

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208411Orig1s006

OTHER REVIEW(S)

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:	March 28, 2023
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 208411/S-006
Product Name, Dosage Form, and Strength:	Narcan (naloxone hydrochloride) nasal spray, 4 mg per spray
Applicant/Sponsor Name:	Emergent Biosolutions
OSE RCM #:	2022-2688-2
DMEPA 2 Human Factors Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator (for labels & labeling evaluation):	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 Director:	Danielle Harris, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted professional sample carton labeling and revised blister labeling, carton labeling, and Directions leaflet received on March 24, 2023 for Narcan. The Division of Nonprescription Drugs I (DNPDI) requested that we review the professional sample carton labeling and the revised blister labeling, carton labeling, and Directions leaflet for Narcan (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions to the blister labeling, carton labeling, and Directions leaflet are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The professional sample carton labeling is acceptable from a medication error perspective. The Applicant implemented all of our recommendations for the blister labeling, carton labeling, and Directions leaflet. We have no additional recommendations at this time.

^a Shah, M. Label and Labeling Review Memorandum for Narcan (NDA 208411/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 15. OSE RCM No.: 2022-2688-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 24, 2023

Directions Leaflet

Available in EDR via: <\\CDSESUB1\EVSPROD\nda208411\0660\m1\us\114-labeling\draft\labeling\narcan-otc-quick-start-guide.pdf>

Blister Labeling



2 Pages 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/

MILLIE B SHAH
03/28/2023 12:02:15 PM

LOLITA G STERRETT on behalf of GRACE JONES
03/28/2023 12:36:25 PM

COLLEEN L LITTLE
03/28/2023 12:58:17 PM

LOLITA G STERRETT
03/28/2023 01:00:06 PM

DANIELLE M HARRIS
03/28/2023 01:32:52 PM

Draft Labeling Review for Narcan (Naloxone Hydrochloride 4 mg) Nasal Spray

SUBMISSION DATES:	September 29, 2022; January 05, 2023, February 17, 2023, February 21, 2023, March 08, 2023, March 24, 2023, March 28, 2023
NDA:	208411/S-006 (Rx-to-OTC Switch)
ACTIVE INGREDIENTS:	Naloxone hydrochloride 4 mg
DOSAGE FORM:	Nasal spray
SPONSOR:	Emergent Operations Ireland Limited
REVIEWER:	Robert Bahde, PhD, DNPD I/ONPD
TEAM LEADER:	Kevin Lorick, PhD, RAC, DNPD I/ONPD
PROJECT MANAGER:	Phong Pham, PharmD, MBA, DRO-NPD/ORO/OND

I. BACKGROUND

Emergent Operations Ireland Limited submitted, on September 29, 2022, an efficacy supplement (i.e., an Rx-to-OTC Switch) for NDA 208411, Narcan Nasal Spray (naloxone hydrochloride 4 mg). This product will be the first nonprescription drug product for the emergency treatment of opioid overdose. Sponsor proposed new labeling to change the marketing status of their 4 mg nasal spray product from prescription to nonprescription. While the labeling has changed, the 4 mg nasal spray drug/device marketed under this NDA remains unchanged for this supplement. Finally, Sponsor informed the Agency that they will withdraw their 2 mg nasal spray drug product from this NDA, see supplement 007.

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 actions address the stigma that is associated with purchasing naloxone drug products. By introducing a nonprescription drug product, naloxone would be placed on store shelves, thus mitigating the 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 a model DFL. 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) was critical for proper consumer use during an emergency, for example indication, “**Directions**”, “**Warnings**” 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 information, importantly, does not comply with the requirements of 21 CFR 201.66. “**Warnings**”, which usually are provided before telling a consumer how to use a product, were placed after the directions, since the trial data suggested that warnings may deter people from using the product in an emergency. Pictograms, whose presence 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.

The model DFL developed by FDA would need to be modified by an applicant to provide device-specific instructions for their drug product. These changes could then be evaluated in a human factors validation study (HFVS) that demonstrates users can safely and effectively use the drug product when following a Sponsor’s modified DFL. In this case, Sponsor modified step 2 of the “**Directions**” for their nasal spray device. Steps 1, 3, 4, and 5 remain unchanged from the model DFL in Sponsor’s labeling submission (a revision to the pictogram in step 4 was later requested by the Agency).

Division of Medication Error Prevention and Analysis 2 (DMEPA 2) reviewed the results of the HFVS for Narcan Nasal Spray and made the following findings and recommendations.

They found that dividing the “**Directions**” section over two panels of the outer carton is likely to result in use errors as consumers may have difficulty locating where the “**Directions**” begin or continuing “**Directions**” from the back panel to the side panel. They recommended Sponsor redesign the carton so that the “**Directions**” are entirely present on a single panel and that each blister package contain a Quick Start Guide (QSG) that displays Steps 1 through 5 of the Directions from the DFL.

Directions on back and side panel

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

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

Revised Directions on Single Panel

Drug Facts (continued)
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 in the nose

- HOLD the nasal spray device with your thumb on the bottom of the plunger
- INSERT the nozzle into either NOSTRIL
- PRESS the plunger firmly to give the 1st dose
- 1 nasal spray device contains 1 dose

Step 3: CALL

- CALL 911 immediately after giving the 1st dose

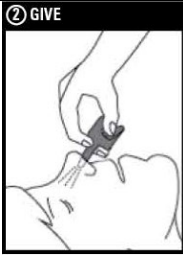
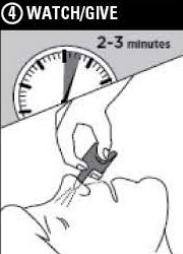
Step 4: WATCH & GIVE

- 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

DMEPA 2 found that the pictogram image for Step 2 may have contributed to a use error during the HFVS. This image is identical to the image from the FDA model DFL and was intended to serve as a placeholder that would be replaced by images specific for each drug product. They recommended 1.) replacing the image for Step 2 and the bottom-half image of Step 4 with a pictogram from Narcan prescription labeling and 2.) adding a figure to the outer carton, outside of the DFL, and QSG that shows the correct hand and finger position on the device. The revised pictures for Steps 2 and 4 are closer views of the nasal spray being inserted to the nose. It also appears as if the nasal spray is fully inserted (as opposed to just the tip).

Step 2 First Proposed Image	Step 2 Revised Image from Rx Labeling
	
Step 4 First Proposed Image	Step 4 Revised Image from Rx Labeling
	

DMEPA 2 determined that a use error in the HFVS occurred because a participant did not fully insert the nozzle into the nostril. They recommended revising the second bullet in Step 2 of the “Directions” and QSG to: “Insert the nozzle into either nostril” (i.e., remove “the tip of”).

During this review, the image of a hand on the side panel of the outer carton was added to address observed user errors in the HFVS. This image, including labels that point to the nozzle and plunger, and the five important statements accompanying the graphic image (see below) should be included in labeling to ensure easy, consistent, safe, and effective use of this drug product.

- For use in 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



Labeling Advice Letters**FDA Comment (March 02, 2023)****Sponsor response in italics (March 08, 2023).****Labeling**

1. Submit clean labeling free of proprietary information. The labeling submitted on February 21, 2023, contains private information, such as the typesetter's name, and therefore is unsuitable for public display and Freedom of Information Act (FOIA) requests. Ensure any clean labeling is free of private and proprietary information by removing your contractor's production notes.

Sponsor

Emergent has updated all product labeling to be clean, free of proprietary information (i.e., removed contractor's production notes).

2. Confirm the print and format specifications for the Drug Facts label (DFL) by annotating your labeling with format specifications required in 21 CFR 201.66(d). For instance, you may include a legend that denotes type sizes and character spacing with each label submitted to module 1.14.1.1 (see example below or see <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> for approved nonprescription labeling examples of DFL annotation).

Drug Facts Label	Size
Drug Facts Title	x pt
Drug Facts Continued	x pt
Headings	x pt
Subheadings	x pt
Body Text	x pt
Leading	x pt
Characters Per Inch	x
Bullets	x pt
Space Before Bullet	x ems
Barlines	x pt
Hairlines	x pt
Space between Hairlines	x spaces

Sponsor

Emergent has confirmed the print and format specifications for the DFL and annotated accordingly. Refer to Section 1.14.1.2 for the annotated DFL.

Principal Display Panel (PDP)

3. Ensure the statements displayed on the PDP are displayed with clarity and conspicuousness, per 21 CFR 201.60. As currently proposed, the carton has insufficient contrast, which may decrease legibility of the text.¹ For example, the established name (pink text on a white background) and remaining statements on the PDP (white text on pink background) are difficult to read. Revise the font color and/or background color of the carton so statements are legible and contrast distinctly with the PDP background.

Sponsor

Emergent acknowledges the Agency's feedback regarding contrast and legibility of the

PDP. In order to improve the readability of the PDP, Emergent has implemented the following:

- *Modified the background color of the Carton to increase contrast*
- *Increased the size and weight of the product claims in the upper right hand corner*
- *Updated the established name to black text*
- *Changed the font style and font size of the text on the bottom half of the PDP*

4. The proposed statement of identity (SOI), “(naloxone HCl) nasal spray 4 mg OPIOID OVERDOSE RESCUE” must include an established name, for example “Naloxone HCl Nasal Spray 4 mg,” that is immediately followed by the general pharmacological category, “Emergency Treatment of Opioid Overdose,” which matches the **Purpose** found in the DFL. This format must be used wherever your labeling includes the established name of the drug. Revise your labeling by 1) removing the parentheses around “naloxone HCl,” 2) capitalizing the first letter of each word in the established name 3) changing the pharmacological category from “Opioid Overdose Rescue” to “Emergency Treatment of Opioid Overdose,” and 4) placing the pharmacological category so that it immediately follows the established name.

Sponsor

The statement of identity on the Carton has been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton. Additionally, the presentation of the established name has been updated throughout all of the product labeling.

5. The declaration of net quantity statement displayed in lower right corner of the PDP must include a useful measurement of the dosage form “Nasal Sprays.” Unlike other nonprescription nasal spray devices, the naloxone nasal spray devices contain only a single dose. Per 21 CFR 201.62(a), augment the net quantity statement to inform that each nasal spray contains only 1 dose and is for single use. Revise your labeling by replacing “2 Single-Dose Devices” with “2 Single-Dose Nasal Spray Devices”.

Sponsor

The net quantity statement on the Carton has been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton

6. Errors occurred in the Human Factors validation study (HFVS) due to confusion regarding the number of doses in each device. Add the following statements under the statement, “2 Single-Dose Nasal Spray Devices” (see #5)
 - i. “1 nasal spray device contains 1 dose of medicine”
 - ii. “Device sprays 1 time only”

Sponsor

Emergent acknowledges the Agency’s request to add these two statements under the statement “2 Single-Dose Nasal Spray Devices”. However, Emergent proposes that these two statements (b) (4)

(b) (4) These three statements provided together help Consumers understand why this nasal spray device should not be “tested” or “primed” before use.

Therefore, only the net contents and net quantity statements are provided together on the bottom left-hand corner of the PDP (as follows):

“2 Single Dose Nasal Spray Devices
0.003 fl oz (0.1 mL) each”

7. Rephrase the net content (fill) volume 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”).

Sponsor

The net content statement on the Carton has been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

8. To align with nonprescription nasal spray drug product labeling, place the net fill volume statement (i.e., “0.003 fl oz (0.1 mL) each”) below the net quantity statement (i.e., “2 Single-Dose Nasal Spray Devices”).

Sponsor

The net fill volume statement has been placed below the net quantity statement on the Carton. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

9. Errors occurred in the HFVS related to device orientation, operation, and hand position on the device. Add a figure to the PDP that shows the correct hand and finger position on the device. Include labels on the figure that point to the components of the device, similar to the figure from Step 2 of the prescription Narcan Nasal Spray carton (see Figure 1 below). Add the same figure to the top right portion of the Quick Start Guide (QSG).

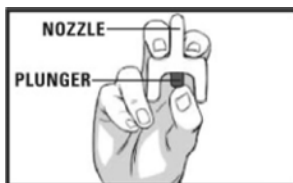


Figure 1. Pictogram from prescription Narcan carton

Sponsor

Emergent proposes that the figure showing the correct hand and finger position on the device be added to the side panel of the Carton. This allows the device figure to be placed in close proximity to the **Directions**. Additionally, as requested in # 27, text (along with an arrow) has been added below this figure directing Consumers to “Read Directions Before Use”. (Refer to Figure 1 for a visual).

Labels have been added that point to the two components of the device, similar to the figure from Step 2 of the prescription NARCAN® Nasal Spray Carton. This same figure has been added to the top right-hand corner of the QSG. Refer to Section 1.14.1.1 for the

updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the updated QSG.

10. Add the statement “For use in the nose only” to the PDP to further promote the correct route of administration.

Sponsor

While the Agency has requested that the statement “For use in the nose only” be added to the PDP, Emergent proposes that this statement be provided on the side panel along with the figure demonstrating the device components and correct hand and finger position on the device. These elements along with the reference for Consumers to “Read Directions Before Use” (see Figure 1) help promote the safe and effective use of NARCAN. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

11. Data are required to support the promotional statements, (b) (4) (b) (4) Provide data to support these two promotional statements.

Sponsor

(b) (4) conducted a Consumer Awareness Trial and Usage study on behalf of Emergent to support potential promotional claims. It was an online survey including 201 participants (consisting of primary care physicians and pain specialists) and was conducted between December 8, 2022 and December 28, 2022. Refer to Appendix A for top-line summary results to support for the promotional claim (b) (4)

Emergent does not intend to market (b) (4) and has removed from the labeling, therefore, no supporting data for this claim is provided.

12. The statement (b) (4) may confuse consumers about the need to follow the “Directions” contained in the DFL. Remove the statement from your PDP.

Sponsor

The statement (b) (4) has been removed from the PDP. This promotional claim has been replaced with “Can Save a Life” consistent with the statement under the **Uses** heading of the DFL. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

Drug Facts Label

13. Follow the order of the DFL headings tested in the “Comprehension for OTC naloxone” or CONFER labeling comprehension study. In other words, use the heading order: **Active ingredient/Purpose, Uses, Directions, Warnings, Other information, Inactive ingredients, Questions?**. We recommend starting the DFL on the side panel to the left of the **Directions** with **Active ingredient/Purpose, Uses** and finishing the DFL on the side panel to the right of the **Directions**. The **Directions** will remain unaffected on the back panel and the remainder of the DFL will be contained on both side panels.

Sponsor

Emergent considers the (b) (4) DFL Carton (b) (4) to be more convenient for Consumers than the proposed Carton that has the DFL content split across 3-panels. (b) (4)

We acknowledge that the order of the DFL content in our alternate proposed (b) (4) Carton would be slightly modified from that tested in FDA's CONFER labeling comprehension study, however, the content of the DFL remains identical to that tested in the CONFER study (with the exception of the device-specific instructions for Step 2). Emergent has updated a version of the Carton to address the Agency's request for the order of the DFL. However, as previously mentioned, Emergent would like to kindly ask the Agency to consider our proposed alternate Carton layout. Emergent recommends the Agency refer to Section 1.14.1.1 for a visual of the (b) (4) DFL Carton (Emergent proposed alternate design) vs. that of the 3-panel DFL Carton (to comply with the Agency's request).

14. Per 21 CFR 201.66(d)(5), arrows are required to signal continuation of the DFL. Add an arrow to the bottom of the **Uses** section on the first panel pointing right to the "**Directions**" on the back panel. Add a second arrow at the bottom of Step 5 in the "**Directions**" that points right to the side panel that contains the **Warnings, Other information, Inactive ingredients, Questions?** sections.

Sponsor

Arrows have been added to signal continuation of the DFL. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

15. The "Active ingredient" heading should read "**Active ingredient (in each spray)**" instead of "**Active ingredient (in each 0.1 mL)**". Per 21 CFR 201.66(c)(2), the parenthetical statement must contain the dosage unit, in this case "spray."

Sponsor

The active ingredient heading has been updated from "**Active ingredient (in each 0.1 mL)**" to "**Active ingredient (in each spray)**". Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

16. Revise the heading of Step 2 of the DFL Directions and QSG to, "Give 1st dose in the nose" to further promote the correct route of administration.

Sponsor

Step 2 of the DFL **Directions** and QSG have been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the updated QSG.

17. The DFL contains the statement “NARCAN Nasal Spray” under Step 2 in the “Directions.” Only nonproprietary names are permitted in the DFL, per Over- The-Counter Human Drugs Labeling Requirements, published on March 17, 1999 (64 FR 13254 at 13268). Revise the bullet “HOLD the Narcan Nasal Spray...” to read “HOLD the nasal spray device...” in the DFL.

Sponsor

*Step 2 of the DFL **Directions** and QSG have been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the updated QSG.*

18. Errors occurred in the HFVS related to device orientation, operation, and hand position on the device. Replace the pictogram in Step 2 of the DFL Directions with the pictogram from Step 2 of the prescription Narcan Nasal Spray carton (see Figure 2) to show correct hand and finger positioning on the device. Incorporate the same image into Step 4’s pictogram, while maintaining the clock image. Make the same revisions to the QSG.



Figure 2. Pictogram from prescription Narcan carton 19.

Sponsor

*Step 2 and Step 4 of the DFL **Directions** and QSG have been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the updated QSG.*

19. Revise the second bullet in Step 2 of the DFL **Directions** and QSG to: “Insert the nozzle into either nostril” (i.e., remove “the tip of”). A use error in the HFVS occurred because a participant did not fully insert the nozzle into the nostril, which may result in partial dose administration of naloxone HCl.

Sponsor

*Step 2 of the DFL **Directions** and QSG have been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the updated QSG.*

20. Add the statement, “1 nasal spray device contains 1 dose” as the last bullet in Step 2 of the DFL **Directions** and QSG. Errors occurred in the HFVS due to confusion regarding the number of doses in each device.

Sponsor

*Step 2 of the DFL **Directions** and QSG have been updated accordingly. Refer to Section*

1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the updated QSG.

21. Add a temperature value to define the “do not freeze” statement under the “**Other information**” section in the DFL (see also request 26 g, below).

Sponsor

The “do not freeze” statement in the DFL has been updated accordingly. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

22. Children may need to administer this drug product, therefore, nullifying the requirement in 21 CFR 330.1(g). Revise your labeling by removing the warning “**Keep out of reach of children**”.

Sponsor

The Drug Facts Label has been updated to remove the statement “Keep out of reach of children”. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

23. Several participants at the Advisory Committee meeting stressed the need to connect overdose victims to care. Consider adding information to direct victims to care under “**Questions?**,” such as the Substance Abuse and Mental Health Services Administration’s (SAMHSA) National Helpline, 1-800-662-HELP (4357) (also known as the Treatment Referral Routing Service) or “FindTreatment.gov.”

Sponsor

Emergent recognizes the importance of connecting victims to care. Emergent will be working to engage cross-functional colleagues and various stakeholders to thoughtfully explore how this could be best implemented.

24. Revise the text font color and/or background color for each numbered heading in the DFL **Directions** (e.g., 1 CHECK, 2 GIVE, etc.). As currently presented, the (b) (4) font text on (b) (4) background has insufficient contrast, which may decrease legibility of the text.2 Make the same changes to the QSG. This recommendation is further supported by the Advisory Committee Panel.

Sponsor

The text font color and background color for each numbered heading in the DFL **Directions** and QSG has been updated to revert back to the black background/white text to provide sufficient contrast. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton, and Section 1.14.1.3 for the QSG.

Blister Label

25. Provide the purpose of the universal product code (UPC) symbol on the blister label.

Sponsor

Bar codes (e.g., UPC bar code on the blister label) are scanned by the on-line vision inspection systems during labeling operations to ensure the correct label is being applied every time. NARCAN® is not produced on a dedicated packaging line and the bar code scanning provides quality control measures to prevent labeling errors.

26. The information on the blister label is disorganized. Revise your label to clearly convey important information that includes content, storage conditions, instruction to use in the nose only, and to not test nasal spray device before use.

We have the following recommendations:

- a. To further promote the safe use of the proposed product related to the route of administration, increase the type size of the statement “For use in the nose only” and, if possible, add a figure of a nose near it.
- b. Remove the parentheses around “(naloxone HCl)” and follow the established name used on the PDP. The displayed established name must be “Naloxone HCl Nasal Spray 4 mg”. It cannot be interrupted by parentheses and should include the strength.
- c. Remove the statement “Each dose contains 4 mg naloxone HCl (equivalent to 3.6 mg naloxone) in 0.1 mL nasal spray”. This statement is redundant because the strength is displayed in the established name and its removal will create space for statements that emphasize safe use and proper storage conditions.
- d. Replace the statement, “1 spray per device” with the following three statements “Do not test nasal spray device before use”, “1 device contains 1 dose of medicine” and “Device sprays 1 time only”. Ensure these statements are on separate lines and have the same prominence. Errors occurred in the HFVS due to confusion regarding the number of doses in each device.
- e. Remove the statement, “Excursions permitted up to 104 °F (40 °C)” and add a temperature value to define the statement “do not freeze”. The storage conditions on the blister package must match the conditions listed under “Other information” in the DFL.
- f. Use bullets to better organize the storage conditions statements.
- g. Present the temperature ranges first in centigrade followed by Fahrenheit within the parenthesis (e.g., Store at 20°C to 25°C (68°F to 77°F)), per USP official compendia, < 659> Packaging and Storage Requirements and USP General Notices and Requirements.
- h. Replace the statement “Use for known or suspected opioid overdose in adults and children” with the Purpose/general pharmacological category to be consistent with the outer carton labeling.

Sponsor

The recommendations in #26 (a through h) have been implemented. Refer to Section 1.14.1.1 for the updated Blister label.

Additional Statements on the Outer Carton

27. Add a message for consumers to familiarize themselves with the Directions found on the back panel before they may need to use this product.

Sponsor

Emergent has added the message “Read Directions before Use” (with an arrow pointing to the Directions) to Carton. Refer to Section 1.4.1.1 for the (b) (4) DFL Carton and the 3-panel DFL Carton.

28. The outer carton labeling should warn against testing the spray device before use and instruct consumers not to use the naloxone spray until needed.

Sponsor

The bullet “Do not test nasal spray device before use” has been added (b) (4) warning against testing the spray device before use. This language aligns with that recommended in #26 to be added to the blister labeling.

29. The statement (b) (4) overstates the efficacy of your product. Remove this statement.

Sponsor

Emergent has updated the statement to just read (b) (4) Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

30. As currently presented in the proposed container labels (blister and device labels) and carton labeling, the format for the expiration date is presented as “MM_YYYY” and “MMM YYYY,” respectively. 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 YYYYMMM-DD format, 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 slash or a hyphen be used to separate the portions of the expiration date.

Sponsor

The expiration date format has been updated to YYYY-MMM-DD. Refer to Section 1.14.1.1 for the updated (b) (4) DFL Carton and the 3-panel DFL Carton.

Quick Start Guide

31. We acknowledge your plan to add a “QUICK START GUIDE” to the blister package. For the purposes of the proposed nonprescription product, and to align with the DFL, retitle this labeling as “**Directions**” to help users quickly identify that this piece of paper

contains identical instructions to the DFL ***Directions***.

Sponsor

The titling of the QSG has been updated accordingly. Refer to Section 1.14.1.3 for the updated QSG.

