Initial Approval Date	N/A
Active Ingredient	Naloxone hydrochloride
Indication (intended use)	Drug Facts Label (DFL) <i>Uses</i> : • To “revive” someone during an overdose from many prescription pain medications or street drugs such as heroin • This medicine can save a life
Route of Administration	nasal
Dosage Form	Nasal spray
Strength	3 mg per spray
Dose and Frequency	3 mg once, may repeat every 2-3 minutes until person wakes up (See DFL Figure 4)
How Supplied/Packaging	• Each nasal spray device contains 3 mg naloxone HCl per spray and is packaged in a blister along with a Quick Start Guide (QSG), which has text and pictograms that are identical to the Directions of the Drug Facts Label (DFL). • Each carton contains 2 nasal spray devices See Figure 2 Figure 2. RiVive Packaging  (b) (4)

Storage	(b) (4) do not refrigerate or expose to high temperatures
Device Constituent	Figure 3. (b) (4) nasal spray device 
Intended Users	Adolescents and adult lay people (friends, family, bystanders, caregivers) without medical training who may encounter someone experiencing an opioid overdose and acquire or purchase the proposed product without the supervision of a licensed healthcare provider.
Intended Use Environment	Community settings where opioids may be present

Figure 4. RiVive nasal spray DFL, carton back panel and bottom panel (left), side panel (right)



1.1.3 Select Regulatory History Related to the Proposed Product's Human Factors Program (See Appendix A for Detailed Regulatory History)

We previously evaluated HRT's proposed December 23, 2020 HFVS protocol and communicated advice and clarified HRT's questions for our recommendations throughout 2021.^{c, d}

^c Olagundoye-Alawode, A. Human Factors Validation Study Protocol Advice Letter for Naloxone. Silver Spring (MD): FDA, CDER, OSE (US); 2021 FEB 20. IND 134611.

^d Stewart, S. Meeting Request-Written Responses for RiVive (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, DNPD1 (US); 2021 MAY 04. IND 134611.

We previously also evaluated HRT's revised HFVS protocol submitted on September 2, 2021 and September 14, 2021; and communicated advice and clarified HRT's questions for our recommendations in late 2021 and 2022.^{e,f,g}

On September 30, 2022, HRT submitted the HFVS report, and on October 28, 2022, HRT submitted the labels and labeling, which are the subject of this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review. The Appendices provide additional information for each material reviewed.

Table 2. Materials Considered for this Review

Material Reviewed	Appendix Section
Detailed Regulatory History Related to the Proposed Product's Human Factors Development Program	A
Human Factors Validation Study Results Report	B
Information Requests Issued During the Review	C
Labels and Labeling	D

3. DISCUSSION ON HUMAN FACTORS VALIDATION STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design and our detailed discussion of the HFVS methodology.

3.1 Summary of Study Design

Table 3 presents a summary of the HFVS methodology. See Appendix C for more details on the study design.

Table 3. Study Methodology for Human Factors Validation Study (HFVS)

Study Design Elements	Details
Participants	60 participants in the following user groups: • Adolescents, 12-17 years (n=20) ○ 30% Limited literacy (LL) • Adults, 18 years and older, general population (n=20) ○ 35% LL

^e Olagundoye-Alawode, A. Human Factors Validation Study Protocol Advice Letter for Naloxone. Silver Spring (MD): FDA, CDER, OSE (US); 2022 JAN 21. IND 134611.

^f Pham, P. Meeting Minutes for RiVive (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, DNPDI (US); 2021 DEC 01. IND 134611.

^g Pham, P. Meeting Minutes for RiVive (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, DNPDI (US); 2022 JUN 09. IND 134611.

	- Adults, 18 years and older, opioid users or family/friends (associates) of opioid users (n=20) 45% LL
Training	None-All participants were untrained
Test Environment	The room had ambient lighting and background noise to simulate environmental stressors (e.g., common noises such as music, people talking).
Test Materials	- RiVive carton printed with labeling (i.e., principal display panel (PDP) and Drug Facts Label (DFL)) - Placebo nasal spray devices (filled with water) inside each blister pack. Two blister packs per carton. Quick Start Guide (QSG) inside each blister pack - Adult-sized mannequin (for demonstrations of drug administration) - A phone on a desk. The phone was not connected, there was no dial tone, and the phone could not place an outgoing call, nor receive an incoming call. - A digital clock in the room
Sequence of Study	- Screening - Confirmation of inclusion/exclusion criteria - Demographics - Informed consent - Reconfirmation of inclusion/exclusion criteria and demographics - Literacy test (Rapid Estimate of Adult Literacy in Medicine (REALM) for adults, REALM-Teen for ages 12-17) - Moderator presented brief study overview (study purpose) - The participant was told to follow the instructions on the box and demonstrate what they would do if this was an actual emergency. - User demonstration of simulated administration of RiVive on mannequin - Trained Moderator conducted debriefing interview to obtain root causes for any incorrect actions - Trained Moderator conducted comprehension interview - Trained Moderator conducted debriefing interview to obtain root causes for any responses that were not correct - Trained Moderator conducted interview about the user's experience with the product and labeling

3.1.1 DMEPA's Discussion and Evaluation of HFVS Methodology

Based on our advice for the HFVS protocol (see Section 1.1.3), the Applicant implemented most of the Agency's recommendations for the HFVS methodology. However, it is important to note the following study limitations when interpreting the study results.

Leading Language

Participants in the HFVS were instructed by the study moderator to, "follow the instructions on the box" prior to demonstrating use of the product in a simulated overdose scenario. Use of leading language might impact study participant performance and is not representative of actual use (i.e., no one will instruct or remind a user to use the packaging directions during actual use). Thus, we generally recommend that the moderator refrain from using leading language.

Although use of the leading language does not preclude our review of the HFVS results, this method may have introduced a bias towards positive performance, which should be taken into consideration when interpreting the HFVS results. We have informed the review team of this study limitation.

Pediatric Users

The Applicant proposed the pediatric user group's age range of 12 to 17 years in the HFVS protocol submitted to the Agency for review. The Agency has identified cognitive and moral development in children as young as 10 years of age that can perform mental operations and thoughts using formal concrete concepts.^h Upon further consideration, we now generally recommend the HFVS include pediatric participants 10 to 17 years old. This study method does not preclude our review of the HFVS results, but because pediatric users between 10 to 11 years old were not tested, the data collected cannot be generalized to the untested age range of the pediatric user group. We have informed the review team of this study limitation.

4. RESULTS AND ANALYSES

This section provides our analysis of the results contained in the HFVS results report.

As discussed in Section 1.1.1 above, Applicants who elect to use the Agency's model DFL have been advised to replace the model DFL placeholders with the device-specific information for evaluation in the HFVS. In this case, because the Applicant has elected to use the model DFL, we have focused our detailed analysis of the HFVS results on Steps 2, 3 and 4. Thus, we provide both a high-level summary and our detailed analysis for Steps 2, 3, and 4 of the DFL Directions in section 4.1, whereas our assessment for Steps 1 and 5 is provided in Section 4.2 below. We also evaluated the HFVS results submitted by the

^h Hollan-Hall, C., & Burstein, G. (2016). Adolescent Development. In R. Kliegman, B. Stanton, J. Geme, & N. Schor, Nelson Textbook of Pediatrics 20th edition (pp. 926-936). Elsevier.

Applicant for opening the blister packaging, removing the QSG, and removing the nasal spray from the package.

4.1 ANALYSIS OF STEP 2, STEP 3, AND STEP 4

The high-level summary of results for Steps 2, 3, and 4 is provided in Table 4 below.

Table 4. Summary of HFVS Results for Steps 2, 3, and 4

60 participants in the following user groups: General Population: Adult General Population, age 18 or older (n=20); Adolescent: Adolescent, ages 12-17 (n=20); Opioid User/Opioid User Associate: Adult Opioid Users/Associates, age 18 or older (n=20)			
	Number of Use Errors (UE)	Number of Close Calls (CC)	Number of Use Difficulties (UD)
Step 2: GIVE a dose of this medicine	9 UE: - General Population (n=3) - Adolescent (n=4) - Opioid User/Associate (n=2)	5 CC: - General Population (n=2) - Adolescent (n=2) - Opioid User/Associate (n=1)	2 UD: - Adolescent (n=1) - Opioid User/Associate (n=1)
Step 3: Call 911	11 UE: - General Population (n=2) - Adolescent (n=7) - Opioid User/Associate (n=2)	17 CC: - General Population (n=8) - Adolescent (n=3) - Opioid User/Associate (n=6)	0 UD
Step 4: Watch & Give	42 UE: - General Population (n=15) - Adolescent (n=15) - Opioid User/Associate (n=12)	2 CC: - General Population (n=1) - Adolescent (n=1)	4 UD: - General Population (n=1) - Adolescent (n=2) - Opioid User/Associate (n=1)

Table 5 further describes the study results for opening the blister packaging, removing the QSG, removing the nasal spray from the package, and Steps 2, 3, and 4 of the DFL, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 5. HF Validation Study Results and Analysis

Legend: UE = use error; CC = close call; UD = use difficulty; URR = use-related risk analysis; RCA = root cause analysis; LL = Limited Literacy Participant; NL = Normal Literacy Participant

Open the Blister Packaging

Information Supplied by Applicant		
Total number of UE, CC, UD		
UE (n=0), CC (n=0), UD (n=4)		
Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA, and in quotation marks Participants' Relevant Subjective Feedback (if available)
UD: Difficulty opening the blister package (n=2)	Adult General Population NL 01-103	Device/Action "I think it's just the way it's made, and I usually have trouble with these types of packages anyway, especially with my nails."
	Opioid User or Associate NL 01-126	Not provided
UD: Dropped device on the floor (n=2)	Opioid User or Associate NL 01-155	Not provided
	Opioid User or Associate LL 01-406	Device/Action "It just slipped out. I picked it back up."
Based on the Applicant's URR, performing the task incorrectly or not at all may result in:		
Respiratory/central nervous system depression, coma, death		
Applicant's Comments and Proposed Mitigations (if available):		
Not provided		
DMEPA's Analysis and Findings		
DMEPA Finding #1		

The Applicant did not provide the root cause analysis or subjective feedback for one participant who experienced difficulty with opening the package. However, although two participants experienced difficulty with opening the blister, both participants were eventually able to open the blister packaging. Thus, based on our review of the available subjective feedback and root cause analysis, we did not identify areas of improvement and have **no recommendations** at this time to address these use difficulties.

DMEPA Finding #2

The Applicant did not provide the root cause analysis or subjective feedback for one participant who dropped the device on the floor. However, both participants successfully opened the blister packaging despite dropping the device on the floor. Also, in these 2 instances, dropping the device did not result in premature activation of the devices or damage to the devices such that it prevented administration of a dose. Thus, based on our review of the available subjective feedback and root cause analysis, we did not identify areas of improvement and have **no recommendations** at this time to address these use difficulties.

Remove Nasal Spray from Package

Information Supplied by Applicant		
Total number of UE, CC, UD		
UE (n=0), CC (n=0), UD (n=3)		
Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA, and in quotation marks Participants' Relevant Subjective Feedback (if available)
UD: Difficulty removing the nasal spray from package (n=2)	Adolescent LL 01-159	Device/Action "I think my nails are a little too long for gripping, it was hard to get a hold of it."
	Opioid User or Associate LL 01-132	Device/Action: Difficult to open with one hand
UD: Dropped nasal spray on the floor (n=1)	Opioid User or Associate NL 01-155	
The Applicant did not evaluate removing the nasal spray from the package in the URR.		

Applicant's Comments and Proposed Mitigations (if available):

Not provided

DMEPA's Analysis and Findings

Although the Applicant did not evaluate removing the nasal spray from the package in the URR, our evaluation finds that respiratory/central nervous system depression, coma, or death may result from performing this task incorrectly or not at all.

DMEPA Finding #3

Although these participants experienced use difficulty while removing the nasal spray device from the blister packaging (e.g., opening with one hand, having long nails), all participants were eventually successful in removing the nasal spray device from the blister packaging. Our review of the study results did not identify subjective feedback or root cause analysis that indicates the user interface contributed to the use difficulties. Thus, based on our review of the subjective feedback and root cause analysis, we did not identify areas of improvement and have **no recommendations** at this time to address these use difficulties.

Remove and Open the Quick Start Guide (QSG)**Information Supplied by Applicant**

Total number of UE, CC, UD

UE (n=12), CC (n=0), UD (n=7)

Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA, and in quotation marks Participants' Relevant Subjective Feedback (if available)
UE: Does not remove QSG (n=12)	Adult General Population LL 01-104	Sensory/Perception: Did not look like instructions/Did not see QSG "I thought it was just some paper back there. Should be with the yellow side up so you see that." "I ignored it because I didn't know it was instructions, but the instructions were on the box." "I didn't even know this had anything to do with it. I thought all the instructions were on the label." "I did not even notice it. It should be like on top when you open it up."

	Adult General Population NL 01-108		
	Opioid User or Associate LL 01-132		
	Opioid User or Associate LL 01-156		
	Adult General Population NL 01-402		
	Opioid User or Associate LL 01-406		
	Adult General Population NL 01-223	Sensory: Could not get QSG open so went to back of box	
	Adult General Population LL 01-204	Behavior: Used to following DFL on OTC drugs "I was trying to read the instructions on the back. That's what I do when I buy over the counter medicine."	
	Adult General Population NL 01-207	Behavior: Focused on reviving the patient "I tried to be as quick as possible."	

	Adult General Population NL 01-103	Behavior: QSG fell out of box
	Adolescent NL 01-213	Behavior: Focused on the back label
	Opioid User or Associate LL 01-208	Not provided
UD: Difficulty removing QSG (n=7)	Adult General Population LL 01-205	Not provided
	Adolescent LL 01-112	Not provided
	Adolescent LL 01-141	Sensory/Perception: Sticky part made it hard to open
	Adult General Population LL 01-205	Sensory/Perception: Did not want to rip it since it was glued “Don’t have glue. Don’t have sticky. Just have it folded.”
	Adolescent LL 01-218	Sensory/Perception: Did not look like anything; just had a sticker; sticker too sticky “The sticky part really sticks. If that would have been easier in the beginning that would have been helpful.” “I don’t know if the stickiness is necessary, it’s very strong, and seems stronger than it should be, if it was just folded I think it would be fine.”
	Adolescent LL 01-227	
	Adolescent NL 01-235	
Based on the Applicant’s URRRA, performing the task incorrectly or not at all may result in: No Harm		

Applicant's Comments and Proposed Mitigations (if available)

The QSG was frequently not used by the study participants. It is folded and tucked into the blister behind the nasal spray. They either did not notice it or did not realize what it was or its purpose. The QSG is clearly marked 'Unfold for User Instructions' in large font, blue ink against a yellow background (see Figure 5).

Figure 5



However, this above QSG instruction is printed on one side only and may not have been noticed by all subjects. The opposite side of the folded QSG is nondescript, repeat pattern of a caduceus (see Figure 6). This nondescript side can be seen by the user through the clear blister; but it is behind the nasal spray.

Figure 6



Harm Reduction Therapeutics is considering printing the notice (Unfold for User Instructions) on both sides of the QSG, to increase visibility to the user of the product. In addition, it should be noted that for those who did remove and attempt to open the QSG, the glue was too strong, making it harder to open the QSG. This resulted in some tearing of the QSG while trying to open it, in some cases, causing the study participant to stop trying to open the QSG because it was taking too long. HRT will explore a less tacky glue to allow the QSG to be unfolded more easily.

DMEPA's Analysis and Findings

DMEPA Finding #4

Our review of the study results identified subjective feedback and root cause analysis that indicated the user interface may have contributed to some use-related events. Specifically, some participants had difficulty seeing the QSG or identifying that the folded paper contained instructions. Additionally, some participants had difficulty opening the QSG or tore the QSG while opening. We considered the participant's subjective feedback and root cause analysis. We acknowledge the Applicant is considering printing the statement, "Unfold for User Instructions" (see Figure 5) on both sides of the QSG. Additionally, we acknowledge the Applicant is exploring a less tacky glue to allow the QSG to be unfolded more easily.

While we agree with the Applicant's URRR for this step as "no harm" under the intended use (carrying nasal spray in carton around until use), we anticipate that some users will carry the blister and not the complete carton. As such, we provide recommendations to ensure the QSG is designed to support safe and effective use.

DMEPA Recommendation for Finding #4:

We recommend the Applicant to implement the improvements they were considering, by adding the statement "Unfold for Directions" in large font with blue ink against a yellow background to both sides of the folded up QSG and use of less sticky glue to mitigate errors associated with unfolding the QSG.

Step 2a: Hold nasal spray with thumb on plunger and a finger on each side of the nozzle

Information Supplied by Applicant

Total number of UE, CC, UD

UE (n=4), CC (n=1), UD (n=0)

Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA and Participants' Relevant Subjective Feedback (if available)
UE: Held the nozzle	Adult General Population LL 01-204	Cognition: Misunderstood instructions [Participant]: "I think it's a habit. Cause that's how I hold most of my devices." [Moderator]: "Is that how it was comfortable for you to hold?" [Participant]: "Yes."

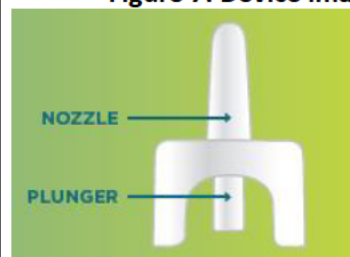
UE: Inserted plunger in nostril	Opioid User or Associate LL 01-208	Cognition: Did not fully read instructions; was nervous with emergency situation "I was nervous. After I was doing it I was reading and after reading I saw it should go the other way around."
UE: Unable to hold nasal spray with thumb on plunger and finger on each side of the nozzle	Adult General Population NL 01-207	Sensory/Perception "It was what was comfortable for me. I have poor blood flow to my hands."
UE: Held with one finger on and the other hand	Adolescent LL 01-215	Sensory/Perception: It was hard to push out and he tried to adjust, and it worked. "It was kind of hard to push out at first, so I tried it that way and it worked. I saw the way they said to do it. It wasn't really confusing."
CC: Did not initially hold the nasal spray with thumb on plunger and finger on each side	Adolescent LL 01-112	Sensory/Perception: Trying to figure out how to best hold and how it felt best.
Based on the Applicant's URR, performing the task incorrectly or not at all may result in: No harm (assuming the user is still able to administer the dose into the nose of the patient)		
Applicant's Comments and Proposed Mitigations (if available): The FDA considers this to be a critical task; however, HRT continues to disagree with this classification. As HRT explained in our protocol and URR, the way a user holds the device is not critical as long as they successfully administer naloxone. In short, if a life-saving dose of naloxone is administered to an opioid overdose victim, then how the device was held during administration does not matter. Of central importance, in this study, 3 of 4 participants who did not hold the device exactly as instructed on the label were still able to successfully administer the drug. Activation of the device is what is critical, not the way that the device was held during administration.		
DMEPA's Analysis and Findings		
DMEPA Finding #5 All participants except for participant #01-208 were successful in administering a full dose despite holding the nasal spray device in a manner inconsistent with the DFL (i.e., thumb not on plunger and a finger not on each side of the nostril). The subjective feedback and root cause analysis indicates the user interface may have contributed to some use-related events. Specifically, for one participant (#01-215) the plunger was "hard to push out." The participant's incorrect hold of the device may have contributed to the plunger being difficult to push initially; however, the participant adjusted the hold of the nasal spray device and was successful in administering a dose.		

The user interface depicts the correct hand and finger orientation of the nasal spray device in the Step 2 pictogram and Step 4 pictogram; however, the carton labeling may be further improved to communicate correct hand and finger orientation and hold on the nasal spray.

DMEPA Recommendation for Finding #5:

We recommend the Applicant revise the device image on the top flap of the carton by adding a depiction of the hand holding the device to show the correct hand and finger orientation and hold (see Figure 7).

Figure 7. Device image on the top flap of the carton



Step 2b: Insert nozzle into one nostril and press plunger firmly

Information Supplied by Applicant		
Total number of UE, CC, UD		
UE (n=5), CC (n=4), UD (n=2)		
Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA and Participants' Relevant Subjective Feedback (if available)
UE: Administered dose into mannequin's mouth	Adult General Population LL 01-104	Cognition: Skipped over some instructions; reacted to tube in mannequin's mouth "Because I saw the little tube in the mouth of the mannequin."

UE: Put device in mouth and sprayed. Looked back over DFL and then put in nose and tried to spray again correctly but plunger was already down. Proceeded to use second device correctly	Adolescent NL 01-234	Cognition “I didn’t see it was a nasal spray. On the device, put on both sides, nose only.”
UE: Did not press plunger firmly enough to release spray (n=2)	Adolescent NL 01-213	Cognition: Thought instruction indicated inserting into both nostrils. “That’s what I think the back says, to insert it into both nostrils, call the ambulance and wait 2-3 minutes.”
	Adolescent NL 01-206	Sensory/Perception “I was all kind of confused and then I looked at the instructions and saw how to do it. Tried it before looking at the instructions.”
UE: Put plunger in nostril, pressed arms of device multiple times in both nostrils. Never successfully released spray or put nozzle in nostril	Opioid User or Associate LL 01-208	Behavior: Did not read instructions and just acted before reading “Did it before reading because I was nervous.”
CC: Did not initially press plunger but self-corrected and pressed plunger (n=2)	Adult General Population LL 01-102	Sensory/Perception: Did not press plunger hard enough to release spray [Moderator]: “Did you notice it didn’t give the dose?” [Participant]: “No. If it had a red thing to let you know. If it had a pop. It sounded like it did pop.”
	Adolescent NL 01-150	“I went to push the nasal spray in the nose and then went back and read it and saw the plunger needed to be pushed down and then did it. Put the words bigger, like step 2. I thought with the pictures he just put it in the nose instead of pushing the middle part (plunger) down.”
CC: Had difficulty pressing the plunger but self-corrected and pressed the plunger	Adult General Population NL 01-110	Sensory/Perception: Was waiting for a click; didn’t push plunger hard enough to release spray “Once I realized I had to push a little harder, that's what I did and then I did hear it.”
CC: Puts device in the mouth but corrects and puts in the nostril and sprays the device	Opioid User or Associate LL 01-156	Cognition: Too much to read “I thought it was the mouth by the drawing. I was in too much of a rush to read all that stuff. It should just have a picture of a nose, spray and the time.”
UD: Held with finger on one side and pressed plunger with thumb (unsuccessfully); added other hand to	Adolescent LL 01-215	Not provided

help steady it and then successfully pressed plunger with thumb		
UD: Put nozzle in second nostril after administering dose to the first	Opioid User or Associate NL 01-136	Behavior: Wanted to be sure delivered full dose "Because I didn't think you had gotten the full dose, so put it back in to make sure I had gotten it all out."
- Based on the Applicant's URRR, performing the task incorrectly or not at all may result in: - No harm (due to delivery of drug into the mouth) - Death, Respiratory/central nervous system depression, coma, slowed respiratory rate, miotic pupils, lethargy (due to incomplete drug delivery-insufficient dose volume delivered)		
Applicant's Comments and Proposed Mitigations (if available): Not provided		
DMEPA's Analysis and Findings		
We disagree with the Applicant's URRR that no harm would result due to delivery of the drug into the mouth. Failure to administer the drug into the nostril may result in respiratory/central nervous system depression, coma, or death. DMEPA Finding #6 The subjective feedback and root cause analysis indicates the user interface may have contributed to some use-related events. Specifically, one participant did not see that the device was a nasal spray and expected to find this information on the label, one participant thought the Step 2 pictogram depicted administration into the mouth and one participant did not think the Step 2 pictogram depicted the plunger being pressed. We find the user interface can be improved to better convey that the drug is for nasal administration. DMEPA Recommendation for Finding #6: We recommend the Applicant: - Add the statement "For nose only" to the carton labeling, blister labeling, and container label. This statement is consistent with approved prescription naloxone nasal spray products with similar device designs. - Revise the heading of Step 2 of carton DFL and QSG to state, "Give 1st dose in the nose" instead of "Give a dose of this medicine" (Also see Step 3, finding #8 below). - Revise the pictogram in Step 2 of the DFL and QSG to show the plunger being pressed, similar to the model DFL Step 2 figure evaluated in CONFER.		

Figure 8. Step 2 Pictograms of RiVive DFL (left) and CONFER DFL (right)



Step 3: Call 911

Information Supplied by Applicant

Total number of UE, CC, UD

UE (n=11), CC (n=17), UD (n=0)

Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA and Participants' Relevant Subjective Feedback (if available)
UE: Did not simulate calling 911 or verbalize that 911 should be called at any time (n=11)	Adolescent LL 01-112	Environment: Did not call 911 because "he was not actually taking the drug"
	Adolescent LL 01-120	Environment: Did not realize they should use the phone
	Adult General Population LL 01-205	"I didn't know if you wanted me to actually pretend to call or to pull my phone out actually"
	Adolescent NL 01-228	"I wasn't sure if I was supposed to. Obviously, the person didn't wake up because it was a mannequin."

	Adult General Population NL 01-402	
	Adolescent LL 01-159	Cognition: Did not see “call 911” on the labeling. Focused on giving the dose.
	Adolescent LL 01-215	[Moderator]: “Did you see that instruction?” [Participant]: “No.” [Moderator]: “What could they do so people don’t miss that?” [Participant]: “I am not sure, make it bigger. I looked past it. I was looking at giving the second dose. I was thinking the person will wake up faster if I give them the second dose.” “I think it is clear, I just think I didn’t see it. Just make it bigger.”
	Adolescent LL 01-218	Cognition: Interpreted directions as “do not dial” vs. “do not delay.” “I didn’t know, since I read do not dial.”
	Opioid User or Associate LL 01-208	Behavior: Reacted to emergency situation and acted vs looking at directions
	Opioid User or Associate LL 01-209	Behavior: Forgot to look at directions because he was nervous in an emergency situation
	Adolescent NL 01-213	Unknown “I don’t know.”
CC: Simulates or verbalizes calling 911 during/after Step 4 (n=11)	Adult General Population LL 01-102	Environment: Did not realize he was actually supposed to use the phone [During the first dose]: “I didn’t see the phone, the second time, I saw the phone there, so I did it. I didn’t know if it was a real phone or not.”
	Adult General Population NL 01-110	Behavior: Assumed that both doses should be given before calling 911.
	Adolescent NL 01-234	Behavior: Did not think phone was working so did not use it to simulate calling 911 “I didn’t know if it [phone] would give a response. I probably would have called 911 and then tried step 1, 2, 4 and 5.”

	Opioid User or Associate NL 01-136	Behavior: did not want to hesitate in giving the second dose "I didn't feel like they woke up and it says to do it right away."
	Opioid User or Associate LL 01-152	"You don't want to hesitate. You told me to act like a real-life situation and I panicked."
	Opioid User or Associate NL 01-161	Cognition "I thought you should be able to give a dose in each nostril and I panicked when there was no more in the first one thinking it misfired and got the second device out for the other nostril right away. Then I saw I was supposed to call 911 after the first dose. I think in an emergency situation, you see 2, you think you give both. I think if it said ONE Nostril, and then say STOP after Step 2."
	Adolescent NL 01-206	Cognition: thought "dose" meant giving both doses and then calling 911 "[Instructions] should say just give one dose and then call 911 and then give the second dose."
	Adolescent NL 01-235	"I think it would be more clear if they said give "1 dose" instead of "a dose" on step 2. I interpreted giving both as a dose."
	Adult General Population NL 01-212	Cognition: thought one "dose" meant one spray in each nostril "It says each nasal spray contains only one dose so I thought one spray for each nostril and gave both at the same time, so maybe it should say 'just give one dose in Step 2,' so you know that it's just one dose at first."
	Opioid User or Associate LL 01-406	Cognition "I would highlight the wait 2-3 minutes and the call 911."
	Opioid User or Associate LL 01-156	Cognition: "It was a lot going on the label. It was hard to me."
CC: Simulates or verbalizes calling 911 before administering the first dose (n=4)	Adult General Population NL 01-103	Behavior: wanted 911 to get there first "My first instinct is to get someone on the way who knows what they are doing instead of me figuring it out first."

