

Rx-to-OTC Switch for NARCAN[®] (naloxone HCl) Nasal Spray 4 mg

Presentation to the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

NDA 208411/S-006

Emergent BioSolutions
February 15, 2023

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Introduction

Manish Vyas
Senior Vice President, Regulatory Affairs
Emergent BioSolutions



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About Emergent BioSolutions

We develop, manufacture, and deliver vaccines and therapeutics that address public health threats.

- OPIOID REVERSAL
- TRAVEL HEALTH
- ANTHRAX
- BOTULISM
- SMALLPOX
- NERVE AGENT ANTIDOTES
- CHEMICAL AGENTS



VACCINES
(injectable, oral)



THERAPEUTICS
(hyperimmune/mAb)



DRUG-DEVICE COMBINATIONS
(device, drug-device combination product)



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NARCAN® Nasal Spray 4 mg and the OTC Development Program

Gay Owens, PharmD, MBA
Global Medical Affairs Lead, Opioid Antidote
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Medical Need for OTC Nasal Naloxone

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Chief, Division of Adolescent and Young Adult Medicine
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Human Factors Study

Sarah Farnsworth, PhD
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NARCAN® Nasal Spray Benefit-Risk Overview

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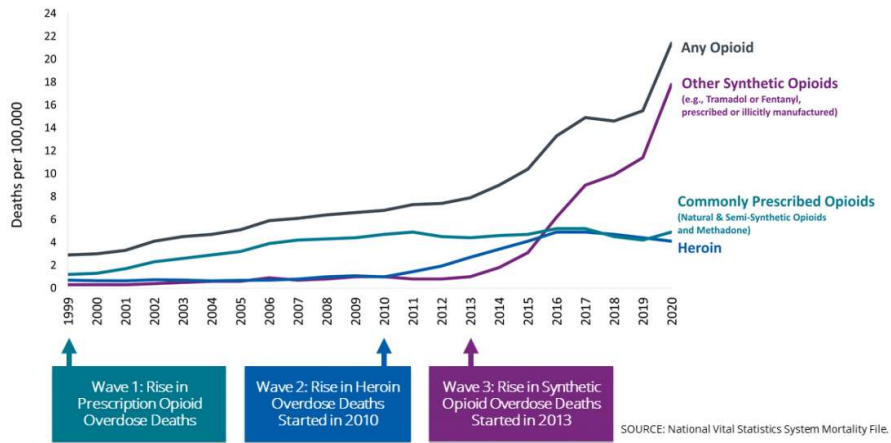
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The Opioid Epidemic is a Critical Public Health Issue in the U.S.

Three Waves of Opioid Overdose Deaths



CDC. Understanding the epidemic. <https://www.cdc.gov/drugoverdose/epidemic/index.html>.

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During an Opioid Overdose, Response Time Matters

Opioid-Induced Respiratory Depression:

An opioid-induced overdose event characterized by hypoxic injury or death¹



EVERY SECOND COUNTS: Permanent brain damage begins after only 4 minutes without oxygen, and death can occur as soon as 4–6 minutes later²

7
minutes

US National average EMS response time (911 call to EMS arrival)³

14
minutes

Response time increases to >14 minutes in rural settings³

EMS, emergency medical services.

1. Nadel, J. Clinical and regulatory perspectives on naloxone products intended for use in the community. 2016. <https://www.fda.gov/media/100648/download>. Accessed May 27, 2021; 2. US National Library of Medicine. CPR – adult and child 9 years and older. <https://medlineplus.gov/ency/article/000013.htm>. Accessed May 27, 2021; 3. Mell HK, et al. JAMA Surg. 2017;152(10):983-984.

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OTC Naloxone Could Help Increase Access

- Various stakeholders have proposed OTC switch of naloxone:
 - OTC status is widely considered to enhance access and use of naloxone in an opioid emergency
- Preliminary FDA opinion:
 - Naloxone nasal spray up to 4 mg has the potential to be safe and effective for use as directed in a non-prescription setting without guidance from a medical practitioner (November 15, 2022; 87 FR 68702)

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NARCAN[®] (naloxone HCl) Nasal Spray 4 mg

NARCAN[®] Nasal Spray proposed as OTC has the **same indication** as the FDA approved prescription (Rx) product:

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

NARCAN[®] Nasal Spray [prescribing information], Plymouth Meeting, PA: Emergent Devices Inc.; 2020.

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NARCAN® Nasal Spray is Designed for Community Use



NARCAN® Nasal Spray proposed as OTC is the same as the FDA approved Rx product

- A single dose device delivers 4 mg naloxone
- Each carton has two devices (8 mg total)
 - allows for repeat dose (administered every 2-3 minutes, as needed)
- Administration requires no specialized training
- Inhalation not required
- Assembly not needed, needle-free, easy to carry

NARCAN® Nasal Spray [prescribing information]. Plymouth Meeting, PA: Emergent Devices Inc.; 2020.

