Joint

Nonprescription Drugs Advisory Committee (NDAC) and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting for

sNDA 208411 / S-006 Narcan (naloxone hydrochloride) nasal spray, 4 mg

Introduction

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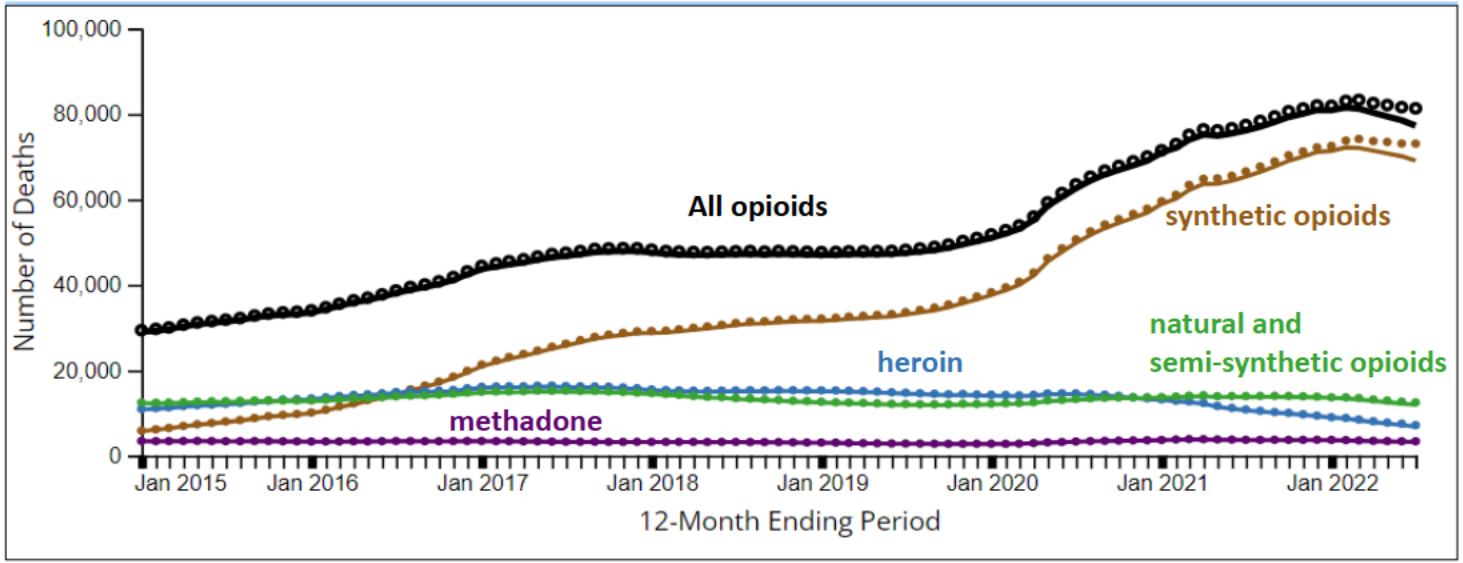
February 15, 2023

Opioid Overdose and Death Is a Public Health Crisis

- The United States is experiencing a devastating public health crisis
- Opioid overdose can occur in:
  - patients prescribed an opioid medication
  - people who misuse or abuse opioids
  - victims of accidental exposure
- Drug overdose is currently the leading cause of accidental death in the United States
- Between 1999 and 2016 nearly 9,000 children and adolescents died from opioid poisoning, with the highest annual rates among those ages 15-19

Opioid Overdose Deaths in the United States

12-Month Ending Provisional Number of Drug Overdose Deaths by Opioid Class 2015-2022



Source: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Narcan (Naloxone HCl)

Approved in 1971 as Narcan

- Solution labeled for intravenous (IV), intramuscular (IM), or subcutaneous (SC) use
- A nonselective opioid receptor antagonist
- Indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids
- Not optimized for use by nonhealthcare practitioners

Current FDA-approved Presentations of Naloxone

- Ampoules and vials
  - for intramuscular, subcutaneous, intravenous use
- Prefilled syringes
- Autoinjectors
- Nasal Sprays 4 mg and 8 mg

Narcan Nasal Spray 4 mg for Community Use

- Developed for ease of administration in community by laypeople
- No additional supplies or assembly needed before use
- May be administered to all ages including children and neonates
- When administered as soon as opioid overdose is suspected, naloxone can prevent hypoxia-associated injury and death and reverses the life-threatening effects of an opioid overdose
- Can be obtained by prescription from healthcare provider, prescription under statewide naloxone standing orders, or through harm reduction groups

Naloxone Distribution Far Greater Than Typical Pharmacy Supply Chain

- Traditional pharmacy supply chain includes hospitals, clinics, retail outlets, mail-order, and government facilities
- Other distribution channels allow naloxone distribution to harm reduction programs and prisons
- These supply routes are not captured in databases available to FDA

Potential Barriers to Prescription Status

- Some pharmacists find standing orders more complicated, may choose not to stock naloxone, and may not carry
- Difficult for harm reduction groups to obtain bulk purchases
- Stigma of opioid dependence may inhibit purchase requiring interacting with pharmacist
- Nonprescription naloxone may help address these barriers

If Naloxone Becomes a Nonprescription Product

- It may be sold at many venues besides pharmacies, such as:
  - Vending machines
  - Convenience stores
  - Supermarkets
  - Big Box stores

87 FR Notice 68702 November 2022

FDA made a preliminary assessment that certain naloxone drug products – up to 4 mg nasal spray (NS) and up to 2 mg autoinjector – may be approvable as safe and effective for nonprescription use pending FDA review of additional supportive information and data.

- If and when FDA approves a nonprescription naloxone product, naloxone products labeled as “Rx only” with no clinically meaningful difference from the approved nonprescription product will be considered misbranded.
- The Notice encourages application holders of prescription (Rx) naloxone products to contact FDA as early as possible to initiate discussion about a possible switch to nonprescription.
- The Notice solicited comments and information from the public. The public comment period closed on January 17, 2023.

Nonprescription Products

- Safe (acceptable safety margin)
- Low misuse and abuse potential
- Condition to be treated is self-diagnosable
- Does not require a healthcare practitioner for safe and appropriate use
- Adequate labeling so that consumers can:
  - Self-diagnose
  - Self-select
  - Self-administer
  - Know when to stop use

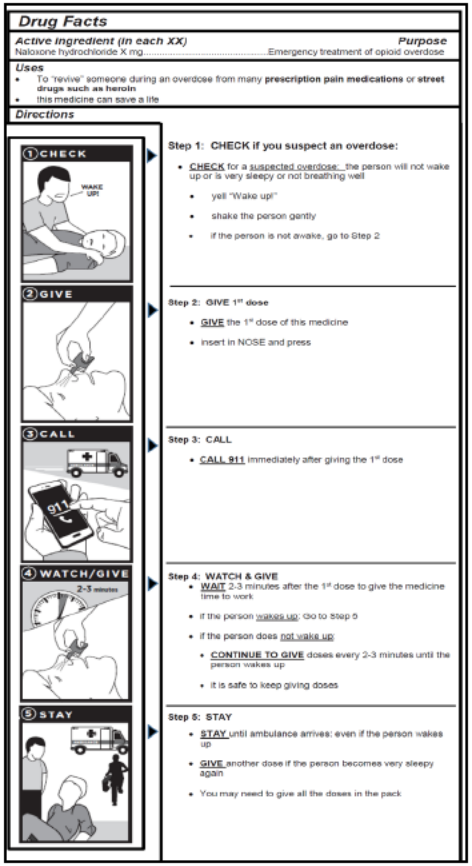
Often requires consumer behavior studies to support this

Additional Supportive Information Submitted With Application

The same drug/device combination product is proposed for the prescription and nonprescription product. What's new is:

1. Postmarketing safety review of data (2016 – 2021)
2. Validated Drug Facts Label with appropriate directions for use
3. Evidence from a simulated use human factors validation study performed by Applicant that the drug product can be used correctly by the intended user

FDA Model DFL With Pictograms



Drug Facts

Active ingredient (in each XX) — **Purpose**
Naloxone hydrochloride X 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

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

5 Steps	
Step 1	CHECK if you suspect an overdose
Step 2	GIVE 1st dose
Step 3	CALL 911
Step 4	WATCH AND GIVE
Step 5	STAY

Product-Specific Directions for Administration

Issues to Consider During AC Meeting

- Efficacy
  - Narcan NS's efficacy as a prescription drug is well established, but is the proposed design of the user interface, including labeling, for the nonprescription drug optimized so that consumers will use it correctly without the help of a healthcare intermediary?
- Safety
  - Narcan NS's safety is well established, but is it likely that the product will remain safe in the nonprescription setting?