	Adult General Population NL 01-230	“Getting someone on the phone and on the way right away is best.”
	Adult General Population NL 01-125	Behavior: assumed he should call 911 first and have them online while he was administering the drug “Called 911 and then I left it online so the 911 operator could hear what was going on. Then I went by the instructions and administered the drug and then went to the phone to try to explain to the 911 operator what was happening and gave the second dose.”
	Adult General Population NL 01-223	Behavior: Did not see the phone right away “I do CPR training every year and the first thing you do when you find someone unconscious, you instruct someone to call 911, and I didn’t see the phone right away.”
CC: Forgets to call 911 but self-corrects before Step 4 (n=2)	Opioid User or Associate NL 01-126	Behavior: did not use phone because it was not a cell phone but a desk phone
	Adult General Population LL 01-401	Cognition: waited a bit (30 seconds to 1 minute) and looked at DFL a few times and then called 911 (simulated) “When I first read that step, I skimmed it. I did that step, then read the next step to see what it was and to wait to see if you would respond and then I called 911.”
Based on the Applicant’s URR, performing the task incorrectly or not at all may result in		
No harm		
Applicant’s Comments and Proposed Mitigations (if available): The fifth critical performance-based task, (Call 911), scored slightly lower (82% error-free) with evidence that most errors were attributed to an artifact of the study in which the participants were expected to “pretend” to call 911. Several participants chose not to simulate the step, but in the debriefing, most stated that they would call 911 in a real-life situation. With regard to calling 911, it is important to note that in some communities, calling 911 for a police response may be perceived as endangering, or actually endanger, those on the scene. Studies have also shown that calls to report overdoses result in incarceration in		

10% of opioid overdose cases.ⁱ Thus, the instruction to Call 911 is not a uniform or neutral call to action and should be seen in appropriate sociopolitical context.

Also, important to note, limited literacy (LL) participants scored lower on the critical task, Step 3 - Call 911 (64% correct - 8 errors among 22 LL subjects) compared to 92% correct for normal literacy (NL) participants (only 3 errors among 38 NL subjects).

DMEPA's Analysis and Findings

We disagree with the Applicant's URRRA that no harm would result from failure to call 911 or delaying the call to 911 as it may result in delayed medical care for the opioid overdose victim and possible continuation of opioid overdose symptoms.

DMEPA Finding #7

The Applicant modified the text in Step 3 of the DFL; however, the pictogram remains the same (see Figure 9 and Figure 10).

Figure 9. RiVive Step 3 DFL evaluated in HFVS

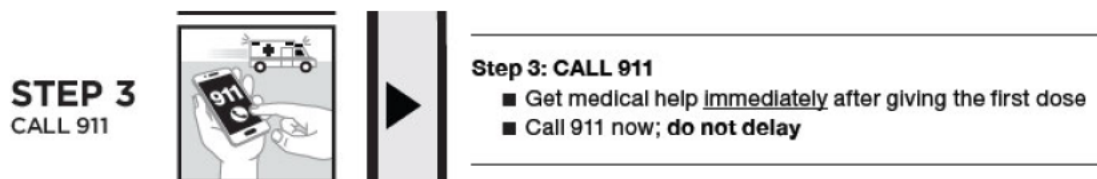


Figure 10. Step 3 of Model DFL Evaluated in CONFER

ⁱ Ray B, Hedden BJ, Carroll JJ, et al. Prevalence and correlates of incarceration following emergency medical services response to overdose. Drug Alcohol Depend. 2022;238:109571. <https://doi.org/10.1016/j.drugalcdep.2022.109571>



Step 3: CALL

- CALL 911 immediately after giving the 1st dose

The subjective feedback and root cause analysis indicates the user interface may have contributed to some use-related events. Specifically, one participant with low literacy misread “do not delay” in Step 3 as “do not dial.” We find that “do not delay” is unnecessary in Step 3 because the instructions state to “Get medical help immediately after giving the first dose” and “Call 911 now.”

DMEPA Recommendation for Finding #7

We recommend the Applicant remove the statement, “do not delay” from the carton DFL and QSG.

DMEPA Finding #8

Some participants experienced a CC in **Step 3** (Call 911) because they thought one dose referred to administering both nasal spray devices which led them to administer both nasal sprays and then call 911 during or after administering the second dose, rather than calling 911 immediately after administering the first dose. Although calling 911 after administration of the first dose is ideal, we acknowledge that these participants called 911 at some point during the use scenario. The subjective feedback and root cause analysis indicates the user interface may have contributed to some use-related events.

We discussed the clinical impact of administering two 3 mg nasal sprays at once (total of a one-time 6 mg dose) with our clinical colleagues, who disagree with the Sponsor’s assertion that no harm would result from this use error. For some opioid overdose victims, administration of 6 mg may result in precipitation of withdrawal symptoms such as vomiting, increased heart rate, pulmonary edema, seizures, or cardiac arrest.

We determined revision of and addition of labeling statements to convey that one dose is equivalent to one device may further reduce the risk of confusion and use errors.

DMEPA Recommendation for Finding #8

We recommend the Applicant:

- Revise the statement, “Each nasal spray contains one dose of medicine” to read “1 nasal spray device contains 1 dose of medicine” on the top flap of the carton and in the third bullet in Step 2 of the DFL to convey that one dose is equivalent to one device. We recommend relocating this statement to the fifth panel of the carton labeling. This statement is similar to other approved products with the same device.
- Revise the heading of Step 2 in the DFL and QSG from “Give a dose of this medicine” to state, “Give 1st dose in the nose.” (Also see Step 2b, finding #6 above).
- Use consistent terminology (i.e., “nasal spray device” to replace “nasal spray”) across the labels and labeling, including the DFL (e.g., in Step 2 and Step 4).

Step 4a: WATCH & GIVE

- **WAIT 2-3 minutes after the 1st dose to give the medicine time to work**

Information Supplied by Applicant

Total number of UE, CC, UD

UE (n=33), CC (n=0), UD (n=0)

Use-Related Event	Participant Type, Literacy, and ID number	Applicant’s RCA and Participants’ Relevant Subjective Feedback (if available)
UE: Does not indicate waiting at all (n=19)	Adult General Population LL 01-102	Behavior: Frustrated because was waiting for a cue like a click or pop “I was getting frustrated because it is a little confusing at first. Tell them to wait until you hear a pop to make sure you gave the dose. Or hear the click sound. Make it bigger print. Put color or put it at the top. You have to really look at the fine print.”
	Adult General Population NL 01-103	Behavior: Estimated wait time “I did step back a bit , and waited, and it probably was not 2-3 minutes.”
	Adult General Population NL 01-110	Behavior: Reacted to emergency to act quickly and give medicine “I was trying to wait but was also thinking if this is family and this could save them and the ambulance wasn’t here yet, I thought, let me just go ahead and try this next.”

Adolescent LL 01-159	"Went ahead and gave second dose. I thought maybe it will work faster."
Opioid User or Associate LL 01-152	Behavior "I am rushing through this demonstration because it is kind of acting thing. Step 4 should be bold letters in red and have caution."
Adult General Population NL 01-202	Behavior "I was thinking the 911 call would have taken the 2 minutes, so after that I was ready to give the dose."
Adult General Population NL 01-207	"I feel like I waited long enough making the phone call and reading the instructions, but I must have sped it up a little."
Opioid User or Associate LL 01-208	Behavior "He wasn't moving. So, I thought try one more time."
Adolescent NL 01-213	Behavior "I was too stressed out about what I was supposed to do, about the product and the nose."
Opioid User or Associate NL 01-136	Cognition "I totally missed that you are supposed to wait 2-3 minutes. They weren't waking up, so I immediately gave another dose. There are so many instructions for a person to see in the emergency situation. Have 3 simple steps at the top. Put WAIT real big in between the doses. Put it in red."
Opioid User or Associate LL 01-156	Cognition "I was just frustrated with reading and trying to help somebody at the same time."
Opioid User or Associate NL 01-161	Cognition: "I was panicky and needed that STOP word after Step 2."
Adult General Population	Cognition

	LL 01-205	"I didn't read the instructions all the way to see that it says wait 2-3 minutes, to see if they wake up. I just saw 2 of them in the package and instantly just thought you use 2 of them. Should put call the police first, then step 2 and then you would see the wait step right after that."
	Opioid User or Associate LL 01-209	Cognition "I thought the words said to give both doses right away, one in each nostril, on step 2."
	Adult General Population NL 01-212	Cognition "It said each spray contains one dose, so I just assumed one for each nostril and went ahead and gave both. Say just give one dose, in step 2 so you know to start with just one."
	Adolescent NL 01-228	Cognition: did not find information on waiting "Put it higher up like in the second step to wait 2-3 minutes"
	Adolescent NL 01-234	RCA not provided "I didn't know there was 2 in there, and when I put it in the mouth I thought I messed it up and immediately thought I have to do it right this time and immediately put it into the nose. I was going as fast as I could. Maybe on the front say please read carefully or something like you have to time this."
	Adolescent NL 01-235	RCA not provided "It is not clear exactly that only one dose is supposed to be given at first. It should say in step 2 only give one dose at first and then wait."
	Opioid User or Associate LL 01-406	RCA not provided "I was going too fast. I seen the second dose with the other nostril and skipped the wait 2-3 minutes. I would put for the first step give dose. I would put MAKE SURE to wait 2-3 minutes before giving another dose. I would put that with the first nostril spray. Wait 2-3 minutes to see if they respond."
UE: Waits less than 2 minutes (n=14)	Adult General Population NL 01-108	Behavior "You kind of have to judge on your own how much time that is and so I waited until I thought 2 minutes passed and then I gave the next dose." "I would wait if I knew the time. I didn't watch the time on the clock." "If someone was in that position, I would want them to hurry and wake up. Have a timer marking. Mark the devices number one and the second one say wait 2-3 minutes."
	Adolescent LL 01-120	
	Opioid User or Associate	

NL 01-133	"In the actual situation I would have waited, but to speed up the process in there I went ahead and gave it."
Adolescent NL 01-162	"I didn't know how long 2 minutes was. I figured by the time I called 911 and went back it should have been 2 minutes. In real life I would guess on the 2 minutes. I wouldn't look for a clock or stopwatch."
Opioid User or Associate NL 01-167	"I didn't pay attention to the clock. I have seen it on TV and haven't seen them wait 2 minutes. I probably panicked and in a real situation it would awaken the person faster depending on how much of an overdose they would be in. Put the time in bold, the 2-3 minutes. Or put 'if the person wakes up go to step 5' in bold."
Opioid User or Associate NL 01-169	"I wasn't sure exactly what time I gave the first dose so that's why tried to give a little bit of time between each dose."
Opioid User or Associate NL 01-170	"I didn't time it. I was rushing and panicking."
Adolescent NL 01-201	
Adolescent NL 01-206	
Opioid User or Associate LL 01-220	
Adolescent LL 01-215	Behavior: Did not read carefully. Did what he thought he should do
Adult General Population NL 01-125	Environment "In a real-life situation, most clocks don't have seconds. I was watching the clock and timing it by the minute."
Adult General Population NL	Cognition: Was looking for information on the device to guide use "Put it in Red. It in red it would have been the first thing I saw and made it obvious that it is important."

	01-230	
	Adult General Population NL 01-402	RCA not provided “I got nervous and thought more time went by.”
Based on the Applicant’s URR, performing the task incorrectly or not at all may result in: No harm		
Applicant’s Comments and Proposed Mitigations (if available): Scores were lower for the instruction to wait 2–3 minutes before administering the second dose, but this was due to most users estimating the time, assuming it was not necessary to simulate the entire waiting time or concluding that it was better to give both doses in quick succession to enhance the odds of a successful overdose reversal. It is known that in real-life opioid reversal situations with prescription naloxone products today, bystanders often do not wait the full 2–3 minutes before giving a 2nd dose of naloxone.^j As this “error” may result in a greater likelihood of a successful opioid overdose reversal, HRT believes no further action required. In the majority of cases, a single administration of intranasal naloxone will reverse most opioid overdoses^k. However, failing to wait 2–3 minutes before administering a second dose should be put in the appropriate medical and public health context. Opioid overdose victims are on the brink of death and often appear to be dead.^l While the administrator of naloxone waits for the medicine to take effect, the urge to give another dose of naloxone is understandable. Not waiting a full 2–3 minutes between doses of naloxone is a common occurrence in the real world.^m Further, it may, in fact, help to save the victim’s life if a second dose is required to achieve the reversal. In the artificial setting of a HFVS study, participants are required to imagine the entire emergency situation and waiting 2–3 minutes serves no purpose other than to extend the experimental session.		

^j Parkin, S., Neale, J., Brown, C., Jones, J.D., Brandt, L., Castillo, F., Campbell, A.N., Strang, J., & Comer, S.D. (2020). A qualitative study of repeat naloxone administrations during opioid overdose intervention by people who use opioids in New York City. *The International Journal on Drug Policy*, 87, 102968.

^k Avetian GK, Fiuty P, Mazzella S, Koppa D, Heye V, Hebbar P. Use of naloxone nasal spray 4 mg in the community setting: a survey of use by community organizations. *Curr Med Res Opin*. 2018;34(4):573-576. Epub 2017 Jun 7.

^l Michael Hufford, Cofounder and CEO of Harm Reduction Therapeutics, Inc., personal communication, July, 2022.

^m Parkin, S., Neale, J., Brown, C., Jones, J.D., Brandt, L., Castillo, F., Campbell, A.N., Strang, J., & Comer, S.D. (2020). A qualitative study of repeat naloxone administrations during opioid overdose intervention by people who use opioids in New York City. *The International Journal on Drug Policy*, 87, 102968.

Further, adhering to the minimum time to pass prior to administering a 2nd dose is not required from a safety perspective. In the majority of real-world cases where intranasal naloxone is used to reverse an opioid overdose, no adverse events (AEs) are reported.^{no} While there is a chance that side effects could be magnified when a second dose is given, when one dose might have sufficed (which is unknowable at the time of administration), there is little to no safety risk in doing so. And, since it is unknowable whether one dose would be sufficient to reverse an overdose, the safest course of action would be to give a second dose of naloxone, even if it is before 2–3 minutes have elapsed since the first dose of naloxone. Note that the AE profile associated with the real-world use of intranasal naloxone in the minority of cases where any AEs are reported include effects like agitation, nausea, vomiting, and headache.^p Thus, these safety data should be placed in the context that the opioid overdose victim must, by definition, be alive to report any AEs, thus the opioid reversal was successful.

One final note, in the context of the artificial situation where study participants assume the victim did not respond to a first dose (because a mannequin does not move or awaken like an overdose victim might), it is a positive result that 96.7% (58/60) participants did attempt to give a 2nd dose of medicine. In sum, the waiting period is inevitably confounded by the artificial situation of the HFVS.

DMEPA's Analysis and Findings

DMEPA Finding #9

Subjective feedback that showed participants felt rushed given the simulation was for an emergency situation thus chose not to wait 2-3 minutes, which is consistent with the Applicant's discussion on prescription naloxone's real-life use by users who do not wait 2-3 minutes. The first bullet under Step 4 "WAIT 2-3 minutes after the 1st dose to give the medicine time to work" is identical to the model DFL evaluated in CONFER, thus, validated for comprehension. We did not identify areas of improvement and have **no recommendations** at this time to address the residual risk that users may chose not to wait 2-3 minutes between doses.

DMEPA Finding #10

ⁿ Avetian GK, Fiuty P, Mazzella S, Koppa D, Heye V, Hebbar P. Use of naloxone nasal spray 4 mg in the community setting: a survey of use by community organizations. *Curr Med Res Opin.* 2018;34(4):573-576. Epub 2017 Jun 7.

^o Thompson J, Salter J, Bui P, et al. Safety, Efficacy, and Cost of 0.4-mg Versus 2-mg Intranasal Naloxone for Treatment of Prehospital Opioid Overdose. *Ann Pharmacother.* 2022;56(3):285-289.

^p Thompson J, Salter J, Bui P, et al. Safety, Efficacy, and Cost of 0.4-mg Versus 2-mg Intranasal Naloxone for Treatment of Prehospital Opioid Overdose. *Ann Pharmacother.* 2022;56(3):285-289.

One participant thought one dose referred to administering both nasal spray devices which led to him/her to give both doses without waiting 2-3 minutes. Please see DMEPA Finding #8 under Step 3 Call 911 above for our recommendations for these use-related events.

Step 4b: WATCH & GIVE

- **If the person does not wake up:**
 - **Give a second dose of medicine using a new nasal spray**
 - **It is safe to keep giving doses every 2-3 minutes until the person wakes up**

Information Supplied by Applicant

Total number of UE, CC, UD

UE (n=9), CC (n=2), UD (n=4)

Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA and Participants' Relevant Subjective Feedback (if available)
UE: Administered second dose into mouth (n=2)	Adult General Population NL 01-104	Cognition: Skipped over some instructions; reacted to tube in mannequin's mouth "Because I saw the little tube in the mouth of the mannequin."
	Opioid User or Associate NL 01-136	Environment: Thought he did the first dose wrong when he saw the tube in the mannequin's mouth "Saw the round thing in the mouth and thought I was really supposed to put it in there. I thought I had done it wrong the first time and then put it in there."
UE: Administered second dose into mouth and reused first device (n=1)	Adult General Population LL 01-204	Cognition "I saw the hole in the mouth and thought it had to go there instead of the nostrils. I just glanced at the directions. I picked up the wrong one. I wasn't trying to use the same one. I just made a mistake."
UE: Administered second dose with first device (n=2)	Adult General Population NL 01-103*	Behavior: Used first device as if it had more medicine in it

	*Applicant categorized as correct; however, we consider this a UE based on the subjective feedback and RCA.	
	Adult General Population NL 01-110*	Cognition: Thought 2 doses might come out of one device (tried to give multiple sprays out of each device) "I was wondering if you can use the same device on each side then how come there aren't 2 doses coming out. I was thinking I need to put it in each side to help revive the person but only felt it come out once and then I thought in real life 2 doses would have come out and I had issues with the instructions, the blue piece stuck it together and I was trying to open, so maybe not have the sticky part that makes the instructions stick together."
UE: Does not verbalize giving second dose at all (n=2)	Opioid User or Associate LL 01-156	Cognition: Did not see the second device and thought he needed to use the first device twice
	Adolescent NL 01-213	Cognition: Did not know to use 2 devices "I don't know why I didn't know."
UE: Administered second dose outside of nostril (n=1)	Adolescent NL 01-206* *Applicant categorized as correct; however, we consider this a UE based on the subjective feedback and RCA.	Device/Action "I really didn't know how to do it. I tried to put it inside the nostril and accidentally squirted it outside. Say how to use the device, like you don't gently push it, you really got to push it in."
UE: Tried to "pump" arms down instead of pressing plunger (n=1)	Opioid User or Associate LL 01-208	Behavior: due to being nervous in the simulation
CC: Administered second dose with first device and then corrected to use second device (n=2)	Adult General Population LL 01-102* *Applicant categorized as correct; however, we consider this a CC based on the subjective feedback and RCA.	Behavior: Focused on if the person was awake "I tried to see if they were awake. I just picked the wrong one up and it was already opened, so then I took the other one out."

	Adolescent LL 01-112	Cognition "Because of the device, you can only do it once. So that is why I went back to get the other device."
UD: Tried to reuse second device a couple of times (n=1)	Opioid User or Associate NL 01-133	Behavior "I was just trying to make sure I got all the liquid out. I felt like I hadn't given enough since they hadn't woken up."
UD: Tried to spray again in second nostril (n=1)	Adult General Population NL 01-230	RCA not provided "I have seen Narcan used, and I think they did it in a second nostril so that is what led me to do the second nostril."
UD: Struggled to open the blister (n=2)	Adolescent LL 01-159	Very long fake nails
	Adolescent LL 01-215	RCA and subjective feedback not provided
Based on the Applicant's URRAs, performing the task incorrectly or not at all may result in: Respiratory/central nervous system depression, coma, death		
Applicant's Comments and Proposed Mitigations (if available): Not provided		
DMEPA's Analysis and Findings		
DMEPA Finding #11 The subjective feedback and root cause analysis indicates the user interface may have contributed to some use-related events. Specifically, some participants thought the nasal spray device contained more than one dose and tried to reuse the nasal spray device previously used to administer the first dose. We find addition of labeling statements to convey that the nasal spray device is single dose may further reduce the risk of confusion and use errors.		
DMEPA Recommendation for Finding #11		

We recommend the Applicant add the statement “Each device sprays one time only” to the PDP of the carton immediately below the statement “1 device contains 1 dose of medicine” (See Step 3, findings #2 above) and to the blister labeling. This statement is similar to other approved products with the same device.

4.2 STEP 1 AND STEP 5

Step 1 Check and Step 5 Stay are identical to the model DFL evaluated in CONFER in terms of both text and pictograms. In our Human Factors Validation Study Protocol Advice Letter, we recommended the Applicant remove evaluation of Step 1 and Step 5.⁹ Thus, the Applicant did not submit HFVS data for Step 1 and Step 5.

4.3 RESULTS AND ANALYSIS OF KNOWLEDGE-BASED QUESTIONS

The Applicant asked 5 knowledge-based questions to evaluate participants' understanding of information. Table 6 includes the results and our analysis of the knowledge-based questions.

Table 6. Results and Analysis of Knowledge-Based Questions

Number	Question and Correct Response	Number of Use Errors (UE)	DMEPA's Analysis
1.	<u>Question:</u> According to the label, each device contains how many doses of medicine? <u>Correct Response:</u> one	20 UE: (n=11 NL, 9 LL) • Adolescents (n=6) • General Population (n=7) • Opioid Users/Associates (n=7)	This knowledge-based question is related to Step 3 and Step 4b. Thus, see our analysis and findings under Step 3 and Step 4b.
2.	<u>Question:</u> Emily was given a carton of this product and wants to store it in the refrigerator. According to the label, is it okay or not okay for Emily to store this product in the refrigerator? <u>Correct Response:</u> not okay	6 UE: (n=2 NL, n=4 LL) • Adolescents (n=1) • General Population (n=3) • Opioid Users/Associates (n=2)	(b) (4) the labeling statements should be updated to include the temperature ranges. We defer to IDS on the storage statement in the DFL.

⁹ Olagundoye-Alawode, A. Human Factors Validation Study Protocol Advice Letter for Naloxone. Silver Spring (MD): FDA, CDER, OSE (US); 2022 JAN 21. IND 134611.

3.	<u>Question:</u> Janet's cousin is overdosing on a prescription pain medicine. Janet gave her a dose of medicine, called 911 and then gave her a second dose of medicine. Now, her cousin is starting to wake up. What, if anything, does the label say Janet should do now?	5 UE: (n=3 NL, n=2 LL) • Adolescents (n=1) • General Population (n=1) • Opioid Users/Associates (n=3)	See our assessment of Step 5 in Section 4.1 above. Step 5 Stay is identical to the model DFL evaluated in CONFER in terms of both text and pictograms and we do not have recommendations.
	<u>Correct Response:</u> Stay until the ambulance arrives even if the person wakes up/stay until the ambulance arrives		
4.	<u>Question:</u> John purchased a carton of this product at the store. When he got home, he noticed that the package was torn. What, if anything, does the label say about this?	7 UE: (n=3 NL, n=4 LL) • Adolescents (n=2) • General Population (n=2) • Opioid Users/Associates (n=3)	Our review of the labeling statement did not identify areas for improvement.
	<u>Correct Response:</u> Do not use if sealed package is torn or opened		
5.	<u>Question:</u> True or False: According to the label, this product should be stored at room temperature.	1 UE: 1 LL Opioid User/Associate (n=1)	(b) (4) the labeling statements should be updated to include the temperature ranges. We defer to IDS on the storage statement in the DFL.
	<u>Correct Response:</u> True		

5. CONCLUSION AND RECOMMENDATIONS

Our review of the HFVS results for RiVive (naloxone HCl) nasal spray identified use-related issues with critical tasks; however, we find the residual risk can be further mitigated by additional changes to the user interface. Although we identified issues with the HFVS methodology, the methodology issues did not preclude our review of the HFVS results. Thus, we carefully reviewed each use-related event, the Applicant's use-related risk analysis, the root cause analysis, the participants' subjective feedback, and the Applicant's additional proposed risk mitigations (if applicable) to inform our recommendations for the user interface. In this instance, our recommendations are carefully targeted to address the root causes of use errors that occurred in the HFVS and draw upon our experience with other similar marketed products. Thus, we find the recommendations pose a low likelihood of introducing new risks during use of the product and can be implemented without submitting additional HFVS data for the Agency's review.

Based on the totality of information submitted and taking into consideration the public health benefit of this proposed product, we find the potential benefit of RiVive (naloxone HCl) nasal spray to "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin outweighs the potential residual risk of use errors.

5.1 RECOMMENDATIONS FOR HARM REDUCTION THERAPEUTICS, INC. (HRT)

We recommend the following be implemented prior to approval of the NDA:

A. Container Label, Blister Labeling, Carton Labeling

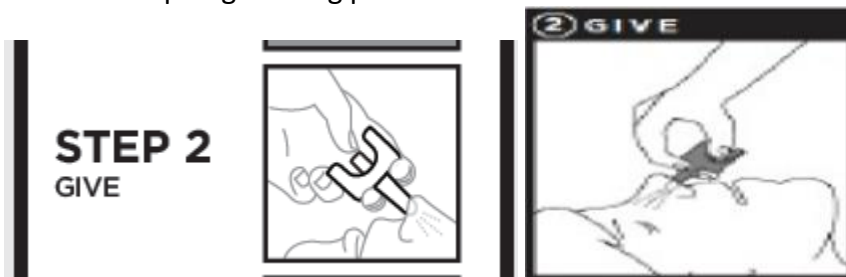
1. Add the statement, "For use in the nose only" to the principal display panel (PDP) of the carton labeling, blister labeling, and to the container label. Use errors in the human factors validation study (HFVS) occurred due to wrong route of administration.
2. Identify the location for the lot number on the labels and labeling. Identify the expiration date format you intend to use and the location on labels and labeling. To reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Carton Labeling, Blister Labeling and Drug Facts Label (DFL)

1. Revise the statement, “Each nasal spray contains one dose of medicine” to read “1 nasal spray device contains 1 dose of medicine” on the top panel of the carton and in the third bullet in Step 2 of the DFL to convey that one dose is equivalent to one device. We recommend relocating this statement to the “fifth” panel of the carton labeling. Add the statement to the blister labeling. Use errors in the HFVS occurred due to confusion about one dose referring to administration of both nasal spray devices prior to calling 911.

C. Drug Facts Label (DFL) and Quick Start Guide (QSG)

1. Revise the pictogram in Step 2 of the DFL (see figure left below) to show the plunger being pressed, similar to the model DFL Step 2 figure evaluated in CONFER where the thumb appears to press down on the device (see figure right below). Incorporate the same image into Step 4’s pictogram, while maintaining the clock image. Make the same revisions to the QSG. A participant in the HFVS did not think the pictogram showed the plunger being pressed.



2. Revise the heading of the Step 2 Directions to “Give 1st dose in the nose”. Use errors in the HFVS occurred due to wrong route of administration. Additionally, use errors in the HFVS occurred due to confusion about a dose referring to administration of both nasal spray devices prior to calling 911.
3. Remove the statement, “do not delay” from Step 3 Directions. A use error occurred in the HFVS because a participant misread “do not delay” as “do not dial.”
4. Use “nasal spray device” instead of “nasal spray” in Step 2 and Step 4 for consistency and to minimize confusion.

D. Carton Labeling

1. Add the statement, “Each device sprays one time only” to the “fifth” panel of the carton. Use errors in the HFVS occurred because some participants thought the nasal spray device contained more than one dose and tried to reuse the device.
2. Add the statement, “Do not test nasal spray device before use” to the “fifth” panel of the carton to minimize the risk of premature activation. Some participants in the HFVS thought the nasal spray device contained more than one dose.
3. Revise the device image on the top “fifth” panel to show an image of a hand holding the device (see image below). This image should show correct hand and finger positioning on the device. Due to space constraints on the top “fifth” panel, we recognize that this may require relocating the graphic image. We recommend relocating the graphic image to the PDP. Add the same image to the top right corner of the Quick Start Guide (QSG). Incorrect hold of the device may have contributed to a use error in the HFVS.



E. Quick Start Guide (QSG)

1. For the purposes of the proposed nonprescription product, and to align with the DFL, retitle the “Quick Start Guide” labeling as “DIRECTIONS” to help users quickly identify that this piece of paper contains identical instructions to the DFL Directions.
2. Revise the statement “Unfold for User Instructions” to read “Unfold for Directions” to help users quickly identify that this piece of paper contains identical instructions to the DFL Directions. We acknowledge you were considering presenting the statement in large font with blue ink against a yellow background such that the statement appears on both sides of the folded QSG per your human factors validation study report, and we agree that the statement should appear on both sides of the folded QSG. Use errors in the HFVS occurred because users had difficulty seeing the QSG or identifying that the folded paper contained directions.
3. Use less sticky glue to keep the QSG folded. We acknowledge you are exploring less sticky glue per your human factors validation study report, and we agree that less sticky glue should be used. Users in the HFVS had difficulty opening the QSG because the glue was too sticky.
4. Revise the last bullet in Step 4 “It is safe to keep giving minutes until the person wakes up” to read, “It is safe to keep giving doses every 2-3 minutes until the person wakes up.” As currently presented, the statement is inconsistent with the carton DFL and there appears to be a typographical error, which may result in confusion.

6. APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. DETAILED REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On August 10, 2017, the Applicant submitted a Pre-IND (PIND) Type B written response only (WRO) meeting request for Naloxone nasal spray, (b) (4), under IND 134611. The Applicant requested to seek advice and discuss the development program for Naloxone nasal spray. Specifically, the Applicant proposed to conduct a Human Factors validation study (HFVS) and to submit a HFVS protocol for Agency's comment prior to conducting the HFVS. The Agency agreed that a HFVS was needed to support NDA submission. We advised the Applicant to complete a comprehensive use-related risk analysis (URRA) to inform their HFVS and to submit their HFVS protocol for Agency review and feedback.^r

(b) (4)

^r Kapoor, S. Meeting Request- Written Responses (IND 134611). Silver Spring (MD): FDA, CDER, ODEII, DAAAP (US); 2017 AUG 10.

^s Stewart, S. Memorandum of Meeting Minutes (IND 134611). Silver Spring (MD): FDA, CDER, ODEIV, DNDP (US); 2018 DEC 20.

- On May 26, 2020, we provided a response to the Applicant's January 27, 2020 request to waive the HFVS after reviewing the Applicant's justification.^t (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

As a result, we advised the Applicant that HF data is needed to confirm that the proposed user interface can be used safely and effectively for its intended uses by intended users in the intended use environments along with ensuring that the associated risks with the proposed product have been mitigated accordingly.

- On June 25, 2020, the Agency sent an email request to the Applicant requesting a submission of their proposed DFL no later than July 6, 2020.^u In particular, the Applicant was asked to provide a line-by-line comparison between their proposed DFL and the FDA-tested model DFL and justification for the acceptability of the identified differences.
- On July 28, 2020, the Agency recommended that the Applicant consider using the FDA proposed naloxone DFL to streamline their product's development. Since the FDA proposed naloxone DFL had already been tested and validated in an LCS, any additional changes made to their product's DFL would require supporting data from a pivotal LCS.
- On August 28, 2020, we sent a Human Factors Validation Study Protocol Incomplete Letter to the Applicant as a response to their request for feedback on their HFVS Protocol that was originally received on August 21, 2020.^v Based on our preliminary review, we stated that the submitted proposed HFVS protocol was incomplete and provided advice on submitting a complete HFVS protocol.
- On December 23, 2020, the Applicant resubmitted their HFVS protocol for the Agency's review.
- On February 20, 2021, we sent the Applicant the Human Factors Validation Study Protocol Advice Letter for the resubmitted HFVS protocol.^w

^t Little, C. Human Factors Review for Naloxone Nasal Spray, IND 134611. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 26. RCM No.: 2020-206.

^u Stewart, S. FDA Communication: IND 134611 Naloxone Nasal Spray, Request for Information, Response Required. Silver Spring (MD): FDA, CDER, DNPDI (US); 2020 JUN 25. IND 134611.

^v Olagundoye-Alawode, A. Human Factors Validation Study Protocol Incomplete Letter for Naloxone. Silver Spring (MD): FDA, CDER, OSE (US); 2020 AUG 28. IND 134611.

^w Olagundoye-Alawode, A. Human Factors Validation Study Protocol Advice Letter for Naloxone. Silver Spring (MD): FDA, CDER, OSE (US); 2021 FEB 20. IND 134611.

- On May 4, 2021, we provided a written response to the Applicant for a Type B Pre-NDA meeting regarding conduct of a remote HF study.^x
- On July 16, 2021, the Applicant submitted a Type C meeting request that included questions relating to their revised HF validation study protocol. These questions were in response to recommendations made in the Human Factors Validation Study Protocol Advice Letter sent on February 20, 2021. On August 20, 2021, in an effort to provide a comprehensive review of the planned HF validation study, we issued an Information Request (IR) to request the revised HFVS protocol. On September 2, 2021, the Sponsor submitted the revised HFVS protocol.
- On November 10, 2021, we provided comments regarding validation of the DFL during the Type C teleconference meeting.^y
 - The Agency acknowledged their HF Formative study results, considered changes made to the DFL due to these study results, and made the following recommendations:
 - Given no changes were made to Step 1 (check) in the DFL, the Agency recommended that it was unnecessary to repeat an evaluation on Step 1 of their DFL in their HFVS.
 - Since the wording changes to Steps 2 (give) and 3 (call 911) of the DFL appeared reasonable, the Agency recommended to continue to evaluate users' comprehension and performance of these steps in their HFVS.
 - Since the wording changes to Step 4 (watch/give) appeared reasonable, the Agency agreed that evaluating Step 4 in their HFVS.
 - In regard to Step 5 (stay), the Agency recommended to use the same wording as stated in the FDA proposed naloxone DFL. As a result, it would be unnecessary to repeat this evaluation as a knowledge-based assessment in their HFVS.
 - The Applicant asked whether the Agency found the proposed RiVive DFL acceptable. The Agency stated their proposed DFL was not acceptable and provided additional comments in regard to the DFL contents and format.
 - The Applicant asked whether the Agency agreed that their proposed RiVive DFL does not require a pivotal label comprehension testing and that statements unique to the DFL (compared to the FDA model DFL) could be validated in the proposed HFVS.
 - The Agency recommended that the currently proposed DFL requires a pivotal LCS. Additionally, if changes to the FDA proposed naloxone DFL are limited to only Steps 2, 3, and 4, then an additional LCS would not be necessary but would ultimately be a review issue.

^x Stewart, S. Meeting Request-Written Responses for RiVive (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, DNPDI (US); 2021 MAY 04. IND 134611.

^y Pham, P. Meeting Minutes for RiVive (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, DNPDI (US); 2021 DEC 01. IND 134611.

- o The Applicant asked whether the Agency agreed with the updated HFVS protocol.
 - The Agency stated that the review of their revised HFVS was ongoing and a separate response would be provided when the review is complete.
- o The Applicant asked whether the URRRA was acceptable to the Agency.
 - The Agency stated that the review of their revised URRRA was ongoing and a separate response would be provided when the review is complete.
- On January 21, 2022, we sent the Applicant the Human Factors Validation Study Protocol Advice Letter for the resubmitted HFVS protocol.²
- On May 12, 2022, we provided comments regarding the Applicant’s proposal to submit the HFVS results prior to the NDA submission during the Type C teleconference meeting. We agreed to provide high-level comments in an advice letter, provided the submission includes the necessary elements to facilitate our review.^{aa} The Applicant did not submit the study results for Agency review prior to NDA submission.
- On September 30, 2022, the Applicant submitted the HFVS report under the program for stepwise submission of sections of a marketing application and on October 28, 2022, the Applicant submitted the labels and labeling, which are the subject of this review.

APPENDIX B. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HFVS results report and background information on human factors engineering process can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda217722\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\emerg-trt-opioid-od\5354-other-stud-rep\20054\study-20054.pdf>

APPENDIX C. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On 1/27/2023, we issued an Information Request (IR) to request clarification on whether the intend-to-market blister labeling contains a quick response (QR) code. On 2/1/2023, the Applicant responded that the intend-to-market blister labeling does not contain a QR code. The response can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda217722\0011\m1\us\response-qr-code-2023jan27.pdf>

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

² Olagundoye-Alawode, A. Human Factors Validation Study Protocol Advice Letter for Naloxone. Silver Spring (MD): FDA, CDER, OSE (US); 2022 JAN 21. IND 134611.

^{aa} Pham, P. Meeting Minutes for RiVive (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, DNPDI (US); 2022 JUN 09. IND 134611.

Using the principles of human factors and Failure Mode and Effects Analysis,^{bb} we reviewed the following RiVive (naloxone HCl) nasal spray labels and labeling submitted by Harm Reduction Therapeutics, Inc. (HRT) on October 28, 2022.

- Container label accessible in EDR via:
<\\CDSESUB1\EVSPROD\nda217722\0002\m1\us\11411-02-revive-nasal-spray-device-lbl.pdf>
- Blister labeling accessible in EDR via:
<\\CDSESUB1\EVSPROD\nda217722\0002\m1\us\11411-01-revive-nasal-spray.pdf>
- Carton labeling accessible in EDR via:
<\\CDSESUB1\EVSPROD\nda217722\0002\m1\us\11411-04-revive-nasal-spray-retail-panel.pdf>
- Quick Start Guide (QSG) accessible in EDR via:
<\\CDSESUB1\EVSPROD\nda217722\0002\m1\us\11411-03-revive-nasal-spray-quick-start.pdf>

D.2 Label and Labeling Images

Container labels



^{bb} Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

MILLIE B SHAH
05/02/2023 08:27:37 AM

GRACE JONES
05/02/2023 10:47:12 AM

COLLEEN L LITTLE
05/02/2023 11:07:14 AM

LOLITA G STERRETT
05/02/2023 11:39:42 AM

CHI-MING TU
05/02/2023 11:45:31 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Ndidi Nwokorie, MD, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic & Reproductive
Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Nonprescription Drugs I (DNPD1)
Office of Nonprescription Drugs (ONPD)

Subject: Review of pediatric assessment and preparation for an advisory
committee meeting

Drug: Naloxone hydrochloride

Proprietary Name: RiVive Nasal Spray

Application Number: NDA 217722

Applicant: Harm Reduction Therapeutics (HRT)

Indications: Over-the-counter emergency treatment of opioid overdose

Dosage Form Solution for intranasal delivery

Proposed Dosage Strength: 3 mg/spray

Proposed Dosage: One 3 mg-dose in one nostril, may repeat every 2-3 minutes¹

Route of Administration: Intranasal (IN)

Consult Request:

DNPD1 consulted DPMH to inform FDA's background materials in preparation for a Joint Nonprescription Drugs Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting to be held on March 20, 2023, to obtain independent expert advice regarding the appropriateness of marketing a nonprescription naloxone product. However, based on the unanimous decision by the same AC at a public meeting held in February 2023 for FDA to approve the prescription to nonprescription switch of another IN naloxone product for the same indication, DNPD1 determined that the Advisory Committee meeting was no longer needed and a Federal Notice to that effect was published on March 2, 2023. DNPD1 additionally requested assistance from DPMH to address pediatric related issues in the review of the Applicant's submission.

I. Acute Opioid Overdose in the U.S. Pediatric Population

Acute opioid overdose in pediatric patients is a preventable public health problem, and increased availability of effective naloxone drug products has the potential to reduce morbidity and mortality in pediatric patients who acutely overdose on opioids both inside and outside of controlled medical settings. Between 1997 and 2012, hospitalizations for opioid poisonings nearly doubled across all pediatric age groups and approximately 5000 patients less than 6 years of age presented to emergency departments for opioid exposures annually.² Between 1999 and 2016, mortality rates increased nearly 3-fold², and nearly 9000 children and adolescents died from opioid poisonings. The highest annual rates were among adolescents aged 15 to 19 years, but time trends revealed a steady linear increase in mortality rates among younger children in the following age groups:

- Adolescents aged 15 to 19 years of age – increased by 252.6%

¹ Appendix 1

² [JAMA Network Open. 2018;1\(8\):e186558. doi:10.1001/jamanetworkopen.2018.6558](https://doi.org/10.1001/jamanetworkopen.2018.6558)

- Children 10 to 14 years of age – increased by 150.0%
- Children aged 5 to 9 years of age – increased by 100.0%
- Children from birth to 4 years of age – increased by 225.0%

During the same timeframe, 7263 (80.8%) of all opioid-related pediatric deaths were unintentional. The majority of these deaths occurred outside of any medical setting; 5537 (61.6%) occurred outside of a medical facility, with 3419 (38.0%) of those children dying at home or another residential setting due to opioid overdose.²

II. Regulatory Framework and Basis for Pediatric Approval of Novel Naloxone

Efficacy of naloxone HCl in pediatric patients was established with the approval of Narcan (naloxone HCl for injection) in 1971. Approved Narcan labeling contains weight-based dosing recommendations for pediatric use, including neonates.

Given the ethical and logistical challenges with conducting controlled efficacy trials evaluating naloxone for the proposed indication in all patients regardless of age, FDA established a plan for the clinical development of novel naloxone drug products relying on a pharmacokinetic (PK) standard in lieu of conducting efficacy trials. FDA publicly shared this clinical development plan in 2012³ and again in 2015⁴. Reliance on a PK standard requires novel naloxone drug products to demonstrate comparable or greater bioavailability to an approved naloxone dose and route of administration in healthy adult volunteers along with data supporting the safety of the proposed naloxone dose. The novel naloxone drug product must match or exceed the PK profile of the approved naloxone product, especially during the early critical period of opioid overdose when prolonged apnea can lead to permanent hypoxic brain injury or death. The key PK parameters include the peak plasma concentration [C_{max}], time to C_{max} [T_{max}], and systemic exposure as measured by the area under the concentration time curve [AUC] during the first few minutes post-dosing.⁵ The PK studies supporting approval of novel naloxone drug products are conducted in adults and do not typically rely on PK evaluation in pediatric patients.

Using this approach, FDA has approved 6 new drug applications for novel prescription naloxone drug products to date for the emergency treatment of known or suspected opioid overdose. Five of 6 products were FDA approved in all ages down to birth. Approved doses have ranged from 0.4 mg to 10 mg. In addition, multiple injectable naloxone drug products are currently marketed under approved abbreviated new drug applications. See Table 1.

³ Transcript from April 12, 2012 Public Workshop on Role of Naloxone on Opioid Overdose Fatality Prevention: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM304621.pdf>;

⁴ Exploring Naloxone Uptake and Use Public Meeting July 1 and 2, 2015: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM469456.pdf>;

⁵ DPMH Memorandum entered in DARRTS under NDA 208411 S001 on 11/10/2015

Table 1. FDA Approved Novel Naloxone Drug Products Based on PK Standard

Product	Application Number	Initial US Approval	Route of Administration	Dose	IN Spray Volume	Approved Population	Marketing Status
Evzio	NDA 205787	2014	IM, SC	0.4 mg	N/A	All ages	Discontinued
Narcan	NDA 208411	2015	IN	4 mg	0.1 mL	All ages	Prescription
		2017		2 mg		All ages	Discontinued
Evzio	NDA 209862	2016	IM, SC	2 mg	N/A	All ages	Discontinued
Kloxxado	NDA 212045	2021	IN	8 mg	0.1 mL	All ages	Prescription
Zimhi	NDA 212854	2021	IM, SC	5 mg		All ages	Prescription
Naloxone HCl Autoinjector	NDA 215457	2022	IM, SC	10 mg	N/A	12 years and older	Discontinued

Source: Adapted by this reviewer from Drugs@FDA.

IM: intramuscular; SC: subcutaneous; IN: intranasal; HCl: hydrochloride

III. Key Pediatric Considerations Specific to RiVive Nasal Spray

Harm Reductions Therapeutics (HRT) included an Agreed iPSP in the new drug application (NDA) it submitted on September 30, 2022. In the Agreed iPSP, HRT agreed to address the following key issues in the planned marketing application:

1. Justify safety and effectiveness of proposed naloxone dose for all pediatric age ranges, including neonates
2. Justify safety of proposed dosing volume in all pediatric patients, including neonates
3. Justify why absorption of drugs through nasal mucosa will not be different in pediatric patients, including neonates, compared to adults
4. Justify device can appropriately deliver intended dose to all pediatric patients, including neonates (e.g., achieve correct placement of device, evidence that device is appropriately sized, evidence that the correct volume is delivered)
5. Address relevance of statements “high exposure to naloxone in neonates may have fatal consequences” and “in neonates, the level of naloxone exposure achieved after administration of a single dose of NARCAN can be 100-fold higher than highest end of range of established safe and effective dose for an adult”

The NDA contains a 12-page document entitled, “RiVive Pediatric Assessment” addressing these key issues. This memorandum focuses on DPMH’s review of the pediatric assessment provided by HRT.

A. Key Issue # 1: Justify safety and effectiveness of proposed naloxone dose for all pediatric age ranges, including neonates.

The Applicant did not provide any new clinical data, published or otherwise, to justify the safety and effectiveness of the proposed 3 mg dose for all pediatric age groups. The Applicant cited

FDA's precedent of approving other naloxone nasal spray products⁶ at higher doses down to birth to support the safety of their 3 mg dose and noted that no new safety signals have been identified since approval of these higher dose naloxone nasal products.

Although the Applicant did not provide any clinical data justifying the pediatric safety and effectiveness of the proposed dose, the lack of post-marketing serious adverse events associated with other naloxone products approved at higher doses⁷ is supportive of the safety of this product. Additionally, the proposed product does not contain any novel excipients requiring non-clinical evaluation for safety.

B. Key Issue #2: Justify safety of proposed dosing volume in all pediatric patients, including neonates.

The Applicant submitted 5 publications to justify the safety of the proposed IN dosing volume of (b) (4). These publications consisted of one controlled trial, 3 reviews, and one organization's information webpage. See Appendix 2. The 3 reviews encompassed published studies supporting the pediatric use of other IN drugs for mainly sedation and analgesia; one review described the practice of medicine as it pertains to the use of IN medications in the pediatric emergency department. None of the 3 reviews specifically discussed the safety of IN dosing volumes, which included recommended volumes ranging from 0.2 mL to <1.0 mL per nostril based on expert opinion and clinical practice.

The controlled single-blinded trial was designed to evaluate the optimal volume of IN midazolam to achieve pre-procedural sedation in a pediatric emergency department at a single center.⁸ The trial population consisted of pediatric patients 1-7 years of age who required laceration repair. Patients were randomized to receive IN midazolam at volumes of 0.2 mL, 0.5 mL, and 1.0 mL. The primary outcome was time to onset of minimal sedation. Secondary outcomes included procedural distress; time to procedure start; deepest level of sedation achieved; adverse events, which included vomiting, apnea (no breath for > 20 seconds); paradoxical reaction (i.e., agitation precipitated by midazolam); and the need for supplemental oxygen, airway repositioning or bag-mask-valve ventilation. Additional secondary outcomes included inadequate sedation during the procedure and clinician and caregiver satisfaction. The procedure was videotaped from 1 minute prior to administration of IN midazolam and throughout the procedure to 1 minute after the procedure was completed. Three trained physician outcome assessors independently scored each video, blinded to the volume of administration used. The trial enrolled a total of 99 patients.

The investigators found a statistically shorter time to onset of minimal sedation (0.9 minutes) between 0.5 mL and 1.0 mL but found this difference to not be clinically meaningful based on the a priori threshold of 1.5 minutes. There were no statistically or clinically meaningful differences

⁶ Narcan NS 4mg (NDA 208411) and Kloxxado NS 8 mg (NDA 212045)

⁷ Cite OSE Post-Marketing Safety Review (Pending)

⁸ Tsze DS, Ieni M, Fenster DB, Babineau J, Kriger J, Levin B, Dayan PS. Optimal Volume of Administration of Intranasal Midazolam in Children: A Randomized Clinical Trial. *Ann Emerg Med*. 2017 May;69(5):600-609. doi: 10.1016/j.annemergmed.2016.08.450. Epub 2016 Nov 4. PMID: 27823876; PMCID: PMC5406242.

in time to onset of minimal sedation between the remaining groups. There were no significant differences regarding the secondary outcomes between groups. There were no serious adverse events (SAEs). The only AEs observed were vomiting and inadequate sedation with no difference between the groups. The authors concluded that this trial supports the acceptability of IN volumes of administration (VOA) up to 1 mL in patients down to 1 year of age. The authors noted that the trial results refute concerns about suboptimal efficacy resulting from run-off from instillation of larger IN volumes; the trial demonstrated that the largest VOA produced clinical outcomes comparable to the smaller VOAs.

The Applicant notes that Narcan Nasal spray, which delivers an IN-spray volume of 0.1 mL, was approved down to birth in 2015. The Applicant also noted that, since that time, other IN products with identical spray volumes of 0.1 mL have been approved for pediatric use down to birth.

Given the lack of any new clinical data provided by the Applicant, the acceptability of the proposed IN spray volume relies on FDA's previous approval of IN products with similar nasal spray volumes down to birth and the pediatric post-marketing safety experience for these products.

C. Key Issue #3: Justify why absorption of drugs through nasal mucosa will not be different in pediatric patients, including neonates, compared to adults.

The Applicant noted that, in general, IN administration of drugs is considered standard practice in adult and pediatric populations in medical settings. Naloxone exhibits certain qualities such as high lipophilicity and small molecular size that make it suitable for IN administration. The Applicant acknowledged that the anatomy of nasal cavity from age 10 days to 53 years undergoes a 5-fold increase in airway surface area, with the greatest increase occurring within the first 5 years.⁹ However, the Applicant stated that determining how these differences impact IN absorption of medications between adults and pediatric patients is difficult. Although conducting a PK study of IN naloxone to compare PK profiles in a study population consisting of both adults and pediatric patients is not feasible for obvious ethical and logistical reasons, the Applicant cited a study for another small molecule, dexmedetomidine¹⁰, which demonstrated comparable PK between the adult and pediatric populations studied after IN drug administration. The cited study described the PK profile of dexmedetomidine after IN administration in 18 patients, 6 to 48 months of age, presenting for elective cardiac surgery who required postoperative sedation with dexmedetomidine. The patients were randomized to 3 arms: 1 µg/kg nasal spray, 2 µg/kg nasal spray, and 1 µg/kg IV infusion over 10 minutes.

In a recent publication in 2021, investigators evaluated the PK profile of naloxone 0.4 mg/mL administered intranasally in a pediatric population. Twenty children 6 months to 10 years of age undergoing surgery received naloxone IN spray at a dose of 20 µg/kg divided into repeated doses

⁹ Xi J, Si X, Zhou Y, Kim JW, Berlinski A. Growth of Nasal and Laryngeal Airways in Children: Implications in Breathing and Inhaled Aerosol Dynamics. *Respiratory Care* 2014;59(2).

¹⁰ Miller JW, Balyan R, Dong M, et al.. Does intranasal dexmedetomidine provide adequate plasma concentrations for sedation in children: a pharmacokinetic study. *British Journal of Anaesthesia* 2018;120(5):1056e1065

of 0.1 mL per nostril up to a maximum total dose that did not exceed the 0.4 mg approved dose for the IV/ IM naloxone formulations. Blood samples were collected at 5,10, and 20 minutes after the end of IN administration. All patients had quantifiable plasma concentrations at 5 minutes, and 14/20 patients had reached their observed peak concentration by 20 minutes. The observed maximum plasma concentrations of naloxone were dose-normalized by body surface area ($C_{max}/\mu\text{g}/\text{m}^2$) and found to be higher in children compared to that observed in adults. The authors concluded that “there is a rapid uptake of naloxone after intranasal administration and suggests that the nasal uptake of naloxone is higher in children than in healthy adults”.¹¹

- D. Key Issue #4: Justify device can appropriately deliver intended dose to all pediatric patients, including neonates (e.g., achieve correct placement of device, evidence that device is appropriately sized, evidence that the correct volume is delivered).

The Applicant provided no new objective information to further support the use of this device and relied on prior approval of other products with same device.

DPMH has had concerns that the device would not fit very young patients appropriately and could result in the delivery of an ineffective dose. However, DPMH is unaware of any post-marketing pediatric safety signals identified to date with use of the same device, which was subsequently approved for multiple other IN products following Narcan Nasal Spray’s initial US approval in 2015. The lack of a safety signal related to the use of the same device for approved products does not currently warrant further evaluation of the safety of the device component in this product for the intended pediatric population.

- E. Key Issue #5: Address relevance of statements “high exposure to naloxone in neonates may have fatal consequences” and “in neonates, the level of naloxone exposure achieved after administration of a single dose of NARCAN can be 100-fold higher than highest end of range of established safe and effective dose for an adult”

The Applicant did not provide any new objective information to address concerns of the proposed fixed dose IN drug product in neonates and again relied on the naloxone products already approved at higher doses for use down to birth. The Applicant stated the safety of the proposed RiVive 3 mg IN dose is supported by the exposure which is expected to be lower than that produced from the 4 mg and 8 mg approved doses of Narcan and Kloxxado, respectively.

The Applicant did not provide any objective information to support the phrase, “high exposure to naloxone in neonates may have fatal consequences” included in the iPSP. Instead, the Applicant acknowledged that caution should be used when treating neonates with an opioid antagonist and that neonates should be treated with naloxone in a hospital setting to avoid inducing opioid

¹¹ Malmros Olsson E, Lönnqvist P-A, Stiller C-O, Eksborg S, Lundeberg S. Rapid systemic uptake of naloxone after intranasal administration in children. *Pediatr Anaesth*. 2021;31:631–636. <https://doi.org/10.1111/pan.14175>

withdrawal because newborn neonates may have been chronically exposed to opioids in utero. The Applicant had taken the phrase “in neonates, the level of naloxone exposure achieved after administration of a single dose of NARCAN can be 100-fold higher than highest end of range of established safe and effective dose for an adult” in the Agreed iPSP from a DPMH memorandum completed in 2015 for Narcan Nasal Spray¹² in which the reviewer compared the estimated naloxone exposure, assuming 100% bioavailability of the 4 mg IN dose, to exposures resulting from doses recommended in the approved naloxone for injection labeling (0.01 mg/kg IV)¹³ and approximately 10-fold higher than the dose recommended by the American Academy of Pediatrics’ Committee on Drugs (0.1 mg/kg parenteral)¹⁴ if it were administered to a low-birth neonate weighing 2 kg. Since completion of the 2015 memorandum, DPMH engaged with the AAP to determine the basis for the AAP naloxone pediatric dosing recommendations and concluded that the AAP recommendations are not evidence-based. Despite the lack of objective data provided by the Applicant, FDA’s subsequent approval of 5 novel naloxone drug products, (see Appendix 3) all of which are labeled for use down to birth with no post-marketing safety concerns identified in the pediatric population, support the safety of the proposed 3 mg IN dose in pediatrics.

IV. Pediatric Specific Consideration for Nonprescription Use

Nonprescription availability of the proposed product will result in the potential for widespread use by consumers, who are not limited to adults. One factor to consider when assessing the Nonprescription suitability of this product for all ages is whether adolescents 12 years of age and older, school aged children less than 12 years of age, and caregivers of the youngest children from birth to less than 2 years of age can reliably administer the drug product without the supervision of a licensed healthcare provider.

Children less than 12 years of age may potentially be the first and only responder in a household if a medical crisis occurs. Almost 1 in 3 children in the United States (US) live with one parent.¹⁵ Approximately 11% of US children under 14 years of age live with at least one family member who is or was addicted to opioids.¹⁶ Teaching these children how to correctly administer naloxone could be life-saving – particularly for families consisting of single parents who abuse opioids or in families where a school-aged child is left at home with an older sibling and/or their friends who use opioids. Additionally, caregivers of the youngest children who inadvertently are exposed to opioids in the home should be able to effectively use this product if the need arises. Between 2000 and 2015, children from birth to 5 years accounted for almost 90% of buprenorphine exposures reported in patients less than 20 years of age.¹⁷ Ideally, consumer use studies and human factors validation studies evaluating the safe and effective use of this drug product by the “intended users,

¹² DPMH Memorandum entered in DARRTS under NDA 208411/s-001 on 1/04/2017

¹³ SPL Labeling accessed from FDALabel on 1/19/2023

¹⁴ American Academy of Pediatrics Committee on Drugs. Naloxone Use in Newborns. Pediatrics 65: 667- 669, 1980.

¹⁵ <https://www.census.gov/newsroom/press-releases/2016/cb16-192.html>

¹⁶ DPMH Memorandum entered in DARRTS under (b) (4) on 12/11/2018

¹⁷ Jakob D. Allen, Marcel J. Casavant, Henry A. Spiller, Thiphalak Chounthirath, Nichole L. Hodges, Gary A. Smith; Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000–2015. Pediatrics April 2017; 139 (4): e20163382. 10.1542/peds.2016-3382

for the intended uses and for the intended use environment”¹⁸ should have included children potentially as young as 8 years of age¹⁶, using both adult and pediatric mannequins to assess effective use under both conditions. The HFS submitted with this application excluded users younger than 12 years of age and did not validate that caregivers of younger children, birth to 2 years of age, would be able to effectively use this product if needed. In addition, studies validating the DFL did not enroll patients younger than 15 years of age. Whether results from these studies can be generalizable to users less than 15 years is questionable. The lack of understanding of how younger user groups would perform on critical tasks as well as how all user groups would perform on patients less than 5 years of age constitutes a gap in our knowledge. However, the benefit/risk profile for such life-saving intervention for a life-threatening condition readily available to consumers may outweigh any potential risk that may exist due to the exclusion of younger user groups from these studies.

V. Conclusion

The pediatric assessment provided by the Applicant in this NDA submission addressed the key issues identified in the Agreed iSP. The Applicant largely relied on FDA’s precedent of approving other naloxone nasal spray products down to birth that deliver higher doses with the same IN volume per actuation using the same device as that proposed for RiVive to support the safety of this product. The lack of post-marketing serious adverse events associated with other naloxone products approved at higher doses further supports the safety of this product.

The Applicant did provide limited data from recent publications supporting IN volumes of administration of 0.2 mL to up to 1 mL per nostril in pediatric patients based on clinical practice. However, most of the submitted publications consisted of general reviews that did not specifically discuss the safety of these IN volumes down to birth. The single controlled trial¹⁹ included with this submission does support the safety of IN volumes up to 1 mL in patients down to 1 year of age but does not address the safety of these volumes in patients less than 1 year of age.