Product Samples (received February 28, 2023)

32. On your product sample carton, the NDC number format appears to be incorrect (i.e., NDC 02-627-69547). Ensure the NDC number format appears correctly on the intend-to-market carton labeling.

Sponsor

Emergent apologizes for the error that was included in the Product Samples. The NDC number (69547-627-02) appears correctly on all of the intend-to-market labeling and will be presented correctly in any future production samples.

33. On your product sample DFL, there is a typographical error in the first and fourth bullets of DFL Directions Step 4, that state, “Wait 3-2 minutes..” and “...every 3-2 minutes....” Ensure the statements are revised to state “...2-3 minutes...” on all relevant aspects of labeling.

Sponsor

Emergent apologizes for the error that was included in the Product Samples. Emergent has confirmed that the statements read “Wait 2-3 minutes” on all relevant aspects of labeling and will be presented correctly in any future production samples.

34. On your product sample carton, there is a half-circle shaped perforation on the top of the back panel, which does not appear in the carton labeling submitted on February 21, 2023. Clarify whether the intend-to-market carton will include a perforation and the purpose of the perforation.

Sponsor

The intend-to-market Carton does include an “easy open” perforation on the back panel to aid the User in being able to quickly open the top of the Carton and remove the blister packs. The initial Carton proofs submitted in Seq 0626 included the perforation detail. It appears this detail was inadvertently excluded from the subsequent Carton proofs. Emergent will work with our Vendor to add the perforation details back in the next revision of the Carton proof which we will submit to FDA once available.

35. In the product sample blister, the nasal spray device was placed in the blister package such that the front device container label is not visible through the blister (i.e., the device label visible through the clear plastic is the back of the device). Clarify whether the intend-to-market product’s placement of the nasal spray device will allow the front device label to be viewed through the blister packaging.

Sponsor

We acknowledge the Agency's comment regarding the Product Samples. Emergent confirms that the current NARCAN® Nasal Spray (Rx) and the intend-to-market NARCAN® (OTC) are assembled and packaged so that the front device label is visible through the Blister.

36. In the product sample blister, the QSG packaged inside the blister package is inconspicuous, thus, users may not realize that the folded paper contains directions. Add the statement, "Unfold for Directions" in prominent text such that it appears on both sides of the folded QSG. Note that you may need to relocate the barcode on the QSG to implement this recommendation.

Sponsor

The statement "Unfold for Directions" has been added in prominent text so that it appears on both side of the folded QSG. Refer to Section 1.14.1.3 for the updated QSG.

37. On your product sample QSG, the text on Step 3 bullet 1 is difficult to read because it appears directly on the fold line of the paper. We are concerned users may not see the instruction to call 911 clearly. Revise the header (b) (4) to read "Step 3: Call 911" to help mitigate this risk.

Sponsor

Step 3 of the QSG has been updated accordingly. Refer to Section 1.14.1.3 for the updated QSG.

38. Also, consider if minor modifications can be made to placement of the Directions on the paper such that the text in this bullet is not directly on the fold line. Ensure any such modifications do not create similar risks for other text on the QSG.

Sponsor

The sub-heading of Step 3 has been shifted up slightly to move it away from being directly on the fold line. Refer to Section 1.14.1.3 for the updated QSG.

FDA Comment (March 21, 2023)**Sponsor response in italics (March 24, 2023)****Principal Display Panel and Side Panels**

1. Refer to the graphic image on the side panel of the carton and Directions leaflet that shows the correct hand and finger position for handling the nasal spray device. As currently presented, it is difficult to determine (b) (4)

 - a. Revise your image to clearly depict the entire hand, for example, by aligning more closely with the figure from step 2 of the prescription Narcan Nasal Spray carton and/or by zooming out so all fingers and entire hand are displayed.
 - b. Additionally, revise the labeling of the graphic image so that the words “Nozzle” and “Plunger” are directly next to the line pointing to each component rather than under the line (similar to how the components are labeled in the figure from step 2 of the prescription Narcan Nasal Spray carton).
 - c. Revise the image on the Directions leaflet so that the color of the plunger is consistent with the color of the actual nasal spray device (i.e., pink/red).

Sponsor

- a. *As recommended, Emergent has updated the previously provided graphic image by zooming out so that all fingers, the entire hand, and wrist are now displayed. To accommodate this request and those provided in #2 and #3, Emergent has moved this graphic image to the opposite side panel. Refer to Section 1.14.1.1 for the revised carton.*
 - b. *As recommended, Emergent has updated the graphic image so that the words “Nozzle” and “Plunger” are directly next to the line pointing to each component. Refer to Section 1.14.1.1 for the revised carton.*
 - c. *As recommended, Emergent has updated the graphic image on the Directions leaflet so that the color of the actual nasal spray device (i.e., pink/red) is visible. Refer to Section 1.14.1.3 for the revised leaflet.*
2. We acknowledge the side panel includes the statement, “For use in the nose only;” however, to further promote the correct route of administration, add this statement to the principal display panel (PDP) of the carton and increase the font size of the statement on the side panel.

Sponsor

The statement “For use in the nose only” has been added to the principal display panel (PDP). Additionally, as requested, this same statement that appears on the side panel has been increased in font size. Refer to Section 1.14.1.1 for the revised carton.

3. We acknowledge the (b) (4) section includes the statements (b) (4) (b) (4) however, to further minimize the risk of confusion regarding the number of doses in each device, add these statements to the PDP of the carton or to the side panel nearby the graphic image demonstrating hand/finger position on the nasal spray device.

Sponsor

The three device statements that were previously provided under the (b) (4) (b) (4) section have been removed and added to the side panel adjacent to the graphic image demonstrating hand/finger position on the nasal spray device.

Per an email clarification received on 22 March 2023, the three statements have been revised to read as follows:

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

Refer to Section 1.14.1.1 for the revised carton. These three device statements have also been updated accordingly in the blister and quick start guide. Refer to Section 1.14.1.1 and Section 1.14.1.3, respectively for the revised blister label and quick start guide.

4. It appears that the letter height of the net quantity statement is less than one-eighth inch. Increase the type size of the net quantity statement so that the letter height is greater than one-eighth inch, per 21 CFR 201.62(h)(2).

Sponsor

The letter height of the net quantity statement has been increased to comply with 21 CFR 201.62(h)(2). Refer to Section 1.14.1.1 for the revised carton.

5. Modify the statement (b) (4) to include “when used as directed” so that it reads “Effective when used as directed”.

Sponsor

Emergent acknowledges the Agency’s request to add a disclaimer with the use of a statement (b) (4). In place of adding this disclaimer, Emergent proposes to remove the (b) (4) portion of the claim so that it now only reads “Easy to Use”.

Refer to Section 1.14.1.1 for the revised carton.

6. We note that you modified the statement (b) (4)

Remove the statement (b) (4)

Sponsor

The statement (b) (4) has been removed from the carton. Refer to Section 1.14.1.1 for the revised carton.

7. Remove (b) (4) from the PDP statement (b) (4)

(b) (4)
Consider instead “Original Prescription Strength”.

Sponsor

The (b) (4) has been removed from the PDP statement (b) (4)
(b) (4) Refer to Section 1.14.1.1 for the revised carton.

8. Clarify whether the top perforation on the outer carton damages the Drug Facts label (DFL) when pulled/used.

Sponsor

Emergent confirms that the perforation provided on the top of the back panel of the carton doesn't damage the Drug Facts Label (DFL) when pulled/used. The carton artwork proof has been updated to demonstrate where the perforation is located. Refer to Section 1.14.1.1 for the revised carton.

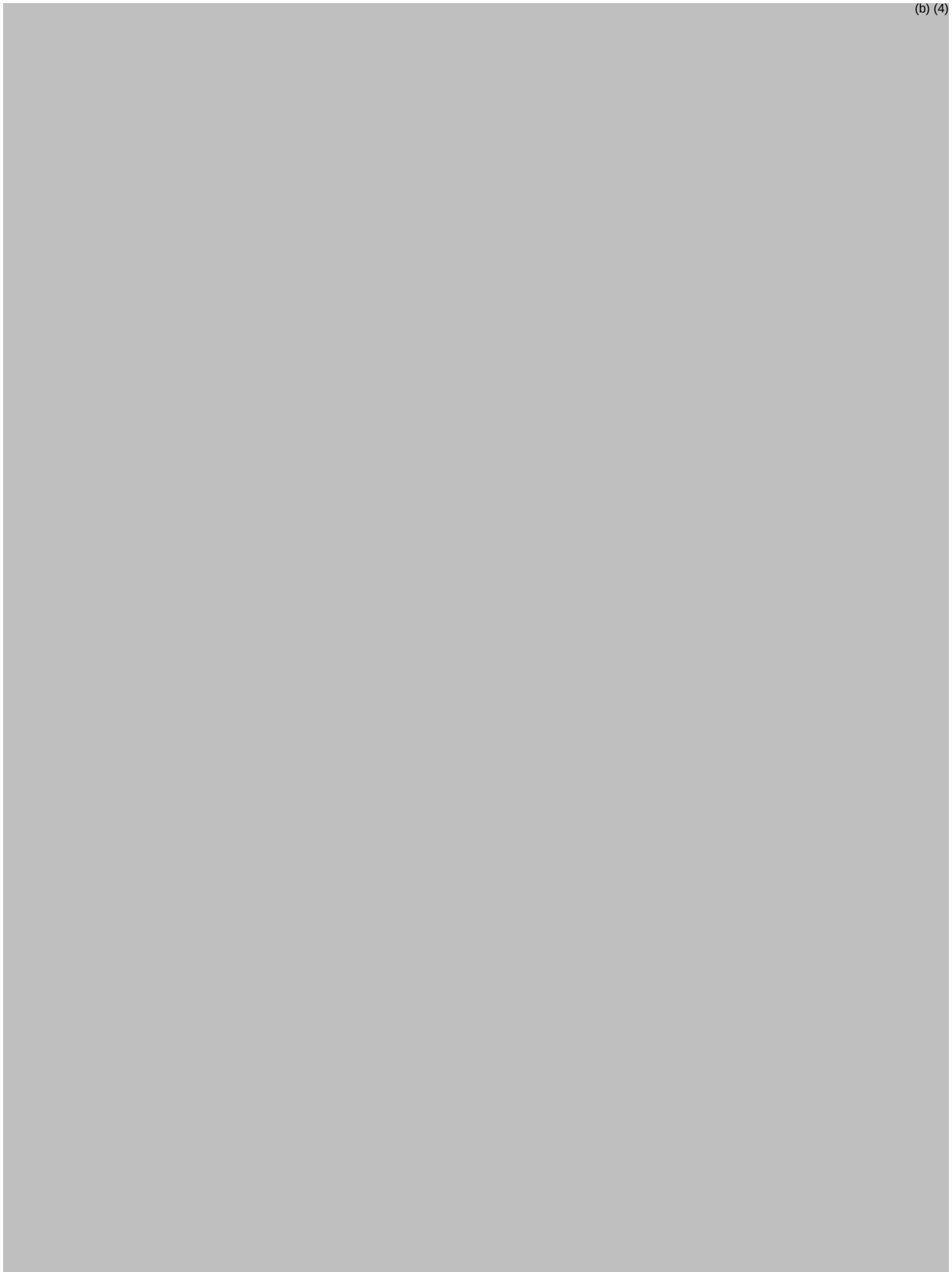
9. Information request regarding your proposed (b) (4)
(b) (4) labeling statement:

The high-level summary provided (b) (4)

(b) (4) labeling claim. More information is needed on the survey data and methods to support the claim. Provide a complete study report of the survey, including the full protocol explaining the objective(s), scope, design, sampling and analysis plans, response rate, demographics, validation method(s), survey items, number of participants, and other necessary details about the study conduct and outcomes, which should be submitted for review if you still wish to make the (b) (4)
(b) (4) claim.

(b) (4)

(b) (4)

Sponsor

Emergent acknowledges the Agency's feedback regarding the study design to support the

use of the proposed (b) (4) claim. Based on the feedback provided and the indication that the Agency may have additional concerns, Emergent proposes removing this claim from the proposed carton at this time. Should Emergent pursue in the future, we will plan to proactively engage the Agency for comprehensive advice to ensure alignment ahead of submitting a Prior Approval Supplement. Refer to Section 1.14.1.1 for the revised carton

Drug Facts Label

10. We acknowledge your addition (at our request) of temperature values (b) (4) for the “do not freeze” storage condition statement to create a range of temperatures for the consumer to store your drug (b) (4). The freezing point, however, may create confusion. Revise your labeling, both outer carton and blister, to present the storage conditions in a clear range of temperatures:
- store at 20 to 25°C (68 to 77°F)
 - do not freeze
 - avoid excessive heat above 40°C (104°F)

Sponsor

As recommended, Emergent has removed the temperature value for the “do not freeze” storage statement on the carton and blister label. Per an email clarification received on 23 March 2023, the “store at” storage statement has been revised to read “store at room temperature or refrigerated, between 2°C to 25°C (36°F to 77°F). Refer to Section 1.14.1.1 for the revised carton and blister label.

11. We note that the tamper evident statement occupies the 9th and 10th bullets of the “**Other information**” section. To improve its prominence, remove the statement, “● replace before the expiration date on the box,” and combine the last two bullets so that they read, “● the product is packaged in individually-sealed blisters. Do not use if the blister is open or torn, or if the device appears damaged.”

Sponsor

The “**Other information**” section of the DFL has been updated accordingly. Refer to Section 1.14.1.1 for the revised carton.

12. It appears that there is a typo in the DFL annotation file. The DFL annotation states that there are 150 characters per inch, which appears incorrect by our count. 21 CFR 201.66(d)(3) requires that DFL text contain no more 39 characters per linear inch. Update your DFL annotation with the correct number of characters per inch.

Sponsor

Emergent confirms there was an inadvertent typographical error in the value provided for characters per inch. The document has now been updated appropriately. Refer to Section 1.14.1.2 for the revised annotated DFL document.

13. We note that you use “disodium ethylenediaminetetraacetate” as an inactive ingredient. This nomenclature is not currently used by a nonprescription drug product. The shorter

“edetate disodium” is user-friendly and will save space. Under “**Inactive ingredients**” change “disodium ethylenediaminetetraacetate” to “edetate disodium”.

Sponsor

*The “**Inactive ingredients**” section has been updated accordingly. Refer to Section 1.14.1.1 for the revised carton.*

14. Remove the text, “**Drug Facts (continued)**,” prior to the arrows at the bottom of the DFL panels that were added to signal continuation of the DFL. This text is unnecessary, per 21 CFR 201.66(d)(5), and clutters the DFL.

Sponsor

*The text “**Drug Facts (continued)**” prior to the arrows at the bottom of the DFL panels that were added to signal continuation of the DFL have been removed. Refer to Section 1.14.1.1 for the revised carton.*

15. The Agency acknowledges your proposed outer carton layout that contains the DFL on (b) (4) and your justification. However, we lack evidence to support the (b) (4) (b) (4) format. The CONFER labeling comprehension study supports a DFL that presented information in the following order: **Active ingredient/Purpose, Uses, Directions, Warnings, Other information, Inactive ingredients, Questions?**. Provide labeling that follows the order of the DFL headings presented in your 3-panel presentation.

Sponsor

Emergent acknowledges the Agency’s request to implement the 3-panel presentation of the DFL headings. Therefore, the changes requested in this Information Request have only been implemented on the 3-panel version of the proposed OTC carton. Refer to Section 1.14.1.1 for the revised 3-panel DFL carton.

16. The Agency acknowledges your proposal to add (b) (4) to the **Uses** statement, “● to “revive” someone during an overdose from many prescription pain medications or street drugs such as heroin”. The term (b) (4) has not been tested for consumer understanding. Because the (b) (4) was not included in the **Uses** statement of the DFL prototype tested in FDA’s CONFER Label Comprehension Study (LCS), it is unknown how consumers will respond to this term if it is included in the **Uses** statement. Without support for such a statement from a well-designed and adequately powered LCS, there is no empirical evidence to support its inclusion in the **Uses** statement for Narcan specifically, or all future nonprescription naloxone products, more generally. Doing so would go beyond the scope of the CONFER LCS. Therefore, the Agency recommends adhering to the language in FDA’s naloxone DFL prototype as a sensible, data-driven approach.

If you would like to add this statement, or something similar, we recommend proposing a labeling prior approval supplement (PAS).

Sponsor

*Emergent acknowledges the Agency's feedback regarding the lack of data to support the inclusion of the word (b) (4) to the **Uses** statement to "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin". We would like to thank the Agency for their time and consideration of this proposal.*

FDA Comment (March 27, 2023)**Sponsor response in italics (March 28, 2023).**

1. We note (b) (4) has been removed from the principal display panel (PDP) statement (b) (4) as requested in the March 21, 2023, information request letter. Because (b) (4) the statement may lead to confusion in the marketplace. Remove the statement and consider instead "Original Prescription Strength".

Sponsor

As recommended, Emergent has updated the PDP to read "Original Prescription Strength". Refer to Section 1.14.1.1 for the revised retail and non-retail cartons.

2. Please refer to your March 08, 2023, response to comment #23 in our March 02, 2023, information request letter. We note that labeling in your March 24, 2023, submission was not updated with information to connect those who required naloxone to additional care. Please explain how you plan to implement your commitment to connect what you referred to as victims to care.

Sponsor

See 1.11.4 Multiple Module Information Amendment, dated March 28, 2023.

3. Because there is only one warning in the Drug Facts label, the heading for the "Warning" section must be singular, per 21 CFR 201.66(c)(5). Change the warning heading from "Warnings" to "Warning".

Sponsor

As recommended, Emergent has updated the Drug Facts label heading to read "Warning" to comply with 21 CFR 201.66 (c)(5). Refer to Section 1.14.1.1 for the revised retail and nonretail cartons.

Submitted Labeling		Dates Submitted
2-Count Outer Carton	(b) (4) (WITHDRAWN)	September 29, 2022 February 17, 2023 February 21, 2023
2-Count Outer Carton for Retail Distribution (retail)		September 29, 2022 March 08, 2023 March 24, 2023 March 28, 2023
2-Count Outer Carton-Not for Retail Distribution (i.e., non-retail)		September 29, 2022 March 24, 2023 March 28, 2023
Quick Start Guide (QSG)		February 17, 2023 March 08, 2023 March 24, 2023
Immediate Container (Blister Package) Label		September 29, 2022 March 08, 2023 March 24, 2023
Drug-Delivery Device Label		September 29, 2022 March 08, 2023

II. REVIEWER'S COMMENTS

A. Outer Carton Label

Sponsor proposed secondary container labeling for blister packages (two in each outer carton) that contain nasal spray devices. Two outer carton labeling files were submitted for final review, non-retail (i.e., labels intended for first responders, government agencies, and community-use organizations) and retail outer cartons. These outer cartons differ by background color, red (retail) vs white (non-retail), and the promotional statements on the retail carton (i.e., “Original Prescription Strength,” “Easy to Use,” and “Can Save a Life”) are replaced by a yellow box that contains the statements, “NOT FOR RESALE” and “FOR NON-RETAIL DISTRIBUTION.”

Retail Outer Carton

(b) (4)



Non-Retail Outer Carton

(b) (4)



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, Narcan, was reviewed by the Division of Medication Error Prevention and Analysis-2 (DMEPA 2), which found it to be acceptable (see the March 07, 2023, review by DMEPA 2). In their review, DMEPA 2 noted that naloxone hydrochloride injection was marketed under the proprietary name Narcan but did not anticipate medication errors from confusion between the previous injection dosage form and the proposed nonprescription nasal spray dosage form. The review also noted that adequate labeling for the nonprescription product will readily communicate the dosage form and the nasal route of administration to the user (see Reviewer Comments below for the multiple examples of labeling statements that refer to the dosage form and route of administration).

Narcan is displayed in either black color print that contrasts distinctly with a white flag in the center of the PDP (retail) or white color print that contrasts distinctly with a red flag in the center of the PDP (non-retail). The retail example is depicted below under the statement of identity (SOI). The proprietary name is the most prominent text on the PDP. Its letter height (about 0.47 in) appears almost three times larger than the letter height of the established name (about 0.14 in) and almost five times larger than the letter height of the pharmacological category (about 0.11 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 March 07, 2023, review by DMEPA 2).

b. Statement of Identity



The proposed statement of identity (SOI) was revised from “(naloxone HCl) nasal spray 4 mg OPIOID OVERDOSE RESCUE” to “Naloxone HCl Nasal Spray 4 mg Emergency Treatment of Opioid Overdose.” The SOI is immediately beneath the proprietary name.

The established name is displayed in black color print against a white background and the pharmacological category is displayed in white print against a dark maroon background.

Comment: This labeling statement is acceptable. The SOI now consists of an established name, “Naloxone HCl Nasal Spray 4 mg,” and the pharmacological category that 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 NDA labeling. The pharmacological category matches the purpose included in FDA's model DFL, which was tested during the CONFER study. Overall, the SOI meets the requirements found in § 201.61 and § 299.4.

c. **Net Quantity**



The net quantity numerical count was revised from “2 Single-Dose Devices” 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 now displayed in the lower left corner in white-color type against a red background, and it sits below and to the left of the graphic images of two nasal spray devices. Below the net quantity numerical count is the net content (fill) volume, “0.003 fl oz (0.1 mL) each.”

The prominence of the net quantity statement was increased to meet the requirements in 21 CFR 201.62(h)(2).

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”).

d. **For Use in nose only**



Sponsor added the statement “For use in the nose only” at the Agency’s recommendation to the PDP.

Comment: This labeling is acceptable. This statement further promotes the correct route of administration

e. Image Depicting Correct Hand and Finger Position



The above image was added to address user errors identified in the HFVS. This image includes labels that point to the nozzle and plunger. Five important statements accompany the graphic image:

- For use in 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

Comment: This labeling is acceptable. The statements that accompany the image above (see bullet list above) should be included in future labeling to ensure consistent, safe, and effective use of this drug product.

The images and statements were added to address the uniqueness of this drug product in the OTC market and to reduce user error (see DMEPA 2 reviews dated March 09, 2023 and March 15, 2023). 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.

f. Expiration Dating and Lot Number



A placeholder for the expiration date, YYYY-MMM-DD, and lot number is indicated on the bottom panel of the outer carton.

Comment: This labeling is acceptable. Sponsor 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).

g. **Place of Business of Distributor**

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

The place of business of distributor statement, “Distributed by Emergent Devices Inc. Plymouth Meeting, PA 19462 USA,” is contained at the bottom of a side panel.

Comment: This labeling is acceptable per 21 CFR 201.1

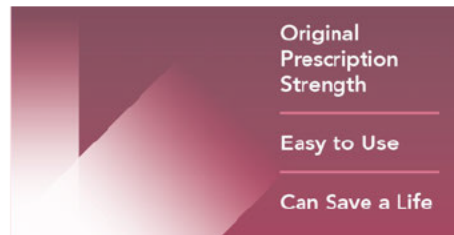
h. **NDC Number**

Distributed by Emergent Devices Inc.
Plymouth Meeting, PA 19462 USA
©2023 Emergent Devices Inc. Plymouth Meeting, PA.
All rights reserved.
NARCAN® is a registered trademark of Emergent Operations
Ireland Limited.
NDC 69547-627-02

Sponsor included the NDC number 69547-627-02, below the distributor address and copyright and trademark statements.