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External Experts for NARCAN® Nasal Spray Rx-to-OTC Switch



Scott Hadland, MD, MPH, MS
 Chief, Division of Adolescent and Young Adult Medicine
 Massachusetts General Hospital – Harvard Medical School
Expertise: adolescent and young adult substance use disorder prevention and treatment



Orman Trent Hall, DO
 Clinical Assistant Professor of Psychiatry and Behavioral Health
 The Ohio State University Wexner Medical Center
Expertise: addiction medicine, overdose epidemiology, neurobiology of pain and addiction, OUD stigma



Joshua J. Lynch, DO, EMT-P, FAAEM, FACEP
 Clinical Associate Professor of Emergency Medicine
 University at Buffalo Jacobs School of Medicine and Biomedical Sciences
Expertise: emergency medicine, addiction medicine, treatment access, first responder



Anita Jacobson, Pharm.D.
 Clinical Professor, Program Director of the Community First Responder Program
 The University of Rhode Island, College of Pharmacy
Expertise: pharmacist-directed patient care, pharmacy regulations, opioid emergency response

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



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Brief History of Naloxone*


Naloxone is on the World Health Organization's (WHO) List of Essential Medicines¹


- 

1961 Jack Fishman, an immigrant from Poland, invented naloxone in 1961 while trying to come up with a way to treat constipation caused by chronic opioid use^{2,3}
- 

1966 Synthesis of naloxone was patented in the United States⁴
- 

1971 FDA approves naloxone for treating opioid overdoses by IV, IM, SC injection in a healthcare setting⁵
- 

2008 Initial experiments with "community" naloxone: prefilled syringes with atomizers for nasal administration (not FDA approved)⁶
- 

2014 Evzio[®] Auto-Injector gains fast-tracked FDA approval as first community-use naloxone⁷
- 

2015 NARCAN[®] (naloxone HCl) Nasal Spray, the first intranasal (IN) naloxone, gained fast-tracked FDA approval⁸

*up until approval of NARCAN[®]

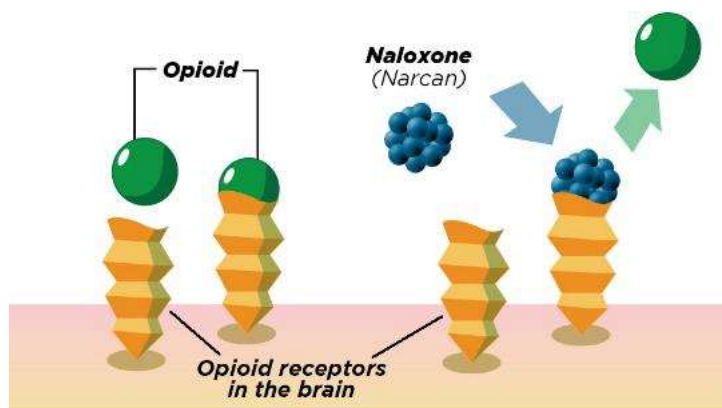
FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; SC, subcutaneous; IN, intranasal.

1. WHO. WHO model list of essential medicines, 21st list, 2019. <https://www.who.int/publications/i/item/WHO/MVP/EMPIAU2019.06>. Accessed May 27, 2021; 2. Castillo T. Who invented naloxone. http://www.huffingtonpost.com/terrie-castillo/meet-jack-fishman-the-man-b_6329512.html. Accessed June 1, 2020; 3. Garfield D. *Essays Information Scientist*. 1983;16:121-130. 4. US Patent Office. 3,254,088 morphine derivative. <https://patentimages.storage.googleapis.com/a6/72/d6/cabe2af652cdd7/US3254088.pdf>. Accessed June 22, 2020; 5. Lloyd J. The clinical use of naloxone. <https://www.fda.gov/media/92994/download>. Accessed June 6, 2020; 6. Dowling J, et al. *The Drug Monitor*. 2008;30(4):490-496; 7. FDA. NDA 205787. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205787Orig1s000ltr.pdf. Accessed May 27, 2021; 8. Data on File. ADAPT Pharma, Inc. Radnor, PA, 2019. License: CC BY-NC-SA 3.0 IGO.

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Naloxone Mechanism of Action



- Naloxone is a competitive mu-opioid receptor antagonist used to reverse an opioid overdose¹⁻³
 - Blocks opioid receptor sites, displacing opioids from receptors and blocking their biological effects
 - Can reverse all signs of opioid toxicity², including respiratory depression, sedation, and hypotension
- Single doses may achieve transient effects because the duration of action (20–90 minutes) is shorter than that of many opioids

1. Straus MM et al. *Subst Abuse Rehabil*. 2013;4:65-72; 2. Boyer EW. *N Engl J Med*. 2012(2);367:146-155; 3. NARCAN (naloxone HCl). Full Prescribing Information. Emergent Devices Inc, 2020.

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Naloxone Has a Long History of Safe and Effective Use

- Intramuscular (IM), subcutaneous (SC), and intravenous administration (IV) for hospital setting
- Naloxone has over 50 years of data in support of efficacy and safety¹
- Initial recommended dose in labeling: 0.4 mg to 2 mg IM/SC/IV
 - This became the reference range for subsequent naloxone products

Goals for Nasal Naloxone Development Program (NARCAN®)

- Establish bioequivalence to the current standard
- Demonstrate no safety concerns

1. NARCAN NDA 016636, Approved 1971.

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Definitive Pharmacokinetic Study for Rx NARCAN® Nasal Spray

Objective:

- Pharmacokinetic (PK) evaluation and comparison of intranasal (IN) and intramuscular (IM) naloxone

Primary Endpoint:

- To determine the PK (relative bioavailability) of 4 IN doses and deliveries compared to a single dose of 0.4 mg naloxone hydrochloride IM injection
- Identify an appropriate IN dose that could achieve systemic exposure comparable to an approved parenteral dose

Secondary Endpoint:

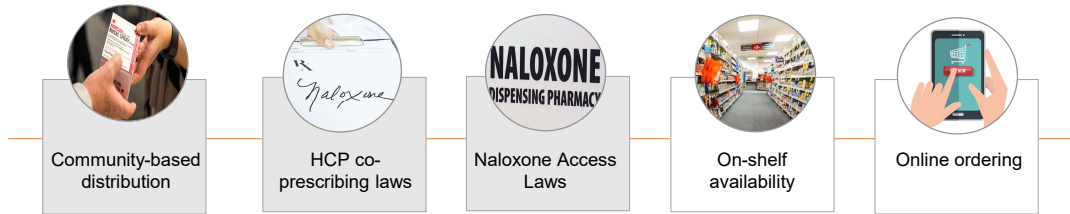
- To determine the safety of IN naloxone, particularly with respect to:
 - Nasal irritation (erythema, edema, & erosion)
 - Evaluations of adverse events
 - Vital signs (heart rate, blood pressure, and respiration rate), ECG, clinical laboratory changes

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Broader Access & Availability of Naloxone Is Needed

Under the current distribution model, federal and state policies and regulations enable naloxone access; by adding OTC channels, naloxone can be made available to an even broader population:



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“OTCness” General Principles

Criteria
User must be able to self-diagnose*
Product is adequately labelled to drive correct use by the consumer
Benefits of increased access outweigh potential risks
Health practitioners are not needed for the safe and effective use of product
Low potential for misuse and abuse

* For NARCAN® Nasal Spray, bystander/caregivers can diagnosis potential overdose and administer/treat. NARCAN® Nasal Spray is indicated for use in known and suspected cases of opioid overdose.

The ABCs of OTCs, Little Known Facts About Over-the-Counter Drugs, Karen Murry Mahoney, MD, FACE, Deputy Director, Division of Nonprescription Drug Products, CDER, US Food and Drug Administration [Nonprescription Drug Products: The Basics and New Initiatives \(fda.gov\)](#); [www.fda.gov](#): The ABCs of OTCs; Little-Known Facts About Over-the-Counter Drugs

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Overview of the OTC Development Program for NARCAN® Nasal Spray

- Development of NARCAN® Nasal Spray OTC Drug Facts Label (DFL)
 - Leveraged FDA-developed intranasal model DFL
- Conducted Human Factors Validation Study of NARCAN® (OTC) DFL
- Reviewed Real World Post-Marketing Data
 - Utilization Data
 - Post-Marketing Safety Surveillance

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Medical Need for OTC Nasal Naloxone

Scott E. Hadland, MD, MPH, MS
Chief, Division of Adolescent and Young Adult Medicine
Mass General for Children / Harvard Medical School



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Disclosures/ Funding Source

- **Conflict of interest statement:**

- I am presenting as an independent expert in pediatric addiction medicine and public health
- Views presented today do not represent those of my employers (Massachusetts General Hospital and Harvard Medical School)

- **Funding Sources:**

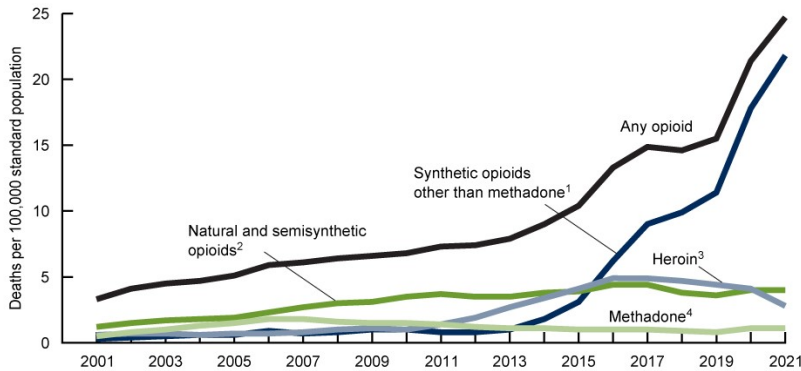
- I receive research funding from the National Institute on Drug Abuse, Patient-Centered Outcomes Research Institute, and US Centers for Disease Control and Prevention
- None of these funders had any role in my decision to present or in the preparation of this presentation

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Scope of the US Overdose Crisis

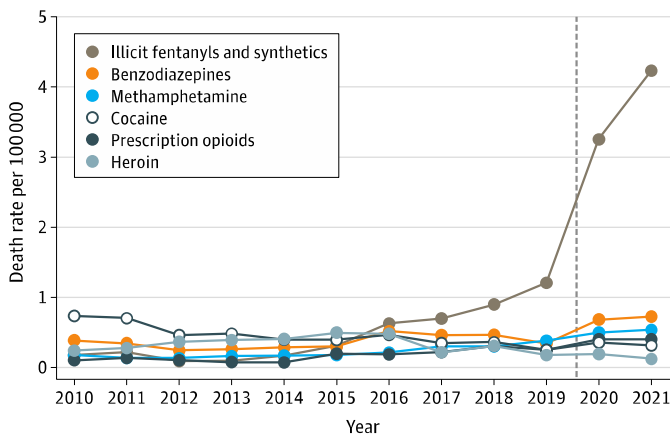
- More than 1,000,000 overdose deaths since the turn of the century
- 107,000 overdose deaths in 2021 alone, the highest on record, driven by fentanyl



MR Spencer, et al. NCHS Data Brief, no 457. Hyattsville, MD: National Center for Health Statistics, 2022.