¹⁸ Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff. February 2016

¹⁹ Tsze DS, Ieni M, Fenster DB, Babineau J, Kriger J, Levin B, Dayan PS. Optimal Volume of Administration of Intranasal Midazolam in Children: A Randomized Clinical Trial. *Ann Emerg Med*. 2017 May;69(5):600-609. doi: 10.1016/j.annemergmed.2016.08.450. Epub 2016 Nov 4. PMID: 27823876; PMCID: PMC5406242.

Appendix 1:



Source: RiVive Nasal Spray Quick Guide submitted to DocuBridge on October 28, 2022

Appendix 2: Applicant Submitted Publications to Support (b) (4) in Spray Volume

Publication Type	Inclusion/Exclusion Rationale	Age Range	VOA* (mL)	Comment / Notable Findings	Publication Year	Reference
Research Paper	Randomize, Prospective, Clinical Trial to evaluate optimal volumes of administration of intranasal drug (midazolam)	1 to 7 years of age	0.2, 0.5, 1.0	- Using a VOA of 0.2 mL, 0.5 mL, or 1 mL produced comparable and acceptable outcomes. - No difference in AEs between groups	2017	Tsze DS et al.
Review Article	Literature review focusing on PK and Therapeutic aspects of opioids available for IN use in cancer patients	Silent	0.2 to 0.3 per nostril	Not relevant as did not provide scientific rationale for the recommended volume of 0.2 to 0.3 mL.	2019	Triarico S et al
Review Article	Literature review focusing on the efficacy and safety of several IN sedatives and analgesics in pediatrics	≥ 1 year of age	< 1.0 mL per nostril	This is a review article with focus on the specific drugs used IN and not on the appropriateness of volumes used	2013	Buck, ML

Publication Type	Inclusion/Exclusion Rationale	Age Range	VOA* (mL)	Comment / Notable Findings	Publication Year	Reference
CME Review Article	Review of the practice of medicine	Silent	0.2 to 0.3	Not relevant to this review	2014	Del Pizzo et al
Webpage information	Informational Page for emergency physicians	Silent	< 1.0 mL per nostril (ideally 0.2 to 0.5)	- Opinion piece found on https://www.aliem.com/pet-pearls-intranasal-medications/. - PEM Pearls - Not relevant to this review	2020	Church A, Tat S, Ziatan C

Source: Created by Reviewer.

*VOA -Volume of administration

Appendix 3: Approved Novel Naloxone Drug Products in Pediatric Patients Birth and Older

Drug Name	Year Approved	Dosage	Dosage Form	Route of Administration
Evzio	2014	0.4 mg	Pre-filled auto-injector	IM/SC*
Narcan	2015	2 mg, 4 mg	Pre-filled IN solution	Intranasal
Evzio Autoinjector	2016	2 mg	Pre-filled auto-injector	IM/SC*
Kloxxado	2021	8 mg	Pre-filled IN solution	Intranasal
Zimhi	2021	5 mg	Pre-filled syringe for injection	IM/SC*

Source: Created by Reviewer

*IM/SC- Intramuscular/ Subcutaneous

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Integrated Review

Date: February 24, 2023

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Product Name: Naloxone hydrochloride, intranasal spray

Subject: Adverse Events, Device Use Errors, and Drug Utilization
Patterns

Application Type/Number: NDA 208411 (naloxone 4 mg)
NDA 217722 (naloxone 3 mg)

Applicant/Sponsor: Emergent Biosolutions Inc. (naloxone 4 mg)
Harm Reduction Therapeutics (naloxone 3 mg)

TTT Record ID:

2022-2857, 2022-2812, 2022-2750, 2022-2700

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

*We would like to acknowledge Sarah Kang, PharmD, BCPS and Jamie Klucken, PharmD, MBA, BCPS, BCACP for their contributions to this document.

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EXECUTIVE SUMMARY

A joint Nonprescription Drug Advisory Committee (AC) and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting convened on February 15, 2023 to discuss the safety and efficacy of over-the-counter (OTC) Narcan Nasal Spray (naloxone hydrochloride spray) 4 mg/0.1 mL (first in class RX-to-OTC switch). RiVive Nasal Spray (naloxone hydrochloride spray) 3 mg/0.1 mL (Direct-to-OTC) is a second OTC naloxone product currently being evaluated. The Office of Nonprescription Drugs (ONPD) requested this Office of Surveillance and Epidemiology (OSE) review to support the briefing document for the AC meeting and the integrated reviews for both OTC intranasal (IN) naloxone products.

This OSE review from the Divisions of Pharmacovigilance II (DPV II), Mitigation Assessment and Medication Error (DMAMES), and Epidemiology II (DEPI II) describes U.S. drug utilization patterns of naloxone products (all formulations), adverse events (all routes of administration and subset analysis of IN), and device use errors (IN) from postmarket data sources between January 1, 2016, and November 17, 2022. Per the Division of Nonprescription Drugs' (DNPD) request, additional safety topics of interest are addressed for the IN route, including precipitation of severe opioid withdrawal (herein referred to as naloxone-induced precipitated withdrawal), risk of limited efficacy (will also be referred to as drug ineffective), and medication errors related to the intranasal products.

Since Narcan NS was launched in 2016, it has been sold and distributed widely across healthcare settings and by harm reduction groups. Narcan NS is also increasingly dispensed through retail pharmacies via individual prescriptions as well as through state actions such as standing order prescriptions which has increased administration in non-health care settings. This increased utilization of the IN product correlates with the increase in number of adverse event reports in recent years. Overall, the FAERS aggregate analysis of all routes of naloxone, and the subset IN naloxone analysis did not identify any new safety issues related to the adverse events. The focused analysis of naloxone-induced precipitated withdrawal, limited efficacy, and device use errors similarly revealed no major areas of concern, although it did yield observations that could inform labeling and product design.

DPV Findings

Our FAERS (318) and literature (11) subset analysis represents U.S. community use of IN naloxone. We note that about half the cases were administered by the general public, about a third of the doses were self-administered, and the majority of the outcomes reported were non-serious. Very few cases described administration by trained laypeople or health care providers (HCPs). Most cases described using one to two doses up to 8 mg, which is what is contained in the package. Most cases reported use for emergency treatment of known or suspected opioid overdose, reflecting appropriate use of IN naloxone by the general public.

Both data sources support the known adverse event of naloxone-induced precipitated withdrawal, which is included in the Narcan nasal spray labeling under Section 5, Warnings and Precautions. We used the Clinical Opiate Withdrawal Scale (COWS) to analyze cases of reported precipitated withdrawal. One or more withdrawal symptoms (e.g., gastrointestinal (GI) upset, anxiety/irritability, sweating) were apparent in at least a third of the IN cases. Other more severe

non-COWS withdrawal symptoms such as pulmonary edema and seizures were also reported to FAERS and the literature (pulmonary edema only). Pulmonary edema and seizures are included in the Narcan nasal spray labeling under **Section 5, Warnings and Precautions**, and described as a potential consequence of abrupt postoperative withdrawal; however, this was not the situation for these cases that occurred in the community setting.

The IN subset analysis also supports the known risk of limited efficacy with partial agonists or mixed agonists/antagonists where larger or repeat doses may be required, which is included in the Narcan nasal spray labeling under Section 5, Warnings and Precautions. Multiple factors contribute to the effectiveness of IN naloxone including the severity of the overdose, if other substances are involved, time elapsed between when the overdose occurred and when naloxone is administered, and the administration technique. Our analysis of the subset of limited efficacy cases was challenging, as 75% of cases did not report the specific opioid intended to be reversed (e.g. partial agonists) or if other substances were involved in the overdose, both of which could affect the efficacy of naloxone.

DMAMES Findings

DMAMES identified multiple device use errors related to wrong technique of IN naloxone administration: not waiting for two to three minutes between two doses, spraying medication into the air instead of patient's nostril and thus, wasting a dose (but IN naloxone user had more than one device in possession), general confusion about the use of the device, and administering medication to the same nostril. All cases were reported as non-serious, and majority of the cases reported patient recovery after administration of IN naloxone despite the device use errors. Additionally, the majority of the cases reported laypeople as the device users. However, it is unclear from the majority of cases whether users referred to the instructions for use, quick start guide, or carton labeling for the information on how to administer the product correctly.

Additionally, beyond the device use errors, we identified wrong indication medication error cases. These cases involved administration of the IN naloxone thinking it is used for indications other than suspected or known opioid overdose (e.g., sinus issues, congestion, asthma, etc.) or thinking it is another drug product (e.g., Flonase). Furthermore, we identified accidental wrong storage medication error cases that reported patients leaving the product in freezing temperatures or temperatures over 104°F.

Drug Utilization Findings

Drug utilization analyses of nationally estimated number of naloxone products sold in the U.S. and the number of prescriptions dispensed for naloxone provide insight into the changing market of naloxone distribution and use over the most recent six years. From 2016 to 2021, manufacturer sales and dispensed prescriptions of all naloxone formulations increased dramatically. Manufacturers sold approximately (b) (4) units of naloxone in 2016, which more than doubled to nearly (b) (4) units sold in 2021. These increases were largely driven by increases in sales of nasal spray formulation, which increased from approximately (b) (4) units in 2016 to (b) (4) units sold in 2021. We saw a similar shift towards nasal spray in the dispensed prescription analysis. The number of naloxone prescriptions dispensed increased from

approximately (b) (4) prescriptions in 2016, to (b) (4) prescriptions in 2021, mainly due to an increase in dispensed prescriptions for the nasal formulation. However, these data underestimate total distribution and availability because the data sources do not capture donations, purchases, or distribution by community programs such as harm reduction programs and organizations.

Conclusion

Overall, the FAERS aggregate analysis of all routes of naloxone and the subset IN naloxone analysis did not identify any new safety issues related to the adverse events. The increase in number of adverse event reports in recent years correlates with increased drug utilization of the IN product. The postmarketing safety data we analyzed for IN naloxone overall and with community use of IN naloxone does not indicate any new safety issues despite an increase in the utilization of IN naloxone. Our cases demonstrated that the general public administered IN naloxone in the community for emergency use of known or suspected opioid overdose and the majority of cases had non-serious outcomes. The known adverse events of naloxone-induced precipitated withdrawal and limited efficacy identified in this FAERS and literature review do not outweigh the potential benefit of increased community availability of an OTC IN naloxone product.

The safety assessment related to the postmarket device use errors indicates that testing the device or spraying naloxone into the air can result in dose omission of naloxone nasal spray and hence, delay an emergency treatment for the opioid overdose, which can potentially lead to death. Although additional device use errors such as not waiting two to three minutes between doses and using the product in the same nostril occurred and can result in overdose and underdose respectively, wasting a dose, especially if that is the only naloxone nasal spray available to the user, appears to be the most significant safety risk related to the device use errors.

Recommendation

Based on the postmarketing safety analysis related to naloxone-induced precipitated withdrawal and limited efficacy, we recommend that the Drug Facts Label (DFL) for any IN naloxone product contain language describing the common symptoms associated with withdrawal (e.g., GI upset, anxiety/irritability, sweating), as well as directions to continue giving doses every two to three minutes until the person wakes up or medical personnel arrive, consistent with what is included in the prescription labeling for naloxone products.

Based on the safety risk assessment related to the postmarketing device use errors, specifically involving the missed dose due to the device testing or spraying naloxone outside of the patient's nostril, we agree with the Applicants' intention of supplying OTC naloxone nasal spray products in a package containing two units together and not as a single unit provided there is one dose per nasal spray device. We also recommend that the labels and labeling clearly and prominently display the product's name, indications, and storage information as we identified multiple cases related to the administration of the product for the wrong indication as well as wrong storage temperatures.

1 INTRODUCTION

On October 5, 2016, the Agency held a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSARM) to discuss what is known about the safety of using naloxone and the risk of precipitating an acute opioid withdrawal syndrome, issues specific to dosing in pediatric patients, the clinical pharmacology of naloxone, and information about the use of naloxone. On December 17 and 18, 2018, the Agency held a second joint meeting to discuss ways in which the Agency could increase the availability of naloxone products intended for use outside of the healthcare setting.

On November 16, 2022, FDA issued a Federal Register Notice (FRN 68702 Vol. 87, No. 220, Docket No. FDA-2022-N-2673) titled, *Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use; Request for Comments*. The FRN announced FDA's "preliminary assessment that certain types of naloxone hydrochloride ("naloxone") drug products may be approvable as safe and effective for nonprescription use including naloxone nasal spray up to 4 mg, naloxone autoinjector for intramuscular or subcutaneous use up to 2 mg have the potential to be safe and effective for use as directed in nonprescription drug labeling without the supervision of a healthcare practitioner."

A joint Nonprescription Drug Advisory Committee (AC) and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting convened on February 15, 2023 to discuss the safety and efficacy of over-the-counter (OTC) Narcan Nasal Spray (naloxone hydrochloride spray) 4 mg/0.1 mL (first in class RX-to-OTC switch). RiVive Nasal Spray (naloxone hydrochloride spray) 3 mg/0.1 mL (Direct-to-OTC) is a second OTC naloxone product currently being evaluated. The Office of Nonprescription Drugs (ONPD) requested this Office of Surveillance and Epidemiology (OSE) review to support the briefing document for the AC meeting and the integrated reviews for both OTC intranasal (IN) naloxone products.

This OSE review from the Divisions of Pharmacovigilance II (DPV II), Mitigation Assessment and Medication Error (DMAMES), and Epidemiology II (DEPI II) describes U.S. drug utilization patterns of naloxone products (all routes of administration), adverse events (all routes of administration and subset analysis of IN), and device use errors (IN) from postmarket data sources between January 1, 2016, and November 17, 2022. Per the Division of Nonprescription Drugs' (DNPd) request, additional safety topics of interest are addressed for the IN route, including precipitation of severe opioid withdrawal (herein referred to as naloxone-induced precipitated withdrawal), risk of limited efficacy, and medication errors related to the intranasal products.

1.1 BACKGROUND

For additional context, the following relevant background text (i.e., Use of naloxone in reversal of opioid overdose, Opioid withdrawal: abstinence-related versus precipitated, and Polysubstance overdose) is replicated from the OSE/DPV review RCM 2022-119, completed recently on May 17, 2022:

1.1.1 Use of naloxone in reversal of opioid overdose

Opioid overdose death is most commonly the result of opioid-induced respiratory arrest with resultant cardiac arrest. Opioid toxicity can be managed with or without opioid antagonist administration.¹ Reversal of opioid toxicity with naloxone can be a life-saving intervention. However, there are no studies demonstrating improvement in patient outcomes from administration of naloxone during cardiac arrest. Early activation of emergency medical services and provision of cardiopulmonary resuscitation are of highest priority.^{2,3} Management without antagonist administration, such as naloxone, requires interventions to restore and/or support respiratory status and airway protection. Naloxone is currently available as parenteral and IN formulations. Over time, the unit dose of naloxone products has increased, including recently approved (2021) products designed to deliver 5 mg intramuscular (IM) or subcutaneous (SC) or 8 mg IN in a single dose.⁴

Naloxone is a pure competitive opioid receptor antagonist. It reverses all receptor-mediated opioid actions including central nervous system (CNS) and respiratory depression due to opioid toxicity.¹ Naloxone administration to opioid-naïve individuals typically produces no clinical effects. However, if given in higher doses to these individuals, reversal of endogenous opioids may produce symptoms.¹ Naloxone administration to individuals with exposure-related opioid receptor neuroadaptations may precipitate withdrawal from a resultant catecholamine increase.^{1,5} Manifestations of precipitated withdrawal overlap with those of abstinence-related withdrawal but are of higher acuity and severity and may also include delirium. The practice of rapid and ultrarapid opioid detoxification is intentional precipitation of withdrawal during sedation or general anesthesia.⁶ Rapid and ultrarapid detoxification are not currently recommended due to the risks of the massive catecholamine surge and related adverse issues.¹

1.1.2 Opioid withdrawal: abstinence-related versus precipitated

For this review, “abstinence-related opioid withdrawal” will refer to that which occurs spontaneously in opioid-dependent individuals when opioid exposure ceases or decreases below a threshold level (i.e., without the use of an opioid antagonist). Symptoms are typically well managed with supportive measures and/or nonopioid medications. Precipitated withdrawal is produced by administration of an opioid antagonist. With acute onset, it is often challenging to manage and associated with much more significant, even life-threatening, clinical features due to the resultant catecholamine surge, especially in hypercapneic individuals.⁷

The Clinical Opiate Withdrawal Scale (COWS) is an 11- item scale (total score range 0 to 45) that provides a reproducible assessment of signs and symptoms of opioid withdrawal.⁸ COWS is a tool for clinicians to diagnose and manage opioid withdrawal. It was developed in the late 1990s, initially as a guide for buprenorphine treatment. It is most frequently used for differentiating the presence versus absence of withdrawal as well as identifying clinically significant withdrawal. Since the early 2000s, it has become more widely used as a clinical tool due to ease of administration and consistency between evaluators (see **Appendix A**).⁹

1.1.3 Polysubstance overdose

An alternate or co-etiology of precipitated withdrawal or other naloxone-related adverse events may be toxicity of a co-exposure in a polysubstance overdose.^{10,11} Stimulant toxidrome includes agitation, cardiac arrhythmias, and seizure. In the event of an opioid and stimulant co-exposure,

administration of naloxone with resulting precipitated withdrawal or reversal of opioid toxicity will leave unopposed stimulant toxicity. The onset of the clinical effects can be severe, life threatening, and difficult to manage, especially in a non-health care setting. In other polysubstance situations, ongoing non-opioid CNS depression could be complicated by vomiting post opioid reversal.¹

1.2 REGULATORY HISTORY OF NALOXONE DRUG APPROVALS

- 1971, FDA first approved naloxone injectable solutions, for intravenous (IV), IM, and SC administration in adult and pediatric patients.
- 2014, the first IM/SC auto-injector, EVZIO (NDA 205787), 0.4 mg/0.4 mL was approved 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. EVZIO was voluntarily discontinued in 2020. EVZIO (NDA 209862), 2 mg/0.4 mL was approved in 2016, but was also discontinued.
- 2015, NARCAN Nasal Spray (NDA 208411) 4 mg/0.1 mL was approved for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. It is administered intranasally as a single spray into one nostril. NARCAN Nasal Spray (NDA 208411), 2 mg was approved in 2017, but was discontinued.
- 2021, ZIMHI (NDA 212854) 5 mg/0.5 mL single dose prefilled syringe for IM or SC use, was approved 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.
- 2021, KLOXXADO (NDA 212045) 8 mg/0.1 mL nasal spray was approved for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, for adult and pediatric patients.
- 2022, Naloxone Hydrochloride (NDA 215457) 10 mg/0.4 mL single dose, pre-filled auto-injector for IM or SC use, was approved for emergency treatment and temporary prophylaxis in patients, military personnel, and chemical incident responders where use of or exposure to high-potency opioids such as fentanyl analogues as a chemical weapon is suspected.

The IM (EVZIO, ZIMHI) and IN (NARCAN, KLOXXADO) naloxone products are allowed for community use of naloxone by laypersons. Per FRN 68702,

“Community-use” products are specifically designed to facilitate use by laypersons, without the need for additional supplies or assembly before use. Because “community-use” naloxone products, such as prefilled auto-injectors (Ref. 9), nasal sprays (Ref. 10), and syringes with an integrated needle presentation, do not require other medical supplies prior to administration, safe and effective use by laypersons in the community may be facilitated. In addition, as part of the approval process, data were required to demonstrate that these “community use” naloxone products administered using the integrated device can achieve naloxone blood levels appropriate to reverse an opioid overdose.

1.3 PRODUCT LABELING

Multiple sections of the Narcan prescription product label include warnings about precipitated withdrawal and limited efficacy (See relevant label sections in **Appendix B**).

The Applicant's proposed OTC Narcan DFL includes warnings about precipitated withdrawal and limited efficacy (See **Appendix C**).

2 METHODS

2.1 DPV METHODS AND MATERIALS

To conduct this evaluation, DPV first selected reports for the aggregate analysis that included any U.S. FAERS reports of naloxone, administered by any route, using the case selection criteria in **Section 2.1.1**.

2.1.1 Case Selection Criteria for Aggregate Analysis of FAERS Reports of all Naloxone Routes

Inclusion Criterion

- U.S. reports^a of naloxone (single ingredient)

Exclusion Criteria

- Duplicates
- Not U.S. reports
- Did not receive naloxone single ingredient/unclear if received naloxone (e.g., naloxone not administered, buprenorphine/naloxone combination product, naltrexone)

2.1.2 Case Selection Criteria for Subset Analysis of FAERS Cases of IN Naloxone Use in the Community Setting

To conduct a subset analysis, DPV reviewed all reports identified in the aggregate analysis in **Section 2.1.1** for mentions of naloxone administered IN and included cases that described use in the community setting using the case selection criteria below:

Inclusion Criteria

- U.S. cases of IN naloxone use with narrative description of use in the community setting (e.g., family member/bystander/self-administration, EMS or law enforcement response, or harm reduction group involvement)

Exclusion Criteria

- Naloxone was administered in an inpatient or outpatient clinic setting or narrative did not provide a description of use in the community setting
- Route of naloxone administration was not IN or unknown

^a Some FAERS reports may include more than one patient but are counted as one report in this aggregate analysis.

- Unassessable/insufficient information
- Literature cases reported to FAERS (reviewed in the literature **Section 3.1.3**)

2.1.2.1 Case Definitions for Naloxone-induced Precipitated Withdrawal and Limited Efficacy Analysis of FAERS Cases of IN Naloxone

The subset of IN naloxone cases identified in **Section 2.1.2** were then evaluated further for mentions of adverse events associated with precipitated withdrawal and limited efficacy, using the case definitions below:

Naloxone-Induced Precipitated Withdrawal Case Definition

Inclusion Criteria

Opioid withdrawal post naloxone administration as reported by a health care provider (HCP) OR reported by a layperson and supported by case details [e.g., specific signs/symptoms associated with the COWS] provided in the report.

To calculate COWS scores, we replicated the same strategy as described in the OSE/DPV review RCM 2022-119, completed recently on May 17, 2022, as described below:

For all cases meeting selection criteria above, we calculated a COWS score (see **Appendix A**) to support the determination of opioid withdrawal and if possible, quantify severity. For cases not reporting on specific elements of the COWS score, for the purposes of calculation, we assumed the individual did not demonstrate that sign/symptom. For cases reporting specific elements, we assumed the individual met the lowest point total for that sign/symptom unless enough detail was provided to meet a higher point value. As such, the COWS scores we derived represented the minimum score; actual COWS scores for the cases may have been higher.^{1,8,9,12}

Limited Efficacy Case Definition

Inclusion Criteria

Naloxone reported as ineffective in the narrative and supported by case details.

2.1.3 DPV FAERS Search Strategy

DPV searched the FAERS database for cases of adverse events with the strategy described in **Table 1**.

Table 1. DPV FAERS Search Strategy*	
Date of search	November 18, 2022
Time period of search	January 1, 2016 [†] to November 17, 2022
Search type	<i>RxLogix PV Reports Quick Query</i>
Product terms	Product active ingredient: naloxone, naloxone hydrochloride
MedDRA search terms (Version 25.1)	All
Other Criteria	U.S. reports only
* See Appendix D for a description of the FAERS database.	
[†] 2016 was the marketing launch year of Narcan Nasal Spray.	
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

2.1.4 DPV Literature Search Strategy

DPV searched the medical literature for cases of adverse events with the strategy described in Table 2.

Table 2. DPV Literature Search Strategy		
Date of search	November 17, 2022	
Database	Embase	PubMed
Search terms	('naloxone'/exp OR naloxone) AND (2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py) AND 'human'/de AND 'case report'/de	'naloxone' Filters applied: Case Reports, Humans, from 2016/1/1 – 2022/11/16
Years included in search	2016-2022	
Other criteria	U.S. reports only	

2.2 DMAMES METHODS AND MATERIALS

2.2.1 DMAMES Case Inclusion and Exclusion

On December 1, 2022, DMAMES searched FAERS using criteria below in Table 3 to identify device use errors. We individually reviewed 395 cases, and used the National Coordination Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors to describe the type of medication error and contributing factors.¹³ We excluded FAERS cases for the following reasons:

- Naloxone hydrochloride nasal spray device malfunction;
- Insufficient information provided to determine whether a use error occurred or device malfunctioned;
- Use of naloxone injection and not the naloxone nasal spray;
- Administration of the expired product;
- Unclear which dosage form of naloxone was used;
- A medication error involved another product, not naloxone nasal spray

We note that in one case, a healthcare provider complained about the illustrations in the Instructions for Use for Narcan Nasal Spray. The user found them unclear and thought that they “show a person with two left hands administering the nasal spray AT AN ANGLE” as well as shows an illustration of “nozzle [being] vertical instead of horizontal.” Upon further investigation of this case, we could not identify either a currently approved or previously approved version of the IFU that fit the description in the narrative. Thus we question whether the report was submitted for the correct product. As such, this case was not further considered in our evaluation and was also excluded.

2.2.2 DMAMES FAERS Search Strategy

DMAMES searched the FAERS database for device use error cases with the strategy described in **Table 3**

Table 3. DMAMES FAERS Search Strategy	
Initial FDA Receive Dates:	January 1, 2016 [†] to November 17, 2022
Product Name:	N/A
Product Active Ingredient (PAI):	Naloxone, Naloxone Hydrochloride
Event Lists:	SMQ <i>Medication errors (Narrow)</i> ; SMQ <i>Medication errors (Broad)</i> ; Event List: DMEPA Device Use Error vs. Malfunction Terms
Country (Derived):	U.S.
* See Appendix D for a description of the FAERS database. † 2016 was the marketing launch year of Narcan Nasal Spray. Abbreviations: SMQ=Standardized MedDRA Query	

2.3 DRUG UTILIZATION METHODS AND MATERIALS

We used proprietary databases available to the FDA to conduct these drug utilization analyses. See **Appendix D for full database descriptions**.

2.3.1 Data Sources

The IQVIA National Sales Perspective™ database was used to obtain the annual estimated number of naloxone units (vials, pre-filled syringes, auto-injectors, and nasal sprays) sold from manufacturers to various channels of distribution in the U.S. from 2016 through 2021.^b We used the Symphony Health Metys™ database to obtain the annual estimated number of naloxone prescriptions dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies, stratified by product formulation, from 2016 through 2021.

^b The National Sales Perspectives™ database does not capture distribution of drugs outside of the typical pharmaceutical distribution supply chain, such as donations or direct sales from manufacturers. Also, the analyses provided in this review may not provide any visibility into distribution to harm reduction programs and the settings impacted by them. The data shown in this review may vary from previous/other analyses due to timing of data source updates and when data were retrieved from the tool.

3 RESULTS

3.1 DPV RESULTS

3.1.1 DPV FAERS Aggregate Results (all routes)

DPV retrieved 1248 reports, and after excluding 196 duplicate reports, 6 non-U.S. reports, and 51 reports where the patient did not receive naloxone or it was unclear if received (e.g., naloxone not administered, buprenorphine/naloxone combination product, naltrexone), we included a total of **995 reports** in this aggregate analysis of FAERS reports of naloxone (all routes). A hands-on review of these reports was not conducted due to the volume of reports retrieved. **Table 4** provides descriptive characteristics of the 995 reports of naloxone (all routes) in this aggregate analysis.

Table 4. Descriptive Characteristics of Adverse Event Reports of Naloxone by Route in FAERS, Received by FDA From January 1, 2016 to November 17, 2022 (N=995)								
Characteristics	Intranasal (n=446, 44.8%)		Injection (n=144, 14.5%)		Unknown (n=405, 40.7%)		All Routes (N=995, 100%)	
	n	%	n	%	n	%	n	%
Age (years)								
<18	2	0.4	7	4.9	22	5.4	31	3.1
18 - <40	70	15.7	40	27.8	84	20.7	194	19.5
40 - <65	52	11.7	23	16.0	79	19.5	154	15.5
≥65	15	3.4	9	6.3	46	11.4	70	7.0
Not reported	307	68.8	65	45.1	174	43.0	546	54.9
Sex								
Male	214	48.0	62	43.1	182	44.9	458	46.0
Female	160	35.9	35	24.3	179	44.2	374	37.6
Not reported	72	16.1	47	32.6	44	10.9	163	16.4
Report type*								
Direct	4	0.9	37	25.7	37	9.1	78	7.8
Expedited (15-Day)	189	42.4	77	53.5	282	69.6	548	55.1
Periodic	253	56.7	30	20.8	86	21.2	369	37.1

Characteristics	Intranasal (n=446, 44.8%)		Injection (n=144, 14.5%)		Unknown (n=405, 40.7%)		All Routes (N=995, 100%)	
	n	%	n	%	n	%	n	%
Initial FDA received year								
2016	100	22.4	15	10.4	19	4.7	134	13.5
2017	25	5.6	12	8.3	27	6.7	64	6.4
2018	33	7.4	24	16.7	31	7.7	88	8.8
2019	8	1.8	22	15.3	36	8.9	66	6.6
2020	115	25.8	22	15.3	123	30.4	260	26.1
2021	65	14.6	23	16.0	79	19.5	167	16.8
2022†	100	22.4	26	18.1	90	22.2	216	21.7
Serious outcome(s) ‡	n=133		n=88		n=347		n=568	
Death	23	-	11	-	91	-	125	-
Life Threatening	16	-	27	-	74	-	117	-
Hospitalization	47	-	55	-	167	-	269	-
Disability	1	-	0	-	25	-	26	-
Congenital Anomaly	0	-	0	-	2	-	2	-
Other	93	-	47	-	215	-	355	-
Required Intervention	1	-	1	-	1	-	3	-

* Direct reports are those that are submitted directly to FDA by patients, caregivers, HCP, etc. and not to the manufacturer. Under 21 CFR 314.80 postmarketing safety reports must be submitted to FDA by the manufacturer for the following: 1) Expedited (15-day) reports – both serious and unexpected adverse events from all sources (domestic and foreign) and 2) Periodic (non-expedited) reports – domestic spontaneous adverse events that are serious and expected (i.e., labeled event); non-serious and unexpected; or non-serious and expected.