U.S. FOOD & DRUG ADMINISTRATION

Joint Nonprescription Drugs Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee Meeting

Regulatory Overview of Narcan Nasal Spray & Postmarketing Safety Data

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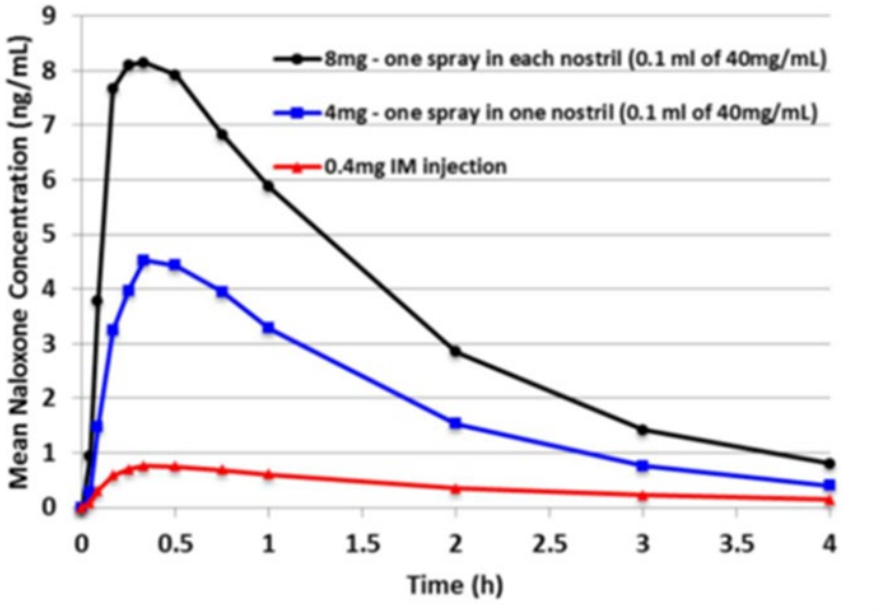
February 15, 2023

Outline

- Brief Regulatory History of Narcan Nasal Spray (NNS)
- Postmarketing Safety Data
  - Applicant's General Analyses from ARGUS
  - FDA's Analyses of Safety Topics of Interest from the FDA Adverse Event Reporting System (FAERS)
- Conclusions

Regulatory History of NNS, NDA 208411

- Approved in 2015 as the first approved intranasal naloxone (INN) product
- Approval relied upon safety and efficacy of an approved naloxone product (NDA 016636)
  - Exceeded exposure achieved by naloxone 0.4 mg IM, including in the early critical period
- Product launched February 2016

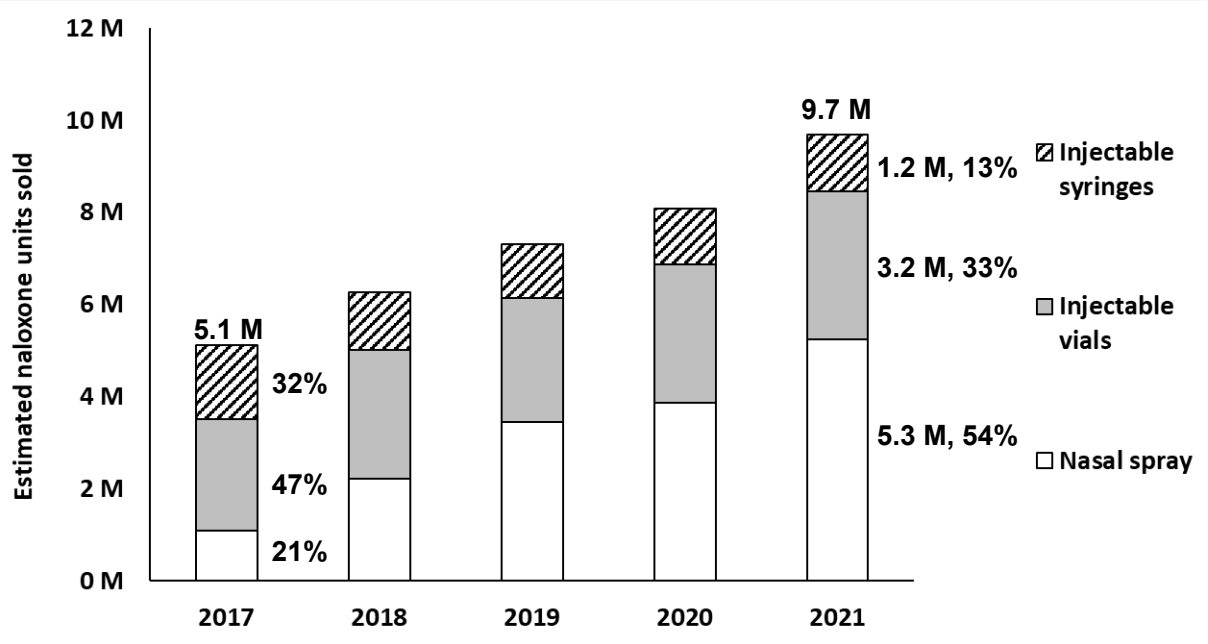


Source: FDA Review

Pharmacovigilance Database Limitations

- Spontaneous reporting
  - Adverse events (AEs) underreported
  - Possibility for multiple reporters and duplicates
  - Variable reporting quality/data often incomplete
  - Reporting biases
  - Causal association is difficult to establish
- Unknown denominator

Manufacturer Sales Data

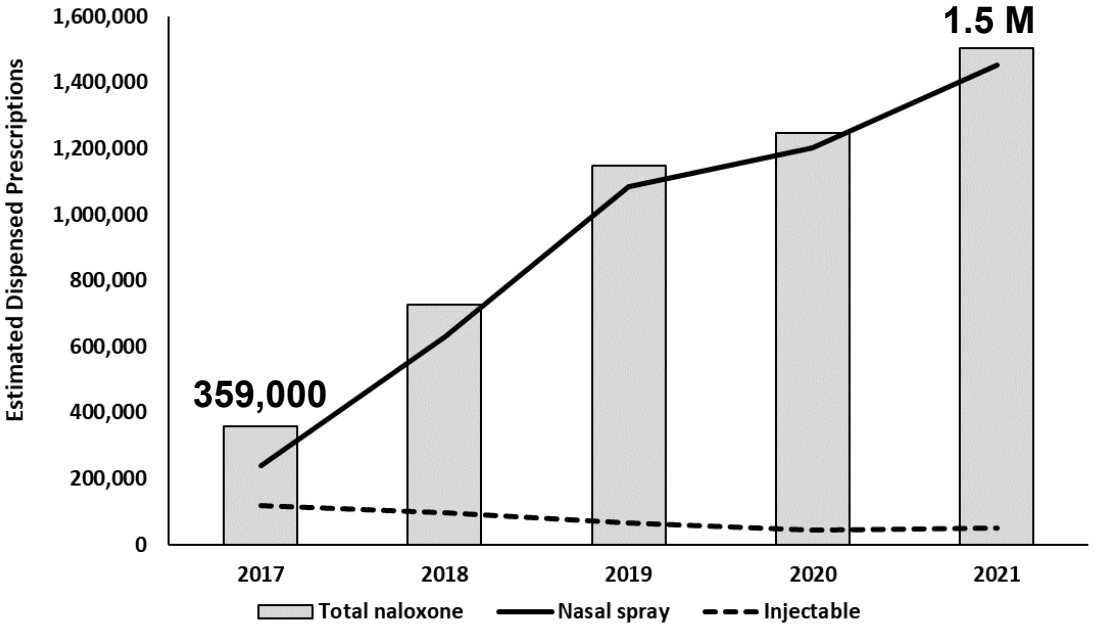


Nationally Estimated Number of Naloxone Units (Vials, Syringes, Nasal Sprays) Sold From Manufacturers to U.S. Channels of Distribution, *Stratified by Product Formulation*, Annually 2017 to 2021.

Source: IQVIA National Sales Perspective™. Time period 2017 to 2021, extracted Jan 2023. M = millions.