Overdose Deaths: Teens Aged 14 - 18

A Overdose mortality among adolescents by substance type

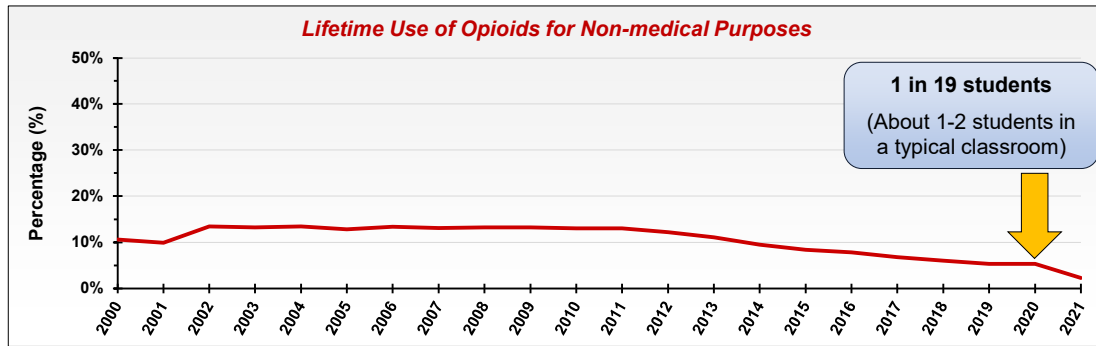


Fentanyl now involved in **5 in 6** of all teen fatalities

Friedman J, et al. JAMA. 2022;327(14):1398-1400; LJ Tanz, et al. MMWR. 2022;71(50):1576-1582

Opioid Misuse Begins Early in Life

2 in 3 individuals in opioid treatment report first use before **age 25**, and **1 in 3** report first use before **age 18**



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Fentanyl in the Drug Supply

- Counterfeit pills in the illicit market: $\geq 60\%$ contain potentially lethal doses of fentanyl



- Increasingly, fentanyl also reported in cocaine, MDMA, methamphetamine
- Result: Many people exposed to fentanyl without their knowledge, including individuals with little to no prior exposure to potent opioids

US Drug Enforcement Administration Fact Sheet, 2021

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Role for Naloxone

- People who overdose usually found unresponsive in their usual settings (e.g., home, work, or in public)
- Emergency care, including opioid reversal and respiratory support, is critical to survival
- Naloxone is safe, effective, and easily administered
- However, many people who use opioids (intentionally or otherwise) are unaware of naloxone and its use, or do not have immediate access

KE Evoy, et al. *Integr Pharm Res Pract.* 2021;10:13-21

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Context of Teen Overdoses

- Most (60%) overdoses of teens aged 10-19 occur at home
- Two-thirds (67%) of the time, someone else is also at home
- 60% of the time, teen is pulseless by the time EMS arrives
- Naloxone given in fewer than 1 in 3 overdose deaths



**Ready availability
of naloxone in US
households
could avert
overdose deaths**

LJ Tanz, et al. *MMWR.* 2022;71(50):1576-1582

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Broader Access to Naloxone is Needed

- Programs that increase community access to naloxone and information save lives
- Many individuals whose lives could be saved by naloxone do not have access or awareness:
 - Persons who use drugs (experience stigma)
 - People without medical insurance or primary care
 - Young people and family members

KE Evoy, et al. *Integr Pharm Res Pract.* 2021;10:13-21

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Why Now? Urgency Due to Fentanyl

- Widespread infiltration of fentanyl into the drug supply requires new approaches
- Many individuals exposed to fentanyl without expecting it (e.g., through counterfeit pills, other drugs like cocaine)
- Secondhand exposures also rising (e.g., toddlers)
- Individuals who knowingly use opioids now at higher risk than ever given variable potency in drug supply

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What Patients, Families & Community Members Say

- Once they know about naloxone, they want it (“fire extinguisher”)
 - But current avenues of access are challenging:
 - Prescription:**
Requires access to a prescriber familiar with naloxone
 - Standing Orders:**
Requires access to a pharmacy, and discretion left to the pharmacist
 - Community Distribution:**
Requires a consistent supply, and currently mainly available in settings for people who use drugs
- ...And many people avoid each of these settings due to stigma

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What OTC Naloxone Offers

- Layperson use of naloxone is safe and effective (and already happening across the U.S.)
- OTC availability will reach people currently unable to access naloxone
- Opioid deaths have been climbing in all age groups and the benefits of naloxone are not age-dependent
 - Indeed, adolescents and their families might, in my view, benefit *most* from OTC naloxone
- Instruction on use of naloxone will be needed, and offering it alongside OTC naloxone availability will decrease stigma

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Human Factors Study

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Background and Introduction

- The OTC NARCAN® Nasal Spray device is identical to the Rx version that was already fully tested in Human Factors (HF) validation studies
- Thus, the primary objective of this HF consumer study was to determine if the proposed OTC labeling appropriately guides correct use of the device

FDA Developed and Tested a Model DFL for Naloxone

THE NEW ENGLAND JOURNAL OF MEDICINE

SPECIAL ARTICLE

FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone

Barbara R. Cohen, M.P.A., Karen M. Mahoney, M.D., Elande Baro, Ph.D.,
Claudia Squire, M.S., Melissa Beck, B.A., Sara Travis, B.S.,
Amanda Pike-McCrudden, M.A., Rima Izem, Ph.D., and Janet Woodcock, M.D.

ABSTRACT

BACKGROUND
The opioid crisis highlights the need to increase access to naloxone, possibly through regulatory approval for over-the-counter sales. To address industry-perceived barriers to such access, the Food and Drug Administration (FDA) developed a model drug facts label for such sales to assess whether consumers understood the key statements for safe and effective use.

METHODS
In this label-comprehension study, we conducted individual structured interviews with 710 adults and adolescents, including 430 adults who use opioids and their family and friends. Eight primary end points were developed to assess user comprehension of each of the key steps in the label. Each of these end points included a prespecified target threshold ranging from 80 to 90% that was evaluated through a comparison of the lower boundary of the 95% exact confidence interval.