Comment: This labeling is acceptable it is the correct number in the correct format.

i. **Promotional Statements**



The outer carton intended for retail sale contains three promotional statements, “Original Prescription Strength,” “Easy to Use,” and “Can Save a Life.” These statements replace the previously proposed promotional statement (b) (4)

- The Agency requested sufficient data to support (b) (4)
(b) (4) And none were received.
- The Agency requested the removal (b) (4)
(b) (4)

- The Agency requested that Sponsor change (b) (4) to (b) (4) “Original Prescription Strength,” because (b) (4) the statement may lead to confusion in the marketplace.

The promotional statements (b) (4) were eventually modified to “Easy to Use.”

Comment: These promotional statements are acceptable. They are truthful and nonmisleading. Sponsor removed the promotional statements that were not supported by data.

“Easy to use” is not fully supported by the Sponsor’s HFVS study, as some use errors occurred. However, the statement “easy to use” may benefit consumers who may be reluctant to purchase a complicated product necessary to save a life; and the informative statements added to the PDP, QSG, and blister package should mitigate future user error, based upon participant feedback from the HFVS. 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 panel to the right of the PDP, with “**Active ingredient**” and “**Uses**”. The DFL then continues to the back panel, which contains only the “**Directions**” in its entirety. Finally, the DFL ends on the panel to the right of the “**Directions**.” This panel contains the “**Warning**,” “**Other information**,” “**Inactive ingredients**,” “**Questions?**”.

Comment: This labeling arrangement is acceptable. The DFL follows the order of the DFL headings tested in the “Comprehension for OTC naloxone” or CONFER labeling comprehension study. A (b) (4) format was proposed by Sponsor and considered by the Agency. (b) (4)

However, it was ultimately (b) (4) dismissed because the Agency lack evidence to support the (b) (4) format.

3-Panel Layout of DFL

Drug Facts (continued)
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 in the nose

- HOLD the nasal spray device with your thumb on the bottom of the plunger.
- INSERT the nozzle into other NOSTRIL.
- PRESS the plunger firmly to give the 1st dose.
- 1 nasal spray device contains 1 dose.

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 awakes up.
- It is safe to keep giving doses.

Step 5: STAY

- STAY until assistance arrives, even if the person wakes up.
- ONE another dose if the person becomes very sleepy again.
- You may need to give all the doses in the pack.

Drug Facts (continued)
Warning
When using this product some people may experience symptoms when they wake up, such as shivering, nausea, muscle, or feeling angry. This is to be expected.

Other information

- store at room temperature or refrigerated, between 2°C to 25°C (36°F to 77°F).
- do not freeze.
- avoid excessive heat above 40°C (104°F).
- protect from light.
- 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, edetate disodium, hydrochloric acid, sodium chloride, water.

Questions?
call 1-888-4NARCAN (1-888-462-7266) or go to www.narcan.com

Original Prescription Strength

Easy to Use

Can Save a Life

NARCAN®
Naloxone HCl Nasal Spray 4 mg
Emergency Treatment of Opioid Overdose

Safe to Use
Even if Opioids are Not Present

Designed to Rapidly Reverse the Effects of a Life-Threatening Opioid Emergency

For use in nose only

Read Directions Before Use

Drug Facts
Active ingredient (in each spray) Purpose
Naloxone hydrochloride 4 mg.....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.

2 Single-Dose Nasal Spray Devices
0.003 fl oz (0.1 mL) each

For use in nose only

a. Drug Facts Title

<i>Drug Facts</i>	
<i>Active ingredient (in each spray)</i>	<i>Purpose</i>
Naloxone hydrochloride 4 mg.....	Emergency treatment of opioid overdose

The Drug Facts title, “***Drug Facts***,” appears at the top of the DFL in italicized, boldface 9-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 “***Active ingredient (in each 0.1 mL)***” 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 4 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, 4 mg, per § 201.66(c)(2). The active ingredient is separated from the purpose by a leader. The appropriate pharmacological category is also found in the SOI, per § 201.66(c)(3).

c. Uses

<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

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

Comment: This labeling was developed for the FDA model DFL. It follows the contents and formatting of the model DFL. The Agency requested a minor formatting change to this section so that it meets regulation. The capitalized letters for the first word of each bulleted statement were changed to lower case.

d. Directions

FDA Model DFL

Directions

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

② GIVE

Step 2: **GIVE** 1st dose

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

③ CALL

Step 3: **CALL**

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

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:
 - **CONTINUE TO GIVE** doses every 2-3 minutes until the person wakes up
 - it is safe to keep giving doses

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

Proposed DFL for Narcan Nasal Spray

Drug Facts (continued)

Directions

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

② GIVE

Step 2: **GIVE 1st dose in the nose**

- **HOLD** the nasal spray device with your thumb on the bottom of the plunger
- **INSERT** the nozzle into either NOSTRIL
- **PRESS** the plunger firmly to give the 1st dose
- 1 nasal spray device contains 1 dose

③ CALL

Step 3: **CALL**

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

④ WATCH/GIVE

Step 4: **WATCH & GIVE**

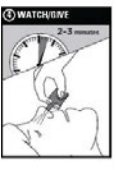
- **WAIT** 2-3 minutes after the 1st dose to give the medicine time to work
- if the person wakes up: Go to Step 5
- if the person does not wake up:
 - **CONTINUE TO GIVE** doses every 2-3 minutes until the person wakes up
 - it is safe to keep giving doses

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 between the 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 step 2). This change in instruction was also accompanied by two pictograms (outside of the DFL) showing a hand holding a device that looks like the Narcan Nasal Spray device into the nostril of an apparently unconscious person (see images for steps 2 and 4).

Step 2 (1 st Submission)	Step 2 (Revised Labeling)
 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	 Step 2: GIVE 1st dose in the nose • HOLD the nasal spray device with your thumb on the bottom of the plunger • INSERT the nozzle into either NOSTRIL • PRESS the plunger firmly to give the 1st dose • 1 nasal spray device contains 1 dose
Step 4 (1 st Submission)	Step 4 (Revised Labeling)
 Step 4: WATCH & GIVE • WAIT 2-3 minutes after the 1st dose to give the medicine time to work • if the person <u>wakes up</u>: Go to Step 5 • if the person does <u>not wake up</u>: • CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up • it is safe to keep giving doses	 Step 4: WATCH & GIVE • WAIT 2-3 minutes after the 1st dose to give the medicine time to work • if the person <u>wakes up</u>: Go to Step 5 • if the person does <u>not wake up</u>: • CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up • it is safe to keep giving doses

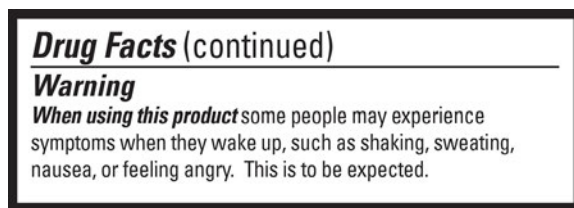
The 2nd bulleted statement in Step 2 was revised from “HOLD NARCAN OTC Nasal Spray with your thumb on the bottom of the plunger” to “HOLD the nasal spray device with your thumb on the bottom of the plunger.” This revision removed the proprietary name Narcan from the DFL.

Comment: This labeling is acceptable. The proposed “*Directions*” mostly follow the “*Directions*” in the model DFL. Step 2 was adapted to provide instructions specific to the Narcan nasal spray device. Four additional revisions to the text in Step were requested by the Agency:

- 1) To address a user error concern, the image for Step 2 and the bottom-half image of Step 4 was replaced with a pictogram from Narcan prescription labeling. A result from the HFVS suggests the pictogram image for Step 2 may have contributed to a use error related to device orientation, operation, and hand position on the device. The image tested in the HFVS was identical to the image from the FDA model DFL. The FDA model image was only intended to serve as a placeholder that would be replaced by images specific for each drug product.
- 2) The second bullet in Step 2 was revised to: “Insert the nozzle into either nostril” by removing the text “the tip of”. A use error in the HFVS occurred because a participant did not fully insert the nozzle into the nostril.
- 3) The heading of Step 2 was revised to, “Give 1st dose in the nose” to further promote the correct route of administration.
- 4) Finally, the statement, “1 nasal spray device contains 1 dose” was added to the last bullet in Step 2 to address errors that occurred in the HFVS due to confusion regarding the number of doses in each device.

The proprietary name, Narcan, was removed from the DFL. Proprietary names are not permitted in the DFL, per Over- The-Counter Human Drugs Labeling Requirements, published on March 17, 1999 (64 FR 13254 at 13268).

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 necessary during the testing of the model DFL.

This warnings 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. Even though the heading “**Warnings**” follows the labeling from FDA’s model DFL, it must be singular because there is only one warning, per 21 CFR 201.66(c)(5).

f. Keep out of reach of children

Sponsor initially included a “**Keep out of reach of children**” warning as set forth in 21 CFR 330.1(g) and 21 CFR 201.66(c)(5)(x). However, it was removed upon request by the Agency.

Comment: This removal is acceptable. Children may need to administer this drug product, therefore, nullifying the requirements in § 330.1(g) and § 201.66(c)(5)(x).

g. Other information

Other information

- store at room temperature or refrigerated, between 2°C to 25°C (36°F to 77°F)
 - do not freeze
 - avoid excessive heat above 40°C (104°F)
 - protect from light
 - the product is packaged in individually-sealed blisters.
- Do not use if the blister is open or torn, or if the device appears damaged.

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 his statement 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). To further improve the statement’s prominence, four statements were removed from the “**Other information**” section, including “replace before the expiration date on the box,” and the last two bulleted statements were combined into a single tamper evident statement.

h. Inactive ingredients

Inactive ingredients

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

This section lists the inactive ingredients in alphabetical order, per 21 CFR 201.66(c)(8), which include benzalkonium chloride, edetate disodium, hydrochloric acid, sodium chloride, water.

The nomenclature for disodium ethylenediaminetetraacetate was revised from “disodium ethylenediaminetetraacetate” to “edetate disodium” to align with other nonprescription drug labeling.

Comment: This labeling is acceptable and compliant with § 201.66(c)(8). Both “disodium ethylenediaminetetraacetate” and “edetate disodium” are listed in official compendia as inactive ingredients. However, disodium ethylenediaminetetraacetate is not currently used in approved nonprescription drug labeling, while the shorter edetate

disodium is found on approved nonprescription labeling. Revision to edetate disodium creates consistency with other approved labeling (i.e., user-friendly) and saves space.

i. Questions or comments?

Questions?

call 1-844-4NARCAN (1-844-462-7226) or go to www.narcan.com

This section includes the telephone number of a source to answer questions about the product call 1-844-4NARCAN (1-844-462-7226) or go to www.narcan.com.

Comment: This labeling is acceptable and compliant with 21 CFR 201.66(c)(9). The Agency recommended adding information to direct consumers to care under **Questions?**, such as the Substance Abuse and Mental Health Services Administration's (SAMHSA) National Helpline. Sponsor informed the Agency that they "will be working to engage cross-functional colleagues and various stakeholders to thoughtfully explore how this could be best implemented."

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).



a. Immediate Container Label

The information on the blister label was originally disorganized and cluttered. The Agency recommended the labeling revisions below to improve the organization of information on the blister label and clearly convey this information that includes drug product content, storage conditions, instruction to use in the nose only, and to not test nasal spray device before use.

Summary of FDA recommendations:

- To further promote the safe use of the proposed product related to the route of administration, increase the type size of the statement "For use in the nose only".

- Remove the parentheses around “(naloxone HCl)” and follow the established name used on the PDP. The displayed established name must be “Naloxone HCl Nasal Spray 4 mg”. It cannot be interrupted by parentheses and should include the strength.
- Remove the statement “Each dose contains 4 mg naloxone HCl (equivalent to 3.6 mg naloxone) in 0.1 mL nasal spray”. This statement is redundant because the strength is displayed in the established name and its removal will create space for statements that emphasize safe use and proper storage conditions.
- Replace the statement, “1 spray per device” with the following three statements “Do not test nasal spray device before use”, “1 device contains 1 dose of medicine” and “Device sprays 1 time only”. Ensure these statements are on separate lines and have the same prominence. Errors occurred in the HFVS due to confusion regarding the number of doses in each device.
- Remove the statement, “Excursions permitted up to 104 °F (40 °C)” and add a temperature value to define the statement “do not freeze”. The storage conditions on the blister package must match the conditions listed under “Other information” in the DFL.
- Use bullets to better organize the storage conditions statements.
- Replace the statement “Use for known or suspected opioid overdose in adults and children” with the Purpose/general pharmacological category to be consistent with the outer carton labeling.

1st Submission Blister Label

Revised Blister Label

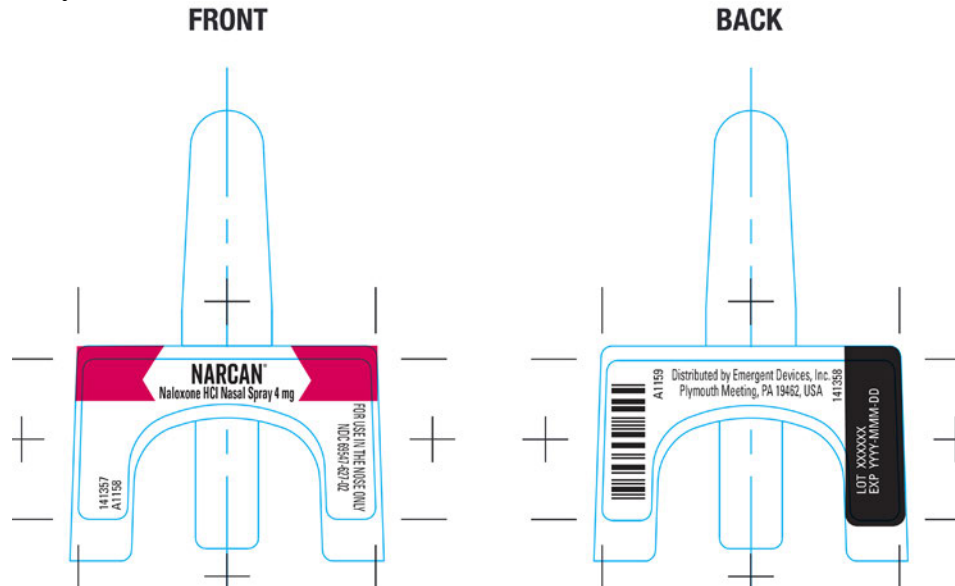


Sponsor informed the Agency that bar codes (e.g., UPC bar code on the blister label) are scanned by an on-line vision inspection systems during labeling operations to ensure the correct label is being applied every time. And that Narcan labeling is not produced on a dedicated packaging line and the bar code scanning provides quality control measures to prevent labeling errors.

Comment: This labeling is acceptable. The SOI is now properly constructed with the established name and pharmacological category. The blister label has been reorganized with

bulleted statements. The first four bulleted statement address user error concerns from the HFVS. The last three statements state the proper storage conditions.

C. Drug-Delivery Device Label



Sponsor proposed a simplistic label for the nasal spray device. It contains 7 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, Narcan
2. The established name, Naloxone HCl Nasal Spray 4 mg
3. Statement, “FOR USE IN THE NOSE ONLY”
4. NDC number, NDC 69547-627-02
5. Bar code
6. Distributor address, Distributed by Emergent Devices, Inc. Plymouth Meeting, PA 19462, USA
7. Expiration Dating and Lot Number

D. Quick Start Guide (QSG)

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

Quick Start Guide (QSG) Label

DIRECTIONS		
 Emergency Treatment of Opioid Overdose Important: • 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 		
 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	Unfold for Directions
 2 GIVE	Step 2: Give 1st dose in the nose • HOLD the nasal spray device with your thumb on the bottom of the plunger • INSERT the nozzle into either NOSTRIL • PRESS the plunger firmly to give the 1st dose • 1 nasal spray device contains 1 dose	Unfold for Directions 
 3 CALL	Step 3: Call 911 • CALL 911 immediately after giving the 1st dose	
 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: • CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up • it is safe to keep giving doses	
 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	
EMERGENT For opioid emergencies, call 911. For questions on NARCAN, call 1-844-4NARCAN (1-844-462-7226) or go to www.narcan.com. ©2023 Emergent Devices Inc. EMERGENT® and NARCAN® are registered trademarks of Emergent BioSolutions Inc. or its subsidiaries.		

Sponsor proposed including a Quick Start Guide (QSG) within each blister package and carton in their February 17 submission. 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, Sponsor made the following modifications.

- Retitled the top of the QSG 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 QSG.
- 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 QSG replicates 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 vertically), 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 Sponsor for the submitted Narcan Nasal Spray (naloxone hydrochloride 4 mg) labeling submitted in NDA 208411/S-006 and request final printed labeling with the following reminder.

Request that the sponsor submit final printed labeling (FPL) identical to the labels submitted on March 08, 2023, March 24, 2023, and March 28, 2023, as outlined in the table below.

Submitted Labeling	Date Submitted
2-Count Outer Carton for Retail Distribution (i.e., Retail)	March 28, 2023
2-Count Outer Carton Not for Retail Distribution (i.e., non-Retail)	March 28, 2023
Immediate Container (Blister Package) Label	March 24, 2023
Quick Start Guide (QSG)	March 24, 2023
Drug-Delivery Device Label	March 08, 2023

IV. SUBMITTED LABELING

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

5 Pages 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
03/28/2023 04:18:31 PM

KEVIN L LORICK
03/28/2023 04:25:20 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:	March 15, 2023
Requesting Office or Division:	Division of Nonprescription Drugs 1 (DNPDP1)
Application Type and Number:	NDA 208411/S-006
Product Name, Dosage Form, and Strength:	Narcan (naloxone hydrochloride) nasal spray, 4 mg per spray
Applicant/Sponsor Name:	Emergent Biosolutions
OSE RCM #:	2022-2688-1
DMEPA 2 Human Factors Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator (for labels & labeling evaluation):	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 Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised blister labeling, carton labeling, and Directions leaflet received on March 8, 2023 for Narcan. The Division of Nonprescription Drugs 1 (DNPDP1) requested that we review the revised blister labeling, carton labeling, and Directions leaflet for Narcan (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

^a Shah, M. Human Factors Study Report and Label and Labeling Review for Narcan (NDA 208411/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 MAR 09. OSE RCM No.: 2022-2688; 2022-2721.

2 CONCLUSION

The revised blister labeling is acceptable; however, the proposed carton labeling and Directions leaflet are unacceptable from a medication error perspective due to the following issues:

- The Applicant added a graphic image to show the correct hand and finger position on the device on the side panel of the carton labeling and top right corner of the Directions leaflet; however, the graphic image can be improved to decrease risk of wrong technique medication error.
- The Applicant added “For use in the nose only” to the side panel of the carton labeling; however, this statement can also be added to the principal display panel (PDP) of the carton labeling to increase the prominence of the correct route of administration.
- The Applicant added the statements, (b) (4)
[REDACTED] however, these statements can be added to the PDP or side panel of the carton labeling to further minimize the risk of confusion regarding the number of doses in each device.

3 RECOMMENDATIONS FOR EMERGENT BIOSOLUTIONS

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

A. Carton Labeling and Directions leaflet

1. Refer to the graphic image on the side panel of the carton and Directions leaflet that shows the correct hand and finger position for handling the nasal spray device. As currently presented, it is difficult to determine (b) (4)
[REDACTED]
 - i. Revise your image to clearly depict the entire hand, for example, by aligning more closely with the figure from step 2 of the prescription Narcan Nasal Spray carton and/or by zooming out so all fingers and entire hand are displayed.
 - ii. Additionally, revise the labeling of the graphic image so that the words “Nozzle” and “Plunger” are directly next to the line pointing to each component rather than under the line (similar to how the components are labeled in the figure from step 2 of the prescription Narcan Nasal Spray carton).
 - iii. Revise the image on the Directions leaflet so that the color of the plunger is consistent with the color of the actual nasal spray device (i.e., pink/red).
2. We acknowledge the side panel includes the statement, “For use in the nose only;” however, to further promote the correct route of administration, add this

statement to the principal display panel (PDP) of the carton and increase the font size of the statement on the side panel.

3. We acknowledge [REDACTED] (b) (4)
[REDACTED]
however, to further minimize the risk of confusion regarding the number of doses in each device, add these statements to the PDP of the carton or side panel nearby the graphic image demonstrating hand/finger position on the nasal spray device.

2 Pages 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/

MILLIE B SHAH
03/15/2023 04:02:23 PM

GRACE JONES
03/15/2023 05:07:07 PM

COLLEEN L LITTLE
03/15/2023 05:23:03 PM

LOLITA G STERRETT
03/15/2023 05:23:21 PM

CHI-MING TU
03/16/2023 11:20:24 AM

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:	March 9, 2023
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 208411/S-006
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength:	Narcan (naloxone hydrochloride) nasal spray, 4 mg per spray
Device Constituent:	Nasal Spray
Rx or OTC:	Prescription to Nonprescription Switch
Applicant Name:	Emergent Biosolutions
FDA Received Date:	September 29, 2022; November 4, 2022, November 23, 2022, December 9, 2022, December 22, 2022, January 4, 2023, February 17, 2023, February 21, 2023
OSE RCM #:	2022-2688; 2022-2721
DMEPA 2 Human Factors Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Safety Evaluator (for labels & labeling evaluation):	Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita White, PharmD
DMEPA 2 Deputy Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS
DMEPA 2 Director:	Danielle Harris, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and user interface (including labels and labeling, packaging, and device design) submitted under NDA 208411/S-006 for Narcan (naloxone hydrochloride) nasal spray, 4 mg. NDA 208411/S-006 proposes a full prescription (Rx) to nonprescription switch for Narcan (naloxone hydrochloride) nasal spray, 4 mg.

1.1 BACKGROUND

Narcan (naloxone hydrochloride) nasal spray, 4 mg, was approved on November 18, 2015 under NDA 208411 for intranasal administration of naloxone for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.^a

As communicated in a 2019 Federal Register Notice 84 (FR 8728), the Agency developed two versions of a model naloxone Drug Facts Label (DFL) (one for nasal spray and one for autoinjector) supported by a Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study to encourage naloxone sponsors to enter the nonprescription market and increase access to naloxone.^b The FDA model DFL directions include placeholders^c (e.g., image of device and Step 2 instructions on how to give a dose) 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-use HF validation study designed to evaluate whether the user interface^d can be used safely and effectively by intended users for the intended use under the expected environment(s) of use.^e

^a The Sponsor submitted a prior approval supplement for the 2 mg strength product on March 25, 2016, which was approved with restrictive labeling for subjects who may be at risk of opioid withdrawal, but the 2 mg strength was never marketed. On November 21, 2022, FDA also received a withdrawal request of the 2 mg dose under NDA 208411. As communicated in Federal Register Notice on February 10, 2023, the Agency withdrew the approval of the sNDA for Narcan nasal spray 2 mg. Information can be found at the following link to the Federal Register notice 88 FR 8873: [Federal Register :: Emergent Biosolutions Inc.; Withdrawal of Approval of a Supplemental New Drug Application for NARCAN \(Naloxone Hydrochloride\) Nasal Spray, 2 Milligrams/0.1 Milliliter.](#)

^b 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>.

^c To reflect the two approved forms of naloxone available in consumer-friendly format at the time the research was designed (nasal spray and auto-injector), two DFLs were prepared, with pictograms for each dosage form. The DFL section related to the particular dosage form was included as a placeholder and was not robustly tested as part of the study. The remaining content was identical for both DFL versions for naloxone.