Distributed products do not provide a direct estimate of use. These data underestimate total naloxone availability as they do not capture direct sales or donations from manufacturers, for example to harm reduction organizations. These data may vary from previous/other analyses due to timing of data source updates and when data were retrieved from the tool.

Dispensed Prescription Data



Nationally Estimated Number of Naloxone Prescriptions Dispensed From U.S. Outpatient Retail, Mail-Order, and Long-Term Care Pharmacies, *Stratified by Product Formulation*, Annually 2017 to 2021.

Source: Symphony Health Metys™. Time period 2017 to 2021, extracted Jan 2023. M = millions.

Dispensed prescriptions do not provide a direct estimate of use. These data underestimate total naloxone availability as they do not include naloxone received outside pharmacy settings, for example from harm reduction organizations.

ARGUS: Introduction and Context

Cases Reported to ARGUS*

Total Cases	NNS	Naloxone
397	300 (75.6%)	97 (24.4%)

*Covers presumed INN only

ARGUS: Descriptive Characteristics

Gender, Age, Seriousness (2016 to 2021)

	< 2 yrs n=1 (0.2)		2 - < 18 yrs n=7 (1.7)		18 - < 65 yrs n=220 (55)		≥ 65 yrs n=21 (5.3)		Unknown n=148 (37.8)		Total N=397 n (%)
	S	NS	S	NS	S	NS	S	NS	S	NS	
Female	0	0	2	0	24	60	3	11	13	50	163 (41)
Male	0	0	2	1	32	94	2	5	7	60	203 (51)
Unknown	0	1	1	1	2	8	0	0	5	13	31 (7.5)
Total	0	1	5	2	58	162	5	16	24	123	397

Abbreviations: S, serious; NS, nonserious

Source: Module 5.3.5.3 Emergent (ARGUS) Safety Database Analysis, submitted November 22, 2022, Table 2, page 5

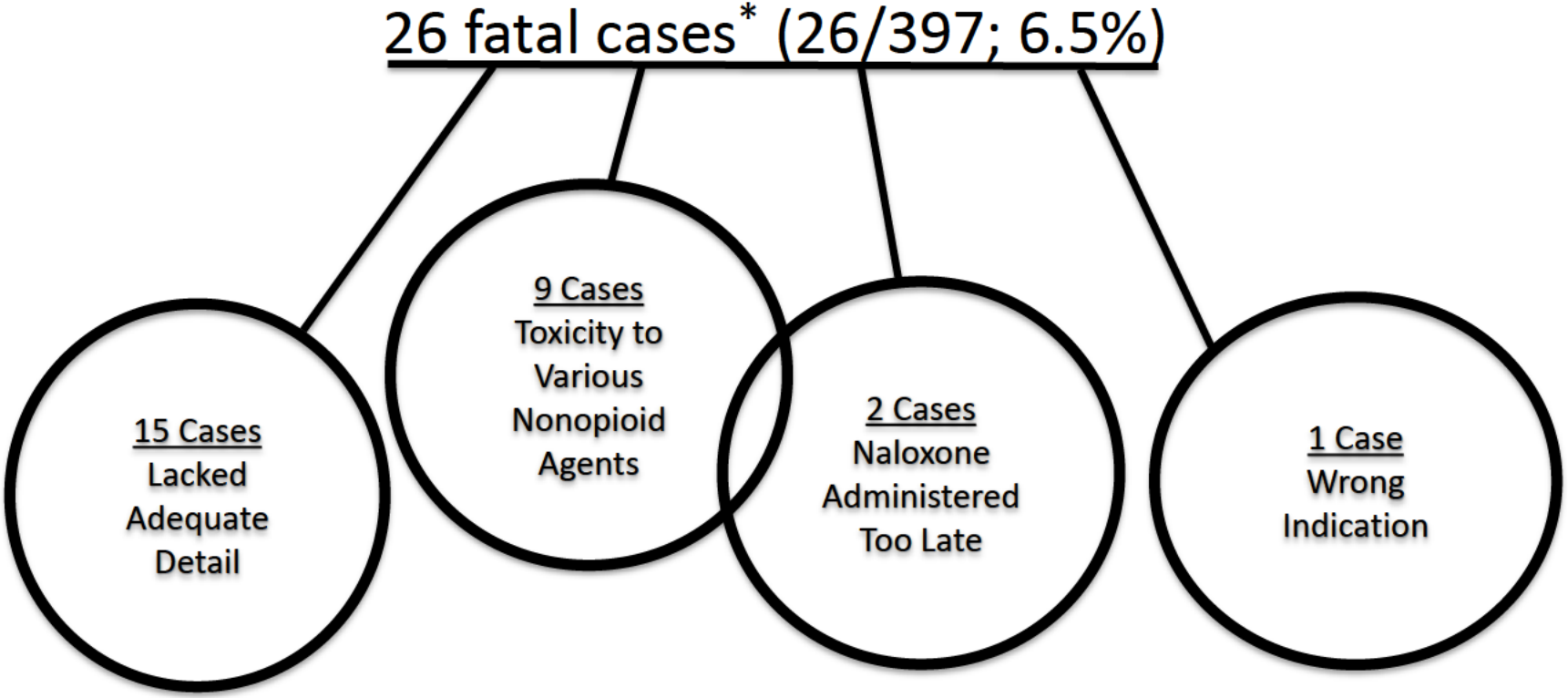
- 93 (23.4%) serious cases
  - Most often occurring in the 18 to < 65-years-old bracket
  - Few serious cases in ≥ 65 years, or < 18 years; no serious cases in < 2 years

ARGUS: Frequent PTs (>1%), Serious Cases

Preferred Term (PT)	< 2 yrs n=0	2 - < 18 yrs n=23	18 - < 65 yrs n=206	≥ 65 yrs n=56	Unknown n=47	Total N=332 n (%)
Death	0	0	5	0	9	14 (4.2)
Drug withdrawal syndrome	0	0	12	0	0	12 (3.6)
Seizure	0	1	9	0	2	12 (3.6)
Drug Ineffective	0	0	6	0	3	9 (2.7)
Loss of Consciousness	0	0	6	1	0	7 (2.1)
Toxicity to various agents	0	2	3	0	1	6 (1.8)
Vomiting	0	0	5	0	1	6 (1.8)
Drug dependence	0	0	5	0	0	5 (1.5)
Overdose	0	0	3	2	0	5 (1.5)
Cardiac Arrest	0	1	3	0	1	5 (1.5)
Unresponsive to Stimuli	0	0	3	2	0	5 (1.5)
Respiratory Failure	0	1	1	0	2	4 (1.2)
Unintentional Use for Unapproved Indication	0	0	2	1	1	4 (1.2)

Source: Adapted from Module 5.3.5.3 Emergent (ARGUS) Safety Database Analysis, submitted November 22, 2022, Appendix I, page 16

ARGUS: Fatal Outcomes



*One case reported more than one etiology

ARGUS: Special Populations

Population of Interest	Total Cases	Serious Cases	Deaths	Case Details from Serious Cases
Pediatrics (< 18)	8	5	2	• 4 serious cases reported AEs related to underlying nonopioid drug of overdose (including 2 fatalities) • One case of seizure/mini-strokes in the setting of naloxone use for opioid overdose

Geriatrics (≥ 65)	21	5	0	• No predominant PT
				  • Blood culture positive (n=3)
				  • Oral candidiasis, pseudomonas, strep infection, unresponsive to stimuli (n=2, each)

Pregnant Women	4	1	0	• Single serious case reported premature delivery, but case was confounded by maternal use of multiple psychoactive medications and nicotine

FDA's Analyses of FAERS

- Focus was to evaluate the safety of INN in the community setting

Safety Topics of Interest

- Naloxone-induced precipitated withdrawal
- Limited efficacy
- Device use errors and additional medication errors

FAERS Analysis- Methods

- Period covering 1/2016 to 11/2022

- Analysis of any U.S. FAERS cases reporting INN in community setting
  - Exclusions: duplicates; non-U.S. reports; cases not involving single-ingredient naloxone/unclear if received naloxone; route of naloxone was not IN or unknown; naloxone administered in a clinic setting; unassessable/insufficient information

Descriptive Characteristics: Community Use INN

N=318	n	%
Serious outcome(s)	**81**	***25.5***
Death	15	4.7
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*
No. of doses administered (range 1 – 7 doses)		
1	104	*32.7*
2	75	*23.6*
≥3	19	*6*
Not reported	120	*37.7*
Naloxone cumulative dose (mg)		
≤8	142	*44.7*
>8	16	*5*
Not reported	160	*50.3*
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*

Source: FDA Review

Naloxone-Induced Precipitated Withdrawal: Methods

- Subset analysis among INN cases
  - 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 Clinical Opiate Withdrawal Scale [COWS]) provided in the report
  - COWS is an 11-item scale that provides a reproducible assessment of signs and symptoms of opioid withdrawal

Naloxone-Induced Precipitated Withdrawal

N=180 (180/318; 56.6%)	n	%
Serious Outcome(s)	**35**	***19.4***
Death	0	*0*
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	2	*1.1*
Naloxone cumulative dose (mg)		
≤8	91	*50.6*
>8	5	*2.8*
Not reported	84	*46.7*
Reported withdrawal or symptom(s) consistent with withdrawal		
COWS score of ≥5‡	21	*11.7*
COWS score <5 or no COWS score	159	88.3

‡ Per COWS scale, scores of 5-12 indicate mild withdrawal.