Cohen BR, Mahoney KM, Baro E, et al. N Engl J Med. 2020;382(22):2129-2136.

Drug Facts	
Active ingredient (in each XX)	Purpose
Naloxone hydrochloride X mg	Emergency treatment of opioid overdose
Uses	
<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> GIVE the 1st dose of this medicine Insert in NOSE and press
3 CALL 	Step 3: CALL <ul style="list-style-type: none"> CALL 911 immediately after giving the 1st dose
4 WATCH/GIVE 	Step 4: WATCH & GIVE <ul style="list-style-type: none"> WATCH 2-3 minutes after the 1st dose to give the medicine time to work if the person gains up: Go to Step 5 if the person does not wake up: <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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

FDA Label Comprehension Study Results

Table 3. Participant Comprehension of Primary and Secondary End Points.^a

End Point	% (95% CI)
Primary	
Step 1: Check for a suspected overdose	95.8 (94.0–97.1)
Step 2: Give the first dose	98.2 (96.9–99.0)
Step 3: Call 911 immediately	90.3 (87.9–92.4)
Composite of steps 1–3	81.1 (78.0–83.9)
Step 4: Repeat doses every few minutes	93.8 (91.8–95.5)
Step 5: Stay with the person	91.1 (88.8–93.1)
Use for treatment of opioid overdose	96.5 (94.0–97.7)
Signs of overdose	94.5 (92.6–96.1)
Secondary	
Some people may have symptoms when they wake up	82.4 (79.4–85.1)
It is safe to keep giving doses	95.6 (93.9–97.0)
Another dose should be given if the person becomes very sleepy again	92.3 (90.0–94.1)
The “call 911” step is completed in the appropriate order	85.2 (82.4–87.7)
Performance of steps 1–5	74.6 (71.3–77.8)

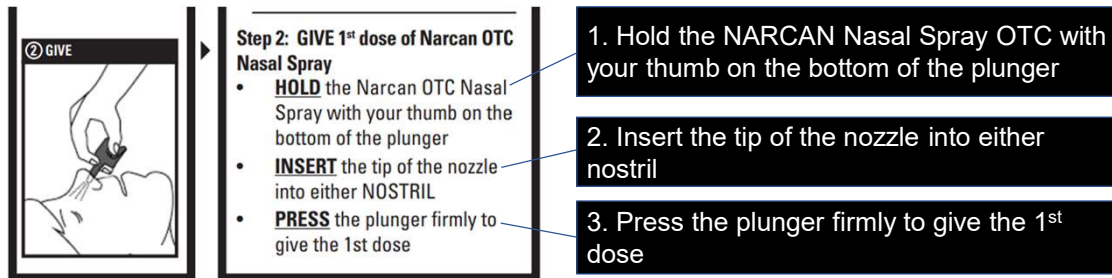
Cohen BR, Mahoney KM, Baro E, et al. N Engl J Med. 2020;382(22):2129-2136.

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Only Product-Specific Directions Require Further Testing

- **Step 2** of the directions for administering NARCAN® Nasal Spray is the only product-specific element in the NARCAN® Nasal Spray OTC DFL vs. the model DFL
- Therefore, three **primary endpoints** evaluated the proportion of participants who could successfully perform these **product-specific** dosing tasks in Step 2 of the proposed NARCAN® Nasal Spray OTC DFL in the HF Study:



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

1. Hold the NARCAN Nasal Spray OTC with your thumb on the bottom of the plunger
2. Insert the tip of the nozzle into either nostril
3. Press the plunger firmly to give the 1st dose

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Target Performance Standards for Primary Endpoints

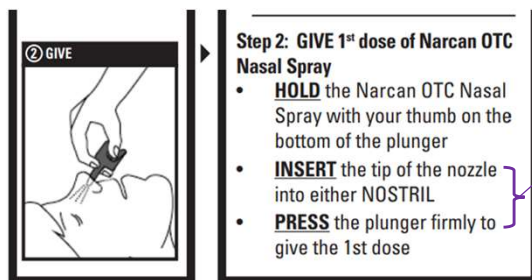
- Each primary endpoint was assigned a target performance standard that was based on an assessment of the clinical risk associated with inadequate performance on that task
- The lower bound of the two-sided 95% Confidence Interval (CI) for each primary endpoint is compared to the target performance standard

Primary Endpoints	Target Performance Standard
Step 2: Give 1st dose of Narcan OTC Nasal Spray	
1. Step 2a: Hold the Narcan OTC Nasal Spray with your thumb on the bottom of the plunger	85%
2. Step 2b: Insert the tip of the nozzle into either nostril	90%
3. Step 2c: Press the plunger firmly to give the 1 st dose	90%

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Secondary Endpoint



The **composite** measure of the proportion of participants who correctly completed Tasks 2 and 3, which are the critical steps in administering nasal naloxone

- Secondary endpoint was presented descriptively, with no target threshold
 - Rationale: the joint probability of success for composite endpoints is directly and inversely related to the number of discrete performance measures that are included in the endpoint

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Other Descriptive Endpoints

Included key directions that are **not specific to NARCAN® Nasal Spray** (OTC) that could be observed or verbally described in an HF demonstration

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

Drug Facts (continued)