† Note 2022 was a partial year through November 17, 2022.

‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

Reviewer comments: Of the reports with age included, the age range of 18 - <40 is the most common across all routes of administration. Of the reports with sex included, a slight male predominance also occurs across all routes.

*For the IN route, the number of adverse event reports was highest in 2020 and continued to have higher numbers of reports in 2021-2022 compared to 2016-2019. This could be a reflection of the increase in severity of the opioid epidemic in recent years or increased awareness and public education surrounding community use of naloxone for opioid overdose. **Section 3.3** shows drug utilization trends with increased sales annually from 2016 to 2021, which could also contribute to the higher numbers of adverse event reports during this time frame. We note that IN reports were also high in 2016, which was when marketing began for intranasal naloxone.*

The IN route has the lowest percentage of serious reports (29.8%) compared to injection (61.1%) and unknown route (85.7%). This difference could be an indicator of community use of intranasal naloxone where patients are likely less sick than hospitalized patients who are more likely to receive naloxone by injection.

Table 5 provides the top 10 preferred terms (PTs) of the 995 reports of naloxone (all routes) in this aggregate analysis.

Table 5. Top 10 Preferred Terms (PTs) of Adverse Event Reports of Naloxone by Route in FAERS, Received by FDA From January 1, 2016 to November 17, 2022 (N=995)			
Intranasal (n=446, 44.8%)	Injection (n=144, 14.5%)	Unknown (n=405, 40.7%)	All Routes (N=995, 100%)
Drug withdrawal syndrome Unintentional use for unapproved indication Vomiting <i>Drug ineffective</i> Withdrawal syndrome Feeling abnormal Overdose Anger Malaise Hyperhidrosis	<i>Drug ineffective</i> Overdose Pulmonary oedema Product label confusion Drug withdrawal syndrome Hypotension Toxicity to various agents Accidental exposure to product Product appearance confusion Bradycardia	Drug dependence <i>Drug ineffective</i> Overdose Toxicity to various agents Drug withdrawal syndrome Pain Emotional distress Drug abuse Drug hypersensitivity Cardiac arrest	<i>Drug ineffective</i> Overdose Drug withdrawal syndrome Drug dependence Vomiting Unintentional use for unapproved indication Toxicity to various agents Withdrawal syndrome Pain Death
Bolded PTs consistent with naloxone-induced precipitated withdrawal. (Symptoms consistent with COWS scoring tool or naloxone nasal spray prescription label). <i>Italicized PT Drug ineffective correlates with the concept of limited efficacy.</i>			

*Reviewer comments: Similar PTs are present across all routes of naloxone related to naloxone-induced precipitated withdrawal and limited efficacy. Other common PTs (i.e., Overdose, Toxicity to various agents, Drug dependence) are related to the underlying opioid overdose and are nonspecific. Note that the PT Unintentional use for unapproved indication is most often associated with accidental use of a product. See **Section 3.1.2** for a discussion of accidental use cases.*

3.1.2 DPV FAERS Case Selection (IN Subset Analysis)

DPV applied the case selection criteria for subset analysis of FAERS cases of IN naloxone (see **Section 2.1.2**) to the 995 aggregate FAERS reports of naloxone (all routes). After applying the exclusion criteria, we included **318** cases of IN naloxone used in the community setting (see **Figure 1**) and performed a hands-on review of these cases. **Appendix E** contains a line listing of the **318** cases.

Figure 1. FAERS Case Selection for IN Naloxone Use in the Community Setting Subset Analysis

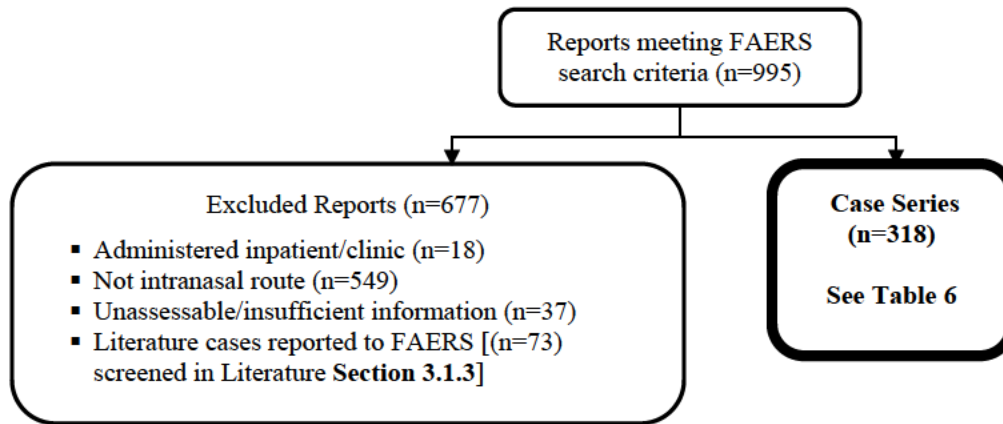


Table 6 summarizes the descriptive characteristics of the 318 FAERS cases of community use IN naloxone.

Table 6. Descriptive Characteristics of Community Use IN Naloxone FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022 (N=318)			
		n	%
Age (years)	<18	1	0.3
	18 - <40	44	13.8
	40 - <65	36	11.3
	≥65	12	3.8
	Not reported	225	70.8
Sex	Male	152	47.8
	Female	122	38.4
	Not reported	44	13.8
Report type	Direct	4	1.3
	Expedited (15-Day)	88	27.7
	Periodic	226	71.1
Serious outcome(s)*		n=81	
	Death	15	-
	Life Threatening	6	-
	Hospitalization	12	-
	Other	60	-
	Required Intervention	1	-
Initial FDA received year	2016	99	31.1
	2017	21	6.6
	2018	31	9.7
	2019	7	2.2
	2020	40	12.6
	2021	45	14.2
	2022†	75	23.6

Table 6. Descriptive Characteristics of Community Use IN Naloxone FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022 (N=318)		
	n	%
Reported reason for use		
Emergency treatment of known or suspected opioid overdose	252	79.2
Accidental use [‡]	58	18.2
Use for non-indicated condition [§]	8	2.5
For the accidental use cases, was the user of naloxone the intended (prescribed) user?	n=58	18.2
Yes	28	8.8
No	3	0.9
Unknown	27	8.5
Naloxone single dose (mg)		
2	4	1.3
4	181	56.9
8	22	6.9
Not reported	111	34.9
Naloxone cumulative dose (mg)		
≤8	142	44.7
>8 to ≤16	8	2.5
>16 to ≤32	8	2.5
Not reported	160	50.3
No. of doses administered (range 1 – 7 doses)		
1	104	32.7
2	75	23.6
≥3	19	6.0
Not reported	120	37.7
Individual administering naloxone[†]		
General public	157	49.4
Trained laypeople	27	8.5
Health Care Professional	13	4.1
Other (multiple types)	2	0.6
Unknown	119	37.4
Administered by self		
Yes	88	27.7
No	140	44.0
Unknown	90	28.3
Most frequently reported preferred terms (n ≥ 5) among serious* cases	n=81	
Drug ineffective	18	-
Drug withdrawal syndrome	12	-
Death	10	-
Vomiting	10	-
Withdrawal syndrome	9	-
Loss of consciousness	7	-
Seizure	7	-
Feeling abnormal	6	-
Headache	5	-
Hyperhidrosis	5	-
Unintentional use for unapproved indication	5	-

Table 6. Descriptive Characteristics of Community Use IN Naloxone FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022 (N=318)		
	n	%
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome. † Note 2022 was a partial year through November 17, 2022. ‡ Examples of accidental use are mistaking the product for another nasal spray (e.g., allergy or sinus nasal spray) or product use error. See Reviewer Comments for further discussion of these cases. § Use for non-indicated condition included known other substance overdose [clonidine (n=2), fluoxetine, marijuana, cocaine, methamphetamine, phencyclidine] and one case of intentional use in a healthy patient to “show it was safe.” All 3 cases were adults using a family member’s IN naloxone. ¶ Refer to Appendix F for definitions of general public, training laypeople, and HCP.		

Reviewer comments: Serious outcomes were noted in 81 cases (81/318; 25.5%). When age information was available, it is noted that most serious cases (21/81; 25.9%) occurred among those ages 18 to 65 years, with no serious cases occurring in children less than 18 years and 3 cases (3/81; 3.7%) occurring in those greater than 65 years. Case reports for deaths were few and not informative with regard to time elapsed between intranasal naloxone administration and the individual’s death, the confirmed substance that the individual had overdosed on, or autopsy information.

*The majority of community use IN naloxone was for emergency use of known or suspected opioid overdose, however almost 20% of cases were accidental use. Examples of accidental use included patients mistaking naloxone nasal spray for other nasal sprays (e.g. for allergies, sinuses, inhaler) and general lack of awareness of what naloxone nasal spray was used for. Some accidental use cases reported naloxone-induced precipitated withdrawal (See **Section 3.1.2.1**) due to patients being on chronic opioids. All but one accidental case were self-administered.*

For Narcan Nasal Spray (NS) each dose is 4 mg and will be available as two doses in a pack for a total of 8 mg. In this case series, the majority of cumulative dose of naloxone administered was ≤8 mg, and very few reported doses greater than 8 mg. In addition, over 50% of cases reported administering 1-2 doses of naloxone nasal spray. Per the prescription label, directions say to “Re-administer NARCAN Nasal Spray, using a new nasal spray, every 2 to 3 minutes if the patient does not respond or responds and then relapses into respiratory depression.”

About half of the cases reported administration by the general public and almost a third were self-administered. The majority (128/157, 81.5%) of the cases where IN naloxone was administered by the general public were non-serious. Of the cases where IN naloxone was administered by the general public, there were three death cases. Two of the death cases reported naloxone being used for emergency treatment of known or suspected opioid overdose and one case reported accidental use, where a patient used IN naloxone thinking it would “help her sinus issues.” In the accidental use case, the patient had multiple comorbidities (chronic pain, “abnormal blood pressure”, “sinus issues”), used multiple medications (furosemide, tramadol, clonazepam, nicoderm, and Cymbalta) for her health conditions, and did not report the date of patient’s death relative to naloxone use. As such, it is difficult to assess whether IN naloxone is related to the patient’s death. In all three death cases, little clinical details pertaining to the death were provided (e.g., time elapsed between IN naloxone administration

and the patient's death, confirmed substance that patient had overdosed on, autopsy information).

The most frequently reported PTs from serious cases appear to be related to naloxone-induced precipitated withdrawal (e.g., drug withdrawal syndrome, vomiting, withdrawal syndrome, hyperhidrosis, seizure) and limited efficacy (i.e., drug ineffective). Other common PTs (e.g., death, loss of consciousness, feeling abnormal, headache) are likely related to the underlying opioid overdose and/or are nonspecific. Note that not all cases with a serious outcome of death (n=15) in this case series reported a PT of death (n=10). Additionally, note that the PT unintentional use for unapproved indication was most often associated with accidental use of a product for the wrong indication in this case series (See Section 3.2.1.)

3.1.2.1 Naloxone-Induced Precipitated Withdrawal

Table 7 describes cases of naloxone-induced precipitated withdrawal in this community use IN naloxone case series.

Table 7. Naloxone-Induced Precipitated Withdrawal, IN Route FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022		
(N=180)		
	n	%
Age (years)		
<18	1	0.6
18 - <40	28	15.6
40 - <65	22	12.2
≥65	10	5.6
Not reported	119	66.1
Sex		
Male	96	53.3
Female	68	37.8
Not reported	16	8.9
Serious Outcome(s)*	n=35	
Death	0	-
Life Threatening	2	-
Hospitalization	7	-
Other	30	-
Required Intervention	1	-
Reported reason for use		
Emergency treatment of known or suspected opioid overdose	156	86.7
Accidental use	22	12.2
Use for non-indicated condition (fluoxetine overdose, methamphetamine exposure)	2	1.1
Naloxone single dose (mg)		
2	4	2.2
4	105	58.3
8	14	7.8
Not reported	57	31.7
Naloxone cumulative dose (mg)		
≤8	91	50.6
>8 to ≤16	4	2.2
>16 to ≤24	1	0.6
Not reported	84	46.7

Table 7. Naloxone-Induced Precipitated Withdrawal, IN Route FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022

(N=180)		
	n	%
No. of doses administered (range 1 – 6 doses)		
1	70	38.9
2	45	25.0
≥3	4	2.2
Not reported	61	33.9
Individual administering naloxone†		
General public	86	47.8
Trained laypeople	15	8.3
HCP	4	2.2
Other (multiple types)	1	0.6
Unknown	74	41.1
Administered by self		
Yes	45	25.0
No	75	41.7
Unknown	60	33.3
HCP reported withdrawal	n=4	2.2
HCP reported withdrawal AND a COWS score of ≥5‡	2	1.1
HCP reported withdrawal AND a COWS score <5 or no COWS score	2	1.1
Non-HCP reported withdrawal/symptom(s) consistent with withdrawal	n=176	97.8
Non-HCP reported withdrawal or symptom(s) consistent with withdrawal AND a COWS score of ≥5‡	19	10.6
Non-HCP reported withdrawal or symptom(s) consistent with withdrawal AND a COWS score <5 or no COWS score	157	87.2
COWS items that received a score >0	n=117§	
GI Upset	61	-
Anxiety or Irritability	46	-
Sweating	30	-
Tremor	15	-
Bone or joint aches	9	-
Restlessness	8	-
Resting pulse Rate	7	-
Gooseflesh skin	5	-
Yawning	4	-
Runny nose or tearing	3	-
Pupil size larger or dilated	2	-
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.		
† Refer to Appendix F for definitions of general public, training laypeople, and HCP		
‡ Per COWS scale, scores of 5-12 indicates mild withdrawal. The 21 cases with a COWS score ≥5 ranged in score from 5-12 (mean 6.7, median 6). No COWS scores were >12.		
§ More than one COWS item can be present in a single case.		

Reviewer comments: The majority of cases report administration by the general public (86/180, 47.8%). No deaths were reported and only 19.4% (35/180) of withdrawal cases reported a serious outcome. There were few cases (4) of HCP-reported withdrawal compared with non-HCP reported withdrawal (176). This may be due to reporting differences between patients/caregivers and HCPs based on their prior knowledge of withdrawal.

COWS Withdrawal Symptoms

Cases with a COWS score of ≥ 5 are highlighted in **Table 7** because according to the COWS scale, scores ≥ 5 indicate mild withdrawal. Per the COWS, scores < 5 do not meet the threshold for withdrawal. However, DPV's COWS scores are likely an underestimation by DPV and may not reflect the actual level of severity due to limited case details. Cases with scores < 5 may still be withdrawal cases and cases with scores ≥ 5 likely represent better documented cases.

However, one or more withdrawal symptoms were apparent in 117 (36.8%) of total IN cases in this case series. GI upset, anxiety/irritability, and sweating were the most commonly scored items on the COWS scale. Overall, with our underestimation of COWS scores, withdrawal symptoms appear to occur as expected with IN naloxone.

Non-COWS Withdrawal Symptoms

In terms of more severe withdrawal symptoms not included in the COWS, we examined cases reporting pulmonary edema or seizure.

3.1.2.1.1 Adverse event: pulmonary edema (n=2)

Two cases (2/318, 0.6%) report the PT Pulmonary oedema in this community IN naloxone case series. Both were non-HCP reported withdrawal and did not report any COWS symptoms. One case (15204710) received two doses of 2 mg IN naloxone from an HCP (EMS) for an overdose that included unspecified opioids (other medications not reported). The naloxone reversed the opioid effects and the patient developed non-cardiogenic pulmonary edema, but left the emergency department against medical advice (AMA) 12 hours after presenting and no further information was provided. The second case (14866638) received an unknown IN naloxone dose from an HCP (EMS) for heroin or fentanyl overdose and refused hospitalization. The following day he received a 2 mg IN naloxone dose from an untrained layperson (family member) for a fentanyl overdose. The family started CPR and was unsure if the patient was breathing while bringing him to the hospital. He was admitted to intensive medical care due to high oxygen requirements and treated with nitroglycerin for "pulmonary edema that occurred after using Narcan", ondansetron, ketorolac, and BiPAP transitioned to high flow nasal cannula. He left the hospital AMA and discharge diagnosis indicated an acute hypoxic respiratory failure likely secondary to aspiration pneumonia in the setting of two opioid overdoses, sepsis secondary to aspiration pneumonia, and altered mental status likely secondary to opioid drug overdose.

3.1.2.1.2 Adverse event: seizure (n=8)

Eight cases (8/318, 2.5%) report the PT Seizure in this community IN naloxone case series. Five of the 8 reported naloxone-induced withdrawal and three did not. One case was an HCP reported withdrawal case and is detailed in **Table 8** below (16201523). Most cases lack detail surrounding the seizure that occurred (e.g. seizure not witnessed or no further information provided in the narrative other than the patient experienced a seizure). Several cases are confounded by other medications involved in the overdose that could cause seizures (e.g. methamphetamine, or unknown medications), or potential misidentification of withdrawal related restlessness for a seizure. Per the COWS scale, restlessness can include frequent shifting or extraneous movements of legs/arms, which could be misidentified as a seizure by an untrained layperson.

Table 8 describes the four cases of HCP-reported naloxone-induced precipitated withdrawal.

Table 8. Cases of HCP-reported Naloxone-induced Precipitated Withdrawal Received in FAERS by FDA From January 1, 2016 to November 17, 2022 (n=4)										
Year/ FAERS Case#	Age/Sex	PMH	Opioid status and current opioid exposure(s)	Initial IN/ cumulative any route naloxone dose (mg)/ reported total number of doses	Person administering naloxone	Signs/symptoms of withdrawal after naloxone	Calculated COWS score/ Reported severity	Adverse event(s) attributed to naloxone exposure	Management of adverse event(s)	Outcome
2019 16201523	64F	Intervertebral disc disorder, chronic back pain, ADD, Bell's palsy, depression, diabetes mellitus, diverticulitis, fatty liver, fibromyalgia, anxiety, narcotic addiction, infectious viral hepatitis, post-traumatic stress disorder, sleep apnea	D/Methadone	4/4/1	General public (self) Patient called nurse who recommended giving the IN naloxone due to altered mental status	“Felt hot, on fire and burning” Yawning Trembling Stomach cramps Sweating Erratic movement of upper extremities (patient attributed to seizure activity, no active seizures occurring during medical exam) Hypertension Extreme panic and anxiety	10/mild	Precipitated withdrawal	Lorazepam NS Bolus KCL (for hypokalemia) Cephalexin (for UTI) ER Care	Recovered
2016 12738733	45F	Unspecified psychiatric history, herniated lumbar intervertebral disc	D/Morphine, Oxycodone, Oxycodone/Aceta minophen	4/4/1	General public (self) Patient called 911 who talked her through how to	“burning all over” Nervous Shaky Bowel incontinence Nausea Piloerection	12/mild	Precipitated withdrawal	Lorazepam ER Care	Recovered

Table 8. Cases of HCP-reported Naloxone-induced Precipitated Withdrawal Received in FAERS by FDA From January 1, 2016 to November 17, 2022 (n=4)										
Year/ FAERS Case#	Age/Sex	PMH	Opioid status and current opioid exposure(s)	Initial IN/ cumulative any route naloxone dose (mg)/ reported total number of doses	Person administering naloxone	Signs/symptoms of withdrawal after naloxone	Calculated COWS score/ Reported severity	Adverse event(s) attributed to naloxone exposure	Management of adverse event(s)	Outcome
					administer IN naloxone	Generalized pain “Flailing about on the stretcher”				
2016 12802058	81M	NR	D/Methadone	4/NR/NR	General public (self)	Agitation Dizziness Mental status change	1/NR	Precipitated withdrawal Encephalopathy	Lorazepam Morphine ICU Care	Recovered
2020 17978708	61F	HIV, chronic pain, history of merkel cell cancer and radiation necrosis of skin and bone, chronic aspiration pneumonitis, SIADH, and mild dementia	D/Oxycodone sustained release and immediate release	NR/NR/1	General public (self) Accidental use – thought was nasal decongestant	NR	NR/severe	Precipitated withdrawal Aspiration pneumonitis	ICU Care	Recovered
Abbreviations: COWS = clinical opioid withdrawal score, D = presumed opioid dependent, EMS = emergency medical services, F = female, HCP = health care professional, M = male, NR = not reported, PMH = past medical history, ADD= Attention Deficit Disorder, ICU = Intensive Care Unit, SIADH = Syndrome of Inappropriate anti-diuretic hormone secretion										

Reviewer comments: Of the HCP-reported withdrawal cases, ages ranged between 45 and 81. Three cases received a 4 mg initial IN naloxone dose, and one did not report the dose. Two cases reported a cumulative dose of 4 mg (both of these were a single 4 mg dose) and the other two cases did not provide enough information to calculate cumulative dose, but one indicated giving a single dose. All of the patients recovered from their overdose, which is consistent with naloxone’s ability to rapidly reverse the life-threatening consequences of opioid overdose (i.e. respiratory depression) and all patients recovered from their subsequent naloxone-induced precipitated withdrawal. All cases described administration by the general public and by self-administration.

3.1.2.2 Limited Efficacy

Table 9 describes the 24 cases of limited efficacy in this IN naloxone case series.

Table 9. Naloxone Limited Efficacy, IN Route FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022		
(N=24)		
	n	%
Age (years)		
<18	0	0
18 - <40	1	4.2
40 - <65	3	12.5
≥65	0	0
Not reported	20	83.3
Sex		
Male	8	33.3
Female	11	45.8
Not reported	5	20.8
Serious Outcome(s)*	n=14	
Death	2	-
Life Threatening	1	-
Hospitalization	1	-
Other	14	-
Required Intervention	0	-
Reported reason for use		
Emergency treatment of known or suspected opioid overdose	24	100.0
Accidental use	0	0
Use for non-indicated condition	0	0
Naloxone single dose (mg)		
2	1	4.2
4	11	45.8
8	2	8.3
Not reported	10	41.7
Naloxone cumulative dose (mg)		
≤8	10	41.7
>8 to ≤16	1	4.2
>16 to ≤32	1	4.2
Not reported	12	50.0
No. of doses administered (range 1 – 6 doses)		
1	2	8.3
2	14	58.3
≥3	5	20.8
Not reported	3	12.5
Individual administering naloxone[†]		
General public	13	54.2
Trained laypeople	3	12.5
HCP	2	8.3
Other (multiple types)	1	4.2
Unknown	5	20.8
Administered by self		
Yes	1	4.2
No	18	75.0
Unknown	5	20.8

Table 9. Naloxone Limited Efficacy, IN Route FAERS Case Series, Received by FDA From January 1, 2016 to November 17, 2022

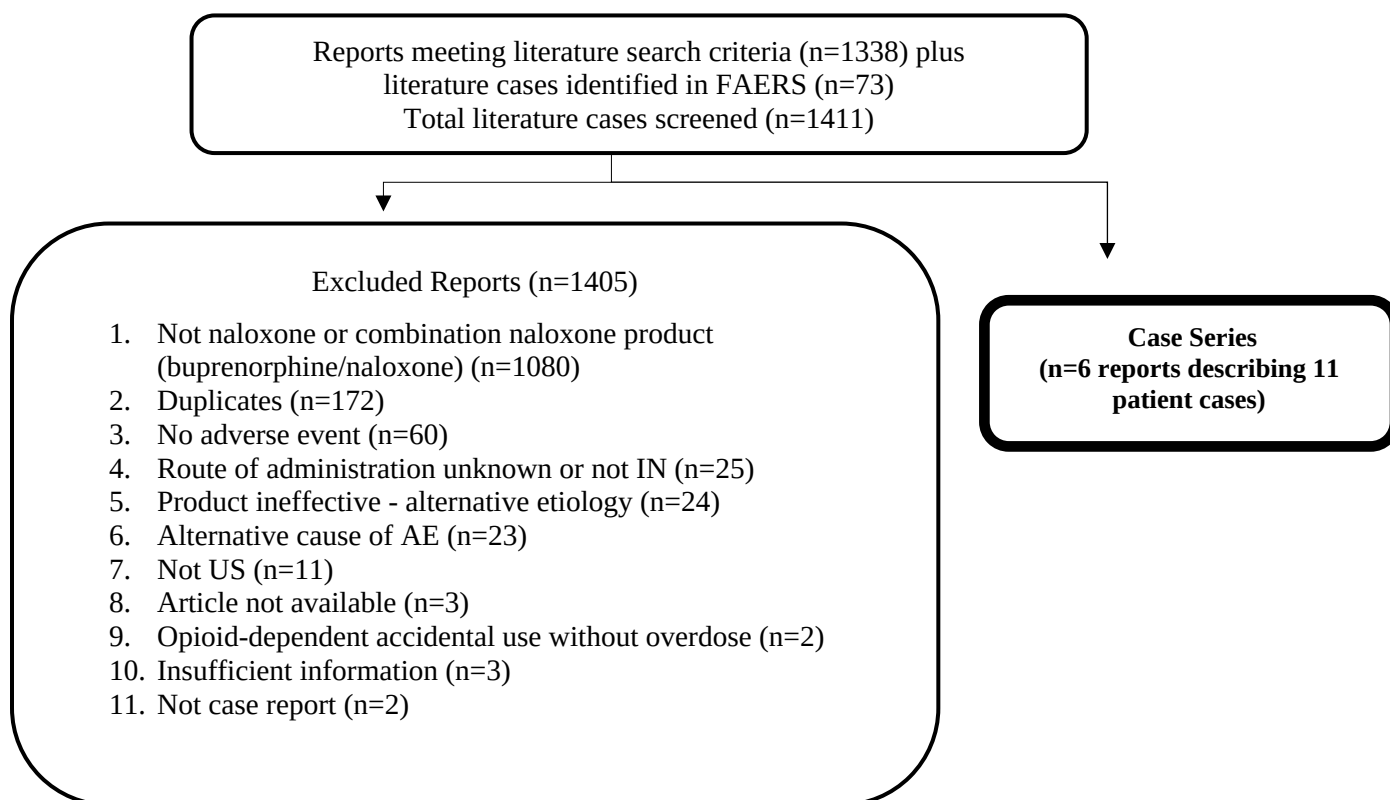
(N=24)		
	n	%
Reasons reported for limited efficacy		
Unknown how long since overdose occurred/ “too late”	6	25.0
No response to 1st dose, but response to second dose	5	20.8
Various product issues (e.g. “nothing came out”, “completely empty”)	5	20.8
Did not have enough naloxone	2	8.3
No reason reported	6	25.0
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.		
† Refer to Appendix F for definitions of general public, training laypeople, and HCP		

Reviewer comments: Of the 318 cases in this IN naloxone case series, 24 (7.5%) reported limited efficacy. Although 7.5% is a low number, there are limitations to these data. We would not expect a large number of reports for a well-known, labeled adverse event, such as limited efficacy. A low number of reports for an adverse event does not reflect its true incidence. Two fatal cases were reported: one involved a polysubstance overdose including alprazolam, alcohol, and oxymorphone and noted naloxone was administered “too late”; the second noted that the patient did not respond after three doses and there was not any more naloxone available. The reported product issues could be use error, but limited information precludes a meaningful assessment. Multiple factors contribute to the effectiveness of IN naloxone including the severity of the overdose, if other substances are involved, the time elapsed between when the overdose occurred and when naloxone is administered, and administration technique. Polysubstance overdoses may not respond to naloxone. Naloxone needs to be administered as quickly as possible after overdose to prevent death. Per the prescription naloxone label in the Warnings and Precautions, reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine may be incomplete and larger or repeat doses of naloxone may be needed due to buprenorphine’s long duration of action. This could have played a role in our limited efficacy cases, as 18 cases did not report the specific opioid intended to be reversed.