Source: FDA Review

Limited Efficacy: Methods

- Subset analysis among INN cases
  - Naloxone reported as ineffective in the narrative and supported by case details

Limited Efficacy

N=24 (24/318; 7.5%)	n	%
Serious Outcome(s)	**14**	***58.3***
Death	2	*8.3*
Naloxone cumulative dose (mg)		
≤8	10	*41.7*
>8	2	*8.4*
Not reported	12	*50.0*
No. of doses administered (range 1 – 6 doses)		
1-2	16	*66.6*
≥3	5	*20.8*
Not reported	3	*12.5*
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*

Source: FDA Review

Device Use Errors and Medication Errors: Methods

- Period covering 1/2016 to 11/2022
- Any U.S. FAERS case involving device use errors or medication errors for naloxone nasal spray devices*
  - Exclusions: device malfunction, cases with insufficient information, cases not involving INN, administration of expired product

*FDA uses 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 factor

Device Use Errors

Wrong Technique of Administration (n=9)	n	%
Serious Outcome(s)	0	0
Description of Error		
Spraying NS into the air instead of patient's nose	3	*33.3*
Not waiting 2-3 minutes between doses	3	*33.3*
General confusion about the use of the device	2	*22.2*
Administering two doses of the medication to the same nostril	1	*11.1*
Reason for Use		
Emergency situation	6	*66.7*
Nonemergency situation (e.g., training in case of emergency)	3	*33.3*

Source: FDA Review

*FDA uses the NCC MERP Taxonomy of Medication Errors to describe the type of medication error and contributing factor

Additional Medication Errors

Wrong Indication

- Multiple cases (58/318; 18.2%) of use for the wrong indication
  - INN was used instead of another nasal spray or due to general lack of knowledge regarding naloxone's indication
  - 3 cases (3/318; 0.9%) reported a serious outcome

Wrong Storage Condition

- Four cases (4/318; 1.25%) of accidental wrong storage conditions
  - No serious outcomes reported

Conclusions

- The postmarketing safety data for INN do not indicate any new safety issues
- Consumers generally administered INN for the correct indication and the majority of cases had nonserious outcomes
- Relatively few cases were identified reporting serious naloxone-induced precipitated withdrawal or limited efficacy
- The highest risk device use error was related to users spraying naloxone outside of the patient's nostril
  - The Applicant's plan to co-package 2 nasal spray devices in a carton may help to mitigate this risk
- Wrong indication and accidental wrong storage errors were identified related to use of INN
  - These errors may be mitigated by clear and prominent labeling displaying the product's name, indications, and storage information

Nonprescription Naloxone Model Drug Facts Label Comprehension Study

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Label Comprehension Studies: Overview

- Conducted for many prescription to nonprescription switch NDAs
- Assess consumer understanding of Drug Facts Label (DFL)
- Based upon FDA Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products (2010)

Label Comprehension Studies: Methodology

- Enroll demographically diverse populations; limited literacy subpopulation should be at least 30% of sample
- Participants are given a DFL to read at their own pace
- They are then asked questions about the DFL and can refer to it whenever they want
- Typically, questions are scenario questions based on a hypothetical third party, to assess participant ability to correctly apply information from the DFL
- Ultimately, these studies can only address comprehension, not predict actual behavior

Label Comprehension Studies: Endpoints

- Identify important primary endpoints and establish target thresholds
  - Endpoints should reflect the clinical significance of the DFL statements being assessed
  - Endpoints align with lower bound (LB) of the 95% confidence interval
  - Typically, label comprehension studies (LCS) have multiple primary endpoints and are designed to assess comprehension of all primary endpoints
  - Thresholds are targets, not hard pass/fail thresholds
  - Secondary and exploratory endpoints typically do not have thresholds

Contrasts Between Label Comprehension and Human Factors Studies

Study Type	Study Objective	Sample	Literacy	Assessment of steps in product administration
Label Comprehension	Evaluate consumer comprehension of the DFL	Quantitative, with target thresholds based on 95% confidence interval	30% Limited Literacy	Cognitive walkthrough – verbal description of steps
Human Factors	Evaluate whether the product user interface is safe and effective for the intended users, uses, and use environments	Qualitative, at least 15 participants per user group	Based on the intended user population	Simulated use of steps (e.g., mannequin, injection pad)

Label Comprehension Studies: Roles

- Typically, Applicants conduct the pivotal LCS and FDA analyzes data and reviews findings when an NDA is submitted
- Often, Applicants conduct preliminary formative research to craft and optimize the label before conducting the pivotal study
- In the case of nonprescription naloxone, some potential Applicants in 2015 told FDA that they did not have the resources and bandwidth for label comprehension research

Label Comprehension Studies: Overview

- Therefore, FDA decided to develop a template for a model Drug Facts Label on its own, and contract out for a label comprehension study. Under this paradigm, the only task for Applicants would be to assess those parts of the DFL that pertained to their particular products.

Challenges With Developing a Model DFL

- Nonprescription naloxone is to be used in an emergency, life-threatening situation (atypical for an nonprescription product)
  - Need to assume that consumers might never look at the label prior to the need for use.
    - Therefore, key steps in product administration needed to be presented clearly and succinctly, and with accompanying pictures.

Challenges With Developing a Model DFL (cont'd)

- FDA did not know which dosage forms would be proposed for eventual nonprescription use.
- FDA did not know how nonprescription Applicants would eventually choose to package their products.
- Therefore, general language needed to be utilized in the model; potential Applicants were advised to then test any new information that needed to be added about usage of their specific product.

Nonprescription Naloxone Model DFL Development

- FDA initiated development of the DFL in 2016
  - Consulted with outside experts in addiction treatment and internal communications experts
  - Developed an innovative DFL with adjacent pictograms
- Contract awarded to firm outside FDA for label comprehension formative assessment, pilot study, and pivotal study (CONFER)
- Pivotal study report and accompanying data were reviewed by firewalled FDA team
- Results published in NEJM, May 2020

Label Comprehension Study Populations

- Adults who used opioids (heroin and/or prescription opioids), recruited from community-based organizations, treatment centers, and participant referral
- Friends and family members of adults who used opioids
- “All comer” adults, age 18+
- “All comer” adolescents, ages 15-17

Demographics of Study Population (N=710)

Demographic Category	n (%)
Race (multiple responses)	
White	464 (65.4%)
Black/African American	221 (31.1%)
American Indian/Alaskan Native	20 (2.8%)
Asian	5 (0.7%)
Native Hawaiian /Pacific Islander	5 (0.7%)
Prefer not to answer	20 (2.8%)
Hispanic or Latino	
Yes	70 (9.9%)
No	638 (89.9%)
Prefer not to answer	2 (0.3%)

Demographics of Study Population (N=710)

Demographic Category	n (%)
Under age 18	140 (19.7%)
Gender	
Male	359 (50.6%)
Female	351 (49.4%)
2017 Household Income*	
Less than $20k	344 (60.4%)
$20k-35k	93 (16.3%)
$35k-75k	61 (10.7%)
$75k+	46 (8.1%)
Prefer not to answer/d/k	26 (4.6%)