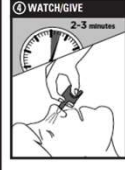
③ CALL



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

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HF Endpoint Calculations

- In OTC HF studies, our experience shows that some people naturally default to explain steps verbally to show understanding of items they think might be harder to demonstrate physically in a research setting. Thus, correct verbal descriptions were considered in endpoint calculations
- Therefore, correct simulated use was calculated for each critical HF task as:
 - The number of participants who were correct or acceptable in their action for that independent task, or
 - Verbally conveyed a clear understanding of the task
- Correct responses to follow-up comprehension questions about each step were included as acceptable in endpoint calculations
- Endpoint findings are presented as % correct + % acceptable for the overall endpoint result

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Methodology

- Conducted in accordance with FDA guidance documents on HF studies¹ and Label Comprehension (LC) Studies²
 - HF Guidance specifies a sample size of 15 participants per user group
- **Inclusion / exclusion criteria and user groups were modeled after FDA's LC study**
 - Adults from General Population
 - Adolescents Ages 15-17 from General Population
 - Adults who reported recent use of opioids
 - Adults who are associated with someone who takes opioids
 - Low literacy target of 30%
- Study was reviewed and approved by an independent IRB

1. Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development; 2. FDA Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products

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Participant Recruitment

- Conducted at research sites in 4 geographically diverse regions in the U.S. (March 2021)
- Participants were recruited by the research sites, via social media, digital advertising, and community outreach groups/clinics
- Participants were re-screened for entry criteria and informed consent was obtained
- Literacy was assessed using the REALM¹ or REALM-Teen² test

1. Murphy et al., *J of Reading*, 1993; 37(2): 124-130; 2. Davis et al., *Pediatrics*, 2006; 118(6): e1707-1714

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HF Demonstration

- Directions provided were very minimal to maintain as much realism as possible for the simulated overdose emergency
- Interviewing room was set up to simulate the experience of walking in to discover a family member in bed and unresponsive
- A movie was playing in the room to create some distraction and stress in the environment to contribute to the naturalism of the simulation
- A carton of NARCAN® Nasal Spray displaying the OTC label and containing two water-filled devices was in the room
- Participants were told to demonstrate how they would use the product to save their family member
- No training or prior exposure to the DFL was provided

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HF Demonstration

- A trained interviewer was in the room carefully observing participant behavior and documenting if each step on the DFL was performed correctly
- Standardized LC questions were asked to assess comprehension of any directions that were not correctly demonstrated
- A second, independent reviewer viewed the recorded interview to also classify correct or incorrect performance
- Any discrepancies between the on-site interviewer and reviewer were resolved by a third independent reviewer

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Participant Characteristics

29.6% low literacy after enrichment

Appropriate user group representation

- Adults (ages 18+), general population (n=18)
- Adolescents (ages 15-17), general population (n=19)
- Adults who reported recent use of opioids (n =16)
- Adults who are friends/family/caregivers of someone who takes opioids (n=18)

Diverse demographics

- 15 to 76 years of age
- 17% Black or African American
- 7% American Indian or Alaska Native
- 10% LatinX
- 25% of adults with high school education or less
- 34% reported an annual household income of \$50,000 or less
- 75% reported that they had not heard of naloxone prior to the study

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Primary Endpoint Results

Primary Endpoint	% Correct / Acceptable	95% CI	Target Performance Standard
1. Step 2a: Hold the NARCAN® Nasal Spray OTC with your thumb on the bottom of the plunger	97.2% (97.2% Correct + 0.0% Acceptable)	(90.3, 99.2)	85%
2. Step 2b: Insert the tip of the nozzle into either nostril	97.2% (97.2% Correct + 0.0% Acceptable)	(90.3, 99.2)	90%
3. Step 2c: Press the plunger firmly to give the 1 st dose	94.4% (93.0% Correct + 1.4% Acceptable)	(86.4, 97.8)	90%

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Primary Endpoint Results by Literacy and Age

Primary Endpoint	All Subjects (n=71)	Normal Literacy (n=50)	Low Literacy (n=21)	Adolescents (n=19)	Adults General Population (n=18)
1. Step 2a: Hold the NARCAN® Nasal Spray OTC with your thumb on the bottom of the plunger	97.2%	96.0%	100%	94.7%	100%
2. Step 2b: Insert the tip of the nozzle into either nostril	97.2%	96.0%	100%	94.7%	100%
3. Step 2c: Press the plunger firmly to give the 1 st dose	94.4%	92.0%	100%	89.5%	100%

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Secondary Endpoint Results

Secondary Endpoint	% Correct / Acceptable	95% CI
Composite measure of the proportion of participants who correctly completed Primary Endpoint Tasks 2 and 3: Insert the tip of the nozzle into either nostril AND Press the plunger firmly to give the 1 st dose	94.4% (93.0% Correct + 1.4% Acceptable)	(86.4, 97.8)

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Descriptive Endpoint Results

Step	% Correct / Acceptable	95% CI
Step 1: Check if you suspect an overdose Yell "Wake up!" Shake the person gently	Correct HF Demonstration: 85.9%	(76.0, 92.2)
	Correct HF Demonstration: 91.5%	(82.8, 98.6)
	+ 9.9% Acceptable Responses to LC Follow-up for Step 1: 95.8%	(88.3, 98.6)
Step 3: Call 911 immediately after giving the first dose Call 911 Immediately after giving the first dose	Correct HF Demonstration: 98.6%	(92.4, 99.8)
	Correct HF Demonstration: 85.9%	(76.0, 92.2)
	+ 5.6% Acceptable Responses to LC Follow-up for Step 3: 91.5%	(82.8, 96.1)

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Descriptive Endpoint Results