^d The term *user interface* refers to all components of the product with which the user interacts, including the device constituent part(s) of the product and any associated controls and displays, as well as product labels, labeling, and packaging.

Drug Facts

Active ingredient (in each XX)

Naloxone hydrochloride X mg.....Emergency treatment of opioid overdose

Purpose

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

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

2 GIVE



Step 2: GIVE 1st dose

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

3 CALL



Step 3: CALL

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

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:
 - **CONTINUE TO GIVE** doses every 2-3 minutes until the person wakes up
 - it is safe to keep giving doses

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

^e 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>

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Figure 1. FDA Model Naloxone Nasal Spray DFL

1.2 PRODUCT INFORMATION

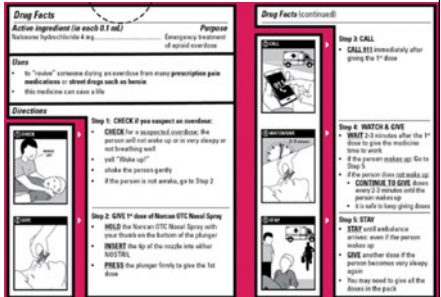
On September 29, 2022, the Applicant submitted efficacy supplement 006 that proposes to change the marketing status of Narcan nasal spray, 4 mg, from prescription (Rx) to nonprescription/over-the-counter (OTC) (i.e., a full Rx-to-OTC switch). The proposed nonprescription Narcan nasal spray device (see Figure 2) is unchanged compared with the Rx Narcan nasal spray device. However, the proposed nonprescription container labels and carton labeling have changed (see Packaging row in Table 1). The Prescribing Information (PI) has been used to inform the Drug Facts Label (DFL) on the carton labeling, the proposed nonprescription blister packaging no longer contains a Quick Start Guide (QSG). Additionally, the proposed carton labeling has been redesigned such that the nonprescription Narcan carton's DFL "Directions" span over 2 different panels that are viewable after rotating the carton box whereas Rx Narcan carton has a flap that opens up to instructions on the same viewable surface on the front of the carton (see Packaging row in Table 1).

We note that Steps 1, 3, 4, and 5 of the proposed nonprescription Narcan nasal spray DFL directions are identical to the DFL directions evaluated in CONFER in terms of both figures and text (see Figure 1 and Figure 3). Step 2 of the proposed Narcan nasal spray DFL directions includes product-specific changes to the text compared to the DFL directions evaluated in CONFER. We also note that the "Directions" section of the proposed nonprescription Narcan DFL is divided across two panels of the Narcan carton. Specifically, the back panel of the carton depicts Steps 1 and 2 of the directions, whereas the side panel depicts Steps 3, 4, and 5.

Table 1 presents relevant product information for nonprescription Narcan (naloxone HCl) nasal spray that Emergent Biosolutions submitted on September 29, 2022 along with a comparison to the relevant product characteristics for Rx Narcan nasal spray.

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

	Nonprescription Narcan nasal spray	Rx Narcan nasal spray
Initial Approval Date	Not applicable	November 18, 2015
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	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Route of Administration	nasal	

Dosage Form	Nasal spray	
Strength	4 mg per spray	2 mg per spray; 4 mg per spray ^f
Dose and Frequency	4 mg once, may repeat every 2-3 minutes until person wakes up (See DFL Figure 3)	
How Supplied	1 single dose nasal spray device packaged in individually sealed blister 2 blisters per carton	
Storage	- store below 25°C (77°F) - do not freeze - avoid excessive heat above 40°C (104°F) - protect from light	
Device Constituent	Aptar Nasal spray (see Figure 2)	
Packaging & User Interface differences between proposed OTC product and Rx product	DFL directions span over 2 different panels that are viewable after rotating the carton box  Quick start guide is <u>not</u> packaged in each blister package	Flap on the front of the carton that opens up to instructions on the same viewable surface  Each blister package contains a quick start guide with instructions

^f The Sponsor submitted a prior approval supplement for the 2 mg strength product on March 25, 2016, which was approved with restrictive labeling for subjects who may be at risk of opioid withdrawal, but the 2 mg strength was never marketed. On November 21, 2022, FDA also received a withdrawal request of the 2 mg dose under NDA 208411. As communicated in Federal Register Notice on February 10, 2023, the Agency withdrew the approval of the sNDA for Narcan nasal spray 2 mg. Information can be found at the following link to the Federal Register notice 88 FR 8873: [Federal Register :: Emergent Biosolutions Inc.; Withdrawal of Approval of a Supplemental New Drug Application for NARCAN \(Naloxone Hydrochloride\) Nasal Spray, 2 Milligrams/0.1 Milliliter](https://www.federalregister.gov/documents/2023/02/10/2023-0210-withdrawal-of-approval-of-a-supplemental-new-drug-application-for-narcan-naloxone-hydrochloride-nasal-spray-2-milligrams-0.1-milliliter)

^g University of Rochester Narcan emergency overdose treatment added to University's AED cabinets. July 24, 2018. Available from: <https://www.rochester.edu/newscenter/narcan-added-to-universitys-aed-cabinets-329492/>. Accessed December 18, 2022.

	(b) (4)	
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.	Adolescents and adult lay people (friends, family, bystanders, caregivers) without medical training, first responders, healthcare professionals who may encounter someone experiencing an opioid overdose
Intended Use Environment	Community settings where opioids may be present	Community and healthcare settings where opioids may be present

^h DailyMed Narcan nasal spray Page. DailyMed November 1, 2020. Available from: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=784a0e98-c2d6-f845-e053-2991aa0ac4b4&type=display>. Accessed December 16, 2022.

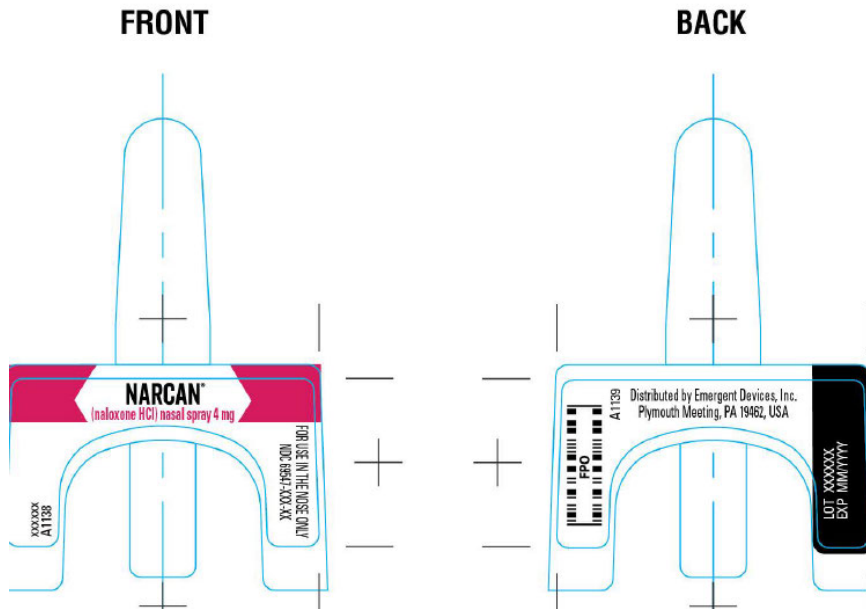


Figure 2: Narcan nasal spray device, 4 mg

Drug Facts		Drug Facts (continued)	
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		Step 3: CALL CALL 911 immediately after giving the 1st dose	
Directions ① CHECK WAKE UP! 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		③ WATCH/GIVE 2-3 minutes	
② GIVE 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		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	
		④ 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	

Figure 3: Proposed Narcan nasal spray DFL Directions, back panel (left), side panel (right)

1.3 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- We previously reviewed the results of the HF validation study for the Rx Narcan nasal spray under NDA 208411. Our review concluded that the HF validation study results supported safe and effective use of the then proposed Rx Narcan nasal spray user interface by the intended users in the intended use environments.ⁱ
- On April 25, 2016, during the pre-IND meeting with the Applicant under IND 130200, we provided responses to questions regarding HF data/information needed to support the proposed market conversion from Rx to nonprescription.^j
- On February 27, 2017, during the Type B meeting with the Applicant under IND 130200, we provided a response to a question regarding HF data/information needed to support the proposed market conversion from Rx to nonprescription.^k
- On May 9, 2019, during the Type B End of Phase 2 Meeting with the Applicant under IND 130200, we provided a response to a question regarding the Applicant's proposal to leverage label comprehension data from the model DFL. We responded that the Applicant needs to validate the proposed DFL in a HF study. We recommended the Applicant conduct a comprehensive use-related risk analysis to inform the design of the HF validation study protocol. We recommended the Applicant submit the HF validation study protocol for feedback before commencing the study.^l
- The Applicant did not submit the HF validation study protocol for review prior to conducting the HF validation study to support the proposed market conversion from Rx to nonprescription.
- On September 29, 2022, the Applicant submitted NDA 208411/S-006 to seek approval for the full prescription to nonprescription switch of Narcan nasal spray, 4 mg, which included the results of a simulated-use HF Validation Study. This submission is the subject of this review.

2 MATERIALS REVIEWED

ⁱ Shah, M. Human Factors, Label, and Labeling Review for Narcan (NDA 208411). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 03. RCM No.: 2015-1531, 2015-1532.

^j Peacock, C. Pre-IND Meeting Minutes for Narcan (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, ONPD, DNPD1 (US); 2016 June 03. IND 130200.

^k Murry, K. Type B Meeting Minutes for Narcan (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, ONPD, DNPD1 (US); 2017 Mar 28. IND 130200.

^l Stewart, S. Type B Meeting Minutes for Narcan (naloxone hydrochloride) nasal spray. Silver Spring (MD): FDA, CDER, ONPD, DNPD1 (US); 2020 APR 03. IND 130200.

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
Applicant's Use-Related Risk Analysis (URRA) and Background Information on Human Factors Engineering (HFE) Process	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 HF validation study methodology.

Summary of Study Design/Methodology

Table 3 presents a summary of the HF validation study design. See Appendix A and B for more details on the study design.

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

Study Design Elements	Details from Applicant's HF Validation Study Results Report
Participants	71 participants^m in the following user groups: • Adult General Population (all comers), age 18 or older (n=18) • 22.2% Limited literacy (LL) • Adolescent, ages 15-17 (n=19) • 36.8% LL • Adult Opioid Users, age 18 or older (n =16) • 31.3% LL • Adult Opioid User Associates, age 18 or older (n=18) • 27.8% LL

^m Based on the Applicant's information request response dated December 9, 2022, 3 participants (b) (6) verbally described tasks instead of performing tasks. Therefore, the HF validation study includes simulated use performance data for 68 participants.

Training	Participants were untrained, but given an unlimited familiarization time period (see “Sequence of Study” row below)
Test Environment	In order to help simulate the stress and distractions found in a real-world environment, a television in the interviewing room was playing a movie in the background.
Test Materials	All participants were provided with a mock nonprescription product in carton with a DFL. Inside the carton were two blister-packaged units each containing one Narcan nasal spray, which contained water or saline solution only. The nasal spray device was identical to the Narcan nasal spray device that is currently manufactured and distributed.
Sequence of Study	• Pre-interview activities ○ Consumers who met initial eligibility criteria scheduled an appointment to complete a brief literacy assessment remotely via audio/video interface with a trained interviewer prior to scheduling an interview at the site • Rapid Estimate of Adult Literacy in Medicine (REALM)/REALM-Teen Test administered via audio/video interface to characterize participants’ health literacy • Rescreening to verify eligibility • Informed consent • Recording initiated • The participant was told that their task was to review the product labeling and to then use the provided medicine and product directions to treat a family member, represented by a mannequin, who had overdosed with pain medication. • Participants were allowed as much time as needed to review the mock nonprescription product and its DFL, and then were asked by a trained interviewer to demonstrate administration of the product in a simulated overdose situation ○ Moderator script includes the following: “If you’d like to you can also verbally tell me what you are doing or would do as you complete the demonstration.” • Questions were asked to assess comprehension of any directions for use that the participant failed to perform correctly (or in the case of pre-specified tasks, to clearly articulate the procedure verbally) in the demonstration portion of the interview. Per the Applicant, this explanation by participants enabled the assessment of whether the participant comprehended the instruction, and only failed to demonstrate the task correctly during the demonstration portion due to limitations of the simulation process. • Debriefing questions:

	o The interviewer next asked debriefing questions about any steps/actions that were performed incorrectly or not comprehended
Data Collection and Analysis	• Interviews were recorded • The interviewer scored each performance in real time as it was demonstrated as “correct”, “acceptable”, “incorrect”, or “could not be observed” • For selected steps, if participants did not perform the step or performed it incompletely, but clearly articulated the procedure they would intend to follow, their performance may have been scored as acceptable. • Responses to debriefing questions were also collected • After completion of interviews, all recordings were transcribed, and coded verbatim responses were used for analysis of study endpoints

3.1 DMEPA’S DISCUSSION AND EVALUATION OF HF VALIDATION STUDY METHODOLOGY

The Applicant did not submit the HF validation study protocol to the Agency for review and guidance prior to conducting the HF validation study. Based on our review of the HF validation study results report, we identified the following issues with the study methodology, data collection, and results report.

User Groups

Pediatric Users:

The Applicant states that the intended users of the product include adolescents and adults. The HF validation study included pediatric participants 15 to 17 years old; however, 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.ⁿ Thus, we generally recommend the HF validation study include pediatric participants 10 to 17 years old. This study method does not preclude our review of the HF validation study results, but because pediatric users between 10 to 14 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.

Limited Literacy Users:

ⁿ 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.

The HF validation study did not include at least 30% limited literacy participants in 2 of the 4 user groups (the Adult General Population (22.2% limited literacy participants) and Adult Opioid User Associates (27.8%) user groups); however, 30% of the total combined participants were limited literacy participants. For HF testing in nonprescription products, we generally recommend that each distinct user group include 30% limited literacy participants in the study to ensure adequate representation of the intended users. The distribution of limited literacy participants does not preclude our review of the HF validation study results but may have introduced bias with tendency towards positive performance in the affected user groups (i.e., Adult General Population and Adult Opioid User Associates), which should be taken into consideration when interpreting the study results. We have informed the review team of this study limitation.

Familiarization Period

All participants in the HF validation study were allowed as much time as needed to review the product labeling before demonstrating use of the product in a simulated overdose situation (i.e., “familiarization period”). While we acknowledge that some users may have the opportunity to familiarize themselves with the product labeling before administration of the product, some users may have limited time to interact with the product labeling when encountering an opioid overdose emergency situation during actual use. Thus, we generally recommend that, at a minimum, some user groups in the HF validation study simulate a scenario that is representative of a high-risk actual use event (e.g., no familiarization prior to encountering overdose emergency). Although the familiarization period used in the study does not preclude our review of the HF validation study results, the data collected does not capture the highest-risk use scenario. We have informed the review team of this study limitation.

Leading Language and Think Aloud Method

Participants in the HF validation study were instructed by the study moderator to, “Please use the package directions” 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.

The moderator script included language for participants to verbally state what they are doing or what they would do as they complete the simulated use scenario. Instructing participants to think aloud is not representative of actual use, as it interrupts the natural sequence and flow of events. Additionally, it may confound the results by affecting how the participant completes the task. Thus, we generally recommend against instructing participants to use a think aloud method during the simulated use scenario in the HF validation study.

Although the leading language and think aloud method do not preclude our review of the HF validation study results, such methods may have introduced a bias towards positive performance, which should be taken into consideration when interpreting the HF validation study results. We have informed the review team of these study limitations.

Test Materials

The carton labeling evaluated in the HF validation study is different from the intend-to-market carton labeling submitted. Most notably, some changes to the intend-to-market carton labeling are in response to the HF validation study results. The carton labeling tested in the HF study displays Steps 3, 4, and 5 of the DFL Directions on the back panel; whereas the intend-to-market carton labeling has been modified post-HF validation such that Steps 1 and 2 of the DFL Directions are on the back panel (see Table 4~~Error! Reference source not found.~~~~Error! Reference source not found.~~). Some changes appear to be cosmetic in nature (e.g., colors, branding, etc.); while other changes to the principal display panel (PDP) include different statements, relocation of important statements, and/or changes to font size of important statements (see Table 5). We generally expect the HF validation study evaluate the intend-to-market user interface, including labels and labeling. Changes to formatting, layout, text size, color, etc. may impact users' performance of critical tasks. Thus, we sent an information request (IR) for the Applicant's rationale for the differences and justification for why the differences in carton labeling do not warrant additional HF validation study data (See Appendix C). Our evaluation of the Applicant's IR response and the post-validation carton labeling changes are provided in Table 7 below.

Table 4. "Mock" Carton tested in HF Validation Study and Intend-to-Market Carton submitted

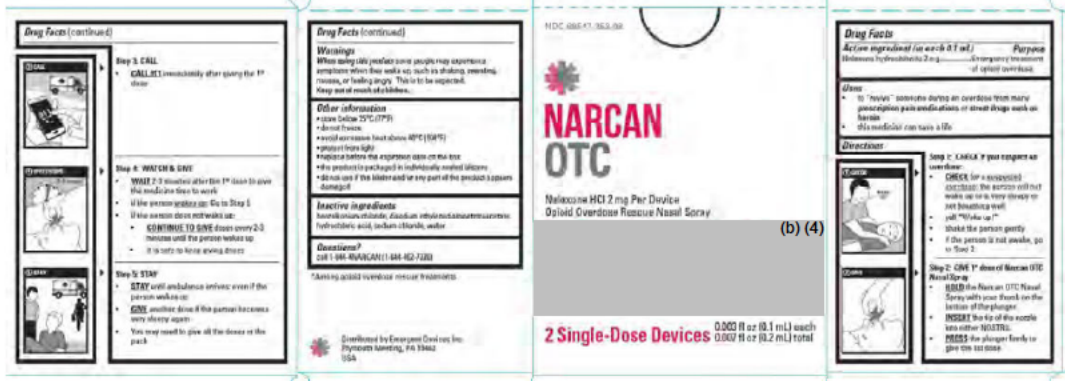
"Mock" Nonprescription Carton Tested in HF Validation Study			
Back panel	Left side panel	Principal Display Panel (PDP)	Right side panel
 The figure displays a side-by-side comparison of two Narcan OTC carton designs. The left design, labeled 'Mock', shows the back panel with 'Drug Facts (continued)' and 'Directions' starting with Step 3: 'CALL 911 immediately after giving the 1st dose'. The right design, labeled 'Proposed Intend-to-Market', shows the back panel with 'Drug Facts' and 'Directions' starting with Step 1: 'CHECK if you suspect an overdose'. The Principal Display Panel (PDP) for both designs is shown in the center, featuring the Narcan OTC logo, the text 'Naloxone HCl 2 mg Per Device', 'Oxycodone Overdose Rescue Nasal Spray', and '2 Single-Dose Devices'. The PDP also includes a warning: '0.002 fl oz (0.1 mL) each 0.002 fl oz (0.2 mL) total'. The right design includes a small illustration of a person using the device, labeled '(b) (4)'.			
Proposed Intend-to-Market Nonprescription Carton submitted September 29, 2022			
Back panel	Left side panel	Principal Display Panel (PDP)	Right side panel



Table 5. Principal Display Panel (PDP) Carton Labeling Differences between HF Validation Study “Mock” Carton and Intend-to-Market Carton Labeling

Principal Display Panel (PDP) Evaluated in HF Validation Study	NDC 69547-353-08  NARCAN OTC Naloxone HCl 4 mg Per Device Opioid Overdose Reversal Nasal Spray (b) (4) 2 Single-Dose Devices 0.003 fl oz (0.1 mL) each 0.007 fl oz (0.2 mL) total
--	--

Intend-to-Market PDP	
Applicant's Identified Differences	• Updated the PDP to a more consumer friendly packaging feel, including the following: ○ Updated primary color from white to pink ○ Added a graphic of the nasal sprayer ○ Updated the indication statement and product claims based on language widely understood by consumers (i.e., based on results from market research) • Updated the statement of identity to comply with 21 CFR 201.61(b) and the <i>Draft FDA Guidance for Industry: Statement of Identity and Strength-Content and Format of Labeling for Human Nonprescription Drug Products (September 2022)</i> • Updated the net contents statement to comply with 21 CFR 201.62(a), (c) and (d) • Moved the National Drug Code from the PDP to the side panel
DMEPA's Assessment	The Applicant did not identify the following differences on the PDP of the intend-to-market carton labeling when compared to carton labeling evaluated in the HF validation study: • Change in font color from pink to white • Relocation and decreased font size of the statement, "2 Single-Dose Devices"

Data Collection and Analysis

The Applicant scored participant performance as "correct", "acceptable", "incorrect", or "could not be observed" and reported the study results using quantitative thresholds for success (e.g., % acceptable). However, HF validation studies are not intended to provide quantitative

information on primary, secondary, or composite outcomes. We generally recommend that HF validation studies are designed to generate qualitative data, using information analyzed from every occurrence of use error^o, use difficulty^p, and close call^q. We expect direct observations, root cause analysis, and subjective feedback from the study to provide valuable qualitative data that can identify vulnerabilities in the user interface and inform appropriate mitigations. The HF validation study report did not include the complete qualitative data sets, including root cause analysis and participants' subjective feedback for all use errors. Additionally, data on close calls and use difficulties was not submitted. Thus, we sent information requests to obtain this information (See Appendix C).

Additionally, the Applicant scored performance as acceptable for instances where participants did not perform the step or performed it incompletely, but clearly articulated the procedure they would intend to follow (i.e., the participant answers a related knowledge-based question correctly). We expect instances where participants fail to perform the step or perform it incompletely to be categorized as either use errors, close calls, or use difficulties; and participants' subjective feedback, the Applicant's root cause analysis, and proposed risk mitigation strategies reported in the HF results study report. Thus, we sent IRs to request this information for our review. The Applicant responded to our IR on December 9, 2022 (See Appendix C).

Tasks

Lastly, the Applicant did not collect data for all tasks the user needs to complete or understand as part of the use sequence:

- opening the carton
- opening the blister
- understanding the product's storage conditions

Given that the proposed carton and blister appear similar to the prescription Narcan product and that understanding the product's storage conditions are not unique to this product,

^o Use error is defined as user action or lack of action that was different from that expected by the manufacturer and caused a result that (1) was different from the result expected by the user and (2) was not caused solely by device failure and (3) did or could result in harm. See Applying Human Factors and Usability Engineering to Medical Devices, Guidance for Industry and Food and Drug Administration Staff. 2016. Available from: <http://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf>.

^p Use difficulty is defined as a difficulty, or struggle, encountered during use, which is typically momentary and overcome by the user. See ANSI/AAMI/IEC 62366-1:2015/(R)2021+AMD1:2020 Medical devices—Part 1: Application of usability engineering to medical devices + Amendment 1

^q Close call is defined as instances in which a user has difficulty or makes a use error that could result in harm, but the user takes an action to "recover" and prevents the harm from occurring. See Applying Human Factors and Usability Engineering to Medical Devices, Guidance for Industry and Food and Drug Administration Staff. 2016. Available from: <http://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf>.

absence of HF validation study data for these tasks does not preclude our review of the HF validation study results.

4 RESULTS AND ANALYSES

We evaluated the HF validation study results submitted by the Applicant for Steps 1 through 5 of the DFL Directions. This section provides our analysis of the results contained in the HF validation study results report and of the qualitative data provided in the Applicant's responses to our IRs (see Appendix C).