**Question was not asked of adolescents. Therefore, N=570 were used when calculating percentage.*

Key Endpoints and Associated Thresholds

Primary Endpoint	Target LB Threshold (%)
Step 1: Check for a suspected overdose	85
Step 2: Give the first dose of the medicine	85
Step 3: Call 911 immediately	**90**
Composite of Steps 1-3	85
Step 4: Repeat doses every few minutes until the person is fully awake or until emergency personnel arrive	85
Step 5: Stay with the person until the emergency personnel arrive	85
Use for the treatment of opioid overdose	80
Signs of overdose	80

Key Endpoints – Results (Steps)

Primary Endpoint	Threshold %	Overall Correct % (LB, UB) N=710	NL Correct % N=473	LL Correct % N=237
Step 1: Check	85	95.8 (94.0, 97.1)	97.9	91.6
Step 2: Give	85	98.2 (96.9, 99.0)	99.8	94.9
Step 3: Call 911 immediately	**90**	**90.3 (87.9**, 92.4)	**94.7**	**81.4**
Composite 1-3	**85**	**81.1 (78.0**, 83.9)	**87.9**	**67.5**
Step 4: Repeat doses until person awakes or emergency personnel arrive	85	93.8 (91.8, 95.5)	97.3	86.9
Step 5: Stay with person until emergency personnel arrive	85	91.1 (88.8, 93.1)	95.1	83.1

Abbreviations: LB, lower bound; LL, Limited Literacy; NL, Normal Literacy; UB, upper bound

Key Endpoints – Results (Other Knowledge)

Primary Endpoint	Threshold %	Overall Correct % (LB, UB) N=710	NL Correct % N=473	LL Correct % N=237
Use for treatment of opioid overdose	80	96.5 (94.9, 97.7)	98.1	93.2
Signs of overdose	80	94.5 (92.6, 96.1)	98.1	87.3

Secondary Endpoints

Secondary Endpoint	Overall Correct % N=710	NL Correct % N= 473	LL Correct% N=237
It is safe to keep giving doses	95.6	98.7%	89.5%
Give another dose if the person becomes very sleepy again	92.3	95.3%	86.1%
Order of the “call 911” step	85.2	89.9%	75.9%
Some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry	82.4	86.5%	74.3%
Steps 1-5 - Composite	74.6	83.1%	57.8%

Exploratory Endpoints

Exploratory Endpoint	Results (Point estimate %)
Wait 2-3 minutes between doses	95.1
What is an opioid	Majority understood Common responses (> 10%) • Heroin – 21.8%, n = 155 • Pain medicine – 21.8%, s = 155 • Drug/type of drug – 12.4%%. N = 88 • Prescription pain medication – 11.0%, n = 78 • Drug with opiates/made from opiates – 10.4%, n = 74

Summary

- The DFL is acceptable, with appropriate changes to address individual products' delivery systems and instructions for use (IFU)
  - "Call 911 immediately" closely approximated but did not reach target
  - Recommend that Applicants further assess whether comprehension of instruction to call 911 immediately may be improved
- Adequate comprehension of IFU would need to be demonstrated through human factors and/or additional label comprehension, if appropriate

U.S. FOOD & DRUG ADMINISTRATION

Joint Nonprescription Drugs Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee Meeting

Human Factors Validation Study (HFVS)

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Center for Drug Evaluation and Research
February 15, 2023

Outline

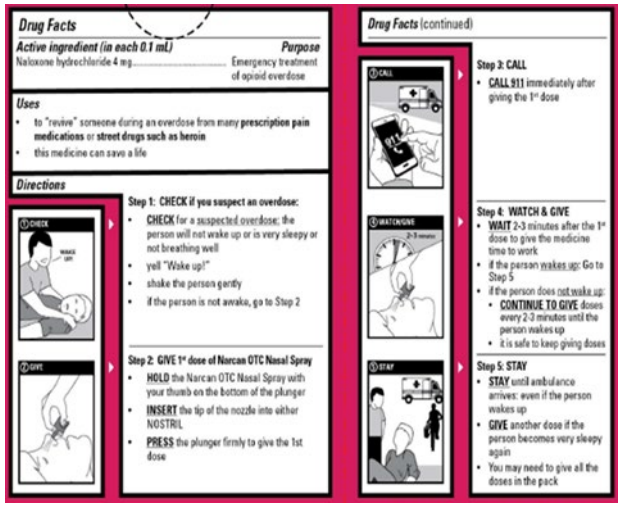
- Product user interface (UI) description
- Human factors (HF) studies - general overview
- Summary of Narcan HF validation study design
- Summary of key HF validation study results
- Recommendations for AC Panel's consideration

User Interface

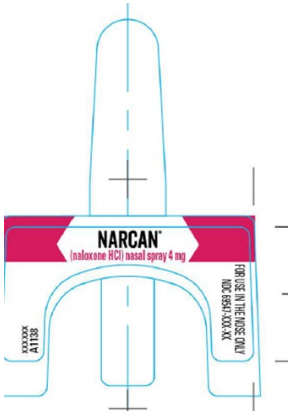
Not only the device

Includes **all** points of interaction between the product and the user(s) including elements such as **packaging** (e.g., blister, carton), **product labels, device**

Blister Packaging



Drug Facts Label (DFL)



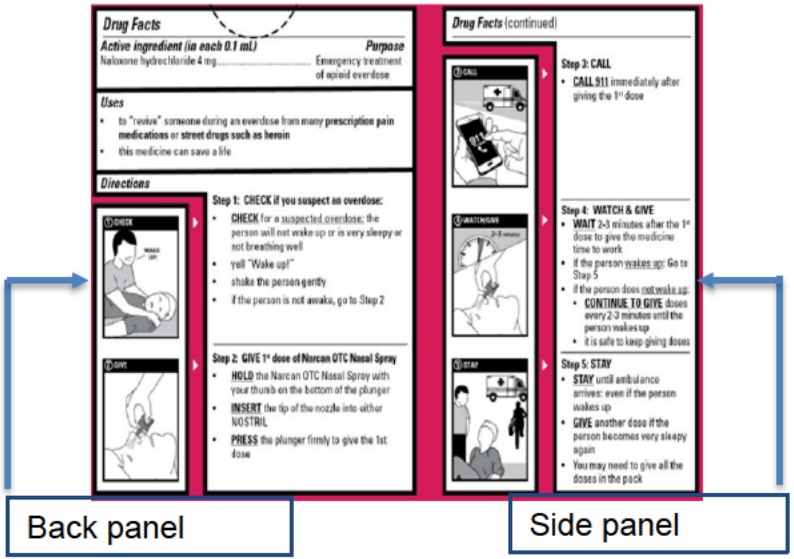
Device

Comparison of Prescription and Nonprescription Carton Directions

Prescription Carton: Flap on the front of the carton opens to instructions on the **same** viewable surface

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.

Nonprescription Carton: DFL directions span over 2 **different** panels (back and side) that are viewable after rotating the carton



Comparison of Nonprescription and Prescription Blister Packaging

- Nonprescription product does <u>not</u> include a Quick Start Guide (QSG) inside each blister package

Prescription product:

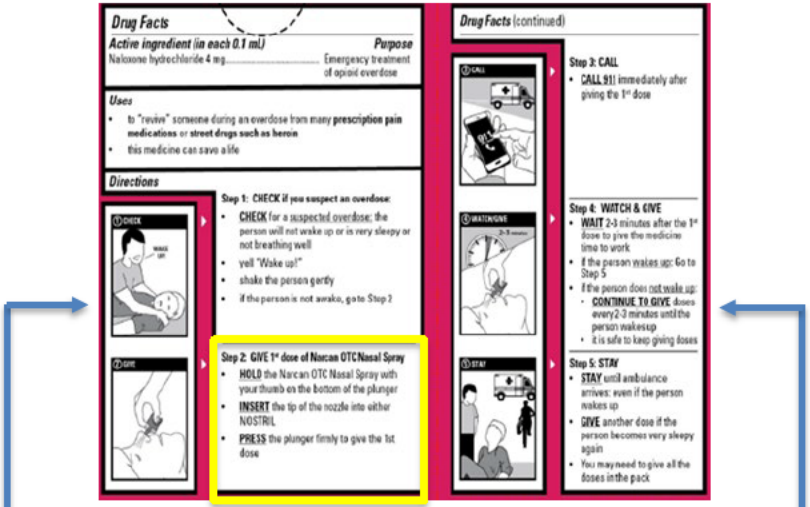
Quick Start Guide (QSG) folded inside the blister package

Nonprescription product:

<u>No</u> Quick Start Guide (QSG) inside the blister package

Comparison of Proposed DFL and Model DFL in CONFER

Nonprescription product DFL:

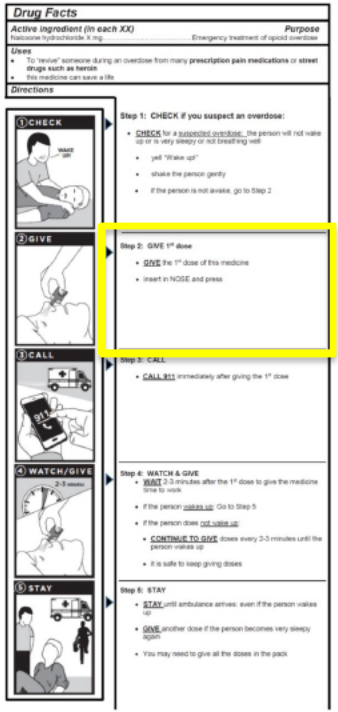


Back panel

Side panel

- Steps 1, 3, 4, and 5 figures and text are identical to model DFL
- **DFL directions split across 2 panels** (Steps 1 and 2 on the back panel and Steps 3, 4, 5 on the side panel)
- Step 2 includes differences in text; however, figure is identical to model DFL

Model DFL evaluated in CONFER:

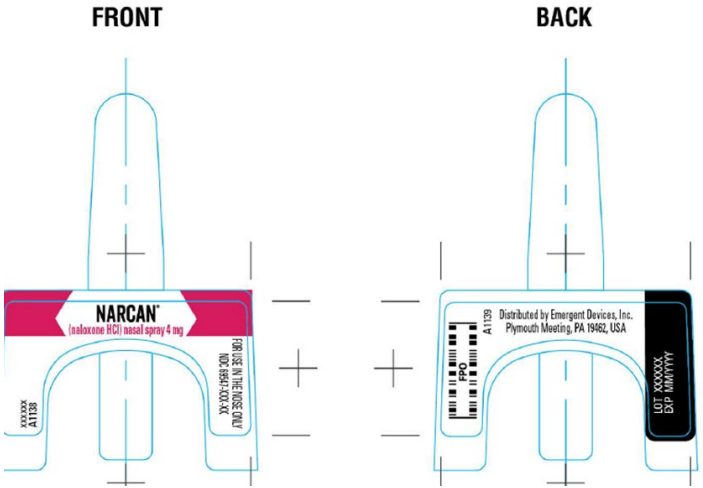


DFL directions Steps 1 to 5 on a single panel

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.

Device

- Proposed nonprescription product's device is the same as prescription product (i.e., Aptar nasal spray device)



Human Factors Validation Study

HF studies:

- conducted under **simulated use** conditions
- evaluate whether the **product user interface is safe and effective** for the intended users, uses, and use environments
- analyzed **qualitatively** to determine if the design of the **user interface** adequately mitigates the use-related risks to acceptable levels

Human Factors Validation Study Design

FDA recommends Sponsors submit the HF validation study protocol for review prior to conducting the HF validation study:

- Ensure the study methodology is acceptable
- Provide recommendations for UI from medication error perspective

The Applicant did not submit the HF validation study protocol for Agency review

- FDA identified several HF validation study methodology limitations

Human Factors Validation Methodology

Study Design Element	General Principles for HFVS Methodology	Details for Narcan HF Validation Study	Narcan HF Validation Study Limitations
User Groups	Minimum of **15 representative users per distinct user group**	71 participants across 4 user groups: • Adult General Population, age 18 or older (n=18) • Adult Opioid User Associates, age 18 or older (n=18) • Adult Opioid Users, age 18 or older (n =16) • Adolescent, **ages 15-17** (n=19)	**Data collected cannot be generalized to the untested age range of the pediatric user group (i.e., users less than 15 years old)**
Limited Literacy (LL) Users	For nonprescription products, each distinct user group include **30% limited literacy participants**	Did not include 30% LL participants in each distinct user group; however, 30% of total combined users LL: • **Adult General Population (22.2%)** • **Adult Opioid User Associates (27.8%)** • Adult Opioid Users (31.3%) • Adolescents (36.8%)	**Distribution of LL participants may have introduced bias with tendency towards positive performance in the affected user groups**

*For HF validation study design elements 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.

HF Validation Study Methodology

Study Design Element	General Principles for HFVS Methodology	Details for Narcan HF Validation Study	Narcan HF Validation Study Limitations
Study Sequence and simulation scenario	Involves **observed performance of tasks**. No drug administered to participants (e.g., placebo-filled device administered to a manikin) in a setting that mimics real world use conditions	**Unlimited Familiarization Period:** Participants were allowed as much time as needed to review the mock OTC product and its DFL	In an actual emergency, some users may have limited time to interact with the product labeling Data **does not capture the highest-risk use scenario**
	Test participants should be given an opportunity to **use the product user interface as independently and naturally** as possible	**Leading language and "Think Aloud" Methods:** Participants were told to use the product labeling and to "**verbally tell me what you are doing… as you complete the demonstration."**	Leading language and Think Aloud Method may have introduced a **bias towards positive performance** – during actual use, users will not have someone reminding them to use the instructions or talk through what they are doing

*For HF validation study design elements 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.

HF Validation Study Methodology

Study Design Element	General Principles for HFVS Methodology	Details for Narcan HF Validation Study	Narcan HF Validation Study Limitations
Data Collection & Analysis	Participants are **observed performing the steps** needed to use the product without interruption and interviewed after the simulation Collects **Qualitative data** for every use error (UE), close call (CC), or use difficulty (UD) • participants' subjective feedback • root cause analysis (RCA) for **why** error occurred **Qualitative** data is used to identify if UI contributed to errors or if mitigation is needed	Used predetermined **Quantitative thresholds** for success used to score each performance as "correct", "acceptable", "incorrect", or "could not be observed" Participants' **verbal descriptions of tasks may have been scored as acceptable, even if participant failed performance**	Some UE, CC, UD, or instances of moderator intervention scored as "correct/acceptable" by Applicant **even if participant failed** RCA/subjective feedback to understand **why** UE, CC, UD occurred **was not collected** in all instances.

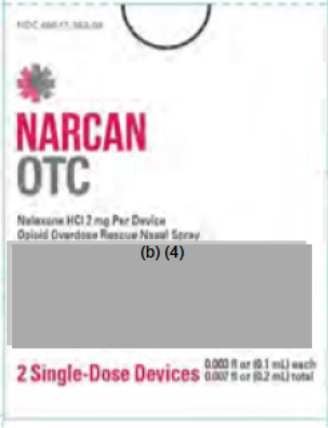
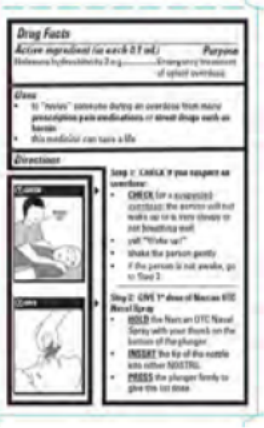
*For HF validation study design elements see Applying Human Factors and Usability Engineering to Medical Devices, Guidance for Industry and Food and Drug Administration Staff. 2016. Available from: http://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf.

HF Validation Study Methodology

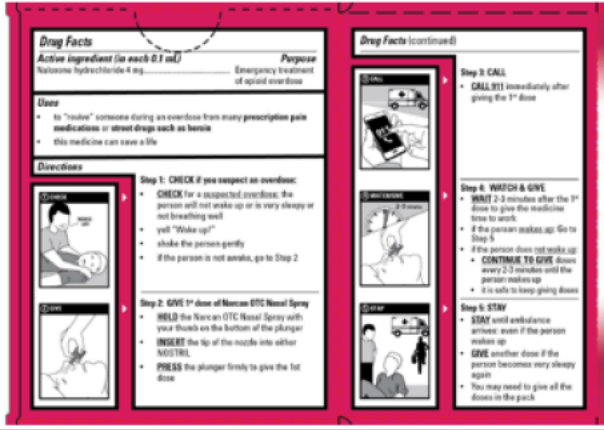
Study Design Element	General Expectations for HF Validation Studies	Details for Narcan HF Validation Study	Narcan HF Validation Study Limitations
Test Materials	**Final intend-to-market user interface (including labels/labeling)** should be evaluated in the HF validation study. • Generally, if changes are made to the UI post-HF validation study, additional HF data may be needed to support the changes	Carton labeling evaluated in the HF validation study is **different** from the proposed intend-to-market carton labeling (see next slides)	**Several changes made post-HF validation (see next slides)** **No HF data to support changes to intend-to-market carton are effective and do not introduce new risks**

*For HF validation study design elements 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.