Step	% Correct / Acceptable	95% CI
Step 4: Watch and Give: Wait 2-3 minutes after the 1 st dose to give medicine time to work Continue to give doses every 2-3 minutes until the person wakes up	84.5% Correct HF Demonstration	(74.3, 91.1)
	97.2% Correct HF Demonstration	(90.3, 99.2)
	+ 1.4% Acceptable Responses to LC Follow-up for Step 4: 98.6%	(92.4, 99.8)
Step 5: Stay Stay until ambulance arrives even if the person wakes up Give another dose if the person becomes very sleepy again*	90.1% Correct HF Demonstration + 2.8% Acceptable Responses to LC Follow-up: 93.0%	(81.0, 95.1) (84.6, 97.0)
	32.4% Correct HF Demonstration	(22.7, 43.9)
	+ 19.7% Acceptable Responses to LC Follow-up: 59.2%*	(47.5, 69.8)

*Results for this sub-step are an artifact of study, as each carton contained 2 doses, and participants had already administered the 2nd dose in Step 4

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HFS Summary

- Participants received minimal directions on what to do or what was expected of them and had no exposure to the DFL prior to entering the opioid overdose simulation
- The lower limit of the 95% CI for 2 of 3 Primary Endpoints exceeded the pre-defined target performance thresholds
- The lower limit of the 95% CI for Primary Endpoint 3 fell just short of the target, but with an observed proportion of 94.4% of participants with acceptable performance of this step

Results indicate that the proposed OTC labeling for NARCAN® Nasal Spray is sufficient to guide correct administration by a diverse group of consumers in an OTC setting

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Agenda

Introduction

Manish Vyas

Senior Vice President, Regulatory Affairs
Emergent BioSolutions

NARCAN® Nasal Spray 4 mg and the OTC Development Program

Gay Owens, PharmD, MBA

Global Medical Affairs Lead, Opioid Antidote
Emergent BioSolutions

Medical Need for OTC Nasal Naloxone

Scott Hadland, MD, MPH, MS

Chief, Division of Adolescent and Young Adult Medicine
Massachusetts General Hospital – Harvard Medical School

Human Factors Study

Sarah Farnsworth, PhD

Vice President, Scientific Affairs
PEGUS Research

NARCAN® Nasal Spray Benefit-Risk Overview

Manish Vyas

Senior Vice President, Regulatory Affairs
Emergent BioSolutions

Conclusion

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NARCAN[®] Nasal Spray Benefit-Risk Overview & Conclusion

Manish Vyas
Senior Vice President, Regulatory Affairs
Emergent BioSolutions



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Post-Market Data Support Favorable Safety of NARCAN[®] Nasal Spray

NARCAN[®] Nasal Spray has a well-established safety profile supported by 7 years of post-marketing safety data with an estimated 44 million doses distributed¹

- The rate of serious adverse events reported is low
 - (0.80 per 100,000 doses)¹
- The rate of medication errors (misuse) reported is low
 - (0.28 per 100,000 doses)¹
- Device failure is also reported infrequently
 - (0.03 per 100,000 doses)¹

1. Emergent Safety Database (Feb 2016 - Oct 2022)

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Since Product Launch in 2016 There Have Been a Total of 1078 Adverse Events Reported in 473 Cases

- Adverse event (AE) reports are consistent with the FDA FAERS and WHO Vigibase
- Overall, AE rate is very low in relation to the large number of doses distributed
- These AE are not unexpected and part of the current NARCAN® Rx label

Most Common Adverse Events (>2% Events) Reported to Emergent	
MedDRA v25.0 Preferred Term (PT)	Total Adverse Events N=1078 events ^a n (% of total events reported)
Drug withdrawal syndrome	78 (7.2%)
Unintentional use for unapproved indication	66 (6.1%)
Vomiting	47 (4.4%)
Drug ineffective	37 (3.4%)
Feeling abnormal	27 (2.5%)
Anger	22 (2.5%)

^a 1078 adverse events reported in 473 cases
Most Common (>2% of Events) from Post market reports of Adverse Events by Preferred Term from February 2016 through October 2, 2022
Source: Emergent Safety Database

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Naloxone Precipitated Opioid Drug Withdrawal is Manageable

- Drug withdrawal is a known effect with naloxone and reflected in current Rx and proposed NARCAN® Nasal Spray OTC labeling
- No pharmacological effect in the absence of opioids¹
- The severity and duration of the withdrawal syndrome are related to the dose of naloxone and to the degree and type of opioid dependence^{1,2}
- While unpleasant, symptoms are generally not life-threatening and are transient^{2,3}
- The comprehensive safety analysis of world-wide data found a low incidence of severe Acute Withdrawal Syndrome associated with serious outcomes
- Precipitation of acute withdrawal symptoms outweighs the risk of the life-threatening consequences of prolonged CNS and respiratory depression

1. NIDA. 2022. January 11. Naloxone DrugFacts. Retrieved from <https://nida.nih.gov/publications/drugfacts/naloxone>; 2. Chiang WK, Goldfrank LR. *Emerg. Med. Clin. N.* 1990;8:3, 613-631; 3. Clarke SFJ, Dargan PI, Jones AL. *Emerg Med J* 2005;22:612-616.