As discussed in Section 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 HF study. In this case, because the Applicant has elected to use the model DFL, we have focused our detailed analysis of the HF study 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 discussion on the results for Steps 1 and 5 is provided in Section 4.2 below.

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 6 below.

Table 6. High-level Summary of HF Validation Study Results for Steps 2, 3, and 4

71 participants* in the following user groups: General Population: Adult General Population (all comers), age 18 or older (n=18); Adolescent: Adolescent, ages 15-17 (n=19); Opioid User: Adult Opioid Users, age 18 or older (n=16); Opioid User Associates: Adult Opioid User Associates, age 18 or older (n=18)			
	Number of Use Errors (UE)	Number of Close Calls (CC)	Number of Use Difficulties (UD)
Step 2: GIVE 1 st dose of Narcan OTC Nasal Spray	5 UE: - Adolescent (n=3) - Opioid User (n=1) - Opioid User Associate (n=1)	2 CC: - Adolescent (n=1) - Opioid User Associate (n=1)	9 UD: - General Population (n=2) - Adolescent (n=2) - Opioid User (n=3) - Opioid User Associate (n=2)
Step 3: Call 911	10 UE: - General Population (n=2) - Adolescent (n=1) - Opioid User (n=3) - Opioid User Associate (n=4)	5 CC: - General Population (n=4) - Opioid User (n=1)	0 UD
Step 4: Watch & Give	12 UE: - General Population (n=1) - Adolescent (n=5) - Opioid User (n=2) - Opioid User Associate (n=4)	0 CC	0 UD

*3 participants verbally described tasks instead of performing tasks. Therefore, the HF validation study includes simulated use performance data for 68 participants

Table 7 further describes the study results for Steps 2, 3, and 4, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

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Table 7. HF Validation Study Results and Analysis – Steps 2, 3 and 4

Legend: NL: Normal Literacy Participant, LL: Limited Literacy Participant, UE: Use Error, CC: Close Call, UD: Use Difficulty, RCA: Root Cause Analysis				
1.	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			
	Information Supplied by Applicant			
	Total number of UE, CC, UD			
	UE (n=5), CC (n=2), UD (n=9)			
	Use-Related Event	Participant Type, Literacy, and ID number	Applicant's RCA and Participants' Subjective Feedback (if available)	Applicant's Discussion of risk mitigation strategies
	UE: Turned the mannequin to the side, which blocked the moderator's view so it cannot be determined whether the participant completed the task correctly.	Adult Opioid User Associate NL # (b) (6)	Turned the mannequin on its side thinking it would help keep the airway open.	Rated this use-related event as a use error conservatively because it could not be verified. No clinical consequence in an actual overdose emergency if the product was administered to a person in a lateral recumbent position.

UE: Did not keep the tip fully inserted up the nostril in the correct upwards orientation	Adult Opioid User NL # (b) (6)	Hand slipped slightly from the correct position into more of a posterior direction at the end of administration. <i>"I used the thumb on the plunger. I'm not sure I understand what you want."</i>	The tip of the device did not entirely exit the nostril, so in a real-world scenario the person would have likely still absorbed at least a partial dose through the nasal mucosa membrane. The participant properly administered a second dose, so no additional mitigation strategies were required.
UE: Squeezed the device without actually pushing in the plunger	Adolescent NL	They held on to just the plunger and bottom of the device without stabilizing	The moderator did not probe further to understand the

		# (b) (6)	the top of the device with two fingers and was thus not able to put enough pressure to push the plunger <i>"Am I [inaudible] to get to squeeze? So, I kind of squeezed out instead of pushing it."</i>	participants' confusion and, therefore, there is not enough information to determine a root cause and/or mitigation strategy. Since this participant was the only one to experience this issue, further mitigation strategies are not required.
	UE: Did not understand that she should actually administer the product in the demonstration	Adolescent NL # (b) (6)	Subjects were given minimal directions to preserve the naturalism of the demonstration. <i>"I didn't really know if we were supposed to fully do it."</i>	This was a research artifact that would not be an issue in an actual overdose emergency, therefore no mitigation strategies were required.
	UE: Held the device inverted, with the bottom of the plunger pointing up	Adolescent NL # (b) (6)	Subject did not understand the orientation of the device. Based on the subject's behavior and feedback, the most likely root cause is that did not carefully review the pictogram associated with Step 2, and that the participant did not attempt to use the device, which may have cued him to his error. The participant assumed for unknown reasons likely that the device was not functional and thus he did not attempt to truly demonstrate, and thought that it was not a functional device. Additionally, the interviewer appears to have prematurely debriefed the participant on what they did wrong, after the HF demonstration but before the LC questions.	N/A, due to participant not fully engaging with the study and is considered an artifact of the research setting

			Stated that the picture of the device on the DFL should be bigger or clarify direction <i>"It just didn't say what direction to put it in."</i>	
	CC: Participant did not depress plunger during initial attempt using the first device. Tried again after a delay and looking at the DFL and was able to press the plunger on a second attempt.	Adult Opioid User Associate LL # (b) (6)	Participant started reviewing the DFL at Step 3 and did not see the first panel before first attempt to administer the product. She seemed to know that she might not have done it correctly so referred to the DFL again, then attempted again after a brief delay using the first device and did push the plunger.	The order of the panels on the DFL was updated after the study so that Step 1 begins on the back of the box, which is more intuitive for consumers. No difficulty with second device/dose.
	CC: Participant did not read Step 2c and press the plunger until 45 seconds after inserting the nozzle into the person's nostril.	Adult General Population LL # (b) (6)	Participant started reviewing the DFL at Step 3 and did not see the first panel before opening the blister pack for the first device and inserting into the nostril. Once he turned the carton to review Step 1, he administered with no difficulty. Participant later made a general statement that the color of the package was hard to see or that it was difficult to see where the steps were.	
	UD: Participant inserted device into nostril, but then removed it, fumbled with it briefly, but then re-inserted and gave the dose. The participant then appeared to see if there was any more medicine in the device by attempting to administer again to the second nostril.	Adult Opioid User Associate NL # (b) (6)	Participant was acting nervous and excited and rushed to dispense the first dose. Additionally, the size of the nostrils of the mannequin were just large enough to accommodate the tip of the nozzle.	Not provided
	UD: Participant struggled to place tip of the nozzle in nostril and had	Adolescent NL	Participant had her thumb on the plunger but did not stabilize the top of the device	

	to refer back to the instructions to confirm how to insert.	# (b) (6)	while inserting into the nostril, which caused the difficulty. Additionally, the nostrils of the mannequin were just large enough to accommodate the tip of the device.	
	UD: At first, the participant thought that the nozzle was a cap that was supposed to be removed before administering the dose.	Adult Opioid User LL # (b) (6)	Participant started reviewing the DFL at Step 3 and did not see the first panel before opening the blister pack for the first device. Once he turned the carton to see Step 1, he administered with no difficulty <i>"I was wondering if there was a cap on the end of that medication that had to be removed, and it doesn't say anything about the cap on here. So anyway, I just put the plunger in the nose, and then I inserted-- or pressed the back side of it, the nasal spray."</i>	The order of the panels on the DFL was updated after the study so that Step 1 begins on the back of the box, which is more intuitive for consumers.
	UD: Participant inserted the tip of the nozzle into the person's nostril and removed their hand, leaving the device in place for a moment while re-reviewing the directions to determine how to deliver a dose.	Adult General Population LL # (b) (6)	Participant reviewed the panel with Step 3 first, then realized something was not right as he was trying to follow the directions and administer. During this pause he left the device in the nostril. Once he reviewed Step 1, he administered the drug appropriately.	
	UD: Brief struggle with plunger before administering the dose.	Adult Opioid User Associate NL # (b) (6)	Struggle with plunger seemed to be an artifact of also having the carton in her hand.	
	UD: Participant used two hands to firmly press plunger. (n=2)	Adult Opioid User NL # (b) (6)	Participant may have been at an odd angle or may have perceived not having the hand strength needed to push the plunger using	Not provided

		Adolescent LL # (b) (6)	just one hand.	
	UD: Participant hesitated to remove nozzle from person's nostril as if they were uncertain that the dose had been completely/fully given. (n=2)	Adult General Population NL # (b) (6) Adult Opioid User LL # (b) (6)	Not provided	
Based on the Applicant's URRAs, performing Step 2 incorrectly or not at all may result in: • Difficulty breathing • Respiratory failure • Death				
DMEPA's Analysis and Findings of Use Related Events for Step 2				
DMEPA Finding #1 Use errors occurred in the study that can be directly attributed to the user interface. Four participants experienced either a close call or use difficulty in giving the first dose because of the layout of the DFL. In each case, these participants turned to the back panel of the carton and initiated their simulation using Step 3 (Call 911) of the DFL "Directions", bypassing Step 1 (Check) and Step 2 (Give 1st Dose) which appear on the side panel of the carton. These use errors indicate that the placement of the DFL directions on the carton, with Steps 1 and 2 on the side panel and Steps 3, 4, and 5 on the back panel contributed to the use errors. Use errors of this nature are likely to result in delayed administration of naloxone if users have difficulty locating where to start on the DFL Directions or understanding the sequence of the steps to give the first dose of naloxone, which may result in negative outcomes. In response to the use errors, the Applicant proposes to implement a post-HF validation revision to the DFL by presenting Step 1 (Check) and Step 2 (Give 1st Dose) on the back panel; and Step 3 (Call 911), Step 4 (Watch & Give), and Step 5 (Stay) on the side panel. We considered the Applicant's proposed mitigation, and we acknowledge that users who refer to the back panel of the carton first will now see Step 1 and Step 2; however, it is unclear if this mitigation will effectively address the use errors observed without introducing new risks				

for error. For example, we are concerned that some users may overlook Steps 3, 4, and 5 on the side panel if they remain divided from Steps 1 and 2 on the back panel. In fact, one participant, who correctly started with Step 1 and gave the first dose successfully spent 50 seconds reading the wrong face of the DFL before proceeding to Step 3 on the next panel. This UE would result in delayed arrival of emergency response healthcare personnel and/or delaying or not giving a second dose that may be needed. The Applicant did not propose to validate this proposed mitigation strategy; thus, we do not have supporting HF data to demonstrate the proposed mitigation will address the use errors and alleviate our concerns. On November 18, 2022 and December 12, 2022, we sent information requests (IRs) to request a description of all changes that were implemented after completion of the HF validation study and the Applicant's justification to support each proposed change and position on whether each change introduces any new use-related risks. Regarding the change in layout of the panels, the Applicant states "no new use-related risk; change will mitigate a minor difficulty that some participants had while navigating package information observed in the HF study." However, we are concerned that some users may overlook Steps 3, 4, and 5 on the side panel. Thus, it is unclear if this mitigation will effectively address the use errors observed without introducing new risks for error.

Proposal for Advisory Committee (AC) Panel Consideration for Finding #1:

We recommend the Applicant redesign the carton such that the back panel includes all 5 steps (Steps 1 through 5) of the DFL "Directions" uninterrupted and in the appropriate sequence. Additionally, we recommend the Applicant package a Quick Start Guide (QSG) within each blister package and carton that displays Steps 1 through 5 of the DFL using text and figures consistent with the DFL Directions. The QSG should include Steps 1 through 5 on a single side page without breaks to minimize the risk of users missing steps.

DMEPA Finding #2

One participant squeezed the device without pushing the plunger and failed to administer a dose. The root cause is unclear based on the HF validation study results report because the study moderator did not probe further to understand the participant's confusion to determine whether any aspect of the user interface (e.g., DFL images or text and/or device design) contributed to the use error. Thus, we cannot determine whether the risk mitigation strategies are appropriate to address this use error. One participant held the device inverted, with the bottom of the plunger pointing up. The participant's subjective feedback indicates that the user interface may have contributed to the use error. Specifically, the participant stated, "It just didn't say what direction to put it in." Use errors of this nature are likely to result in delayed dose or no dose of naloxone if users have difficulty activating the device, which may result in negative outcomes.

Proposal for AC Panel Consideration for Finding #2:

We are aware that the Step 2 image tested by the Applicant is identical to the Step 2 image from the FDA model DFL, which differs from pictograms used in the prescription Narcan labeling. However, Step 2 of the model DFL was a device-specific placeholder and thus was not tested in the CONFER study (See Section 1.1). FDA designed the model DFL such that device-specific instructions may be added to Step 2 and evaluated in a simulated HF validation study. We request the AC panel to consider if the Step 2 pictogram may be further improved to optimize the nonprescription Narcan carton labeling, for example, by incorporating elements of the prescription Narcan pictograms (see

Figure 4). If we elect to revise the Step 2 pictogram for the nonprescription Narcan, we will not have LCS or HVFS data to support effectiveness of the change.

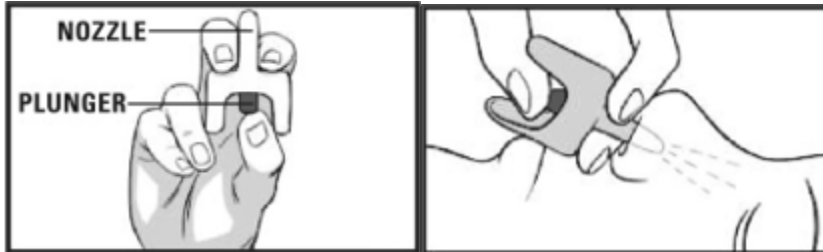


Figure 4. Prescription Narcan Pictograms

DMEPA Finding #3

One participant did not keep the nozzle fully in the nostril while administering a dose, which resulted in a partial dose administration. Although the participant's subjective feedback and root cause analysis did not cite wording in the DFL as a contributing factor to the use error, the second bullet of the step states, "INSERT the tip of the nozzle into either NOSTRIL." The word "tip" may result in users not fully inserting the nozzle into the nostril, which may result in partial dose administration.

Proposal for AC Panel Consideration for Finding #3:

We recommend the Applicant revise the bullet to state, "INSERT the nozzle into either NOSTRIL."

2.

Step 3: Call

- CALL 911 immediately after giving the 1st dose

Information Supplied by Applicant			
Total number of UE, CC, UD			
UE (n=10), CC (n=5), UD (n=0)			
Use-Related Event	Participant Type, Literacy and ID number	Applicant's RCA and Participants' Subjective Feedback (if available)	Applicant's Discussion of risk mitigation strategies
UE: Verbalized calling 911 prior to giving the first dose	Adult Opioid User NL # (b) (6)	Verbally described calling 911, even though they did not simulate it.	Not provided

			<i>"I called 911 at the beginning before I gave the medication."</i>	
	UE: Verbalized calling 911 after the first dose	Adult General Population LL # (b) (6)	RCA not provided <i>"I was checking her airway first after I gave her the first dose."</i>	
	UE: Called 911 prior to administering the first dose	Adult Opioid User Associate NL # (b) (6)	Did not read the directions far enough <i>"I just didn't read them all."</i>	Calling 911 before administering the dose is not a critical error, since the 911 operator could help them through the process if needed and the victim would get the first dose of medicine very shortly thereafter.
		Adult Opioid User Associate NL # (b) (6)	Upon entering the simulation of a family member who is unconscious, some of these subjects acted out or described calling 911 before looking at the Narcan package, which would likely be common in any medical emergency of any kind. This type of error was not due to any fault of the device or labeling, participant was acting on instinct in an emergency.	
		Adult General Population NL # (b) (6)		
		Adult Opioid User Associate NL # (b) (6)	<i>"Because I thought I already called them. I didn't think I needed to call them again."</i>	
		Adolescent NL # (b) (6)		
		Adult Opioid User LL # (b) (6)	Looking at the back of the box (Panel 2 of the DFL) first, rather than Panel 1, which was on the side panel. <i>"Because I didn't see it."</i> <i>"I thought I did call 911 after the first dose-- or before the first dose. And then I waited the second two to three minutes for then to</i>	The DFL flow has been updated across the carton panels to be more intuitive and to better direct consumer attention to starting at Step 1, which is now on the back panel.

			<i>administer the second dose. I didn't know if I should be repeating the call, so."</i>	
	UE: Acted out in the simulation directing someone else to call 911 prior to giving first dose	Adult Opioid User Associate LL # (b) (6)	Assumed that there would be one other person there to call 911 while he attended to the unconscious family member. This was not due to any fault of the device or labeling; participant was acting on instinct in an emergency. <i>"Because upon the first doses I thought that I had given, I had already screamed for somebody to call 911."</i>	Although not technically consistent with the label directions, directing a bystander to call 911 while the participant was orienting themselves to the label and how to administer the product is not a critical error and could expedite contacting emergency services.
	UE: Verbally described calling 911 prior to giving first dose and then demonstrated / simulated calling 911 after the second dose	Adult Opioid User NL # (b) (6)	Participant actually did verbally state the need to call 911 after giving the first dose, but then actually acted out / simulated dialing after the second dose. It appears this was very conservatively scored and was not a true error. <i>"I think that the steps should be bigger and bolder. I just feel like they need to be a little bit bigger than what the writing is next to it, kind of stand out a little bit bigger."</i>	The DFL flow has been updated across the carton panels to be more intuitive and to better direct consumer attention to starting at Step 1, which is now on the back panel.
	CC: Participant called or described calling 911 prior to administering the first dose, but after reading the DFL, administered the first dose and called/stated they'd call 911 at that point or identified they'd still be on the phone with 911	Adult General Population NL # (b) (6) Adult Opioid User NL # (b) (6)	Participants started with the wrong side of the carton, which starts with Step 3 to call 911.	All participants quickly self-corrected after seeing the correct panel. The order of the panels on the DFL was updated after the study so that Step 1 begins on

^r The Applicant's IR response dated December 9, 2022 listed participant ID #9028-00008, which does not exist in the HF validation study report. Based on review of the participant transcripts, this appears to be participant ID #9025-00008.

	(n=4)	Adult General Population NL # (b) (6)		the back of the box, which is more intuitive for consumers.
		Adult General Population LL # (b) (6)		
	CC: Participant did not call 911 until just less than 1 minute after the first dose	Adult General Population NL # (b) (6)	Participant spent about 50 seconds reading the wrong face of the DFL and was trying to determine how long to wait for the person to wake up before proceeding, before reading Step 3 to call 911.	It was a very brief delay and the first dose had been delivered successfully.
Based on the Applicant's URRAs, performing Step 3 incorrectly is not "device related" and the Applicant lists associated harm as:				
"N/A."				
DMEPA's Analysis and Findings of Use Related Events for Step 3				
The Applicant's URRAs categorizes these use errors as "none that are device related" and associated harm as "N/A." We disagree with the Applicant's categorization of the task "Call 911" because performing the task incorrectly or not at all may result in delayed medical care for the opioid overdose victim and possible continuation of opioid overdose symptoms. DMEPA Finding #1 Use errors occurred in the study that can be directly attributed to the user interface. Subjective feedback and root cause analysis indicate that participants called 911 prior to administering the first dose (instead of after administering the first dose). In some cases, these participants turned to the back panel of the carton and initiated their simulation using Step 3 (Call 911) of the DFL "Directions", bypassing Step 1 (Check) and Step 2 (Give 1st Dose) which appear on the side panel of the carton. These use errors indicate that the placement of the DFL directions on the carton, with Steps 1 and 2 on the side panel and Steps 3, 4, and 5 on the back panel contributed to the use errors. Use errors of this nature are likely to result in delayed administration of naloxone if users have difficulty locating where to start on the DFL Directions or understanding the sequence of the steps to give the first dose of naloxone, which may result in negative outcomes.				

	In response to the use errors, the Applicant proposes to implement a post-HF validation revision to the DFL by presenting Step 1 (Check) and Step 2 (Give 1st Dose) on the back panel; and Step 3 (Call 911), Step 4 (Watch & Give), and Step 5 (Stay) on the side panel. We considered the Applicant's proposed mitigation, and we acknowledge that users who refer to the back panel of the carton first will now see Step 1 and Step 2; however, it is unclear if this mitigation will effectively address the use errors observed without introducing new risks for error. For example, we are concerned that some users may overlook Steps 3, 4, and 5 on the side panel. The Applicant did not propose to validate this proposed mitigation strategy; thus, we do not have supporting HF data to demonstrate the proposed mitigation will address the use errors and alleviate our concerns. Proposal for AC Panel Consideration for Finding #1: We recommend the Applicant redesign the carton such that the back panel includes all 5 steps (Steps 1 through 5) of the DFL "Directions" uninterrupted and in the appropriate sequence. Additionally, we recommend the Applicant package a Quick Start Guide (QSG) within each blister package that displays Steps 1 through 5 of the DFL using text and figures consistent with the DFL Directions. The QSG should include Steps 1 through 5 on a single side page without breaks to minimize the risk of users missing steps. DMEPA Finding #2 One participant stated the instructions could be more prominent (i.e., "bigger and bolder"). However, we also acknowledge a discrepancy in the observed performance for this participant. Specifically, the HF report states the participant verbally described calling 911 prior to and then demonstrated calling 911 after administering the second dose. Thus, although the participant experienced use errors by calling 911 prior to administering the first dose and again after administering the second dose, we acknowledge that they called 911 at some point during the use sequence. Thus, we do not have recommendations to address this use-related event. Proposal for AC Panel Consideration for Finding #2: N/A
3.	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

Information Supplied by Applicant

Total number of UE, CC, UD

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

Use-Related Event	Participant Type, Literacy and ID number	Applicant's RCA and Participants' Subjective Feedback (if available)	Applicant's Discussion of risk mitigation strategies
UE: Did not wait 2-3 minutes before administering a second dose or did not verbally describe the need to do so during the HF demonstration.	Adult Opioid User Associate NL # (b) (6)	Participants understood the need for a second dose if the person did not wake up but failed to time a 2–3-minute wait as part of their simulation or verbally articulate the need to wait 2-3 minutes. Upon review of the available participant comments, it appears that this was largely understood that the wait was assumed or implied, and that they didn't need to actually act out waiting for 2-3 minutes, i.e., an artifact of the research setting. <i>"I was waiting. I figure the step three where you're calling 911, the duration of that would probably take you about two to three minutes. So I think it is pretty well placed. I figure someone would probably follow that step immediately."</i>	The act of calling 911 for emergency services after administering the first dose would result in some delay between doses in a real-life setting if a consumer failed to notice or understand this direction. While the label instructs a User to wait 2-3 minutes before delivering a 2nd dose, administering one sooner is not considered a critical use error.
	Adolescent NL # (b) (6)		
	Adult Opioid User NL # (b) (6)		
	Adult Opioid User Associate NL # (b) (6)		
	Adult Opioid User NL # (b) (6)		
	Adolescent NL # (b) (6)		
	Adult General Population NL # (b) (6)		

		Adolescent LL # (b) (6)	<i>"I kind of just went with it as imagining it was two or three minutes."</i>	
		Adolescent NL # (b) (6)	<i>"I didn't even think about that. I guess just because you said to move on that I just assumed I waited two to three minutes."</i>	
		Adult Opioid User Associate LL # (b) (6)	<i>"Just missed a step. I figured wait for 911 to come. That's why I kept listening. If there were two, three minutes of-- I guess. I got lost in it."</i>	
	UE: Did not administer or discuss need to administer a second dose	Adolescent LL # (b) (6)	This participant somewhat modified the scenario provided to them by including in their demonstration a statement that emergency personnel had arrived shortly after giving the first dose, and she stated that in her "scenario," the person would be waking up. However, this participant also did not provide a correct answer to the associated labeling comprehension (LC) question, responding with "It says to check with them again, but make sure you call 911." <i>"Because my patient or family member [laughter] was waking up. So I didn't feel that they needed the second dose."</i>	Not provided
	UE: Failed to administer a second dose	Opioid User Associate LL # (b) (6)	She set down the box after administering the first dose and did not appear to finish reading all directions during the HF demonstration - she appeared to have gotten	This subject failed to demonstrate or verbalize the need to administer a second dose during the HF demonstration but did demonstrate clear understanding of this concept in the LC question

			upset thinking about it being a real-life scenario and focused on all other additional lifesaving measures she could try in addition to Narcan rather than referring to all Steps on the package during the HF demonstration. <i>“Just try to resuscitate him and do this. Try to get him to breathe again through mouth-to-mouth or CPR. That’s all I can [inaudible] to do. Wait for the ambulance to get there.”</i>	by responding to give Narcan twice “Administer the Narcan. Put it in the nose. Spray it one time, it says. Then call 911. Check to make sure they’re breathing. [inaudible] check to make sure they’re breathing and administer the Narcan” and then later: “Call 911 and then proceed to give them a dose every two to three minutes” as well as “I don’t know. I’d say that maybe I could do another dose... Yeah. Yeah. Give another dose of it.” Therefore, no additional mitigation strategies were required.
Based on the Applicant’s URRAs, performing the task incorrectly or not at all may result in: - Excessive therapy, which may result in diaphoresis, drug withdrawal convulsions, cardiac arrest, death - Delayed therapy or no therapy, which may result in death				
DMEPA’s Analysis and Findings for Use Related Events for Step 4				
Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use errors. Based on our review of the subjective feedback and RCA, we did not identify areas of improvement and have no recommendations at this time.				