Mock Carton Tested in HF Validation Study

Back Panel	Left Side Panel	PDP	Right Side Panel
			

Intend-to-Market Carton Submitted September 29, 2022

Back Panel	Left Side Panel	PDP	Right Side Panel
			

Changes to UI Post-HFVS

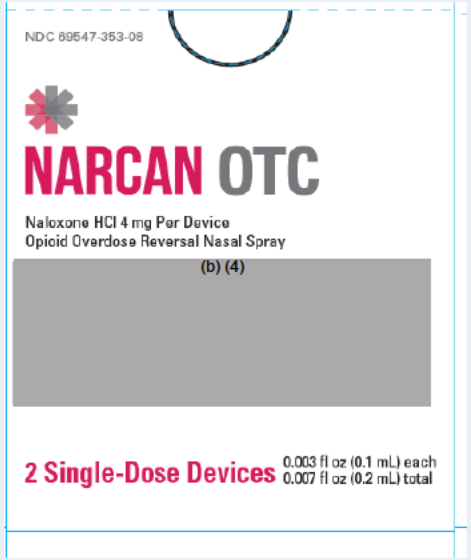
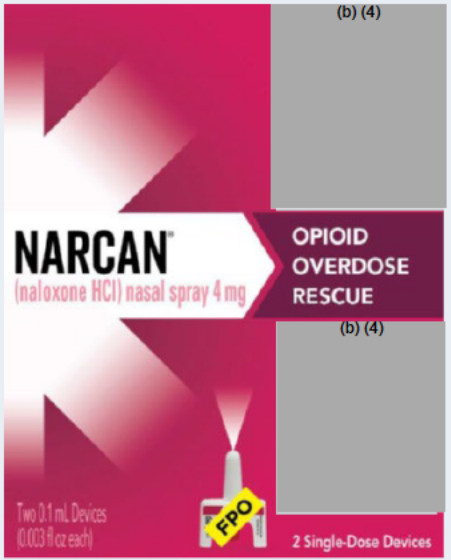
Some **changes are in response to use errors** observed in the HF validation study:

- Intend-to-market carton labeling has been modified post-HF validation by **switching Steps 3, 4, and 5 of the DFL Directions from the back panel to side panel**

Certain labeling claims are redacted in this slide at the Applicant's request

Changes to UI Post-HF

- Some changes appear to be cosmetic (e.g., colors, branding, etc.)
- Other changes include **different statements, relocation and/or changes to font size of important statements** (e.g., "2 Single-Dose Devices")

PDP Evaluated in HFVS	Intend-to-Market PDP
	

Certain labeling claims are redacted in this slide at the Applicant's request

Review of HFVS Results

- Focus on **qualitative** results, root cause analysis (RCA) & subjective feedback
  - Identify the **root cause** for every use error (UE), close call (CC), or use difficulty (UD)
  - Determine if **user interface contributed** to the UE, CC, or UD
  - Determine **potential for harm**
  - Determine whether further **risk mitigation(s)** are needed
  - Determine if **additional data** is needed to support the mitigations (e.g., are the changes effective, do changes introduce new risks?)

- Consider study limitations during results interpretation
  - **Age range** of adolescent user group
  - Inadequate representation of **limited literacy** participants
  - **Familiarization** period, leading language, and think aloud method
  - **Data collection** methods
  - **Changes to UI** post-HF validation

Summary of HF Validation Study Results

- Focus on key results with RCA/participant subjective feedback that indicate the user interface contributed to the UE, CC, or UD
- Complete HF Validation Study qualitative data set available in the FDA AC Briefing Document

Step 1: Check if You Suspect an Overdose

Use-related Events Attributed to User Interface	Observations and Verbatim Responses from Participants

• 5 UE:
  • General Population (n=2)
  • Opioid User (n=3)
• 4 CC*
  • General Population (n=2)
  • Opioid User (n=1)
  • Opioid User Associate (n=1)
 	
*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.
	"**I started on step three**. For some reason, in the panic mode, **I just read the back of the box** and jumped into action."
	
	"So **usually instructions are on one panel**, right? So I just kind of assumed that the first panel that I looked at that had directions was the beginning. It wasn't until later that I realized that there was a second panel-or that I was looking at the second panel. And **it did kind of confuse me because when it says call 911 and wait 2-3 minutes after the first dose, I was like, wait I haven't given the first dose yet. I need to go back to the beginning**."
	
	"Because **I didn't see the step one and step two**. I seen the back of the package, and I felt like that was all the instructions."
	
	"Got on the **wrong side of the box**."
	
	"I was **looking for instructions on the back**."
	
	"**Where is step one**?"

Step 2: Give 1st Dose of Narcan OTC Nasal Spray

Use-related Events Attributed to User Interface	Observations and Verbatim Responses from Participants

• 3 UE:
  • Adult Opioid User(n=1)
  • Adolescent (n=2)
• 2 CC
  • Adolescent (n=1)
  • Opioid User Associate(n=1)
• 2 UD
  • Adult Opioid User (n=1)
  • Adult General Population (n=1)
	Participant **did not keep tip fully inserted** - Hand slipped slightly from the correct position: "I used the thumb on the plunger. **I'm not sure I understand** what you want"
	
	Participant squeezed device without pushing plunger: "Am I [inaudible] to get to squeeze? So, **I kind of squeezed out instead of pushing it**."
	
	Participant held device upside down: "It just **didn't say what direction to put it in**"
	
	Participant **started reviewing the DFL at Step 3** and did not see the first panel before first attempt to administer the product.
	
	Participant **started reviewing the DFL at Step 3 and did not see the first panel**: **"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."
	
	Participant **reviewed the panel with Step 3 first**, then **realized something was not right** as he was trying to follow the directions and administer.

Step 3: Call 911 Immediately After Giving the 1st Dose

Use-related Events Attributed to User Interface	Observations and Verbatim Responses from Participants

• 1 UE:
  • Adult Opioid User(n=1)
 	
• 5 CC:
  • Adult General Population (n=4)
  • Adult Opioid User (n=1)
	Participant called 911 first - **Looked at the back of the box first**, rather than Panel 1, which was on the side panel: "**Because I didn't see it**."
	
	Participants called or described calling 911 prior to administering the first dose because **started with the wrong side of the carton**
	
	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.

Step 5: Stay

Use-related Events Attributed to User Interface	Observations and Verbatim Responses from Participants

• 6 UE:
  • Adolescent (n=1)
  • Opioid User (n=1)
  • Opioid User Associate (n=4)
 	
• 1 CC:
  • Adult General Population (n=1)
	"So **I don't know if there's more than two doses in that.** And the **I'm not sure if there's each single doses**.... I'm not sure if you could get more than one usage"
	
	"I ended up opening up a second package **because I couldn't figure out there was more than one dose in one of these**. So **I tried pushing back to see if it would go again for a another**, but it didn't seem like it to me. So I just went about opening another pack."
	
	"**Is this one dose or is this many doses**? Got one more minute to figure that out…."
	
	" ….There is **nothing that conclusively tells me that there is one dose**, except when the plunger's been plunged, you can't do it anymore.
	
	"**Assuming this is just a single dose**."