3.1.3 DPV Literature Case Selection (IN only)

DPV applied the same case selection criteria in **Section 2.1.2** to the literature cases of IN naloxone. After applying the exclusion criteria, our literature cases series included 6 reports describing 11 patient cases (see **Figure 2**).

Figure 2. Literature Case Selection for IN Naloxone Analysis



The DPV literature search identified six reports describing 11 patient cases who experienced adverse events and device use errors associated with IN naloxone use. These include pulmonary edema, need for higher than typical dose possibly related to a superpotent opioid, precipitated withdrawal, and rapid administration of multiple doses (five additional doses in rapid succession) resulting in overexposure and prolonged precipitated withdrawal. These patient cases are summarized below. An aggregate overview of these cases is provided in **Table 10**.

3.1.3.1 Adverse event: pulmonary edema (n=7)

Kummer et al. Naloxone-associated pulmonary edema following recreational opioid overdose: A case series. Am J Emerg Med, 2022.¹⁴

This is a retrospective case series of naloxone-associated pulmonary edema diagnosed between January 1, 2017, and September 30, 2019. It included 10 patients with opioid intoxication who were reportedly treated with pre-hospital naloxone, five of whom received IN naloxone. Cases were defined by the acute onset of respiratory distress, hypoxemia, and radiographic pulmonary

edema following naloxone administration, provided that gas exchange and radiographic abnormalities rapidly improved over 24 to 48 hours, and pulmonary aspiration of gastric contents was not clinically suspected. Four of the five patients who received IN naloxone reportedly took heroin and received an initial 4 mg IN dose, and one took oxycodone and received an initial 1 mg IN dose. One patient who had taken heroin and received only one dose of naloxone was managed in an intermediate care unit. The remaining four received multiple (ranging from 2-6) subsequent naloxone doses, given by an unspecified route; these patients required critical care. The authors noted that the mechanism of naloxone-associated pulmonary edema is uncertain, but it may be due to an acute catecholamine surge from rapid opioid reversal, which results in increased pulmonary blood flow and pulmonary capillary permeability. Hypoxemia- or catecholamine-induced cardiac dysfunction may also contribute to the pathophysiology.

Reviewer comments: Four of the five cases treated with IN naloxone received a 4 mg dose, which is consistent with the commercially available nasal spray. However, one case reportedly received a 1 mg IN dose as stated in the article, which does not correspond to any available nasal spray product. It is unclear whether they received another product intranasally, or if the dose was administered by another route.

Pulmonary edema is included in the Narcan nasal spray label under Section 5, Warnings and Precautions, where it is described as a potential consequence of abrupt postoperative withdrawal.¹⁵ The hypothesized mechanism is “similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.”

The article provided limited individual case details. The 10 subjects included in this case series were young, with a median age of 23 years. Their past medical histories were not reported, so it is unclear whether they had underlying risks for pulmonary edema. Five of the 10 cases had a urine test positive for a stimulant [i.e., cocaine (n=2) and methamphetamine (n=3)], but the initial route of naloxone administration in these individuals is not available, so it is unclear which, if any, were in the subset receiving an IN dose. Regardless of route, use of naloxone in a person co-intoxicated with a stimulant may unmask or exacerbate a stimulant toxidrome.¹² This, along with the mechanism hypothesized in the naloxone label, may have contributed to the pulmonary edema in these individuals.¹⁵

Yarlagadda et al. Opioid antidote induced pulmonary edema and lung injury. Respir Med Case Rep, 2020.¹⁶

This is a case report of a 23-year-old male who had used “3 bags of heroin” and an unknown amount of alcohol and become somnolent. He was treated in the field with 8 mg of naloxone nasal spray. He began coughing frothy pink sputum, and had chest tightness, shortness of breath, and abdominal pain. He was tachycardic and hypoxic, with an oxygen saturation of 89% on room air, and his lung exam revealed rhonchi and rales. His white blood cell (WBC) count was elevated to 14.9K/ μ L, and brain natriuretic peptide (BNP) was normal. Chest x-ray (CXR) demonstrated “diffuse bilateral interstitial and alveolar density with concerns of asymmetric pulmonary edema or multifocal infiltrative pneumonia.” He was admitted to the ICU and treated with positive pressure ventilation, from which he was quickly weaned. The next day, he became febrile, and a follow-up CXR showed resolution of pulmonary edema and progression of a right

lower lobe pneumonia, for which he received antibiotics for community acquired pneumonia with aspiration.

Reviewer comments: This case has a temporal association between the onset of pulmonary edema and the use of IN naloxone. He rapidly responded to positive pressure ventilation, and his follow-up CXR indicated a resolution of the edema. The mechanism by which pulmonary edema may have developed is presumably similar to the cases described by Kummer et al.

Veet et al. Reversing opiates in a flash: Intranasal naloxone-induced pulmonary edema. J Gen Intern Med, 2017.¹⁷

This is a case report of a 27-year-old man who responded to three doses of IN naloxone (6 mg; unclear if this was per dose or cumulative) administered by paramedics at the scene for respiratory depression related to a suspected opioid overdose. In transit to the emergency department, he was hypoxic and required intubation. CXR showed bilateral infiltrates. Echocardiogram was reportedly normal. His WBC count was 14.2K/ μ L, and the drug screen was positive for oxycodone. He responded rapidly to IV furosemide and was extubated. A follow-up CXR showed resolution of the pulmonary edema.

Reviewer comments: Similar to the cases described above, this patient had acute pulmonary edema. This case responded rapidly to diuresis.

3.1.3.2 Adverse event: limited efficacy (n=2)

Bardsley R. Higher naloxone dosing may be required for opioid overdose. AJHP, 2019.¹⁸

This case series describes two individuals who were suspected to have overdosed on carfentanil, based on community drug use patterns, though the users believed that they were taking IV heroin. A 32-year-old male with a history of schizophrenia and heroin, alcohol, and tobacco abuse, and a 26-year-old female with a history of heroin and tobacco abuse, arrived at the ED in the same vehicle with several other overdose victims. They were both unresponsive and cyanotic and had to be physically removed from the vehicle. Before IV access was obtained, the male was given 4 mg IN naloxone, and the female was treated with 2 mg of IN naloxone. Both required four additional 2 mg IV aliquots of naloxone in order to restore normal respiration. They subsequently remained stable and left the ED against medical advice. The authors speculated that the high naloxone requirement was likely due to the potency of carfentanil, and that clinicians should be prepared to use higher naloxone doses in such suspected exposures.

Reviewer comments: The cases described here illustrates the possibility that use of exceptionally potent opioids like carfentanil may lead to inadequate effectiveness of naloxone use in the field. Carfentanil is a very potent opioid analgesic indicated for use in veterinary medicine. Per the naloxone prescription label, “the requirement for repeat doses of NARCAN Nasal Spray depends upon the amount, type, and route of administration of the opioid being antagonized.” Complicating this is the possibility of an alternative unrecognized cause of somnolence that would not respond to opioid antagonism. This underscores the importance of rapidly activating EMS for further evaluation and management.

3.1.3.3 Adverse event: precipitated withdrawal (n=2)

Brenner et al. Severe prolonged agitation due to intranasal naloxone overexposure. Am J Emerg Med, 2021.¹⁹

This is a case report of a 43-year-old woman with a history of opioid abuse who was found unconscious and apneic by a family member who administered 4 mg of IN naloxone. She did not immediately improve, so the bystander then administered five additional doses in rapid succession, leading to a total dose of 24 mg. Shortly thereafter, the patient awoke and was severely agitated. She was transported to the ED where she was found to have a COWS score of 25. She was diaphoretic, tachycardic, tachypneic, disoriented and screaming incoherently, and retching. Over three hours, she was treated with IV buprenorphine 1.2 mg, haloperidol 10 mg, lorazepam 10 mg, and diphenhydramine 50 mg without resolution of her symptoms. She was then intubated, sedated with an IV propofol drip, and transferred to the ICU. On the following morning, her mental status had returned to normal, and she was extubated without incident. Although her urine was positive for both fentanyl and cocaine, the authors determined that the severe agitation was more likely due to overexposure to naloxone, rather than a sympathomimetic toxidrome from cocaine, which she had not used for several days.

Reviewer comments: This case of precipitated withdrawal reported severe agitation most likely from device use error (i.e., administration of six naloxone nasal spray doses, each 4 mg, in rapid succession). Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia, and have caused agitation.¹⁵ Although the opioid toxicity was reversed, the case resulted in severe withdrawal symptoms due to wrong technique of the product administration. It is unclear whether the user referred to the instructions for use prior to or during the administration of the product, as the labeling clearly states waiting for 2 to 3 minutes between administration of subsequent doses. Additionally, it appears that the user was in possession of multiple naloxone nasal spray devices since one device can administer one dose (e.g., 5 doses=5 devices). As such, we are unable to provide additional comments regarding the labeling based on this case, but device design already limits dosing to help mitigate such over-use.

Carroll et al. Buprenorphine Field Initiation of ReScue Treatment by Emergency Medical Services (Bupe FIRST EMS): A Case Series. Prehosp Emerg Care, 2020.²⁰

This case report describes a 45-year-old female who was found apneic and given a 4 mg dose of IN naloxone by police before EMS arrived. Responsiveness was restored, and her COWS score was documented to be 12, based on tachycardia in the 140s, diaphoresis, and irritability. She was then given buprenorphine 16 mg film as part of a novel field-based treatment program, and 10 minutes later, her COWS score had dropped to 4.

Reviewer comments: This case of precipitated withdrawal is consistent with the labeled effects of intranasal naloxone. It also describes the speed and extent to which administration of buprenorphine mitigated the withdrawal symptoms.

3.1.3.4 DPV Literature Aggregate Results

Table 10 describes the 11 published case reports of naloxone-induced adverse events.

Table 10. Published Case Reports of Naloxone-Induced Adverse Events (n=11)										
Author Year	Age/ Sex	PMH	Opioid status and current opioid exposure(s)	Initial IN/ cumulative any route naloxone dose (mg)/ reported total number of doses	Person administering naloxone	Signs/symptoms of withdrawal after naloxone	Reported COWS score/ severity	Adverse event(s) attributed to naloxone exposure	Management of adverse event(s)	Outcome
<i>Pulmonary edema (n=7)</i>										
Kummer 2022	NR/ NR	NR	NR/Heroin	4/4/1	“pre-hospital provider”	NR	NR/NR	Acute hypoxemic respiratory failure with pulmonary edema	Ventilatory support (type unknown)	R
Kummer 2022	NR/ NR	NR	NR/Heroin	4/10.2/7	“pre-hospital provider”	NR	NR/NR	Acute hypoxemic respiratory failure with pulmonary edema	Ventilatory support (type unknown)	R
Kummer 2022	NR/ NR	NR	NR/Heroin	4/8.5/3	“pre-hospital provider”	NR	NR/NR	Acute hypoxemic respiratory failure with pulmonary edema	Ventilatory support (type unknown)	R
Kummer 2022	NR/ NR	NR	NR/Heroin	4/14/4	“pre-hospital provider”	NR	NR/NR	Acute hypoxemic respiratory failure with pulmonary edema	Ventilatory support (type unknown)	R
Kummer 2022	NR/ NR	NR	NR/Oxycodone	4/2.5/3	“pre-hospital provider”	NR	NR/NR	Acute hypoxemic respiratory failure with pulmonary edema	Ventilatory support (type unknown)	R
Yarlagadda 2020	23/ M	Multiple opioid overdoses	D/Heroin	8/8/1.5	NR – given in field	Heart rate 109	NR/NR	Pulmonary edema and aspiration pneumonia	Positive pressure ventilation, antibiotics	R

Table 10. Published Case Reports of Naloxone-Induced Adverse Events (n=11)										
Author Year	Age/ Sex	PMH	Opioid status and current opioid exposure(s)	Initial IN/ cumulative any route naloxone dose (mg)/ reported total number of doses	Person administering naloxone	Signs/symptoms of withdrawal after naloxone	Reported COWS score/ severity	Adverse event(s) attributed to naloxone exposure	Management of adverse event(s)	Outcome
Veet 2017	27/ M	Chronic neck pain, polysubstance abuse	NR/oxycodone	2/6/3	Paramedics	NR	NR/NR	Pulmonary edema	Intubation IV furosemide	R
Limited efficacy (n=2)										
Bardsley 2019	32/ M	Heroin, alcohol, and tobacco abuse, schizophrenia	D/Carfentanil	4/12/5	Presumed HCP	Nausea and vomiting	NR/NR	Higher than expected naloxone requirement presumed related to carfentanil	Ondansetron, observation	R
Bardsley 2019	26/ F	Heroin and tobacco abuse, infrequent alcohol use	D/Carfentanil	2/10/5	Presumed HCP	None	NR/NR	Higher than expected naloxone requirement presumed related to carfentanil	Observation	R
Precipitated withdrawal (n=2)										
Brenner 2021	43/ F	NR	D/Fentanyl	4/24/6	General public (family member)	Severe agitation Tachycardia Tachypnea Diaphoresis Disorientation Retching	NR/NR	Severe and prolonged agitation due to naloxone overexposure related to layperson administration	Buprenorphine Haloperidol Diphenhydramine Lorazepam Propofol Intubation ICU care	R
Carroll 2020	45/ F	NR	NR/NR	4/4/1	EMS	Heart rate 140 Diaphoresis Dilated pupils Irritability	12/ moderate	Precipitated withdrawal	Buprenorphine on-site with post-treatment COWS score of 4	R
*The articles by Kummer and Yarlagadda described fractional doses that are not consistent with the available products. Abbreviations: COWS = clinical opioid withdrawal score, D = presumed opioid dependent, EMS = emergency medical services, F = female, HCP = health care professional, M = male, NR = not reported, PMH = past medical history, R = recovered										

Reviewer comments: Of those cases reporting, ages ranged between 23 and 45 years, with a mean of 33 years and a median of 30 years. Eight cases received a 4 mg initial IN naloxone dose, two received an initial 2 mg dose, and one received an initial 8 mg dose. The cumulative all-route doses ranged between 2.5 and 24 mg, with a mean of 9.4 mg and a median of 8.5 mg. The naloxone doses (10 mg and 12 mg) in the two cases of carfentanil exposures described by Bardsley were somewhat higher than the mean and median, though not dramatically so. The outlier of 24 mg was related to naloxone overdosing by an untrained bystander. All of the patients in the published cases recovered from the overdose, which is consistent with naloxone's ability to rapidly reverse the life-threatening consequences of opioid overdose (i.e., respiratory depression), and recovered from the subsequent adverse event. A trained person administered naloxone to all but one patient in this series. However, it is difficult to draw any conclusion about the role of naloxone training in the patients' outcomes, particularly in this very limited case series.

3.2 DMAMES RESULTS

3.2.1 DMAMES Case Selection and Findings

The FAERS search retrieved 395 reports. After applying case exclusion criteria described in **Section 2.2.1**, and accounting for duplicate reports, we identified 71 medication errors case relevant to this review. Nine U.S. cases describe Narcan (naloxone) nasal spray device use error (see **Table 11** for detailed information about the cases). No cases were identified for Kloxxado. In addition to device use error cases, we identified 58 cases of wrong indication medication errors and four cases of accidental wrong storage medication errors .

Device Use Error Cases (n=9)

These cases described wrong administration technique related to the device use errors and included:

- not waiting two to three minutes between doses (n=3),
- spraying medication into the air instead of patient's nostril and thus, wasting a dose (n=3),
- general confusion about the use of the device (n=2),
- administering medication to the same nostril (n=1).

In six of the cases, the narratives indicated that the use of naloxone nasal spray occurred during the emergency situation when the person was not breathing or appeared not to breathe. These six cases reported user not waiting 2 to 3 minutes between two doses (n=3), spraying the nasal spray into the air (n=2), or administering the product to the same nostril (n=1). Of these six cases, five reported that users were either a friend or a family member of the affected patient, and the remaining case reported the device user was a police officer. One of the six cases specifically reported that the user panicked. However, the remaining 5 cases did not cite root cause or contributing factor information. In all six cases that reported an emergency situation, the patients recovered. In five cases of the cases, including one in which the drug was sprayed into the air, patients ultimately received and responded to naloxone treatment. In the sixth case, the user sprayed the device into the air, and this resulted in dose omission, but the patient recovered nevertheless. None of the six emergency situation cases reported whether Instructions for Use/Quick Start Guide/carton labeling with the use instructions was referred to during the use of

the product or whether the user read the Instructions for Use/Quick Start Guide at any time prior to using the product.

Three of the nine cases involved nonemergency use of the product. The narratives for these three cases suggested that the users were trying to train themselves on how to use the device in case of an emergency (n=3). One case reported the user “was not sure how to work it out and nothing was coming out of the device” (n=1), in the second case, the user stated they were confused how to use the device and continued pressing the plunger and nothing was coming out of the device (n=1), and in the third case reported a user was confused and sprayed the product into the air and hence wasted a dose (n=1). In two of the three cases, the case narrative did not state whether the person referred to the Instructions for Use/Quick Start Guide/carton labeling with instructions. In the remaining case, the user was referring to the Instructions for Use, but still was confused about taking off a cap and pressing the red plunger. The user in the case reported that “the instructions made it sound like it just need to open and spray in nose. She wanted to know if there were any steps in between”. We note that neither naloxone nasal spray device (i.e., Narcan or Kloxxado) has a “cap” and did not have a cap previously at the time of the approval. The IFU does mention “cap”. Thus, it is unclear from the case narrative why the user thought there would be a cap and a step missing.

Although some device use errors occurred, they reported nonserious outcomes. Additionally, with the exception of one case, the remaining cases were unclear with regards to whether the user referred to the approved labels and labeling during use of the product. We are unable to determine, based on the nine cases discussed above, whether additional changes to the labels and labeling are needed or should be considered in the evaluation of the proposed nonprescription NSS.

Table 11. Reported Characteristics for U.S. FAERS Cases of Device Use Error for Naloxone Nasal Spray submitted to FAERS between January 1, 2016 and November 17, 2022, n=9	
Reported Characteristic	9 Cases
Brief Narrative of the Device Use Error Cases (9 cases reported by the firm, 1 direct report)*	
- Did not wait for 2 to 3 minutes between doses: - a person (not a first responder) “indicated they panicked and did not wait three minutes between the two doses. Patient’s overdose was reversed” (n=1); - female companion administered two IN doses 13 seconds apart and eventually with additional intervention, patient responded to treatment (n=1); - police officer administered two doses of Narcan nasal spray 1 min apart. Patient responded to treatment (n=1).	3
“Was not sure how to use” the device: - female consumer “was not sure how to work it out and there is nothing coming out of it for two days now” (n=1). “The patient couldn't get the NARCAN to work for a long time as she was pressing on the red plunger as hard as she could, but it wouldn't spray, and then finally, she kept trying and it eventually did spray. Reportedly, the patient wanted to know if it had to be twisted or turned for the product to spray. She was not able to understand why the NARCAN was not spraying, and she thought she did not apply enough pressure on the NARCAN plunger. Furthermore, the patient kept reading the NARCAN instructions and wanted to know if she had to take the cap off or pull the red thing on the bottom of NARCAN off. The instructions made it sound like it just need to open and spray in nose. She wanted to know if there were any steps in between” (n=1).	2

- Sprayed nasal spray into the air instead of the nostril: - patient's friend pressed the plunger before it was in patient's nose, "but it still worked" (n=1) - patient's wife "pushed that thing, and it went up into the air, so she wasted the whole thing." She was not sure how to use the device and "could not figure it out and it made no sense to her." She was able to get another "dose... and gave it to him." Patient responded to treatment as she drove him to the hospital (n=1). "The first time she tried using the first device, it did not come out. While trying to work the product in her hands, it just sprayed out and was wasted. She opened the second device and that worked; she sprayed it up her nose but now nothing comes out of this device anymore." It was not an emergency situation. Patient wanted to see how to use the device (n=1).	3
- Sprayed twice in the same nostril: - patient's cousin sprayed Narcan twice in the same nostril. The patient "woke up very soon after administration of second dose."	1
Root Cause/Contributing Factors for the Error	
Was not sure how to use the device	3
Person administering the product panicked	1
Not reported	5
Reported Outcome (all 10 cases reported as non-serious)	
Patient eventually responded to treatment and opioid overdose was reversed	6
Not reported	3
N/A (Complaint)	1
Case Narratives Indicated an Emergency Situation	
Yes	6
No	3
Who Administered the Product or Reported an Issue with the Product	
Friend/family member (administered the product)	5
Self-administration (intended to administer in emergency situation as needed, reported an issue with the use of the device as they were trying to understand how to use it if needed)	3
Police Officer (administered the product)	1
Product Involved	
Narcan Nasal Spray	9
Kloxxado	0
Number of Reported Device Use Error Cases Per Year	
2016	3
2017	1
2018	1
2019	0
2020	2
2021	1
2022	1
*FAERS Case Numbers: 12448503, 12745713, 12745718, 13949627, 15379035, 17791840, 18151337, 19965781, 21026907.	

Additional Medication Errors Findings Wrong Indication (n=58) and Accidental Wrong Storage Errors (n=4)

FDA identified additional medication errors that may help inform the considerations for labels and labeling for the non-prescription IN naloxone:

- Wrong Indication (n=58)
- Accidental wrong storage error (n=4)

Wrong Indication (n=58)

The wrong indication cases reported patients or caregivers mistakenly administering IN naloxone due to lack of knowledge regarding what naloxone is used for and thinking it is used for indications other than stated in the package insert labeling (e.g., sinus issues, allergy, asthma, diabetes) or thinking it is another product (i.e., inhaled morphine, Flonase, Imitrex, or substitute for Percocet). In some cases, patients administered IN naloxone without knowing what the product was for all together, but since it looked like a nasal spray they assumed they were prescribed for one of their conditions. One case stated that the prescription label was wrapped all around the carton and they couldn't understand what the product was for. Other cases did not report whether patients attempted to read and comprehend what this IN naloxone was indicated for. However, several cases reported that patients saw "nasal spray" on the box. In one case that reported administration of Narcan instead of Imitrex. There is a currently marketed Imitrex product that uses the same nasal device configuration as prescription Narcan and thus, the similarity between Imitrex inhaler device and Narcan device appears to be a contributing factor for confusion.

Of the 58 cases that reported wrong indication, 22 cases reported withdrawal symptoms. Additionally, three of the 58 cases reported serious outcome: one cases reported death and two cases reported "other". One case that reported an outcome of death stated that patient used IN naloxone thinking it would "help her sinus issues." The patient had multiple comorbidities (chronic pain, "abnormal blood pressure", "sinus issues"), used multiple medications (furosemide, tramadol, clonazepam, nicoderm, and Cymbalta) for her health conditions, and did not report the date of patient's death relative to naloxone use. As such, it is difficult to assess whether IN naloxone is related to the patient's death. The two cases that reported serious outcome as "other", both reported withdrawal symptoms (COWS score of 4 and 5), after patients used IN naloxone while thinking it was an allergy spray and a spray to relieve congestion respectively.

Accidental Wrong Storage (n=4)

Four cases were identified related to accidental wrong storage of the product in the freezing temperatures or temperatures over 104°F, which is outside the labeled temperature. In all four cases patients were aware of the correct storage temperature, but accidentally left the product either in the freezer or a car either in the freezing temperature or temperature over 104°F. None of the patients administered the product and all of these cases were non-serious.

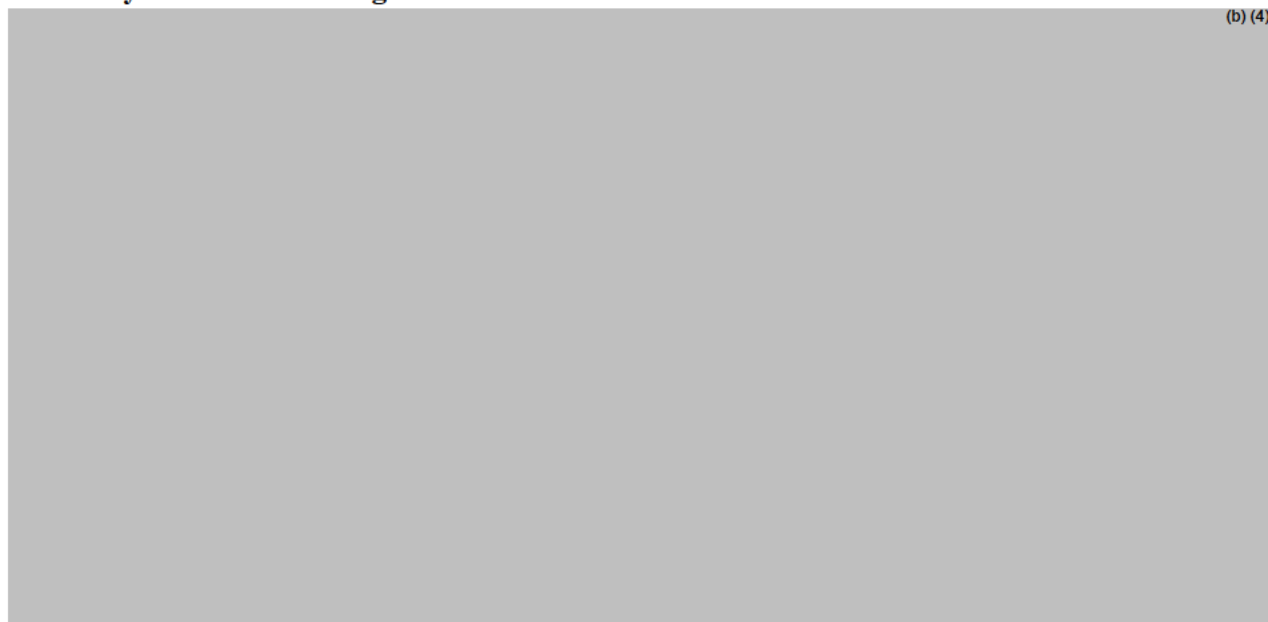
3.3 DRUG UTILIZATION RESULTS

3.3.1 Manufacturer Sales Data

Figure 3 below shows the annual estimated number of naloxone units sold from manufacturers to all U.S channels of distribution, stratified by product formulation, 2016 through 2021. During this time period, manufacturer sales and dispensed prescriptions of all naloxone formulations increased dramatically. Manufacturers sold approximately (b) (4) units of naloxone in 2016, which more than doubled to nearly (b) (4) units sold in 2021. These increases were largely driven by increases in sales of nasal spray formulation, which increased from approximately (b) (4) units in 2016 to (b) (4) units sold in 2021.

The market share for nasal spray increased from 6% in 2016 to 54% in 2021, while the shares for injectable vials and pre-filled syringes decreased from 53% to 33% and 40% to 13% respectively.

Figure 3. Nationally estimated number of naloxone units (vials, syringes, nasal sprays) sold from manufacturers to U.S. channels of distribution, stratified by product formulation, annually from 2016 through 2021.



Source: IQVIA, National Sales Perspective™. Time period 2016 to 2021. Data extracted January 2023. (b) (4)

3.3.2 Prescription Data

Figure 4 below shows the annual national estimated number of naloxone prescriptions dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies, stratified by product formulations from 2016 through 2021. During this study period, the annual number of naloxone prescriptions dispensed increased from approximately (b) (4) in 2016 to (b) (4) in 2021, mostly due to an increase in nasal formulation prescriptions from approximately (b) (4) prescriptions in 2016 to (b) (4) in 2021. The proportion of nasal formulation prescriptions dispensed among the total naloxone prescriptions increased from roughly (b) (4)% in 2016 to (b) (4)% in 2021, while the proportion of injectable naloxone prescriptions dispensed decreased from (b) (4)% to (b) (4)% during the same time period.

Figure 4. Nationally estimated number of prescriptions for naloxone products dispensed from U.S. outpatient retail, mail-order, and long-term care pharmacies, stratified by product formulation, annually from 2016 through 2021.



4 DISCUSSION

Since Narcan NS was launched in 2016, it has been sold and distributed widely across healthcare settings and by harm reduction groups. Narcan NS is also increasingly dispensed through retail pharmacies via individual prescriptions as well as through state actions such as standing order prescriptions which has increased administration in non-health care settings.²¹⁻²⁴ This increased utilization of the IN product correlates with the increase in number of adverse event reports in recent years. Overall, the FAERS aggregate analysis of all routes of naloxone, and the subset IN naloxone analysis did not identify any new safety issues related to the adverse events. The focused analysis of naloxone-induced precipitated withdrawal, limited efficacy, and device use/medication errors similarly revealed no major areas of concern, although it did yield observations that could inform labeling and product design.

DPV Discussion

Our FAERS (318) and literature (11) subset analysis represents U.S. community use of IN naloxone. We note that about half the cases were administered by the general public, about a third of the doses were self-administered, and the majority of the outcomes reported were non-serious. Very few cases described administration by trained laypeople or HCPs. Most cases described using one to two doses up to 8 mg, which is what is contained in the package. Most cases reported use for emergency treatment of known or suspected opioid overdose, reflecting appropriate use of IN naloxone by the general public.