4.2 ANALYSIS OF USE-RELATED EVENTS FOR 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 figures.⁵ Our review of the HF validation study results did not identify subjective feedback or root cause analysis that indicated the content of the DFL (i.e., text and/or figures) contributed to the use-related events observed for Step 1 and Step 5. However, we identified subjective feedback and root cause analysis that indicate other aspects of the user interface contributed to some use-related events for Step 1 and Step 5. Thus, we evaluate the use-related events for Step 1 and Step 5 in this section.

Our review of the study results for Step 1 “Check” identified subjective feedback and root cause analysis that indicated the user interface contributed to some of the use-related events. Specifically, 5 participants experienced a use error, and 4 participants experienced a close call^t whereby they called or almost called 911 prior to administering the first dose because they started reviewing the DFL at Step 3 Call 911, which was on the back panel of the carton instead of Step 1, which was on the side panel of the carton. Please see Table 7 rows #1 and #2 above for our analysis, findings, and recommendations regarding the split DFL across the side and back panel.

Our review of the study results for Step 5 “Stay; Give another dose if the person becomes very sleepy again” identified subjective feedback and root cause analysis that indicated the user interface contributed to some of the use-related events. Specifically, 2 participants experienced a use error, and 6 participants experienced a close call^u because they were confused about whether each nasal spray contained a single dose or multiple doses. For example, one participant provided the following subjective feedback, “I spent 30 seconds trying to figure out if each one of these was one dose or multiple doses. And it never said.” Our review of the user interface finds that the labels and labeling can be improved to further minimize the risk of this use error. Although these use-related events occurred with Step 5, our review finds adding information to convey that each nasal spray contains only one dose on the container label, PDP and early in the DFL (i.e., Step 2) may minimize the risk for confusion on the number of sprays in each nasal spray for subsequent Steps including Step 5.

Proposal for AC Panel Consideration:

⁵ 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>.

^t The Applicant did not categorize these events as close calls; however, we categorized these events as close calls based on our review of the participants’ statements provided in the transcript.

^u The Applicant did not categorize these events as close calls; however, we categorized these events as close calls based on our review of the participants’ statements provided in the transcript.

We recommend the Applicant to add a statement that each nasal spray contains only one dose of naloxone to the container label, Step 2 of the DFL, and the carton labeling. Furthermore, we recommend the carton labeling display an image depicting 2 nasal spray devices to minimize confusion on the number of nasal spray devices in each carton.

5 SUMMARY OF ADVISORY COMMITTEE (AC) MEETING

The Nonprescription Drugs Advisory Committee (NDAC) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met jointly on February 15, 2023 to discuss supplemental NDA 208411/S-006, for Narcan (naloxone hydrochloride) nasal spray and the proposed switch from prescription to nonprescription status. One of the issues discussed included adequacy of HF data to support the nonprescription application and the Agency's potential label/labeling recommendations. We presented the HFVS (human factors validation study) qualitative results, taking into consideration the HFVS study limitations, our analysis, and our proposed recommendations from Section 4.1 and Section 4.2 above to the AC for their consideration.

Overall, the AC panel members agreed that the HFVS design was less than optimal but they acknowledged its utility in informing the optimal product design. Many committee members emphasized that availability of this product as a nonprescription drug should not be delayed to obtain additional data. Many committee members were strongly in favor of implementing the Agency's recommendations, including revising the pictograms. At the meeting, Emergent displayed a mock-up nonprescription QSG for inclusion in the blister and a revised carton label that incorporated the Agency's recommendation to include all 5 steps of the DFL "Directions" on the back panel. The AC panel members supported these revisions and recommended the Agency formally review the mock-up labeling. Some AC panel members provided additional label/labeling recommendations. All comments and recommendations from the AC panel were considered. Following the AC Meeting, on February 17, 2021 and February 21, 2023, Emergent formally submitted a new proposed QSG and carton labeling, respectively (see Appendix D). Section 6.1 includes our label/labeling recommendations based on our review and analysis of the HFVS, our review of the recommendations from the AC panel, and Emergent's proposed labels and labeling.

6 CONCLUSION AND RECOMMENDATIONS

Our review of the human factors (HF) validation study results for Narcan (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 HF validation study methodology, the methodology issues did not preclude our review of the HF validation study 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. Additionally, we considered the AC's recommendations and comments regarding the public health benefit of nonprescription status

of Narcan. 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, including the prescription Narcan. 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 HF validation study 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 switching the status of Narcan (naloxone HCl) nasal spray from prescription to nonprescription 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.

6.1 RECOMMENDATIONS FOR EMERGENT BIOSOLUTIONS

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

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

1. Replace the pictogram in Step 2 of the DFL Directions with the pictogram from Step 2 of the prescription Narcan Nasal Spray carton (see Figure 55 below) to show correct hand and finger positioning on the device. Incorporate the same image into Step 4's pictogram, while maintaining the clock image. Make the same revisions to the Quick Start Guide (QSG). Use errors, close calls, and use difficulties in the human factors validation study (HFVS) occurred that were related to device orientation, operation, and hand position on the device, which may result in no dose or delayed administration of naloxone HCl.



Figure 5. Pictogram from prescription Narcan carton

2. Revise the second bullet in Step 2 of the DFL Directions and QSG to: "Insert the nozzle into either nostril" (i.e., remove "the tip of"). A use error in the HFVS occurred because a participant did not fully insert the nozzle into the nostril, which may result in partial dose administration of naloxone HCl.
3. Revise the heading of Step 2 of the DFL Directions and QSG to, "Give 1st dose in the nose" to further promote the correct route of administration.
4. Add the statement, "1 device contains 1 dose" as the last bullet in Step 2 of the DFL Directions and QSG. Use errors and close calls in the HFVS occurred

due to confusion regarding the number of doses in each device, which may result in delayed administration of additional doses of naloxone HCl.

5. Revise the text font color and/or background color for each numbered heading in the DFL Directions and QSG (e.g., 1. CHECK, 2. GIVE, etc.). As currently presented, the (b) (6) font text on (b) (6) background has insufficient contrast, which may decrease legibility of the text.^v This recommendation is further supported by the Advisory Committee Panel.
 6. On your product samples, received on February 28, 2023, there is a typographical error in the first and fourth bullets of Step 4 on the carton DFL and QSG, that state, “Wait 3-2 minutes...” and “...every 3-2 minutes...” Ensure the statements on the intend-to-market labels and labeling state “...2-3 minutes...”
- B. Quick Start Guide (QSG)
7. We acknowledge your plan to add a “QUICK START GUIDE” to the blister package. For the purposes of the proposed nonprescription product, and to align with the DFL, retitle this labeling as “DIRECTIONS” to help users quickly identify that this piece of paper contains identical instructions to the DFL Directions.
 8. In the product samples received on February 28, 2023, the QSG packaged inside the blister package is inconspicuous, thus, users may not realize that the folded paper contains directions. Add the statement, “Unfold for Directions” in prominent text such that it appears on both sides of the folded QSG. Note that you may need to relocate the barcode on the QSG to implement this recommendation.
On your product sample QSG, the text on Step 3 bullet 1 is difficult to read because it appears directly on the fold line of the paper. We are concerned users may not see the instruction to call 911 clearly. Revise the header (b) (6) to read “Step 3: Call 911” to help mitigate this risk. Also, consider if minor modifications can be made to placement of the DFL on the paper such that the text in this bullet is not directly on the fold line. Ensure any such modifications do not create similar risks for other text on the QSG.
- C. Carton Labeling
9. Add a figure to the PDP that shows the correct hand and finger position on the device. Include labels on the figure that point to the components of the device, similar to the figure from Step 2 of the prescription Narcan Nasal Spray carton (see Figure 6 below). Add the same figure to the top right

^v Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

portion of the QSG. Use errors, close calls, and use difficulties in the HFVS occurred that were related to device orientation, operation, and hand position on the device, which may result in no dose or delayed administration of naloxone HCl.

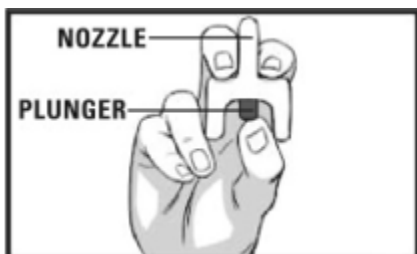


Figure 6. Pictogram from prescription Narcan carton

10. Add the statement “for use in the nose only” to the PDP to further promote the correct route of administration.
11. Use errors and close calls in the HFVS occurred due to confusion regarding the number of doses in each device, which may result in delayed administration of additional doses of naloxone HCl. We recommend the following to mitigate the confusion and mitigate the risk of delay in naloxone administration:
 - a. Add the statement, “1 nasal spray device contains 1 dose of medicine” to the PDP below the images of the devices and the statement, “2 Single-Dose Nasal Spray Devices”.
 - b. Add the statement, “Device sprays 1 time only” to the PDP immediately following the statement, “1 nasal spray device contains 1 dose of medicine”.
12. Revise the white text’s font color and/or pink/red background color of the carton to a text font color and/or background color of the carton so there is adequate contrast. As currently presented, the white text’s font color on the pink/red background color of the carton has insufficient contrast, which may decrease legibility of the text.^w
13. On your product samples, received on February 28, 2023, the NDC number format appears to be incorrect (i.e., NDC 02-627-69547). Ensure the NDC number format appears correctly on the intend-to-market carton labeling.

^w Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

14. There is a perforation on the back panel in the product samples received on February 28, 2023, which does not appear in the carton labeling submitted on February 21, 2023. Clarify whether the intend-to-market carton will include a perforation and the purpose of the perforation.

D. Blister Labeling

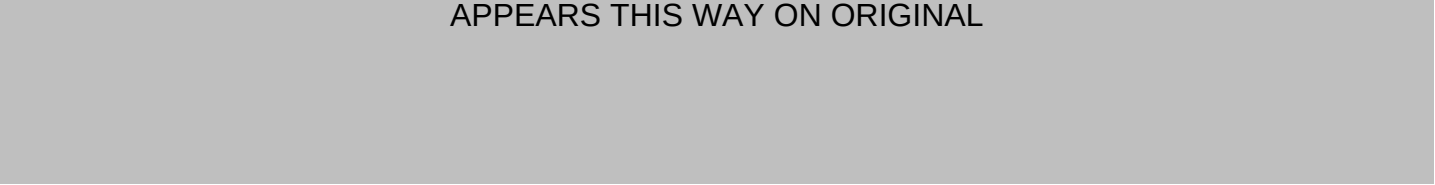
15. Add a figure of a nose near the statement “For use in the nose only” to further promote the safe use of the proposed product related to the route of administration.
16. Use errors and close calls in the HFVS occurred due to confusion regarding the number of doses in each device, which may result in delayed administration of additional doses of naloxone HCl.
 - a. Replace the statement, “1 spray per device” with the statements “Do not test device before use”, “1 device contains 1 dose of medicine” and “Device sprays 1 time only”. Ensure these statements have the same prominence.
17. In the product samples received on February 28, 2023, the nasal spray device was placed in the blister package such that the container label’s principal display panel was not visible through the blister. Clarify whether the intend-to-market product’s placement of the nasal spray device will allow the container label’s principal display panel to be viewed through the blister packaging.

E. Container Labels and Carton Labeling

18. As currently presented in the proposed container labels (blister and device labels) and carton labeling, the format for the expiration date is presented as “MM_YYYY” and “MMM YYYY,” respectively. 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 format, 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 slash or a hyphen be used to separate the portions of the expiration date.^x

^x Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPEARS THIS WAY ON ORIGINAL



7 APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information supplied by the Applicant can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\nda208411\0626\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report-1.pdf>

APPENDIX B. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\nda208411\0626\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report-2.pdf>

APPENDIX C. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On 10/21/2022, we issued an Information Request (IR) to request subjective feedback and root cause analysis for use errors, close calls, and use difficulties for Steps 2, 3, and 4 of the DFL and a discussion of any additional risk mitigation measures implemented or considered to address the identified use errors, close calls, and use difficulties.
 - o On 11/4/2022, the Applicant provided a response. The response can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda208411\0633\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report.pdf>
 - o However, we determined the response did not include subjective feedback and root cause analysis for all use errors, close calls, and use difficulties. Thus, we issued another IR on 11/23/2022.
 - o On 12/9/2022, the Applicant responded with additional use errors, close calls and use difficulties and available subjective feedback and root cause analysis for Steps 2 and 3. The response can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda208411\0643\m1\us\111-information-amendment\clinical-information-amendment.pdf>
- On 11/18/2022, we issued an IR to request the comprehensive, updated Use Failure Modes and Effects Analysis (uFMEA) and the justification for changes made to the user interface after completion of the HF validation study.
 - o On 11/22/2022, the Applicant responded with the uFMEA that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda208411\0638\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report-2.pdf>

[rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report-2.pdf](#).

- o On 12/02/2022, the Applicant responded with the justification for changes made to the user interface after completion of the HF validation study. The response can be accessible in EDR via:
[\\CDSESUB1\EVSPROD\nda208411\0640\m1\us\111-information-amendment\clinical-information-amendment.pdf](#)
- o However, we determined the IR response was inaccurate and incomplete because the IR response did not accurately depict the carton evaluated in the HF validation study; thus, we sent a Filing Communication letter on 12/12/2022.
 - In the 12/12/2022 Filing Communication letter, we requested the Applicant (1) provide a revised carton that includes all 5 steps of the directions on the back panel and (2) if (1) is not feasible given carton dimensions, state whether the carton dimensions or carton design could be modified to accommodate the requested change.
 - On 12/14/2022, the Applicant replied in an email correspondence and stated option (1) is not viable because it will shrink the illustrations considerably and option (2) is not viable because it will cause significant delay.
- o On 12/22/2022, the Applicant provided an amended response to our 11/18/22 IR with a description of the changes from the carton evaluated in the HF validation study and the intend-to-market carton along with the justification for changes. The response can be accessible in EDR via:
[\\CDSESUB1\EVSPROD\nda208411\0647\m1\us\111-information-amendment\clinical-information-amendment- -hf-labeling.pdf](#)
- o On 12/30/2022, we sent the Applicant a General Advice Letter to request the Applicant provide the current carton dimensions and carton dimensions required to place Steps 1 through 5 on a single panel. Additionally, we requested the Applicant describe the manufacturing constraints for placing Steps 1 through 5 on a single panel.
- o On 01/04/2023, the Applicant responded with carton dimensions and a description of manufacturing constraints. The response can be accessible in EDR via: [\\CDSESUB1\evsprod\NDA208411\0648](#)

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

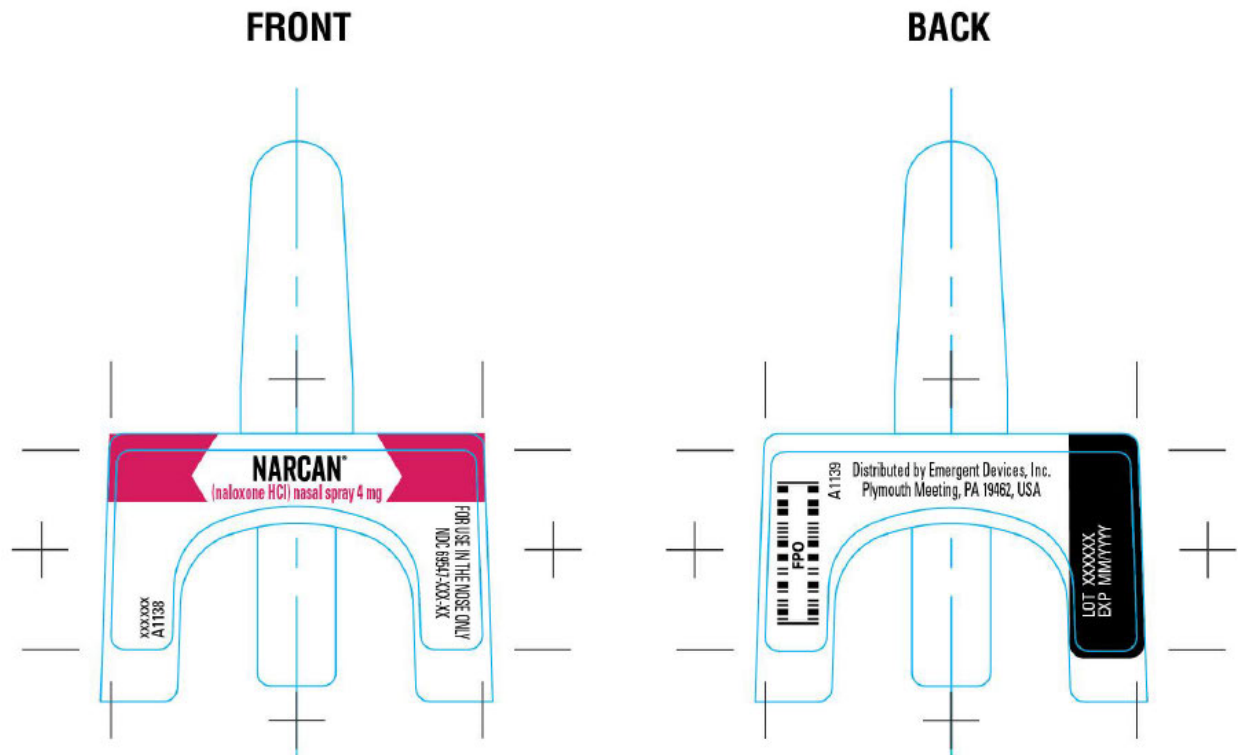
Using the principles of human factors and Failure Mode and Effects Analysis,^y we reviewed the following Narcan labels and labeling submitted by Emergent Biosolutions.

- Container labels submitted on September 29, 2022
- Blister labeling submitted on September 29, 2022
- Carton labeling submitted on September 29, 2022 and February 21, 2023
- Quick Start Guide (QSG) submitted on February 17, 2023, available from <\\CDSESUB1\EVSPROD\nda208411\0656\m1\us\114-labeling\draft\labeling\narcan-otc-quick-start-guide.pdf>

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

D.2 Label and Labeling Images

Container labels submitted on September 29, 2022



Blister labeling submitted on September 29, 2022



4 Pages 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/

MILLIE B SHAH
03/09/2023 03:20:27 PM

GRACE JONES
03/09/2023 03:22:48 PM

COLLEEN L LITTLE
03/09/2023 03:23:34 PM

LOLITA G STERRETT
03/09/2023 03:34:05 PM

CHI-MING TU
03/09/2023 03:59:05 PM

DANIELLE M HARRIS
03/09/2023 04:02:44 PM

**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 (b) (4)

Applicant/Sponsor: Emergent Biosolutions Inc. (naloxone 4 mg)
(b) (4)

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). (b) (4)

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). (b) (6)

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

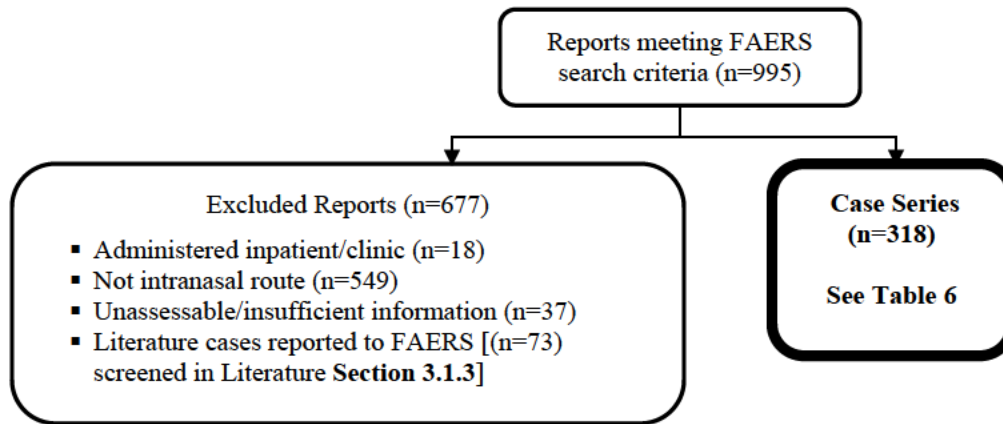


Table 6 summarizes the descriptive characteristics of the 318 FAERS cases of community use IN naloxone.