FDA Analysis for Steps 1, 2, 3 and Applicant's Response

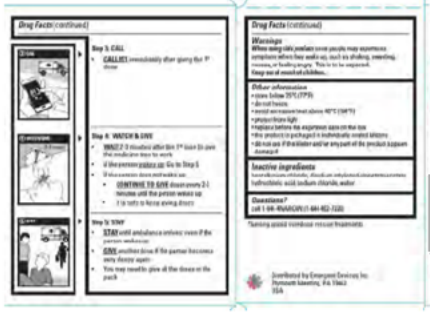
FDA Analysis:

- UE, CC, UD **directly attributed to format of DFL** directions split across side and back panel
- May result in **no dose or delayed administration of naloxone**

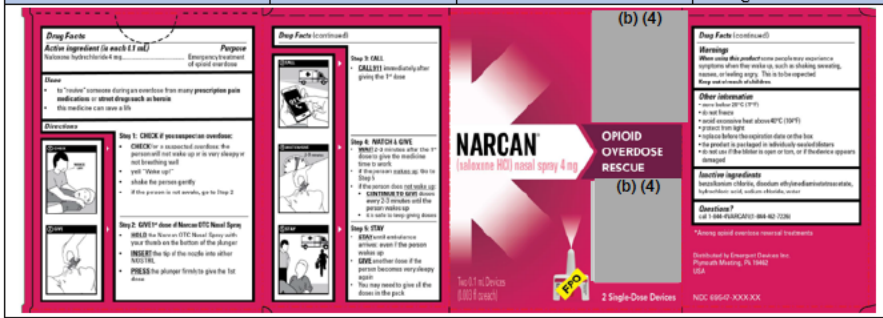
Applicant's Proposed Mitigation:

- Post-HF validation revision to the DFL to switch directions on back and side panel

Mock Carton Tested in HF Validation Study

Back Panel	Left Side Panel	PDP	Right Side Panel
			

Intend-to-Market Carton Submitted September 29, 2022

Back Panel	Left Side Panel	PDP	Right Side Panel
			

Certain labeling claims are redacted in this slide at the Applicant's request

FDA Analysis of Applicant's Response and Proposal for AC Panel Consideration

FDA Analysis of Applicant's Response:

- Users who refer to the back panel of the carton first will now see Step 1 and Step 2
  - Unclear if this mitigation is effective without introducing new risks for error
  - Some users may overlook Steps 3, 4, and 5 on the side panel
- Applicant did not validate this proposed mitigation strategy

Proposal for AC Panel Consideration:

- Redesign Carton so that Steps 1 through 5 appear on back panel uninterrupted
- Package QSG within each blister package and carton that displays Steps 1 through 5 on a single sided page

FDA Analysis for Step 2 and Proposal for AC Panel Consideration

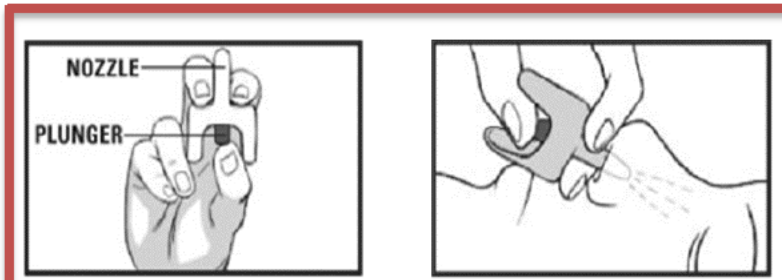
FDA Analysis:

- UE, CC, UD related to device orientation, operation, and hand position on the device
- 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

Proposal for AC Panel Consideration:

- Revise the bullet to state, "INSERT the nozzle into either NOSTRIL."
- Improve carton labeling, including Step 2's pictogram to show hand/finger positioning from prescription Narcan

DFL Pictogram



Prescription Narcan Pictograms

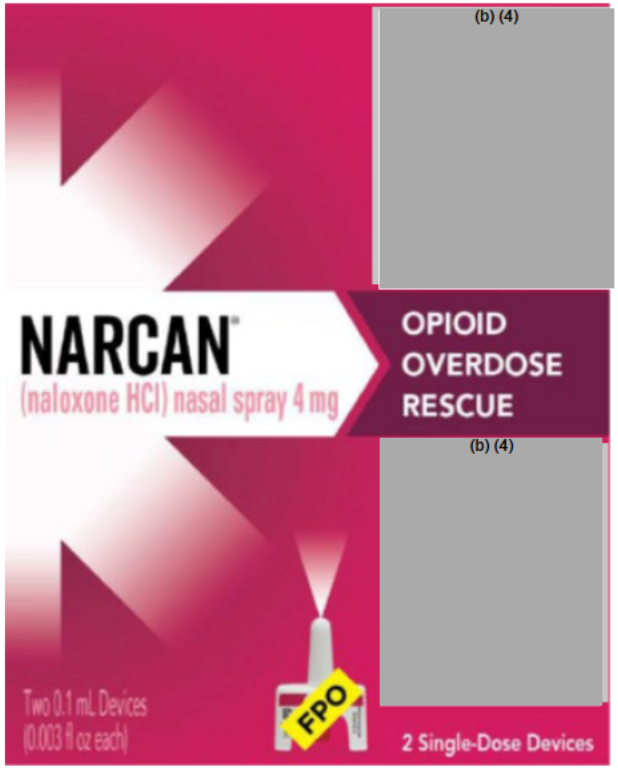
FDA Analysis for Step 5 and Proposal for AC Panel Consideration

FDA Analysis:

- UE, CC due to confusion about whether each nasal spray contains a single dose or multiple doses.

Proposal for AC Panel Consideration:

- Add a statement that each nasal spray contains only one dose of naloxone to labels/labeling.
- Depict 2 nasal spray devices on carton labeling to minimize confusion on the number of nasal spray devices in each carton.



Certain labeling claims are redacted in this slide at the Applicant's request

Conclusion and Considerations for AC Panel

Conclusion:

- HF validation study methodology issues need to be considered when interpreting the HF validation study results:
  - Familiarization period, leading language, and think aloud method
  - Data collection methods
  - Changes to UI post-HF validation
- Several use errors can be directly attributed to the user interface design
- Use errors may result in no dose or delayed dose of naloxone
- Agency has identified some potential recommendations for the user interface design

As the AC panel considers the topics for discussion in the next section, we ask that you take the study limitations, HFVS use-related errors, and our potential mitigations into consideration during your discussions

FDA Joint Meeting

Nonprescription Drugs Advisory Committee

Anesthetic and Analgesic Drug Products Advisory Committee

Meeting for Naloxone Nasal Spray for Nonprescription Use

FDA Charge to the Committee

Jody E. Green, MD
Deputy Director of Safety
Division of Nonprescription Drugs I
Office of Nonprescription Drugs
Center of Drug Evaluation and Research

February 15, 2023

Classes of Drugs in the United States (Section 503(b)(1) of the FD&C Act)

- **Prescription Drug:** not safe for use except under supervision of a practitioner licensed to administer the drug because of
  - Toxicity or other potentially harmful effects
  - Method of use
  - Collateral measures necessary for use
- **Nonprescription Drug**: can be used safely and effectively by a consumer without the supervision of a health care practitioner and does not meet the criteria for prescription-only dispensing

Prescription to Nonprescription Switch (21 CFR 310.200)

- FDA may approve a supplement to an approved prescription drug application requesting to market the drug as nonprescription if:
  - FDA finds that the prescription requirement is not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measure necessary for its use, AND
  - FDA finds that the drug is safe and effective for use in self-medication as directed in the proposed labeling

Key Elements of Nonprescription Drugs

Nonprescription drug products generally have these characteristics:

- Can be adequately labeled such that
  - The consumer can self-diagnose, self-treat, and self-manage the condition being treated
  - No healthcare practitioner is needed for the safe and effective use of the product
- The drug has a low potential for misuse and abuse
- The safety margin is such that the benefit of the nonprescription availability outweighs the risks

Goals for Committee

Discuss:

1. Safety as related to proposed OTC population
2. Human Factors Validation Study and associated user interface as adequate support for approval
3. Need for additional labeling materials to mitigate risk
4. Vote

Question 1

Discuss the safety profile for use of Narcan Nasal Spray (NNS) in the nonprescription setting.

Question 2

Discuss whether the results of the Human Factors validation study (HFVS) support that consumers are able to correctly administer nonprescription NNS in an emergency situation.

(4 subparts)

Question 2a

a. Discuss the HFVS study design, and the interpretability of the study.

Question 2b

b. Discuss the use errors observed in the HFVS where participants started with Step 3 (Call 911) during the simulation and bypassed Steps 1 and 2.

   i. Could the intend-to-market nonprescription carton be further improved to mitigate risk of delayed administration?

Question 2c

c. Discuss the incorrect finger placement on the nasal spray in the HFVS.

i. Could the pictogram be further improved to optimize correct administration?

Question 2d

d. Discuss whether the HFVS data submitted using the "mock" nonprescription user interface support the safe and effective use of:

i. the proposed nonprescription NNS and

ii. the modified intend-to-market user interface

If not, what additional data are needed?

Question 3

Discuss whether there is any additional labeling information that might mitigate risk of use errors.

Question 4: Vote

Is the benefit-risk profile of NNS supportive of its use as a nonprescription opioid overdose reversal agent?

a. If you vote 'No', what further data should be obtained?

Thanks for your attention