Both data sources support the known adverse event of naloxone-induced precipitated withdrawal, which is included in the Narcan nasal spray labeling under Section 5, Warnings and Precautions. As a pure competitive opioid receptor antagonist, naloxone reverses all receptor-mediated opioid actions including central nervous system and respiratory depression due to opioids. Naloxone administration to individuals with exposure-related opioid receptor neuroadaptations may precipitate withdrawal from a resultant catecholamine increase.^{1,5} We used the COWS to analyze cases of reported precipitated withdrawal. One or more withdrawal symptoms (e.g., GI upset, anxiety/irritability, sweating) were apparent in at least a third of the IN cases. Overall, we had few cases with a COWS score ≥ 5 . Per the COWS scale, scores of 5 to 12 indicates mild withdrawal. The utilization of the COWS scoring tool within our case series was not how the COWS tool is intended to be used (i.e., at the bedside), but it provided an objective way to report withdrawal symptoms, which are by their nature, subjective symptoms. We acknowledge the COWS scores are likely an underestimation due to lack of data reported in the FAERS cases. Other more severe non-COWS withdrawal symptoms such as pulmonary edema and seizures were also reported to FAERS and the literature (pulmonary edema only). Pulmonary edema and seizures are included in the Narcan nasal spray labeling under **Section 5, Warnings and Precautions**, and described as a potential consequence of abrupt postoperative withdrawal; however, this was not the situation for these cases that occurred in the community setting. The hypothesized mechanism for pulmonary edema is “similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.”

The IN subset analysis also supports the known risk of limited efficacy with partial agonists or mixed agonists/antagonists where larger or repeat doses may be required, which is included in the Narcan nasal spray labeling under Section 5, Warnings and Precautions. Multiple factors contribute to the effectiveness of IN naloxone including the severity of the overdose, if other substances are involved, and time elapsed between when the overdose occurred and when naloxone is administered. Naloxone needs to be administered as quickly as possible after overdose to prevent death; however, how soon naloxone was administered after the overdose was not reported in most cases. Polysubstance overdoses may also not respond effectively or at all to naloxone. Our analysis of the subset of limited efficacy cases was challenging as 75% of cases did not report the specific opioid intended to be reversed (e.g. partial agonists) or if other substances were involved in the overdose, both of which could affect the efficacy of naloxone.

DMAMES Discussion

In terms of a safety assessment related to the device use errors, if a user chooses to test the device and thereby spray medication into the air, this will waste a dose. If that is the only device/dose available at the time, a person would not get an emergency treatment for the opioid overdose, which can potentially lead to death. Additional device use errors such as not waiting two to three minutes between doses and using the product in the same nostril also occurred. These latter device use errors represent a deviation from labeled dosing and use, which could have an impact on efficacy. However, missed dose appears to be a more significant safety risk from the device use error perspective. As such, postmarket data appear to support packaging of two devices together in one carton as a single sales unit to minimize the likelihood that a dose is not available when needed.

Regarding the wrong indication medication error safety assessment, there are several factors that we considered. Although prescription IN naloxone products state the indication on the carton labeling and instructions for use, it is unclear whether patients read the carton labeling. Additionally, given that the product is prescribed by a doctor and filled by the pharmacy, patients may not realize why they are prescribed this medication. For the non-prescription product, the patients or caregivers will have to select the product for the suspected or known opioid overdose off the shelf, thereby knowing why they are getting the medication. Additionally, labeling comprehension study for these products address that layusers were able to understand that the product is for “use for treatment of opioid overdose”. However, despite these mitigating factors, we recommend the name and the indication of the product is prominently stated on the labels and labeling to ensure layusers are able to see the information.

We also identified four cases of accidental wrong storage that report leaving the product in the freezing temperatures (e.g., car in the winter) or temperatures over 104°F (e.g., hot car or near microwave/heater). As such, we recommend that the OTC products’ labels and labeling should clearly state the storage information to help mitigate these types of errors.

Drug Utilization Discussion

The naloxone distribution and utilization data help provide insight into the changing market of naloxone use in the U.S. From 2016 to 2021, manufacturer sales and dispensed prescriptions of all naloxone formulations increased dramatically. Manufacturers sold approximately (b) (4) units of naloxone in 2016, which more than doubled to nearly (b) (4) units sold in 2021. These increases were largely driven by increases in sales of the nasal spray formulation, which increased from approximately (b) (4) units in 2016 to (b) (4) units sold in 2021. We saw a similar shift towards nasal spray in the dispensed prescription analysis. The estimated number of naloxone prescriptions dispensed increased from approximately (b) (4) prescriptions in 2016 to (b) (4) prescriptions in 2021, mainly due to an increase in dispensed prescriptions for the nasal formulation.

However, findings from this review should be interpreted in the context of the known limitations of the databases used. It is important to note that the proprietary databases used for these analyses underestimate total distribution and availability of naloxone products in the United States. A substantial proportion of naloxone distributed outside the usual channels accessible by prescription is not captured in these databases, such as direct sales or donations from manufacturers to community-based naloxone distribution programs like harm reduction groups. Therefore, it is challenging to provide an accurate estimate of how much naloxone is distributed. Some sources cite that community-based naloxone distribution programs received over two million injectable naloxone doses donated by manufacturers or purchased in bulk at low cost between 2017 and 2021.^{21, 22} It is also important to note that sales distribution and dispensed prescription data do not provide a direct estimate of use (what is administered to individuals). Naloxone is obtained as a preventative measure and stored until use may be needed in an emergency situation. If naloxone is not used before the product expires, the product may end up not being used. Lastly, the estimated prescription counts are based on projections of sample prescription data. These data therefore have some degree of inherent sampling error. These

estimates are not intended to be representations of exact enumerations and should be interpreted with caution, particularly if they are based on a small sample size.

5 CONCLUSION

Overall, the FAERS aggregate analysis of all routes of naloxone and the subset IN naloxone analysis did not identify any new safety issues related to the adverse events. The increase in number of adverse event reports in recent years correlates with increased drug utilization of the IN product. The postmarketing safety data we analyzed for IN naloxone overall and with community use IN naloxone does not indicate any new safety issues. Our cases demonstrated that the general public administered IN naloxone in the community for emergency use of known or suspected opioid overdose and the majority of cases had non-serious outcomes. The known adverse events of naloxone-induced precipitated withdrawal and limited efficacy identified in this FAERS and literature review do not outweigh the potential benefit of increased community availability of an OTC IN naloxone product.

The safety assessment related to the postmarket device use errors indicates that testing the device or spraying naloxone into the air can result in dose omission of naloxone nasal spray and hence, delay an emergency treatment for the opioid overdose, which can potentially lead to death. Although additional device use errors such as not waiting two to three minutes between doses and using the product in the same nostril occurred and can result in overdose and underdose respectively, wasting a dose, especially if that is the only naloxone nasal spray available to the user appears to be the most significant safety risk related to the device use errors.

Additionally, beyond the device use errors, we identified case reports related to the use of the IN naloxone for the wrong indication as well as accidental wrong storage by leaving the product in freezing temperatures or temperatures over 104°F.

6 RECOMMENDATIONS

Based on the postmarketing safety analysis related to naloxone-induced precipitated withdrawal and limited efficacy, we recommend that the DFL for any IN naloxone product contain language describing the common symptoms associated with withdrawal (e.g., GI upset, anxiety/irritability, sweating), as well as directions to continue giving doses every two to three minutes until the person wakes up and medical personnel arrive, consistent with what is included in the prescription labeling for naloxone products.

Based on the safety risk assessment related to the postmarketing device use/other medication errors, specifically involving the missed dose due to the device testing or spraying naloxone outside of the patient's nostril, we agree with the Applicants' intentions to supply OTC IN naloxone products in a package containing two units together and not as a single unit given there is one dose per nasal spray device based on postmarket data. We also recommend that the labels and labeling clearly and prominently display product's name, indications, and storage information as we identified multiple cases related to the use of the IN naloxone for the wrong indication as well as accidentally storing the product at the temperatures beyond labeled temperature recommendations.

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8 APPENDICES

8.1 APPENDIX A. CLINICAL OPIATE WITHDRAWAL SCALE

Wesson & Ling

Clinical Opiate Withdrawal Scale

APPENDIX 1 Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____ Date and Time ____/____/____ : ____	
Reason for this assessment: _____	
Resting Pulse Rate: _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	GI Upset: over last 1/2 hour 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: over past 1/2 hour not accounted for by room temperature or patient activity. 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	Tremor: observation of outstretched hands 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness: Observation during assessment 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	Yawning: Observation during assessment 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches: If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing: Not accounted for by cold symptoms or allergies 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Journal of Psychoactive Drugs

Volume 35 (2), April - June 2003

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253-9.

8.2 APPENDIX B. RELEVANT PRESCRIPTION NARCAN NASAL SPRAY LABEL SECTIONS

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Recurrent Respiratory and Central Nervous System Depression

The duration of action of most opioids may exceed that of NARCAN Nasal Spray resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek emergency medical assistance immediately after administration of the first dose of NARCAN Nasal Spray and to keep the patient under continued surveillance. Administer additional doses of NARCAN Nasal Spray if the patient is not adequately responding or responds and then relapses back into respiratory depression, as necessary [see *Dosage and Administration* (2.2)]. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses of naloxone hydrochloride may be required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor [see *Dosage and Administration* (2.3)]. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of NARCAN Nasal Spray in patients who are opioid-dependent may precipitate opioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.

There are limited data to inform if the 2 mg dose of NARCAN Nasal Spray will avoid precipitation of severe opioid withdrawal in the setting of opioid dependence. However, the 2 mg dose may not provide an adequate and timely reversal in persons who may be exposed to an overdose of a potent or very high dose of opioids.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a

dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

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. In these settings, consider use of an alternative, naloxone containing product that can be titrated to effect and, where applicable, dosed according to weight. [see *Use in Specific Populations* (8.4)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Precipitation of Severe Opioid Withdrawal [see *Warnings and Precautions* (5.3)]

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reactions were observed in a NARCAN Nasal Spray clinical study.

In a pharmacokinetic study of 30 healthy adult volunteers exposed to one spray of NARCAN Nasal Spray in one nostril or two sprays of NARCAN Nasal Spray, one in each nostril, the most common adverse reactions were: increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

The following adverse reactions have been identified primarily during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia, and have caused agitation.

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In some patients, there may be aggressive behavior upon abrupt reversal of an opioid overdose. In the neonate, opioid withdrawal signs and symptoms also included convulsions, excessive crying, and hyperactive reflexes.

8.3 APPENDIX C. PROPOSED NARCAN AND REVIVE DFL

Drug Facts

Active ingredient (in each 0.1 mL)
Naloxone hydrochloride 4 mg

Purpose
Emergency treatment of opioid overdose

Uses

- to "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin
- this medicine can save a life

Directions

Step 1: CHECK if you suspect an overdose:

- CHECK** for a suspected overdose; the person will not wake up or is very sleepy or not breathing well
- yell "Wake up!"
- shake the person gently
- if the person is not awake, go to Step 2

Step 2: GIVE 1st dose of Narcan OTC Nasal Spray

- HOLD** the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger
- INSERT** the tip of the nozzle into either NOSTRIL
- PRESS** the plunger firmly to give the 1st dose

Drug Facts (continued)

Step 3: CALL

- CALL 911** immediately after giving the 1st dose

Step 4: WATCH & GIVE

- WAIT** 2-3 minutes after the 1st dose to give the medicine time to work
- if the person **wakes up**: Go to Step 5
- if the person **does not wake up**:
 - CONTINUE TO GIVE** doses every 2-3 minutes until the person wakes up
 - it is safe to keep giving doses

Step 5: STAY

- STAY** until ambulance arrives: even if the person wakes up
- GIVE** another dose if the person becomes very sleepy again
- You may need to give all the doses in the pack

NARCAN[®]
(naloxone HCl) nasal spray 4 mg

DESIGNED TO RAPIDLY REVERSE THE EFFECTS OF A LIFE-THREATENING OPIOID EMERGENCY

OPIOID OVERDOSE RESCUE

Full Prescription Strength | 4 mg

Effective & Easy to Use

No Training Required

2 Single-Dose Devices

Drug Facts (continued)

Warnings

When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.

Keep out of reach of children.

Other information

- store below 25°C (77°F)
- do not freeze
- avoid excessive heat above 40°C (104°F)
- protect from light
- replace before the expiration date on the box
- the product is packaged in individually-sealed blisters
- do not use if the blister is open or torn, or if the device appears damaged

Inactive ingredients

benzalkonium chloride, disodium ethylenediaminetetraacetate, hydrochloric acid, sodium chloride, water

Questions?

call 1-844-4NARCAN (1-844-462-7226)

*Among opioid overdose reversal treatments

Distributed by Emergent Devices Inc.
Plymouth Meeting, PA 19462
USA

69547-XXX-XX

Drug Facts

Active ingredient (in each pre-filled device)

Naloxone hydrochloride 3.0 mg

Purpose

Emergency treatment of opioid overdose

Uses

- To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin
- This medicine can save a life

Directions

STEP 1 CHECK



STEP 2 GIVE



STEP 3 CALL 911



STEP 4 WATCH/GIVE



STEP 5 STAY



Step 1: CHECK if you suspect an overdose

- **CHECK** for a suspected overdose: the person will not wake up or is very sleepy or not breathing well
 - Yell "Wake up!"
 - Shake the person gently
 - If the person is not awake, go to Step 2

Step 2: GIVE a dose of this medicine

- Hold nasal spray with thumb on plunger and a finger on each side of the nozzle
- Insert nozzle into one nostril and press plunger firmly
- Each nasal spray contains only one dose of naloxone

Step 3: CALL 911

- Get medical help **immediately** after giving the first dose
- Call 911 now; **do not delay**

Step 4: WATCH & GIVE

- **WAIT** 2-3 minutes after the 1st dose to give the medicine time to work
- If the person **wakes up**: Go to Step 5
- If the person does **not wake up**:
 - Give a second dose of medicine using a new nasal spray
 - It is safe to keep giving doses every 2-3 minutes until the person wakes up

Step 5: STAY

- **STAY** until ambulance arrives: even if the person wakes up
- **GIVE** another dose if the person becomes very sleepy again
- You may need to give all the doses in the pack

Drug Facts (continued)

Warnings

When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.

Drug Facts (continued)

Other information

- store at room temperature
- do not refrigerate or expose to high temperatures
- do not use if sealed package is torn or opened

(b) (4)

8.4 APPENDIX D. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Drug Utilization Database Descriptions and Limitations

IQVIA National Sales Perspectives™ (NSP)

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~89% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections.

Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys™

Powered by IDV® (Integrated Dataverse), Metys™ is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point.

Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions; 73% of all U.S. mail order prescriptions, and 75% of all U.S. specialty prescriptions and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data are not projected to the national level. Metys™ Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.

8.5 APPENDIX E. FAERS LINE LISTING OF COMMUNITY USE INTRANASAL NALOXONE CASE SERIES (N=318)

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
1	2016-05-20	12391438	1	US-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-1052585	PERIODIC		MALE	USA	
2	2016-06-08	12448507	2	US-ADAPT PHARMA INC-2016ADP00008	PERIODIC		MALE	USA	
3	2016-06-08	12448499	2	US-ADAPT PHARMA INC-2016ADP00001	PERIODIC		MALE	USA	
4	2016-06-08	12448500	2	US-ADAPT PHARMA INC-2016ADP00002	PERIODIC		MALE	USA	
5	2016-06-08	12448501	2	US-ADAPT PHARMA INC-2016ADP00010	PERIODIC		MALE	USA	
6	2016-06-08	12448502	2	US-ADAPT PHARMA INC-2016ADP00003	PERIODIC		FEMALE	USA	
7	2016-06-08	12448503	2	US-ADAPT PHARMA INC-2016ADP00004	PERIODIC		MALE	USA	
8	2016-06-08	12448504	2	US-ADAPT PHARMA INC-2016ADP00005	PERIODIC		MALE	USA	
9	2016-06-08	12448505	2	US-ADAPT PHARMA INC-2016ADP00006	PERIODIC		FEMALE	USA	
10	2016-06-08	12448506	2	US-ADAPT PHARMA INC-2016ADP00007	PERIODIC		MALE	USA	
11	2016-08-02	12613698	2	US-ADAPT PHARMA INC-2016ADP00017	15-DAY	33	MALE	USA	Death
12	2016-08-30	12697639	1	US-ADAPT PHARMA INC-2016ADP00102	15-DAY	53	FEMALE	USA	Other
13	2016-08-30	12697649	2	US-ADAPT PHARMA INC-2016ADP00051	15-DAY		FEMALE	USA	Death
14	2016-08-30	12697670	1	US-ADAPT PHARMA INC-2016ADP00097	15-DAY	21	MALE	USA	Other