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

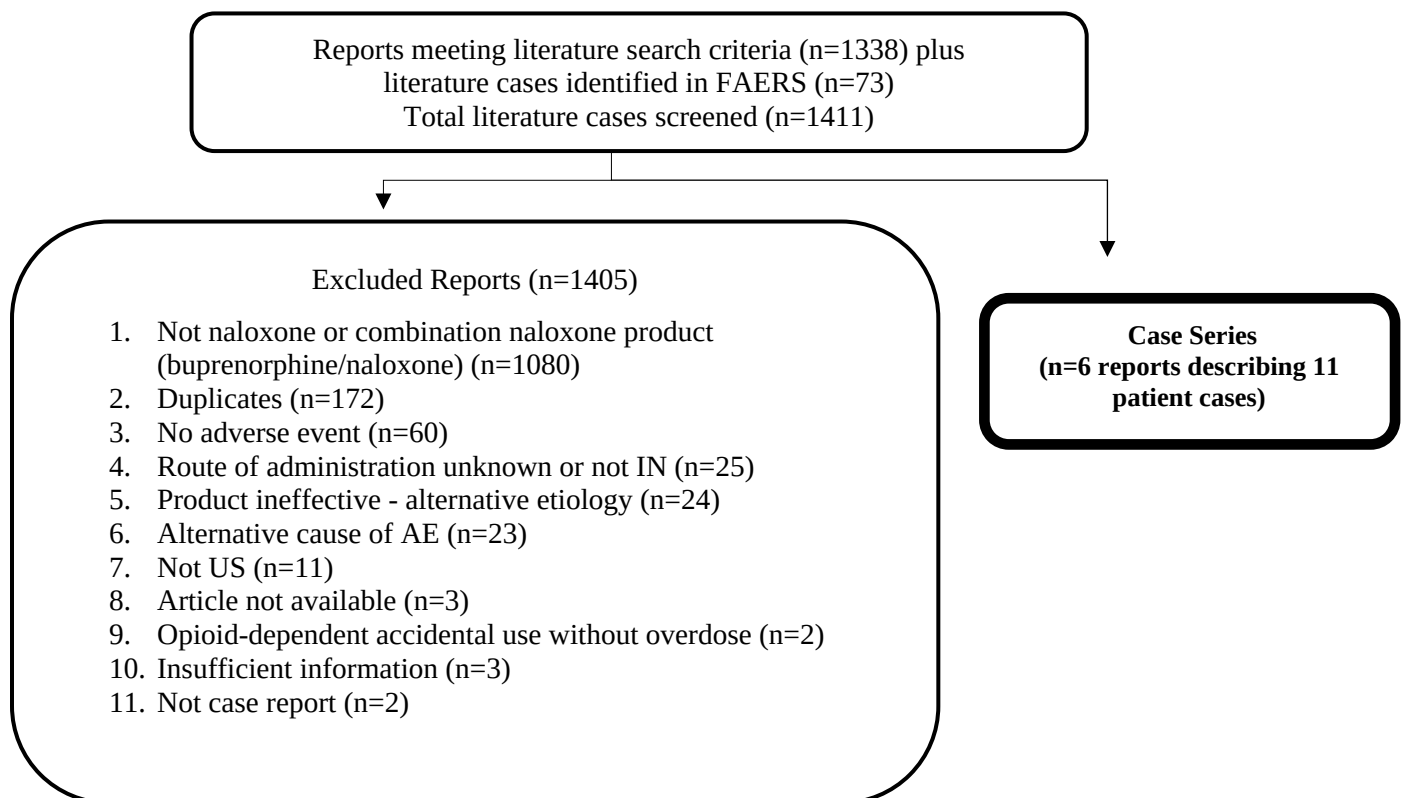
(N=24)		
	n	%
Reasons reported for limited efficacy		
Unknown how long since overdose occurred/ “too late”	6	25.0
No response to 1st dose, but response to second dose	5	20.8
Various product issues (e.g. “nothing came out”, “completely empty”)	5	20.8
Did not have enough naloxone	2	8.3
No reason reported	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 (b) (4)% in 2016 to (b) (4)% in 2021, while the shares for injectable vials and pre-filled syringes decreased from (b) (4)% to (b) (4)% and (b) (4)% to (b) (4)% 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.



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.

7 REFERENCES

1. Nelson LS, Olson D, 2019. Opioids. In Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS (eds.), Goldfrank's Toxicologic Emergencies, 11e. McGraw Hill.
2. Panchal A, Bartos J, and Cabanas, J, 2021. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation, S366-S468.
3. Dezfulian C, Orkin AM, Maron BA, et al., 2021. Opioid-Associated Out-of-Hospital Cardiac Arrest: Distinctive Clinical Features and Implications for Health Care and Public Responses. Circulation, e836-e870.
4. Zimhi - A Higher Dose Injectable Naloxone for Opioid Overdose, 2022. Med Lett Ther Drugs, 61-62.
5. Connors NJ, and Hamilton RJ, 2019. Withdrawal Principles. In Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS (eds.), Goldfrank's Toxicologic Emergencies. McGraw Hill.
6. Singh J, and Debasish B, 2004. Ultra-Rapid Opioid Detoxification: Current Status and Controversies. J Postgrad Med, 227-232.
7. Mills CA, Flacke JW, Miller, JD, Davis LJ, Bloor BC, Flacke WE, 1988. Cardiovascular Effects of Fentanyl Reversal by Naloxone at Varying Arterial Carbon Dioxide Tensions in Dogs. Anesth Analg, 730-736.
8. Wesson D, and Ling W, 2003. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs, 253-259.
9. Tompkins DA, Bigelow GE, Harrison JA, et al., 2009. Concurrent Validation of the Clinical Opiate Withdrawal Scale (COWS) and Single-Item Indices against the Clinical Institute Narcotic Assessment (CINA) Opioid Withdrawal Instrument. Drug Alcohol Depend, 154-159.
10. Duhart Clarke SE, Kral AH, Zibbell JE, 2022. Consuming Illicit Opioids During a Drug Overdose Epidemic: Illicit Fentanyl, Drug Discernment, and the Radical Transformation of the Illicit Opioid Market. Int J Drug Policy, 103467.
11. National Institute on Drug Abuse (NIDA). Trends & Statistics. *Overdose Death Rates*. Accessed December 2022 at <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>
12. Hantsch C, Mundkur M, Diak IL. Pharmacovigilance Review – Naloxone and naloxone-induced precipitated withdrawal. May 17, 2022. RCM 2022-119.
13. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Available from: <https://www.nccmerp.org/taxonomy-medication-errors-now-available>.
14. Kummer RL, Kempainen RR, Olives TD, Leatherman JW, Prekker ME. Naloxone-associated pulmonary edema following recreational opioid overdose. Am J Emerg Med. 2022;53:41-43. doi:10.1016/j.ajem.2021.12.030
15. Narcan Nasal Spray (naloxone hydrochloride). Package Insert. Revised August 2020. Emergent Devices, Inc. Plymouth Meeting, PA. available at: <https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/724df050-5332-4d0a-9a5f-17bf08a547e1/spl-doc?hl=Narcan>
16. Yarlagadda K, Kim J, Kanderi T, Sendil S, Nookala VK. Opioid antidote induced pulmonary edema and lung injury. Respir Med Case Rep. 2020;30:101107. Published 2020 May 29. doi:10.1016/j.rmcr.2020.101107
17. Veet et al. Reversing opiates in a flash: Intranasal naloxone-induced pulmonary edema. in: Abstracts from the 2017 Society of General Internal Medicine Annual Meeting. J GEN INTERN MED 32 (Suppl 2), S583 (2017). <https://doi.org/10.1007/s11606-017-4028-8>
18. Bardsley R. Higher naloxone dosing may be required for opioid overdose. Am J Health Syst Pharm. 2019;76(22):1835-1837. doi:10.1093/ajhp/zxz208
19. Brenner DS, Stolbach AI, Zschoche J, Bright L. Severe prolonged agitation due to intranasal naloxone overexposure. Am J Emerg Med. 2021;42:261.e1-261.e2. doi:10.1016/j.ajem.2020.08.069
20. Carroll GG, Wasserman DD, Shah AA, et al. Buprenorphine Field Initiation of ReScue Treatment by Emergency Medical Services (Bupe FIRST EMS): A Case Series. Prehosp Emerg Care. 2021;25(2):289-293. doi:10.1080/10903127.2020.1747579
21. Direct Relief, Pfizer to Donate 1 Million Naloxone Doses to Direct Relief for Life-Saving Opioid Overdose Reversal, April 15, 2021, available at <https://www.directrelief.org/2021/04/pfizer-to-donate-1-million-naloxone-doses-to-direct-relief-for-life-saving-opioid-overdose-reversal/>.

22. Wheeler, E and M Doe-Simkins, Harm Reduction programs distribute one million doses of naloxone in 2019, January 2, 2020, available at <https://medium.com/@ejwharmreduction/harm-reduction-programs-distribute-one-million-doses-of-naloxone-in-2019-4884d3535256>.
23. Wheeler E, Jones TS, Gilbert MK, Davidson PJ, 2015. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. MMWR MorbMortal Wkly Rep, 631-634.
24. Guy GP, Haegerich TM, Evan ME, et al., 2021. Vital Signs: Pharmacy-Based Naloxone Dispensing - United States, 2012-2018. MMWR Morb Mortal Wkly Rep, 202-207.

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.

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

OPIOID OVERDOSE RESCUE

Two 0.1 mL Devices
(0.003 fl oz each)

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 (1-844-62-7226)

*Among opioid overdose reversal treatments

Distributed by Emergent Devices Inc.
Plymouth Meeting, PA 19462
USA
NDC 69547-XXX-XX

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	

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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	

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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	

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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- (b) (4)	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	

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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	

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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	

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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	

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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	

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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	

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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

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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	

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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



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

Date	1/19/2023		
To:	Avani Patel		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From	Kyran Gibson 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 208411, NARCAN (naloxone hydrochloride) Nasal Spray ICC2200957 00880977		
Recommendation	Final Recommendation Date: 1/19/2023 From a device perspective, the switch from Rx to OTC is supportable as there are no changes to the device constituent, specifications, manufacturing, or control strategy. It is difficult to assess potential for device failures based on an OTC designation; however, this product is emergency-use and should perform to a 99.999% reliability. At this time there are minimal reports of device failures and/or malfunctions regarding the Narcan (naloxone hydrochloride) Nasal Spray.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 208411
Sponsor	Emergent Operations Ireland Limited
Drug/Biologic	NARCAN (naloxone hydrochloride) Nasal Spray
Indications for Use	For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Device Constituent	Nasal Spray
Related Files	ICC1600352, ICC1600450, ICC1700138, ICC1800007, ICC1800190, ICC1800664, ICC1900368, ICC2000632, ICC2100032, DMF (b) (4), IND 114704, NDA 016636, PIND 130200

Review Team		
Lead Device Reviewer		Kyran Gibson
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #

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	
Facilities & Quality Systems			X	

1.1. **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:

1.2. **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:

1.3. **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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2. PURPOSE/BACKGROUND

2.1. Scope

Emergent Operations Ireland Limited is requesting approval of NARCAN (naloxone hydrochloride) Nasal Spray. The device constituent of the combination product is a Choose an item..

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

Input from CDRH with respect to the potential post-market device failures considering this is an OTC product, even though the firm refers most of the Module 3 to NDA 208411 Rx, and states that nasal spray device remains the same.

The goal of this memo is to provide a recommendation of the approvability of the proposed supplement; specifically related to changes that may impact the device constituent of the combination product. The Sponsor is proposing the following [change\(s\) in this supplement](#):

- Replacement of Prescribing Information (PI) with Drug Facts Label (DFL) and a new outer carton graphic configuration (Principal Display Panel) consistent with a non-prescription product.
- Human Factors study to validate the new DFL and user's ability to successfully use NARCAN 4 mg in the intended setting.
- An integrated summary of safety (ISS), including data obtained from FAERS and WHO VigiBase databases.

This review will cover the following [review areas](#):

Labeling, safety

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.

2.2. Prior Interactions

NDA 208411 was approved in November 2015. Since approval, the Sponsor has had multiple interactions with the Agency regarding the Narcan (Naloxone Hydrochloride) Nasal Spray. These interactions include reviews (i.e., changes in dimensions, part changes), meeting requests, and reviews of responses of Post-Marketing Requirements regarding reliability of the combination product.

2.2.1. Related Files

ICC1600352, ICC1600450, ICC1700138, ICC1800007, ICC1800190, ICC1800664, ICC1900368, ICC2000632, ICC2100032, DMF (b) (4), IND 114704, NDA 016636, PIND 130200

2.3. Indications for Use

Combination Product	Indications for Use
NARCAN (naloxone hydrochloride) Nasal Spray	For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Nasal Spray	Delivery of the Drug Product

2.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)

0626	1.2 Cover Letters 1.4 References 1.14 Labeling 2 Common Technical Document Summaries 3.2.P Drug Product 5.3 Clinical Study Reports
0629	1.11.1 Quality Information Amendment
0632	1.14 Labeling 5.3 Clinical Study Reports
0633	5.3 Clinical Study Reports

3. DEVICE DESCRIPTION

3.1. Device Description

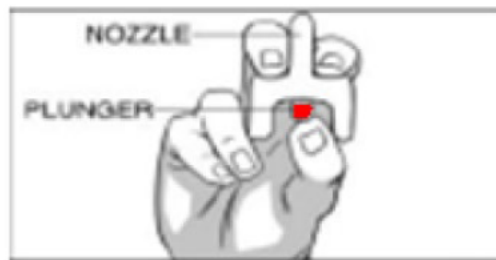
NARCAN® (naloxone hydrochloride) Nasal Spray 4mg is a prefilled 0.1ml, single dose intranasal spray. The drug substance is contained in a Type I borosilicate glass vial closed with a chlorobutyl rubber plunger. The primary container closure system is mounted into a unit-dose nasal spray device. The device is a non-pressurized dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100µl.

Component	Function
Naloxone hydrochloride (b) (4)	Active ingredient
Benzalkonium chloride (b) (4)	Preservative
Disodium edetate	Stabilizer
Sodium chloride	(b) (4)
Hydrochloric acid	
Water (b) (4)	

Component	Quality Standard	Function	Strength: 40 mg/ml	
			Quantity per ml	Quantity per dose (100 µL)
Naloxone HCl	USP, Ph. Eur	Active ingredient	44.0 mg (40.0 mg)	4.4 mg (4.0 mg)
(b) (4) (corresponding to naloxone HCl)				
Benzalkonium Chloride	USP, Ph. Eur	Preservative	(b) (4)	
(b) (4)				
Disodium Edetate	USP, Ph. Eur	Stabilizer		
Sodium Chloride	USP, Ph. Eur	(b) (4)		
Hydrochloric Acid	USP/NF, Ph. Eur			
(b) (4)				
Water	(b) (4) USP, Ph. Eur			

The manufacturing information for the manufacturing, control, and release of the combination product is provided below.

Site Name	Site Address	Manufacturing Step(s) or Type of Testing
(b) (4)		- Bulk and Final Product Manufacturing and Control - Release and Stability Testing - Labeling and Packaging



3.1.1. Specific *Changes* to the Device Constituent

- Replacement of Prescribing Information (PI) with Drug Facts Label (DFL) and a new outer carton graphic configuration (Principal Display Panel) consistent with a non-prescription product.
- Human Factors study to validate the new DFL and user's ability to successfully use NARCAN 4 mg in the intended setting.
- An integrated summary of safety (ISS), including data obtained from FAERS and WHO Vigibase databases.

3.2. Steps for Using the Device

Prescribing Information (Sequence 0645)

- Lay the person on their back to receive a dose of NARCAN Nasal Spray.
- Remove NARCAN Nasal Spray from the box. Peel the tab with the circle to open the NARCAN Nasal Spray.
- Hold the NARCAN Nasal Spray with your thumb on the bottom of the red plunger and your first and middle fingers on either side of the nozzle.
- Tilt the person's head back and provide support under the neck with your hand. Gently insert the top of the nozzle into one nostril until your fingers on either side of the nozzle are against the bottom of the person's nose.
- Press the red plunger firmly to give the dose of NARCAN Nasal Spray.
- Remove the NARCAN Nasal Spray from the nostril after giving the dose.
- Get emergency medical help. Move the person on their side (recovery position) after giving NARCAN Nasal Spray. Watch the person closely. If the person does not respond by waking up to voice or touch, or breathing normally, another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available. Repeat Steps 2 through 6 using a new NARCAN Nasal Spray to give another dose in the other nostril. If additional NARCAN Nasal Sprays are available, Steps 2 through 6 may be repeated every 2 to 3 minutes until the person responds or emergency medical help is received.
- Put the used NARCAN Nasal Spray back into its box.

9. Throw away (dispose of) the used NARCAN Nasal Spray in a place that is away from children.

Drug Facts Label

1. Check if you suspect an overdose
2. Give 1st dose of Narcan Nasal Spray
3. Call 911
4. Watch and give (b) (4)
5. Stay until ambulance arrives

3.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The device constituent is not changing in this PAS.	
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

4. FACILITIES & QUALITY SYSTEMS TRIAGE

4.1. Facilities Inspection Recommendation

Is a new facility or manufacturing process being implemented as a result of this supplement?	☐ Yes ☒ No (No facilities review)
--	---

4.2. Quality System Documentation Triage Checklist

The changes proposed impact the quality systems:	☐ Yes ☒ No QS Review is needed because:
--	--

4.3. Facilities & Quality Systems Review Triage Conclusion

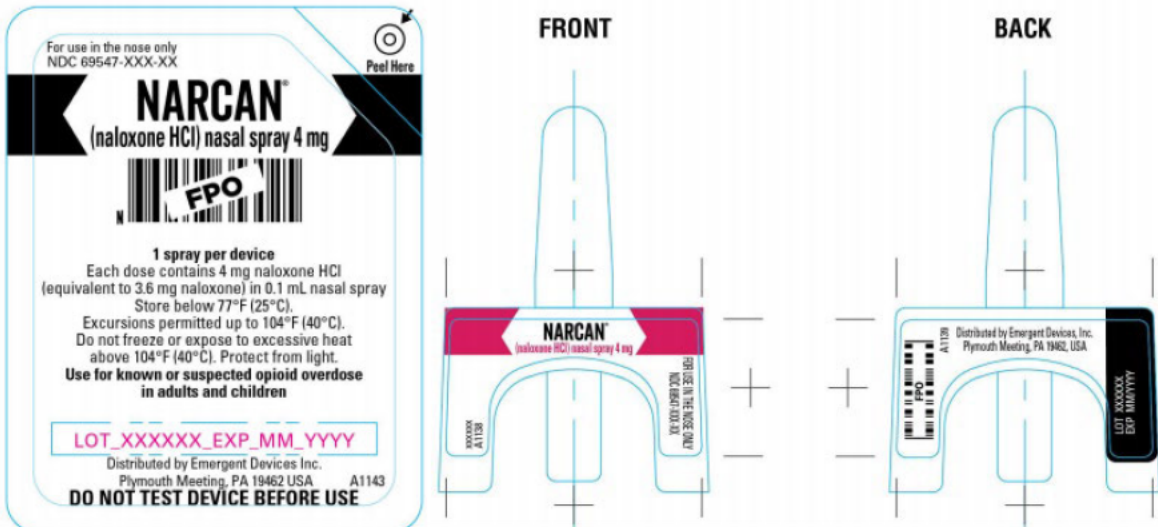
FACILITIES & QUALITY SYSTEMS REVIEW RECOMMENDATIONS
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☒ No Inspection ☐ N/A (Select this if a Facilities review is not being conducted)
Site(s) needing inspection: N/A
Quality System Review Required: ☐ Yes ☐ No ☒ N/A
Reviewer Comments See Section 12 for review of Facilities Inspection and/or Quality Systems Review

5. LABELING

☒ The proposed changes involve changes to the labeling of the device constituent and require review (See review below)
☐ The proposed changes do not impact the labeling and therefore the labeling was not reviewed

5.1. 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:



(b) (4)

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 – OTC
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The purpose of this PAS is a replacement of Prescribing Information (PI) with Drug Facts Label (DFL) and a new outer carton graphic configuration consistent with a non-prescription product.

The Sponsor has provided the proposed Drug Facts Label (DFL) within Sequence 0646. The document contains the combination product name, active ingredient, purpose, uses, warnings, directions, “other information” (e.g., storage conditions, expiration dating, etc.), and inactive ingredients.

The Package Insert provided in Sequence 0645 contains the Prescribing Information including indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, use in specific populations, description, clinical pharmacology, nonclinical toxicology, storage and handling, patient counseling information. The document also includes patient information and instructions.

The device information in the labeling is adequate; however, changes may be requested by CDER and/or DMEPA based on the changes proposed in this PAS.

5.2. Device Specific Labeling Review**Reviewer Comments**

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>) includes a section on labeling recommendations for the label and package inserts. The applicable recommendations outlined by the guidance (e.g., amount of drug, fill weight, storage conditions, manufacturing details, prescription symbols, etc.) were provided in the labeling. Other elements such as number of sprays, shake instructions, priming sprays, and cleaning were not included as this is a single use device that does not require priming or shaking. The Instructions for Use will be further analyzed in the human factors review.

5.3. 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.

5.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The Sponsor has provided the Drug Facts Label for the proposed OTC designation. The labeling includes all requirements from a device perspective.	
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

6. DESIGN CONTROL [SUMMARY](#)

6.1. 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 The proposed changes included in this submission do not affect the device constituent, or combination product, Essential Performance Requirements (EPRs), risk, and verification/validation. The labeling and human factors will be reviewed by DMEPA; as such, DMEPA is responsible for use-based risks.

6.2. Design Inputs and Outputs

[Essential Performance Requirements](#)

Reviewer Comments The Essential Performance Requirements (EPRs) have not changed in this submission.
--

6.3. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> The current submission does not impact design controls.	
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

7. RISK ANALYSIS

7.1. Risk Management Plan

Reviewer Comments The current submission does not impact overall risks. Any use-related risks will be evaluated by DMEPA.

7.2. Risk Analysis Review Conclusion

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

8. Safety Review for Potential Post-Market Device Failures

8.1.1. Integrated Summary of Safety

To support the change in designation from Rx to OTC, the Sponsor has performed an Integrated Summary of Safety (ISS) study to provide a detailed analysis of safety data. This study was completed in August 2021 to demonstrate consistency and reliability of the combination product. The data was obtained from FDA FAERS database, WHO Vigibase, and medical/scientific literature. The review below is focused on device malfunctions and product quality issues as they relate to the device. The data obtained regarding use errors and the naloxone drug constituent are deferred to the respective disciplines. In conclusion of this study, the Sponsor states there is no change to the current known risk-benefit profile of the product.

The data obtained from FEARS and Vigibase is shown below. The focus of review is intranasal administration.

	FAERS	Vigibase
# of Unique case IDs	850	1,292
# of Adverse events	3276	3912
Data lock point of dataset	31MAR2021	05MAY2021
Missing information (from the dataset)	Marketing status Dose formulation Route Duration of use	Marketing status Dose formulation Duration of use
Exclusion criteria applied to data		
Year of report $\geq$ 2016	Yes	Yes
Route of administration = nasal, unknown, other, transplacental and trans-mammary	N/A	Yes

Database	Nasal n (%)	Other* n (%)	Unknown n (%)	Total Cases N
Vigibase	226 (17.5%)	20 (1.6%)	1047 (81.0%)	1292
FAERS	N/A	N/A	N/A	N/A

Table 1 provided in the ISS details adverse events and the amounts for each based on age for reports obtained through FAERS. There are a total of 850 cases in which users reported at least one (1) adverse event. Within this table, there is one (1) report for Device Dispensing Error, two (2) reports for Medical Device Discomfort, two (2) reports of Device Related Infection, two (2) reports of Device Issue, one (1) report of Drug Delivery System Malfunction, one (1) report of Product Delivery Mechanism Issue, one (1) report of Product Label Issue, one (1) report of Product Packaging Difficult to Open, and four (4) reports of Product Quality Issue.

Table 2 provided in the ISS details adverse events and the amounts for each based on year reported for FAERS reports. A majority of the reports totaling at 330 out of 850 were reported in 2020.

Table 4 provided in the ISS details adverse events and the amounts for each based on age for reports obtained through Vigibase. There are a total of 1,292 cases in which users reported at least one (1) adverse event. Within this table, there is one (1) report of Medical Device Discomfort, one (1) report of Device Difficult to Use, one (1) report of Device Issue, one (1) report of Drug Delivery System Malfunction, one (1) report of Product Delivery Mechanism Issue, one (1) report of Product Expiration Date Issue, one (1) report of Product Label Issue, one (1) report of Product Lot Number Issue, one (1) report of Product Packaging Difficult to Open, four (4) reports of Product Quality Issue, and one (1) report of Product Substitution Issue.