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Additional Safety Considerations

- Drug risk behavior has not been observed with current community use
 - In a study¹ among two groups of persons who use heroin, there was no evidence of compensatory drug use following naloxone/overdose training
- Opioid Education & Naloxone Distribution Programs have demonstrated feasibility, increased knowledge and skills and a concomitant reduction in fatal overdoses²
- Naloxone has no effect on someone who does not have opioids in their system³
- Potential for misuse, medication errors, and device failures are minimal⁴

1. Jones JD, Campbell A, Metz VE, Comer SD. *Addict Behav.* 2017;71:104-106; 2. Walley A, et al. *BMJ* 2013;346:f174 3. NIDA. 2022, January 11. Naloxone DrugFacts. Retrieved from <https://nida.nih.gov/publications/drugfacts/naloxone>;
 4. Emergent safety database (pharmacovigilance data); February 2016 – 02OCT2022

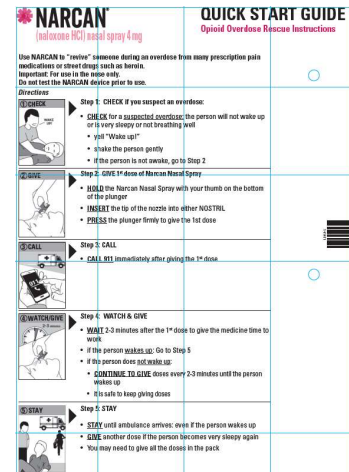
NARCAN® Nasal Spray Especially Suited for OTC Use

- HF Validation Study supports that consumers can be directed only by the DFL
 - Emergent has worked with FDA and will add all 5 Steps of DFL onto the back panel and a Quick Start Guide (QSG) leaflet inside the blister

Updated Proposed Carton (Back Panel)



Proposed QSG



NARCAN[®] Nasal Spray Especially Suited for OTC Use

- NARCAN[®] Nasal Spray has 7 years of post-marketing safety data with low frequency of misuse
- There is no risk of naloxone overdose, making it appropriate for use by layperson bystanders to administer naloxone safely and rapidly until emergency services arrive
- NARCAN[®] Nasal Spray has been specifically designed for community use and is currently used by laypersons without specific training
- Favorable benefit-risk profile is supportive of NARCAN[®] Nasal Spray use as OTC product

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NARCAN[®] Nasal Spray 4 mg Fulfills the Criteria for “OTCness”

OTCness	Criteria
√	User must be able to self-diagnose*
√	Product is adequately labelled to drive correct use by the consumer
√	Benefits of increased access outweigh potential risks
√	Health practitioners are not needed for the safe and effective use of product
√	Low potential for misuse and abuse

* For NARCAN[®] Nasal Spray, bystander/caregivers can diagnosis potential overdose and administer/treat. NARCAN[®] Nasal Spray is indicated for use in known and suspected cases of opioid overdose.

The ABCs of OTCs, Little Known Facts About Over-the-Counter Drugs, Karen Murry Mahoney, MD, FACE, Deputy Director, Division of Nonprescription Drug Products, CDER, US Food and Drug Administration [Nonprescription Drug Products: The Basics and New Initiatives \(fda.gov\)](#); [www.fda.gov](#); The ABCs of OTCs, Little-Known Facts About Over-the-Counter Drugs

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Thank You

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Back Up Slides

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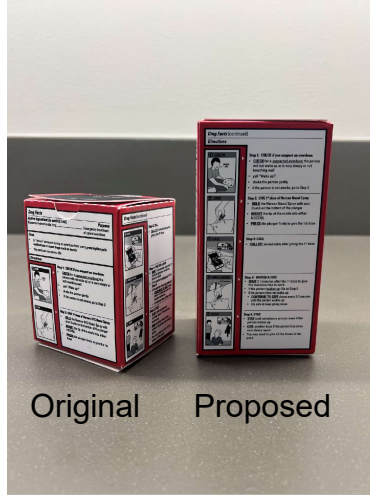
Participants Delivered the First Dose Quickly

- Time from beginning the simulation to delivering the first dose:
 - Mean: 75.9 seconds
 - Median: 67 seconds
 - Range: 22 – 164 seconds
 - 71.4 % gave dose within 90 seconds
- This includes the time for the tasks required before administration:
 - Review the label, try to wake the person, open the carton, retrieve one blister pack, open the blister pack, hold the device / prepare to administer

Original Proposed Drug Facts Label vs. Updated Proposed Drug Facts Label

Back Panel	Side Panel	Directions
<p>Drug Facts</p> <p>Active ingredient (in each 0.1 mL) _____ Purpose Naloxone hydrochloride 4 mg _____ Emergency treatment of opioid overdose</p> <p>Uses</p> <ul style="list-style-type: none"> • to "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin • this medicine can save a life <p>Directions</p> <p>Step 1: CHECK if you suspect an overdose:</p> <ul style="list-style-type: none"> • 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 <p>Step 2: GIVE 1st dose of Narcan OTC Nasal Spray</p> <ul style="list-style-type: none"> • 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 	<p>Drug Facts (continued)</p> <p>Step 3: CALL</p> <ul style="list-style-type: none"> • CALL 911 immediately after giving the 1st dose <p>Step 4: WATCH & GIVE</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up • it is safe to keep giving doses <p>Step 5: STAY</p> <ul style="list-style-type: none"> • 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 	<p>Directions</p> <p>1) CHECK</p> <ul style="list-style-type: none"> • 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 <p>2) GIVE</p> <ul style="list-style-type: none"> • HOLD the Narcan 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 <p>3) CALL</p> <ul style="list-style-type: none"> • CALL 911 immediately after giving the 1st dose <p>4) WATCH & GIVE</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • CONTINUE TO GIVE doses every 2-3 minutes until the person wakes up • it is safe to keep giving doses <p>5) STAY</p> <ul style="list-style-type: none"> • 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

Original Proposed Carton vs. Updated Proposed Carton



Visual representation to scale

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FDA Figure 13: Nonprescription Narcan Blister Labeling



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FDA Figure 16: Prescription Narcan Blister Design with Quick Start Guide



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