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
15	2016-08-30	12697675	1	US-ADAPT PHARMA INC-2016ADP00104	15-DAY	30	MALE	USA	Other
16	2016-08-30	12698629	2	US-ADAPT PHARMA INC-2016ADP00053	15-DAY		FEMALE	USA	Other
17	2016-08-30	12697726	1	US-ADAPT PHARMA INC-2016ADP00093	15-DAY	27	MALE	USA	Other
18	2016-08-31	12704075	1	US-ADAPT PHARMA INC-2016ADP00092	15-DAY	35	MALE	USA	Other
19	2016-09-08	12723555	1	US-ADAPT PHARMA INC-2016ADP00114	15-DAY			USA	Death
20	2016-09-08	12723561	1	US-ADAPT PHARMA INC-2016ADP00115	15-DAY			USA	Death
21	2016-09-12	12738733	2	US-ADAPT PHARMA INC-2016ADP00113	15-DAY	45.505	FEMALE	USA	Other
22	2016-09-15	12745756	1	US-ADAPT PHARMA INC-2016ADP00098	PERIODIC	31	MALE	USA	
23	2016-09-15	12745720	1	US-ADAPT PHARMA INC-2016ADP00020	PERIODIC	24	MALE	USA	
24	2016-09-15	12745778	1	US-ADAPT PHARMA INC-2016ADP00096	PERIODIC	50	MALE	USA	
25	2016-09-15	12745779	1	US-ADAPT PHARMA INC-2016ADP00090	PERIODIC	50	MALE	USA	
26	2016-09-15	12745758	1	US-ADAPT PHARMA INC-2016ADP00083	PERIODIC	25	MALE	USA	
27	2016-09-15	12745769	1	US-ADAPT PHARMA INC-2016ADP00105	PERIODIC	27	FEMALE	USA	
28	2016-09-15	12745724	1	US-ADAPT PHARMA INC-2016ADP00037	PERIODIC	19	FEMALE	USA	
29	2016-09-15	12745776	1	US-ADAPT PHARMA INC-2016ADP00089	PERIODIC	20	MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
30	2016-09-15	12745718	1	US-ADAPT PHARMA INC-2016ADP00019	PERIODIC		MALE	USA	
31	2016-09-15	12745710	1	US-ADAPT PHARMA INC-2016ADP00014	PERIODIC		MALE	USA	
32	2016-09-15	12745711	1	US-ADAPT PHARMA INC-2016ADP00016	PERIODIC	33	MALE	USA	
33	2016-09-15	12745713	1	US-ADAPT PHARMA INC-2016ADP00015	PERIODIC		MALE	USA	
34	2016-09-15	12745714	1	US-ADAPT PHARMA INC-2016ADP00072	PERIODIC			USA	
35	2016-09-15	12745715	1	US-ADAPT PHARMA INC-2016ADP00021	PERIODIC		MALE	USA	
36	2016-09-15	12745716	1	US-ADAPT PHARMA INC-2016ADP00024	PERIODIC	39	MALE	USA	
37	2016-09-15	12745717	1	US-ADAPT PHARMA INC-2016ADP00025	PERIODIC	30	MALE	USA	
38	2016-09-15	12745719	1	US-ADAPT PHARMA INC-2016ADP00022	PERIODIC		MALE	USA	
39	2016-09-15	12745721	1	US-ADAPT PHARMA INC-2016ADP00023	PERIODIC	25	MALE	USA	
40	2016-09-15	12745722	1	US-ADAPT PHARMA INC-2016ADP00038	PERIODIC	17	MALE	USA	
41	2016-09-15	12745725	1	US-ADAPT PHARMA INC-2016ADP00039	PERIODIC	51	MALE	USA	
42	2016-09-15	12745726	1	US-ADAPT PHARMA INC-2016ADP00043	PERIODIC			USA	
43	2016-09-15	12745727	1	US-ADAPT PHARMA INC-2016ADP00042	PERIODIC			USA	
44	2016-09-15	12745728	1	US-ADAPT PHARMA INC-2016ADP00040	PERIODIC	35	FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
45	2016-09-15	12745729	1	US-ADAPT PHARMA INC-2016ADP00066	PERIODIC		MALE	USA	
46	2016-09-15	12745730	1	US-ADAPT PHARMA INC-2016ADP00068	PERIODIC		MALE	USA	
47	2016-09-15	12745731	1	US-ADAPT PHARMA INC-2016ADP00063	PERIODIC		MALE	USA	
48	2016-09-15	12745732	1	US-ADAPT PHARMA INC-2016ADP00058	PERIODIC		FEMALE	USA	
49	2016-09-15	12745734	1	US-ADAPT PHARMA INC-2016ADP00047	PERIODIC		MALE	USA	
50	2016-09-15	12745735	1	US-ADAPT PHARMA INC-2016ADP00060	PERIODIC		MALE	USA	
51	2016-09-15	12745736	1	US-ADAPT PHARMA INC-2016ADP00059	PERIODIC		FEMALE	USA	
52	2016-09-15	12745737	1	US-ADAPT PHARMA INC-2016ADP00048	PERIODIC		MALE	USA	
53	2016-09-15	12745739	1	US-ADAPT PHARMA INC-2016ADP00062	PERIODIC		MALE	USA	
54	2016-09-15	12745740	1	US-ADAPT PHARMA INC-2016ADP00065	PERIODIC		MALE	USA	
55	2016-09-15	12745741	1	US-ADAPT PHARMA INC-2016ADP00057	PERIODIC		MALE	USA	
56	2016-09-15	12745742	1	US-ADAPT PHARMA INC-2016ADP00050	PERIODIC		MALE	USA	
57	2016-09-15	12745743	1	US-ADAPT PHARMA INC-2016ADP00052	PERIODIC		MALE	USA	
58	2016-09-15	12745745	1	US-ADAPT PHARMA INC-2016ADP00045	PERIODIC		FEMALE	USA	
59	2016-09-15	12745746	1	US-ADAPT PHARMA INC-2016ADP00056	PERIODIC		MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
60	2016-09-15	12745747	1	US-ADAPT PHARMA INC-2016ADP00046	PERIODIC		MALE	USA	
61	2016-09-15	12745748	1	US-ADAPT PHARMA INC-2016ADP00049	PERIODIC		FEMALE	USA	
62	2016-09-15	12745749	1	US-ADAPT PHARMA INC-2016ADP00067	PERIODIC		MALE	USA	
63	2016-09-15	12745750	1	US-ADAPT PHARMA INC-2016ADP00061	PERIODIC		MALE	USA	
64	2016-09-15	12745751	1	US-ADAPT PHARMA INC-2016ADP00064	PERIODIC		FEMALE	USA	
65	2016-09-15	12745752	1	US-ADAPT PHARMA INC-2016ADP00054	PERIODIC		FEMALE	USA	
66	2016-09-15	12745753	1	US-ADAPT PHARMA INC-2016ADP00055	PERIODIC		FEMALE	USA	
67	2016-09-15	12745754	1	US-ADAPT PHARMA INC-2016ADP00044	PERIODIC		FEMALE	USA	
68	2016-09-15	12745755	1	US-ADAPT PHARMA INC-2016ADP00094	PERIODIC	46	FEMALE	USA	
69	2016-09-15	12745757	1	US-ADAPT PHARMA INC-2016ADP00084	PERIODIC	25	FEMALE	USA	
70	2016-09-15	12745759	1	US-ADAPT PHARMA INC-2016ADP00086	PERIODIC	23	MALE	USA	
71	2016-09-15	12745760	1	US-ADAPT PHARMA INC-2016ADP00085	PERIODIC	40	MALE	USA	
72	2016-09-15	12745761	1	US-ADAPT PHARMA INC-2016ADP00091	PERIODIC		MALE	USA	
73	2016-09-15	12745762	1	US-ADAPT PHARMA INC-2016ADP00100	PERIODIC	26	MALE	USA	
74	2016-09-15	12745763	1	US-ADAPT PHARMA INC-2016ADP00101	PERIODIC	63	MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
75	2016-09-15	12745765	1	US-ADAPT PHARMA INC-2016ADP00082	PERIODIC	32	MALE	USA	
76	2016-09-15	12745767	1	US-ADAPT PHARMA INC-2016ADP00103	PERIODIC	28	FEMALE	USA	
77	2016-09-15	12745771	1	US-ADAPT PHARMA INC-2016ADP00070	PERIODIC	59	FEMALE	USA	
78	2016-09-15	12745774	1	US-ADAPT PHARMA INC-2016ADP00087	PERIODIC	29	FEMALE	USA	
79	2016-09-15	12745775	1	US-ADAPT PHARMA INC-2016ADP00080	PERIODIC	28	MALE	USA	
80	2016-09-15	12745780	1	US-ADAPT PHARMA INC-2016ADP00079	PERIODIC	56	MALE	USA	
81	2016-09-15	12745773	1	US-ADAPT PHARMA INC-2016ADP00075	PERIODIC	30	FEMALE	USA	
82	2016-09-15	12745770	1	US-ADAPT PHARMA INC-2016ADP00081	PERIODIC	30	FEMALE	USA	
83	2016-09-15	12745766	1	US-ADAPT PHARMA INC-2016ADP00088	PERIODIC	25	MALE	USA	
84	2016-09-15	12745772	1	US-ADAPT PHARMA INC-2016ADP00078	PERIODIC	27	FEMALE	USA	
85	2016-09-15	12745781	2	US-ADAPT PHARMA INC-2016ADP00069	PERIODIC	20	MALE	USA	
86	2016-09-26	12781381	1	US-ADAPT PHARMA INC-2016ADP00118	15-DAY			USA	Death
87	2016-09-30	12802058	1	US-FDA-CDER-OSC-FDA-CDER-CTU-5493	DIRECT	81	MALE	USA	Hospitalization
88	2016-11-23	12968211	2	US-ADAPT PHARMA INC-2016ADP00130	15-DAY	62.54	FEMALE	USA	
89	2016-12-13	13022439	1	US-ADAPT PHARMA INC-2016ADP00107	PERIODIC		MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
90	2016-12-13	13022440	1	US-ADAPT PHARMA INC-2016ADP00109	PERIODIC		FEMALE	USA	
91	2016-12-13	13022441	1	US-ADAPT PHARMA INC-2016ADP00111	PERIODIC		FEMALE	USA	
92	2016-12-13	13022442	1	US-ADAPT PHARMA INC-2016ADP00112	PERIODIC		MALE	USA	
93	2016-12-13	13022443	1	US-ADAPT PHARMA INC-2016ADP00106	PERIODIC		FEMALE	USA	
94	2016-12-13	13022444	1	US-ADAPT PHARMA INC-2016ADP00108	PERIODIC		MALE	USA	
95	2016-12-13	13022445	1	US-ADAPT PHARMA INC-2016ADP00110	PERIODIC		FEMALE	USA	
96	2016-12-13	13022447	1	US-ADAPT PHARMA INC-2016ADP00122	PERIODIC		MALE	USA	
97	2016-12-13	13022448	2	US-ADAPT PHARMA INC-2016ADP00127	PERIODIC	23	FEMALE	USA	
98	2016-12-13	13022449	1	US-ADAPT PHARMA INC-2016ADP00126	PERIODIC		MALE	USA	
99	2016-12-13	13022450	1	US-ADAPT PHARMA INC-2016ADP00128	PERIODIC		FEMALE	USA	
100	2017-03-16	13342356	1	US-ADAPT PHARMA INC-2016ADP00135	PERIODIC	34	MALE	USA	
101	2017-03-16	13342357	1	US-ADAPT PHARMA INC-2017ADP00002	PERIODIC			USA	
102	2017-03-16	13342358	1	US-ADAPT PHARMA INC-2017ADP00003	PERIODIC	57.464	MALE	USA	
103	2017-06-13	13648413	1	US-ADAPT PHARMA INC-2017ADP00007	PERIODIC		MALE	USA	
104	2017-06-13	13648414	1	US-ADAPT PHARMA INC-2017ADP00005	PERIODIC		FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
105	2017-06-13	13648416	1	US-ADAPT PHARMA-2017ADP00009	PERIODIC	50.863	MALE	USA	
106	2017-06-13	13648419	1	US-ADAPT PHARMA INC-2017ADP00013	PERIODIC		FEMALE	USA	
107	2017-06-13	13648418	1	US-ADAPT PHARMA INC-2017ADP00012	PERIODIC		MALE	USA	
108	2017-06-13	13648415	1	US-ADAPT PHARMA INC-2017ADP00008	PERIODIC	50	MALE	USA	
109	2017-09-08	13949621	1	US-ADAPT PHARMA INC-2017ADP00015	PERIODIC	58.36	MALE	USA	
110	2017-09-08	13949624	1	US-ADAPT PHARMA-2017ADP00018	PERIODIC	59.871	FEMALE	USA	Other
111	2017-09-08	13949633	1	US-ADAPT PHARMA INC-2017ADP00021	PERIODIC	32	FEMALE	USA	
112	2017-09-08	13949637	1	US-ADAPT PHARMA INC-2017ADP00024	PERIODIC	40.985	FEMALE	USA	
113	2017-09-08	13949644	1	US-ADAPT PHARMA INC-2017ADP00034	PERIODIC		FEMALE	USA	
114	2017-09-08	13949627	1	US-ADAPT PHARMA INC-2017ADP00017	PERIODIC		MALE	USA	
115	2017-12-12	14279090	1	US-ADAPT PHARMA INC-2017ADP00039	PERIODIC		FEMALE	USA	
116	2017-12-12	14279092	1	US-ADAPT PHARMA INC-2017ADP00042	PERIODIC			USA	
117	2017-12-12	14279094	1	US-ADAPT PHARMA-2017ADP00043	PERIODIC		FEMALE	USA	Other
118	2017-12-12	14279096	1	US-ADAPT PHARMA INC-2017ADP00047	PERIODIC		FEMALE	USA	
119	2017-12-12	14279088	1	US-ADAPT PHARMA INC-2017ADP00037	PERIODIC	30	FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
120	2017-12-15	14298420	1	FDA-CDER-CTU-2017-80849	DIRECT		FEMALE	USA	Life Threatening
121	2018-01-10	14373045	1	US-ADAPT PHARMA INC-2017ADP00048	15-DAY		MALE	USA	Other
122	2018-03-13	14632998	1	US-ADAPT PHARMA INC-2018ADP00009	PERIODIC		FEMALE	USA	
123	2018-04-18	14773106	3	US-ADAPT PHARMA-2018ADP00026	15-DAY	64.591	MALE	USA	Other
124	2018-05-08	14866638	1	US-ALKERMES INC.-ALK-2018-000738	PERIODIC	49	MALE	USA	Hospitalization,Life Threatening
125	2018-06-12	15002313	1	US-ADAPT PHARMA INC-2018ADP00028	PERIODIC	63.123	FEMALE	USA	
126	2018-06-12	15002310	1	US-ADAPT PHARMA INC-2018ADP00023	PERIODIC		MALE	USA	
127	2018-06-12	15002315	1	US-ADAPT PHARMA INC-2018ADP00030	PERIODIC		FEMALE	USA	
128	2018-06-12	15002316	1	US-ADAPT PHARMA INC-2018ADP00032	PERIODIC		MALE	USA	
129	2018-07-26	15204710	1	US-INTERNATIONAL MEDICATION SYSTEMS, LIMITED-2052795	PERIODIC		MALE	USA	Other
130	2018-08-07	15251531	1	US-ADAPT PHARMA INC-2018ADP00048	15-DAY			USA	Death
131	2018-08-16	15284284	1	US-ADAPT PHARMA INC-2018ADP00055	15-DAY	25	FEMALE	USA	Hospitalization
132	2018-08-16	15285255	2	US-ADAPT PHARMA INC-2018ADP00054	15-DAY		MALE	USA	Death,Life Threatening
133	2018-08-29	15329321	2	US-ADAPT PHARMA-2018ADP00058	15-DAY		FEMALE	USA	Other
134	2018-09-13	15379029	1	US-ADAPT PHARMA INC-2018ADP00039	PERIODIC	55.285	FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
135	2018-09-13	15379031	1	US-ADAPT PHARMA INC-2018ADP00041	PERIODIC	24.073	MALE	USA	Other
136	2018-09-13	15379030	1	US-ADAPT PHARMA INC-2018ADP00040	PERIODIC		FEMALE	USA	
137	2018-09-13	15379033	1	US-ADAPT PHARMA INC-2018ADP00046	PERIODIC		MALE	USA	
138	2018-09-13	15379034	1	US-ADAPT PHARMA INC-2018ADP00044	PERIODIC		FEMALE	USA	
139	2018-09-13	15379035	1	US-ADAPT PHARMA INC-2018ADP00049	PERIODIC		MALE	USA	
140	2018-09-13	15379036	1	US-ADAPT PHARMA INC-2018ADP00045	PERIODIC		FEMALE	USA	
141	2018-09-13	15379037	1	US-ADAPT PHARMA INC-2018ADP00047	PERIODIC		MALE	USA	
142	2018-09-13	15379038	1	US-ADAPT PHARMA INC-2018ADP00050	PERIODIC		FEMALE	USA	Death,Hospitalization,Life Threatening,Other
143	2018-09-13	15379039	1	US-ADAPT PHARMA INC-2018ADP00056	PERIODIC		FEMALE	USA	
144	2018-10-10	15485610	4	US-ADAPT PHARMA INC-2018ADP00072	15-DAY	59.304	MALE	USA	
145	2018-10-11	15489160	1	US-ADAPT PHARMA INC-2018ADP00073	15-DAY		MALE	USA	Death
146	2018-11-13	15614597	1	US-ADAPT PHARMA INC-2018ADP00080	15-DAY		FEMALE	USA	Hospitalization,Life Threatening
147	2018-11-20	15637116	1	US-ADAPT PHARMA INC-2018ADP00083	15-DAY		FEMALE	USA	Death,Other
148	2018-12-14	15722751	1	US-ADAPT PHARMA INC-2018ADP00065	PERIODIC	83.923	FEMALE	USA	
149	2018-12-14	15722948	1	US-ADAPT PHARMA INC-2018ADP00068	PERIODIC		MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
150	2018-12-14	15722949	1	US-ADAPT PHARMA INC-2018ADP00081	PERIODIC		FEMALE	USA	
151	2018-12-14	15722950	2	US-ADAPT PHARMA INC-2018ADP00084	PERIODIC		MALE	USA	
152	2019-01-25	15869639	1	US-ADAPT PHARMA-2019ADP00003	15-DAY		FEMALE	USA	Other
153	2019-02-26	16144295	1	FDA-CDER-CTU-2019-23075	DIRECT	75	MALE	USA	Hospitalization
154	2019-04-16	16201523	2	US-ADAPT PHARMA INC-2019ADP00038	15-DAY	64.703	FEMALE	USA	Other
155	2019-06-07	16402598	1	US-MALLINCKRODT-T201902941	PERIODIC	85.593	FEMALE	USA	
156	2019-08-12	16693700	1	US-ADAPT PHARMA-2019ADP00077	15-DAY	64.251	FEMALE	USA	Death
157	2019-10-08	16895065	1	US-INDIVIOR US-INDV-120837-2019	PERIODIC	72.273	MALE	USA	
158	2019-11-20	17053812	1	US-ADAPT PHARMA INC-2019ADP00107	15-DAY	69.111	MALE	USA	Other
159	2020-01-17	17282040	1	US-ADAPT PHARMA INC.-2018ADP00089	PERIODIC	26.655	FEMALE	USA	
160	2020-01-17	17282041	1	US-ADAPT PHARMA INC.-2019ADP00002	PERIODIC	85.878	FEMALE	USA	
161	2020-01-17	17282072	1	US-ADAPT PHARMA INC.-2019ADP00005	PERIODIC		FEMALE	USA	
162	2020-01-17	17282073	1	US-ADAPT PHARMA INC.-2019ADP00009	PERIODIC		MALE	USA	
163	2020-01-17	17282081	1	US-ADAPT PHARMA INC.-2019ADP00057	PERIODIC		FEMALE	USA	
164	2020-01-17	17282083	1	US-ADAPT PHARMA INC.-2019ADP00067	PERIODIC		FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
165	2020-01-17	17282089	1	US-ADAPT PHARMA INC.- 2019ADP00076	PERIODIC		MALE	USA	
166	2020-01-17	17282090	1	US-ADAPT PHARMA INC.- 2019ADP00086	PERIODIC	76.257	MALE	USA	
167	2020-01-17	17282091	1	US-ADAPT PHARMA INC.- 2019ADP00088	PERIODIC	63	FEMALE	USA	
168	2020-01-17	17282092	1	US-ADAPT PHARMA INC.- 2019ADP00103	PERIODIC		FEMALE	USA	
169	2020-01-17	17282095	1	US-ADAPT PHARMA INC.- 2019ADP00018	PERIODIC		MALE	USA	
170	2020-01-17	17282098	1	US-ADAPT PHARMA INC.- 2019ADP00028	PERIODIC		MALE	USA	
171	2020-01-17	17282099	1	US-ADAPT PHARMA INC.- 2019ADP00029	PERIODIC		MALE	USA	
172	2020-01-17	17282074	1	US-ADAPT PHARMA INC.- 2019ADP00014	PERIODIC		MALE	USA	
173	2020-01-17	17282101	1	US-ADAPT PHARMA INC.- 2019ADP00032	PERIODIC	24	MALE	USA	
174	2020-01-31	17356863	1	US-EMERGENT BIOSOLUTIONS,-19000429SP	15-DAY			USA	
175	2020-02-07	17391910	1	US-EMERGENT BIOSOLUTIONS,-19000470SP	15-DAY		MALE	USA	
176	2020-02-20	17442069	1	US-EMERGENT BIOSOLUTIONS,-19000433SP	15-DAY		FEMALE	USA	
177	2020-04-21	17688408	1	US-EMERGENT BIOSOLUTIONS,-20000154SP	15-DAY	57.587	MALE	USA	
178	2020-05-06	17754112	1	US-EMERGENT BIOSOLUTIONS,-20000227SP	15-DAY		FEMALE	USA	
179	2020-05-15	17791839	1	US-EMERGENT BIOSOLUTIONS,-20000125SP	15-DAY		MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
180	2020-05-15	17791840	2	US-EMERGENT BIOSOLUTIONS,-20000240SP	PERIODIC	54.863	FEMALE	USA	
181	2020-06-19	17919431	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-20000397SP	15-DAY			USA	Death
182	2020-06-23	17933087	1	US-EMERGENT BIOSOLUTIONS,-20000338SP	15-DAY	46.091	FEMALE	USA	
183	2020-07-03	17978708	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-20000401SP	15-DAY	61.982	FEMALE	USA	Hospitalization,Other
184	2020-07-03	17978731	1	US-EMERGENT BIOSOLUTIONS,-20000357SP	15-DAY		MALE	USA	
185	2020-07-20	18045362	2	US-EMERGENT BIOSOLUTIONS,-20000421SP	15-DAY	55.953	MALE	USA	
186	2020-07-20	18046709	1	US-EMERGENT BIOSOLUTIONS-20000423SP	15-DAY		MALE	USA	Other
187	2020-07-30	18095571	1	US-EMERGENT BIOSOLUTIONS,-20000431SP	15-DAY			USA	
188	2020-07-30	18095589	1	US-EMERGENT BIOSOLUTIONS,-20000419SP	15-DAY		MALE	USA	
189	2020-07-30	18096513	1	US-EMERGENT BIOSOLUTIONS,-20000177SP	15-DAY		MALE	USA	
190	2020-09-22	18296698	1	US-EMERGENT BIOSOLUTIONS,-20000470SP	15-DAY	38	MALE	USA	Death
191	2020-09-23	18301743	1	US-EMERGENT BIOSOLUTIONS,-20000441SP	PERIODIC	64.876	FEMALE	USA	
192	2020-09-25	18312438	1	US-EMERGENT BIOSOLUTIONS,-20000448SP	PERIODIC		MALE	USA	
193	2020-09-30	18331899	1	US-EMERGENT BIOSOLUTIONS,-20000443SP	PERIODIC		FEMALE	USA	
194	2020-10-01	18336227	1	US-EMERGENT BIOSOLUTIONS,-20000468SP	PERIODIC		FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
195	2020-11-06	18474438	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-20000481SP	15-DAY	38.642	MALE	USA	Other
196	2020-12-04	18581630	1	US-EMERGENT BIOSOLUTIONS,-20000476SP	PERIODIC		MALE	USA	
197	2020-12-21	18643262	1	US-EMERGENT BIOSOLUTIONS,-20000498SP	PERIODIC	22	FEMALE	USA	
198	2020-12-24	18656827	1	US-EMERGENT BIOSOLUTIONS,-20000494SP	PERIODIC	79	MALE	USA	
199	2021-01-05	18703038	1	US-EMERGENT BIOSOLUTIONS,-20000500SP	PERIODIC		FEMALE	USA	
200	2021-01-05	18703584	1	US-EMERGENT BIOSOLUTIONS,-20000501SP	PERIODIC		MALE	USA	
201	2021-01-25	18782942	1	US-EMERGENT BIOSOLUTIONS,-20000518SP	PERIODIC		FEMALE	USA	
202	2021-01-25	18786716	1	US-EMERGENT BIOSOLUTIONS,-20000178SP	PERIODIC	81.42	FEMALE	USA	
203	2021-01-25	18786974	1	US-EMERGENT BIOSOLUTIONS,-20000004SP	PERIODIC		FEMALE	USA	
204	2021-01-26	18789713	2	US-EMERGENT BIOSOLUTIONS,-20000520SP	PERIODIC		FEMALE	USA	
205	2021-01-27	18794912	1	US-EMERGENT BIOSOLUTIONS,-20000543SP	PERIODIC	61	MALE	USA	
206	2021-01-27	18794947	1	US-EMERGENT BIOSOLUTIONS,-20000526SP	PERIODIC		FEMALE	USA	
207	2021-01-27	18795060	1	US-EMERGENT BIOSOLUTIONS,-20000521SP	PERIODIC	56.61	FEMALE	USA	
208	2021-02-26	18946661	2	US-EMERGENT BIOSOLUTIONS,-21000025SP	15-DAY			USA	Other
209	2021-03-03	18964714	1	US-EMERGENT BIOSOLUTIONS,-21000008SP	PERIODIC		FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
210	2021-03-03	18964874	1	US-EMERGENT BIOSOLUTIONS,-21000012SP	PERIODIC		FEMALE	USA	
211	2021-03-05	18974136	1	US-EMERGENT BIOSOLUTIONS,-21000016SP	PERIODIC		MALE	USA	
212	2021-03-09	18986757	1	US-EMERGENT BIOSOLUTIONS,-21000028SP	PERIODIC	57.182	MALE	USA	
213	2021-03-11	18999929	1	US-EMERGENT BIOSOLUTIONS,-21000017SP	PERIODIC		FEMALE	USA	
214	2021-03-29	19068801	1	US-EMERGENT BIOSOLUTIONS,-21000022SP	PERIODIC		FEMALE	USA	
215	2021-04-08	19110029	1	US-EMERGENT BIOSOLUTIONS,-21000023SP	PERIODIC		FEMALE	USA	
216	2021-04-08	19111221	1	US-EMERGENT BIOSOLUTIONS,-21000030SP	PERIODIC		FEMALE	USA	
217	2021-04-13	19128998	1	US-EMERGENT BIOSOLUTIONS,-21000037SP	PERIODIC		FEMALE	USA	
218	2021-04-20	19159267	1	US-EMERGENT BIOSOLUTIONS,-21000044SP	PERIODIC	66.97	FEMALE	USA	
219	2021-04-23	19176391	1	US-EMERGENT BIOSOLUTIONS- 21000045SP	15-DAY	33.96	FEMALE	USA	Hospitalization,Other
220	2021-04-30	19202538	1	US-EMERGENT BIOSOLUTIONS,-21000050SP	PERIODIC		FEMALE	USA	
221	2021-04-30	19202540	1	US-EMERGENT BIOSOLUTIONS,-21000049SP	PERIODIC		FEMALE	USA	
222	2021-05-13	19252809	3	US-EMERGENT BIOSOLUTIONS,-21000051SP	15-DAY	32.468	MALE	USA	Life Threatening,Other
223	2021-05-25	19305923	2	US-EMERGENT BIOSOLUTIONS,-21000061SP	PERIODIC		MALE	USA	
224	2021-06-01	19353000	1	US-EMERGENT BIOSOLUTIONS,-21000063SP	PERIODIC		FEMALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
225	2021-06-02	19363916	1	US-EMERGENT BIOSOLUTIONS,-21000064SP	PERIODIC		MALE	USA	
226	2021-06-09	19396062	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000067SP	15-DAY			USA	Other
227	2021-07-07	19502165	3	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000084SP	15-DAY			USA	Hospitalization
228	2021-07-12	19523792	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000089SP	15-DAY			USA	Death
229	2021-07-19	19581821	2	US-EMERGENT BIOSOLUTIONS,-21000105SP	PERIODIC			USA	
230	2021-07-19	19581822	1	US-EMERGENT BIOSOLUTIONS,-21000091SP	PERIODIC			USA	
231	2021-07-20	19585663	2	US-EMERGENT BIOSOLUTIONS,-21000107SP	PERIODIC			USA	
232	2021-07-23	19605775	1	US-EMERGENT BIOSOLUTIONS,-21000106SP	PERIODIC			USA	
233	2021-07-28	19621929	1	US-EMERGENT BIOSOLUTIONS,-21000116SP	PERIODIC			USA	
234	2021-07-28	19622124	1	US-EMERGENT BIOSOLUTIONS,-21000118SP	PERIODIC			USA	
235	2021-08-18	19720272	2	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000129SP	15-DAY			USA	Other
236	2021-08-24	19742919	1	US-EMERGENT BIOSOLUTIONS,-21000128SP	PERIODIC			USA	
237	2021-09-02	19781412	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000150SP	15-DAY		MALE	USA	Other
238	2021-09-08	19808969	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000157SP	15-DAY		FEMALE	USA	Hospitalization
239	2021-09-14	19829571	1	US-EMERGENT BIOSOLUTIONS,-21000149SP	PERIODIC			USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
240	2021-09-14	19829580	1	US-EMERGENT BIOSOLUTIONS,-21000142SP	PERIODIC			USA	
241	2021-11-08	20045569	1	US-EMERGENT BIOSOLUTIONS,-21000202SP	PERIODIC			USA	
242	2021-11-08	20045583	1	US-EMERGENT BIOSOLUTIONS,-21000214SP	PERIODIC		MALE	USA	
243	2021-12-14	20181078	2	US-EMERGENT BIOSOLUTIONS CANADA INC.-21000277SP	15-DAY		FEMALE	USA	Hospitalization,Other
244	2022-01-07	20311327	1	US-EMERGENT BIOSOLUTIONS,-21000291SP	PERIODIC		MALE	USA	
245	2022-02-22	20503904	1	US-EMERGENT BIOSOLUTIONS,-22000001	PERIODIC			USA	
246	2022-02-22	20503905	1	US-EMERGENT BIOSOLUTIONS,-22000008	PERIODIC		MALE	USA	
247	2022-02-22	20503915	1	US-EMERGENT BIOSOLUTIONS,-22000009	PERIODIC			USA	
248	2022-02-22	20503965	1	US-EMERGENT BIOSOLUTIONS,-22000024	PERIODIC		FEMALE	USA	
249	2022-02-23	20506492	1	US-EMERGENT BIOSOLUTIONS,-22000033	PERIODIC			USA	
250	2022-03-01	20533047	2	US-EMERGENT BIOSOLUTIONS,-22000037	PERIODIC		FEMALE	USA	
251	2022-03-04	20552419	3	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00533	15-DAY			USA	
252	2022-03-04	20553459	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00562	15-DAY		MALE	USA	Other
253	2022-03-04	20553595	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00552	15-DAY		MALE	USA	
254	2022-03-04	20553614	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00559	15-DAY		FEMALE	USA	Other

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
255	2022-03-04	20553652	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00553	15-DAY		MALE	USA	Other
256	2022-03-04	20553653	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00560	15-DAY		MALE	USA	Other
257	2022-03-08	20563494	1	US-EMERGENT BIOSOLUTIONS CANADA INC.-22000038	15-DAY			USA	Other
258	2022-03-09	20570078	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00588	15-DAY		MALE	USA	
259	2022-03-09	20570088	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00587	15-DAY		MALE	USA	Other
260	2022-03-09	20571972	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00594	15-DAY		MALE	USA	Other
261	2022-03-09	20572345	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00595	15-DAY		FEMALE	USA	Other
262	2022-03-09	20572385	3	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00589	PERIODIC		FEMALE	USA	Other
263	2022-03-09	20572389	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00590	15-DAY			USA	Other
264	2022-03-09	20572390	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00591	15-DAY			USA	Other
265	2022-03-09	20572436	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00593	15-DAY			USA	Other
266	2022-03-09	20572893	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00631	15-DAY		MALE	USA	Death,Other
267	2022-03-14	20590377	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00658	15-DAY			USA	
268	2022-03-14	20590378	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00660	15-DAY		MALE	USA	Other
269	2022-03-14	20590381	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00661	15-DAY			USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
270	2022-04-10	20693253	1	US-EMERGENT BIOSOLUTIONS,-22000051	PERIODIC		FEMALE	USA	
271	2022-04-10	20693257	1	US-EMERGENT BIOSOLUTIONS,-22000046	PERIODIC		FEMALE	USA	
272	2022-05-09	20803121	1	US-EMERGENT BIOSOLUTIONS,-22000077	15-DAY	28	MALE	USA	Other
273	2022-05-10	20805752	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00214	PERIODIC			USA	Other
274	2022-05-10	20805753	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00474	PERIODIC		FEMALE	USA	Other
275	2022-05-10	20805754	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00524	PERIODIC		MALE	USA	
276	2022-05-10	20805755	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00525	PERIODIC			USA	
277	2022-05-10	20805756	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00526	PERIODIC		MALE	USA	
278	2022-05-10	20805757	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00528	PERIODIC		MALE	USA	
279	2022-05-10	20805758	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00530	PERIODIC		MALE	USA	
280	2022-05-10	20805759	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00531	PERIODIC			USA	
281	2022-05-10	20805760	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00532	PERIODIC		MALE	USA	
282	2022-05-10	20805761	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00534	PERIODIC		MALE	USA	
283	2022-05-10	20805762	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00536	15-DAY		MALE	USA	Other
284	2022-05-10	20805763	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00537	15-DAY		MALE	USA	Other

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
285	2022-05-10	20805764	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00543	PERIODIC		MALE	USA	Other
286	2022-05-10	20805765	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00558	PERIODIC		MALE	USA	Other
287	2022-05-10	20805766	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00561	PERIODIC		MALE	USA	
288	2022-05-10	20805767	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00563	PERIODIC			USA	
289	2022-05-10	20805768	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00592	PERIODIC		MALE	USA	
290	2022-05-10	20805769	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00612	PERIODIC			USA	Other
291	2022-05-10	20805770	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00615	PERIODIC		MALE	USA	Other
292	2022-05-10	20805771	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00616	PERIODIC		FEMALE	USA	Other
293	2022-05-10	20805773	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00620	PERIODIC		FEMALE	USA	Other
294	2022-05-10	20805774	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00621	PERIODIC		FEMALE	USA	Other
295	2022-05-10	20805775	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00622	PERIODIC		FEMALE	USA	Other
296	2022-05-10	20805776	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00623	PERIODIC		FEMALE	USA	Other
297	2022-05-10	20805777	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00632	PERIODIC		MALE	USA	Other
298	2022-05-10	20805778	1	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-00633	PERIODIC			USA	
299	2022-05-11	20815913	2	US-EMERGENT BIOSOLUTIONS,-22000084	15-DAY		FEMALE	USA	Other

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
300	2022-05-12	20818179	1	US-EMERGENT BIOSOLUTIONS,-22000062	PERIODIC		FEMALE	USA	
301	2022-05-12	20818187	1	US-EMERGENT BIOSOLUTIONS,-22000065	PERIODIC		FEMALE	USA	
302	2022-05-12	20818207	1	US-EMERGENT BIOSOLUTIONS,-22000072	15-DAY		FEMALE	USA	
303	2022-05-12	20818236	1	US-EMERGENT BIOSOLUTIONS,-22000079	15-DAY	39.375	FEMALE	USA	
304	2022-05-12	20821213	1	FDA-CDER-CTU-2022-36602	DIRECT	29	FEMALE	USA	Hospitalization,Required Intervention
305	2022-05-20	20855880	1	US-EMERGENT BIOSOLUTIONS,-22000088	15-DAY			USA	
306	2022-06-30	21026699	1	US-EMERGENT BIOSOLUTIONS,-22000103	15-DAY		MALE	USA	
307	2022-06-30	21026733	1	US-EMERGENT BIOSOLUTIONS,-22000104	15-DAY		MALE	USA	
308	2022-06-30	21026907	1	US-EMERGENT BIOSOLUTIONS,-22000113	15-DAY		FEMALE	USA	
309	2022-07-18	21094058	2	US-Hikma Pharmaceuticals USA Inc.-US-H14001-22-01562	PERIODIC	58	FEMALE	USA	
310	2022-07-26	21130010	1	US-TEVA-2022-US-2057314	PERIODIC	62	MALE	USA	
311	2022-08-08	21187419	1	US-EMERGENT BIOSOLUTIONS,-22000137	15-DAY		MALE	USA	
312	2022-09-08	21308620	1	US-EMERGENT BIOSOLUTIONS,-22000180	15-DAY	84.795	MALE	USA	
313	2022-10-02	21400122	1	US-EMERGENT BIOSOLUTIONS,-22000216	15-DAY		MALE	USA	Other
314	2022-10-02	21400160	1	US-EMERGENT BIOSOLUTIONS,-22000213	PERIODIC		MALE	USA	

Case No.	Initial FDA received Date	FAERS Case #	Version Number	Manufacturer Control #	Report Type	Age in Years	Sex	Country Derived	Serious Outcome(s)
315	2022-10-17	21465660	1	US-EMERGENT BIOSOLUTIONS,-22000233	PERIODIC		MALE	USA	
316	2022-11-12	21586502	1	US-EMERGENT BIOSOLUTIONS,-22000244	15-DAY		FEMALE	USA	
317	2022-11-12	21586512	1	US-EMERGENT BIOSOLUTIONS,-22000254	15-DAY		MALE	USA	
318	2022-11-12	21586513	1	US-EMERGENT BIOSOLUTIONS,-22000266	15-DAY		FEMALE	USA	

8.6 APPENDIX F. DEFINITIONS OF INDIVIDUALS ADMINISTERING NALOXONE

Table A. Definition of Individuals Responding to OA-OHCA Based on Training		
	Definition	Likely educational setting/resources
General public	Untrained lay public	Public service announcements; Stand-alone OEND kits; Virtual/online courses; EMS dispatcher instructions
Trained laypeople	Non-health care personnel with formal training • Naloxone dosing • Basic life support • Other skills	OEND programs; Occupational first-aid programs; Instructional (certification) courses for people likely to encounter overdose
Health care providers	Existing health care professionals with resuscitation capabilities	Formal health care training; resuscitation training; ongoing quality improvement and simulation
EMS = emergency medical services OA-OHCA = opioid-associated out-of-hospital cardiac arrest OEND = overdose education and naloxone distribution		

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/

ALLISON B LARDIERI
02/24/2023 10:59:43 AM

KAREN E KONKEL
02/27/2023 06:05:11 AM

YELENA MASLOV
02/27/2023 09:43:28 AM

JAE WOOK YOO
02/27/2023 09:58:21 AM

CORINNE M WOODS
02/27/2023 10:04:38 AM

LYNDA V MCCULLEY
02/27/2023 10:41:54 AM

RAJDEEP K GILL
02/27/2023 10:47:55 AM

ZACHARY A OLESZCZUK
02/27/2023 10:55:25 AM

IDA-LINA DIAK
02/27/2023 11:06:24 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/18/2023

TO: Division of Nonprescription Drugs I (DNPDI)
Office of Nonprescription Drugs (ONPD)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 217722

OSIS received an inspection request consult from the Division of Nonprescription Drugs I (DNPDI) on November 25, 2022, for the below clinical and analytical sites. The requested review goal date was January 6, 2023. This amends the prior OSIS decline to inspect memos dated December 14, 2022 and January 13, 2023.

Rationale

Inspections of the sites listed below were not able to be completed by the requested review goal date of January 6, 2023. However, the OSIS inspection history for the sites indicate that inspections are not needed based on each site's current compliance status shown below.

Pharma Medica Research, Inc., clinical site: The Office of Regulatory Affairs (ORA) conducted an inspection in December 2022. The inspection was conducted under the following submission: NDA (b) (4)

The following item was discussed with the site:

- (b) (4)

We note that the final OSIS Review is pending for NDA (b) (4).

(b) (4) analytical site: OSIS conducted an inspection in (b) (4). The inspection was conducted under the following submissions: ANDAs (b) (4)

OSIS concluded that data from the reviewed studies were reliable, and thus indicates that the analytical site's study conduct is satisfactory.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Pharma Medica Research, Inc.	4770 Sheppard Avenue East, Toronto, Ontario, Canada
Analytical	(b) (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/

NICOLA M FENTY-STEWART
01/20/2023 12:44:00 PM