Table 5 provided in the ISS details adverse events and the amounts for each based on year reported for Vigibase reports. A majority of the reports totaling at 245 and 401 out of 1,292 were reported in 2017 and 2020, respectively.

Reviewer Comment

The device malfunctions and/or failures obtained through the review of FAERS and Vigibase demonstrate a low occurrence of device-related issues that impact administration of Narcan to those who have a suspected or confirmed overdose.

8.1.2. Integrated Summary of Safety – Comprehensive Literature Evaluation

The Sponsor conducted a comprehensive literature evaluation from January 2016 through June 2021 to support an OTC designation. There was little to no information regarding device performance. There were two (2) references, shown below, that mentioned the device constituent.

Author / Title	Title	Abstract	Synopsis
Storage, Stability and Efficacy			
Hossain 2022	Chemical stability of naloxone products beyond their labeled expiration dates	OBJECTIVE: The purpose of this study was to evaluate the chemical stability of previously dispensed, expired naloxone products. SETTING: When properly stored, certain products maintain stable, defined as within compendia acceptability, beyond their manufacturer's expiration date. Stockpiling life-saving medications such as the opioid overdose reversing agent naloxone nasal spray (NNS) or injection (NIJ) is of utmost importance to ensure public health emergency preparedness and response. Design/interventions/methods: After each naloxone product was stored at room temperature for several months (6-19) past their labeled expiration date, the level of active therapeutic content and the presence of degradation impurity, 2,29'-binaloxone, were evaluated. RESULTS: The mean potency of naloxone in both NNS and NIJ, up to 10 and 19 months post-expiration, respectively, is within the 90-110 percent United States Pharmacopeia acceptance limit (NNS: 102.8 ± 2.6 percent and NIJ: 106.0 ± 1.3 percent). No impurity was detected in any chromatogram of the expired products. CONCLUSION: In summary, since both NNS and NIJ were found to be chemically stable beyond 10 months of the expiration date, shelf-life extension of climate controlled, commercially available naloxone products should be further investigated as a potential cost savings measure for national strategic stockpiles, emergency medical services, hospitals, and public responders.	The stability of naloxone in intranasal spray devices was noted to demonstrate 102.8 ± 2.55 % mean potency after expiration. This indicates that naloxone's chemical stability is significantly longer than directed as per product labels. Reports of naloxone 25+ years after expiry still maintained efficacy at 89% and higher.

Author / Title	Title	Abstract	Synopsis
Community Use and Take Home Programs			
McDonald 2022	Take-Home Naloxone Kits: Attitudes and Likelihood-Of-Use Outcomes from a European Survey of Potential Overdose Witnesses	Background: Injectable naloxone is already provided as take-home naloxone (THN), and new concentrated intranasal naloxone is now being introduced in Europe. Despite evidence of the effectiveness and cost-effectiveness of THN, little is known about the attitudes of key target populations: people who use opioids (PWUO), family/friends, and staff. We examined the acceptability of different naloxone devices (ampoule, prefilled syringe, and concentrated nasal spray) across 5 European countries. Objectives: The aim of this study was to compare THN target groups (PWUO vs. family/friends vs. staff) in their past rates of witnessed overdose and THN administration (as indicators of future use), current THN device preference, and THN carriage on the day of survey. Method: Cross-sectional survey of respondents (age ≥18) in addiction treatment, harm reduction, and recovery services in Denmark, England, Estonia, Norway, and Scotland. A purpose-developed questionnaire (59 items) was administered in the local language electronically or in a pen-and-paper format. Results: Among n = 725 participants, 458 were PWUO (63.2%), 214 staff (29.5%), and 53 (7.3%) family members. The groups differed significantly in their likelihood-of-future THN use ($p < 0.001$): PWUO had the highest rate of previously witnessing overdoses (352; 77.7%), and staff members reported the highest past naloxone use (62; 30.1%). Across all groups, most respondents (503; 72.4%) perceived the nasal spray device to be the easiest to use. Most reported willingness to use the spray in an overdose emergency (508; 73.5%), followed by the prefilled syringe (457; 66.2%) and ampoules (64; 38.2%). Average THN carriage was 18.6%, ranging from 17.4% (PWUO) to 29.6% (family members). Conclusion: Respondents considered the concentrated naloxone nasal spray the easiest device to use. Still, most expressed willingness to use the nasal spray as well as the prefilled syringe in an overdose emergency. Carriage rates were generally low, with fewer than 1 in 5 respondents carrying their THN kit on the day of the survey.	Publication identifies the key populations of potential naloxone carriers: opioid users, family/friends, and staff relating to overdose mitigations. The target to identify preferential route of administration, carrying rates, and likelihood to act in future overdose emergencies. The results identified nasal spray devices were most frequently reported to be willing to use in future overdose emergencies as well as the easiest to use.

Reviewer Comment

The literature provided in the supplemental ISS evaluation does not mention reports of device failures and/or malfunctions.

8.1.3. Integrated Summary of Safety – Summary of Serious Cases

The Sponsor provided a report containing summaries of serious cases obtained through Emergent's pharmacovigilance safety database (Argus), FAERS, and VigiBase data. There are two (2) reports that mention device failure and/or malfunction and are included below.

Case ID ¹ / Country	Report Type	Gender Age (years)	Preferred Terms MedDRA v25.0	Suspect Products	Outcome	Causality (As determined)	Summary / Comments
20000368RG/ United States	Regulatory Authority	UNK/ Male	Drug withdrawal syndrome Abnormal behaviour Amnesia Anxiety disorder Lumbar spinal stenosis Device occlusion (Foley catheter) Lethargy Meningitis Loss of consciousness Psychotic behaviour Psychotic disorder Spinal cord abscess Drug withdrawal syndrome Nausea Aggression	Naloxone	Unknown	Not assessable	The report describes a patient who multiple conditions that include drug dependence, abnormal behaviour, amnesia, anxiety, lethargy, lumbar spinal stenosis (PT: Lumbar spinal stenosis, (Foley) catheter occlusion, meningitis, loss of consciousness, psychotic behavior, intraspinal abscess, drug withdrawal syndrome, nausea, aggressive behavior and drug overdose. From 2011 to 2012 concomitant medications include enoxaparin, cyclobenzaprine, fentanyl (transdermal), hydromorphone, methadone, morphine, oxycodone, paracetamol, pethidine, promethazine, chlorpromazine, alteplase, diazepam, cefalexin, cefazolin. Some of those medications were infused intravenously that usually require a hospital setting but not reported. Information regarding naloxone is limited (no dates of onset, route or dose) other than it was used after the patient presented hypopnea but no description in the report that was due to overdose. However, hypopnea could have been due to concomitant medications that included narcotics that developed dependency from and was showing symptoms of withdrawal. If those events occurred before 2015, Narcan was not in the US market yet and could not have been the naloxone used. The events could not be evaluated and considered not assessable. Hospitalization was not due to naloxone.
17000220SP/ United States	Spontaneous	UNK/ Female	Drug ineffective Product quality issue	Narcan	Recovered / Resolved	Not reported (legacy report)	The patient received an Narcan Nasal Spray (route & dosage unspecified) for treatment of an unspecified drug overdose. After an unspecified period (after the overdose), multiple 4 mg doses were attempted. Apparently, the device malfunctioned and didn't deliver the dose. Information was incomplete to properly assess the case but if the dose was not delivered, lack of effect doesn't apply.

Reviewer Comment

The above reports of serious cases do not contain enough information to determine the exact nature of the device malfunctions/failures or the root causes. For the report 20000368RG, it is unclear what Naloxone product was used (i.e., route) to determine applicability to the current review.

8.1.4. Integrated Summary of Safety – FAERS

The Sponsor provided a supplemental ISS document containing FAERS reports and associated route of administration. The data reviewed in this document was obtained from January 2016 through June 2021. In this time, there were a total of 1,134 cases which contained 4,139 events.

Patient Demographics	Intranasal ^a		Non-nasal ^b		Unknown ^c		Total N=1,134
	Serious N=71	Nonserious N=193	Serious N=205	Nonserious N=27	Serious N=465	Nonserious N=173	
Gender							
Female	27	79	75	10	241	61	493 (43.5)
Male	37	100	73	12	159	79	460 (40.6)
Unknown gender	7	14	57	5	65	33	181 (16.0)
Age							
< 2 years	0	0	1	0	1	0	2 (0.2)
2 to < 18 years	0	1	11	0	13	1	26 (2.3)
18 to < 65 years	38	55	78	15	171	55	412 (36.3)
65 years and older	6	10	21	1	26	15	79 (7.0)
Unknown age	27	127	94	11	254	102	615 (54.2)

Within this report, there are a total of 28 cases that claim a Product Use Issue with none reported directly for Intranasal, two (2) for Non-Nasal, and 26 for Unknown routes. Additionally there are two (2) cases of Wrong Technique reported for Intranasal.

For specific product issues, the breakdown is shown below. There are fewer reports of device failure and/or malfunctions for the Intranasal route.

System Organ Class Preferred Term	Intranasal ^a N=321, n (%)	Non-nasal ^b N=1,029, n (%)	Unknown ^c N=2,141, n (%)	Total N=3,491, n (%)
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Product issue	1 (0.31)	7 (0.68)	3 (0.14)	11 (0.32)
Device malfunction	0	0	1	1
Device occlusion	0	0	1	1
Product dosage form issue	0	1	0	1
Product quality issue	1	0	0	1
Product solubility abnormal	0	1	1	2
Product substitution issue	0	5	0	5

8.1.5. Integrated Summary of Safety – ARGUS

The Sponsor provided a supplemental ISS document containing Argus reports. The data reviewed in this document was obtained from January 2016 through June 2021. Within this timeframe, the following distribution of cases was observed.

	Narcan Nasal Spray	Naloxone	Total Number of Cases
Serious	54	39	93
Non-serious	246	58	304
Total Number of Cases	300	97	397

The following table shows the distribution of cases based on age for the reports obtained through Argus search. The reports of device failures and/or malfunctions are minimal.

System Organ Class Preferred Term	Child^a N=1 n(%)	Adolescent^b N=22 n(%)	Adult^c N=206 n(%)	Elderly^d N=56 n(%)	UNK^e N=47 n(%)	Grand Total N=332 n(%)
Product issues	n=0	n=0	n=2 (1.0)	n=0	n=1 (1.9)	n=3 (0.9)
Device malfunction	0	0	1	0	0	1
Device occlusion	0	0	1	0	0	1
Product quality issue	0	0	0	0	1	1

8.1.6. FDA Database Searches

A search of relevant FDA databases was conducted using the search terms “Narcan” and “Naloxone” to determine if there have been any Medical Device Reports (MDRs), recalls, Manufacturer and User Facility Device Experience (MAUDE), or MedSun reports that may provide insight on post-market issues. These searches did not return applicable information.

Reviewer Comment

Overall, the safety information provided regarding Narcan and Narcan Nasal Spray appear to support the switch from Rx to OTC. Without reported problems of device failures it is difficult to assess the potential of failures. In an attempt to do so, I reviewed the safety data provided by the Sponsor and attempted to obtain additional information through FDA databases. At this time with no changes to the device constituent, specifications, manufacturing, or control strategy, the switch to OTC can be supported from a device perspective. With a wider reach of potential users after an OTC designation, there may be potential for more user errors. However, this aspect will be assessed by DMEPA.

8.2. Potential Post-Market Device Failures Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments There are no indications that a switch to OTC would impact device performance.	
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

8.3. Discipline Specific Sub-Consulted Review Summary

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

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

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

10. HUMAN FACTORS VALIDATION REVIEW

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

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

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

11.2. Quality Systems Documentation Review

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

11.3. Control Strategy Review

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

Essential Performance Requirements Control Strategy Table

Reviewer Comments The Sponsor is not changing the device constituent in this PAS. All specifications and release testing activities have not been changed.
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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

11.4. 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 See above.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

<<END OF REVIEW>>

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/s/

PHONG T PHAM
02/09/2023 12:49:47 PM



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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: Narcan Nasal Spray

Application Number: NDA 208411/s-006

Applicant: Emergent Operations Ireland LTD

Indications:

- an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
- intended for the immediate administration as emergency therapy in settings where opioids may be present
- not a substitute for emergency medical care

Dosage Form Solution for Intranasal Delivery

Dosage Strength: 4 mg/spray

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 February 15, 2023. The content of this DPMH review was incorporated into the FDA Briefing Information provided to the AC members and to the public.

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.¹ Between 1999 and 2016, mortality rates increased nearly 3-fold, and nearly 9000 children and adolescents died from opioid poisonings¹. 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%
- Children 10 to 14 years of age – increased by 150.0%

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

- 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.¹

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 2012² and again in 2015.³ 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.⁴ 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.

² 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>

³ Exploring Naloxone Uptake and Use Public Meeting July 1 and 2, 2015: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM469456.pdf>

⁴ DPMH Memorandum 11/10/2015.DARRTS.under NDA 208411 S001

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

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

Source: Adapted by this reviewer from Drugs@FDA.

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

The Applicant submitted Supplement 006 to NDA 208411 on 9/29/22 seeking to switch Narcan Nasal Spray from prescription to nonprescription status.⁵ The drug and device components proposed for nonprescription use are identical to that currently approved for prescription use. The sNDA contains the following pivotal data:

- Simulated human factors validation study
- Label comprehension study
- Post-marketing safety data

This memorandum summarizes the relevant pediatric regulatory history for Narcan Nasal Spray as well as factors unique to the pediatric population that DPMH previously considered to help inform the benefit-risk assessment for prescription use of the product in all ages.

III. Basis for Pediatric Approval for Prescription Use of Narcan Nasal Spray

The approval of Narcan Nasal Spray was based on results from a single relative bioavailability (BA) study in healthy adult volunteers that was further supported by a human factors validation study in adults and adolescents 12 years of age and older. Relative BA data supporting the approval of Narcan Nasal Spray demonstrated that a 4 mg IN dose provides systemic naloxone exposures equivalent to that achieved with a 2 mg IM dose. FDA approved the fixed dose 4 mg IN product to ensure availability of a non-invasive naloxone formulation to provide a life-saving therapeutic option in the full pediatric age range for emergency use in the community setting. Given the potentially life-threatening nature of this condition if untreated or inadequately treated, conducting controlled efficacy trials pose ethical and logistical concerns. Therefore, no new pediatric efficacy or PK data were required, and the Applicant leveraged efficacy data for the

⁵ Request for Priority Review Designation

previously approved Narcan for injection to support the pediatric approval.⁴ Additional safety data supplied by the NDA holder to support pediatric approval of the proposed Narcan Nasal Spray dose primarily consisted of retrospective reviews, case reports, and case series. Despite their inherent limitations, the available publications provided some insight into how naloxone was being used in healthcare settings.

There have been no well-controlled studies on the optimal dose of naloxone nasal spray for pediatric patients with acute opioid overdose in different clinical settings or publications describing use of naloxone for pediatric patients in the community. Available data are limited to several retrospective case reviews⁴ assessing cardiovascular and respiratory responses and any adverse effects associated with intravenous (IV) naloxone use in pediatric intensive care units and emergency rooms. These reports described clinical improvements in all patients treated with IV naloxone with no serious adverse events. The median (range) total dose used was 0.1 mg (0.01 to 7 mg). None of the patients in the published case reports developed arrhythmias, hypotension, seizures, emesis, or cardiac arrest after naloxone administration. Case reports⁴ cited by the NDA holder for Narcan Nasal Spray included 9 pediatric cases of acute opioid overdose in patients less than 7 years of age; 6 of the 7 patients were less than 3-years of age. Acute opioid overdose in these cases was due to accidental exposure to buprenorphine/naloxone co-formulations (n=5), acetaminophen/codeine co-formulations (n=1), nor-methadone (n=1), fentanyl (n=1), and morphine (n=1). Eight of the 9 patients received naloxone as an IV bolus, IV infusion, or both as part of their medical care. All 9 patients were hospitalized and fully recovered. No naloxone-related adverse events were described.⁴

IV. Unique Pediatric Considerations

a. Intranasal Dosage Delivery

Differences in nasal morphology, nasal cavity dimensions, and pattern of IN particle deposition between adults and pediatric patients exist that may potentially cause the IN deposition of drug in aerosol particles to differ in the two populations.⁴

There is some published evidence⁶ that the differences in nasal morphology are associated with large inter-individual variability in the pattern of deposition of intranasally administered aerosol particles among pediatric patients under age 5 years.

Factors that potentially may decrease IN drug absorption include the following:

- Drug formulations with high molecular weight, low lipophilicity and with a net charge at physiologic pH
- Reduced contact with the nasal mucosa such would occur in the presence of epistaxis or with copious nasal secretions
- Poorly fitted actuator tip, either too small or too large, would potentially lead to inaccurate dose delivery and local and ocular injury to young patients.⁴

⁶ 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).

b. Safety

Despite the potential for developmental differences in nasal anatomy and morphology in pediatric patients to adversely impact delivery of the intended dose, post marketing safety reports received by FDA since the approval of Narcan Nasal spray have shown no evidence suggesting drug failure or safety concerns in the pediatric population.

During the initial review of Narcan Nasal Spray, DPMH raised concerns about the safety of the proposed product as it relates to IN drug delivery. Specifically, DPMH requested DAAP to confirm that the actuator tip may be properly positioned despite differences in nasal morphology and can deliver a minimally effective dose in pediatric patients under five years of age. Further, given the fixed dose, DPMH raised concerns that a single 4-mg dose, assuming 100% bioavailability, could result in exposure in neonates that could be approximately 100-fold higher than the established safe and effective exposures for an adult given the approved naloxone for injection. However, we note that the approved IV labeled dose (0.01 mg/kg IV)⁷ was approximately 10-fold lower than the recommended dose by the American Academy of Pediatric Committee on Drugs (0.1 mg/kg parenteral)⁸. DPMH raised additional concerns for the potential to induce respiratory distress with intranasal instrumentation in the youngest patients because of obligate nasal breathing. Therefore, DPMH recommended a post-marketing requirement (PMR) and a post-marketing commitment (PMC) to capture any treatment failures or serious adverse events (AEs) of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age and to evaluate the pharmacokinetic profile of this product in patients under five years of age, respectively.⁹ FDA issued the following PMR under Section 505(o)(3) of the Food Drug and Cosmetic Act:

2990-2: Establish a post-market monitoring program for detection and evaluation of under-dose and failure-to-dose events, regardless of cause, and provide periodic reports to the Agency which contain descriptions of each reported event along with results of root cause and contributing-cause analyses.

Final Report Submission: January 2018

The NDA holder submitted an Interim Report for NDA 208411 PMR 2990-2 to the Annual Report for the NDA on February 27, 2017. The report showed a total of 5 complaints for Narcan Nasal Spray from November 18, 2015, to November 17, 2016 in adult patients. Two reports were for Lack of Effect in which one user was revived using Narcan Nasal Spray but subsequently died and the other user was not revived using the drug product. The remaining 3 reports were regarding improper device performance; one product broke during package opening, another complained the spray came out too fast and the third report described an empty device. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the two complaints associated with packaging and usability of the product. DMEPA obtained additional narratives through an Information Request showing one user did not follow packaging instructions regarding opening the package and the other user merely was voicing an opinion that the blister packaging was inconvenient. The Office of Surveillance and Epidemiology's review¹⁰ of FDA Adverse Event Reporting System (FAERS), Periodic Safety Reports, and IMSP Newsletters did

⁷ SPL Labeling accessed from FDALabel on 1/19/2023

⁸ American Academy of Pediatrics Committee on Drugs. Naloxone Use in Newborns. Pediatrics 65: 667- 669, 1980.

⁹ Medical Officer review Adapt PMR IN Narcan review under NDA 208411 in DARRTS on 9-11-2018

¹⁰ Medical Error Review under NDA 20841 in DARRTS on 8/1/2017

not identify any relevant safety cases. The Center for Devices and Radiological Health (CDRH) reviewed complaints associated with device performance and found no product deviations or errors in the manufacture of the batch/lot. DMEPA, CDRH, and the DAAP concluded, after reviewing the reports, that labeling for this product was adequate and that the PMR was fulfilled⁹.

V. 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 the pivotal data included in the sNDA support whether adolescents 12 years of age and older, younger 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.¹¹ Approximately 11% of US children under 14 years of age live with at least one family member who is or was addicted to opioids.¹² Teaching these children how to correctly administer naloxone could be lifesaving, 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 those less than 20 years of age.¹³ Ideally, consumer use studies and human factors validation studies evaluating the safe and effective use of this drug product by the “intended users, for the intended uses and for the intended use environment”¹⁴ should include children potentially as young as 8 years of age¹², using both adult and pediatric mannequins to assess effective use under both conditions.

¹¹ <https://www.census.gov/newsroom/press-releases/2016/cb16-192.html>

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

¹³ 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

¹⁴ Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development: Draft Guidance for Industry and FDA Staff. February 2016

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DMEPA 2 FILING 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)

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Date of This Review:	November 28, 2022
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 208411/S-006
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength:	Narcan (naloxone hydrochloride) nasal spray, 4 mg per spray
Device Constituent:	Nasal Spray
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Emergent Biosolutions
FDA Received Date:	September 29, 2022; November 4, 2022; November 23, 2022
OSE RCM #:	2022-2721
DMEPA 2 Human Factors Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita White, PharmD
DMEPA 2 Deputy Division Director:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF REVIEW

On September 29, 2022, Emergent Biosolutions submitted NDA 208411/S-006 for the full prescription-to-OTC (Rx-OTC) switch of Narcan (naloxone hydrochloride) nasal spray, 4 mg. The submission included the human factors (HF) validation study report and the proposed container labels and carton labeling. This review provides our assessment of the supplement's fileability.

2 DISCUSSION

The HF validation study report did not include participants' subjective feedback and root cause analysis for each use error, close call, and use difficulty. Therefore, on 10/21/2022, we issued an Information Request (IR) to request the aforementioned HF study data for Steps 2, 3, and 4 of the Drug Facts Label (DFL) and a discussion of any additional risk mitigation measures to address the identified use errors, close calls, and use difficulties. On 11/4/2022, the Applicant provided a response.^a

The HF validation study report stated the Applicant completed an updated Use Failure Modes and Effects Analysis (uFMEA) but the September 29, 2022 submission instead included a high-level uFMEA. Therefore, on 11/18/2022, we issued an IR to request the comprehensive, updated uFMEA. On 11/23/2022, the Applicant provided a response.^b

3 CONCLUSION

NDA 208411/S-006 for Narcan (naloxone hydrochloride) nasal spray is fileable from DMEPA2's perspective.

^a Human Factors Validation for Narcan NDA 208411-S/006. Dublin, Ireland: Emergent Biosolutions; 2022 NOV 04. Available from: <\\CDSESUB1\EVSPROD\nda208411\0633\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report.pdf>

^b RPT056282 Narcan Unit Dose Use FMEA (OTC) NDA 208411-S/006. Dublin, Ireland: Emergent Biosolutions; 2022 NOV 23. Available from: <\\CDSESUB1\EVSPROD\nda208411\0638\m5\53-clin-stud-rep\535-rep-effic-safety-stud\management-of-suspected-acute-opioid-overdose\5354-other-stud-rep\pivotal-human-factor\pivotal-human-factor-study-report-2.pdf>

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