

Clinical and Regulatory Overview of Naloxone Products Intended for Use in the Community

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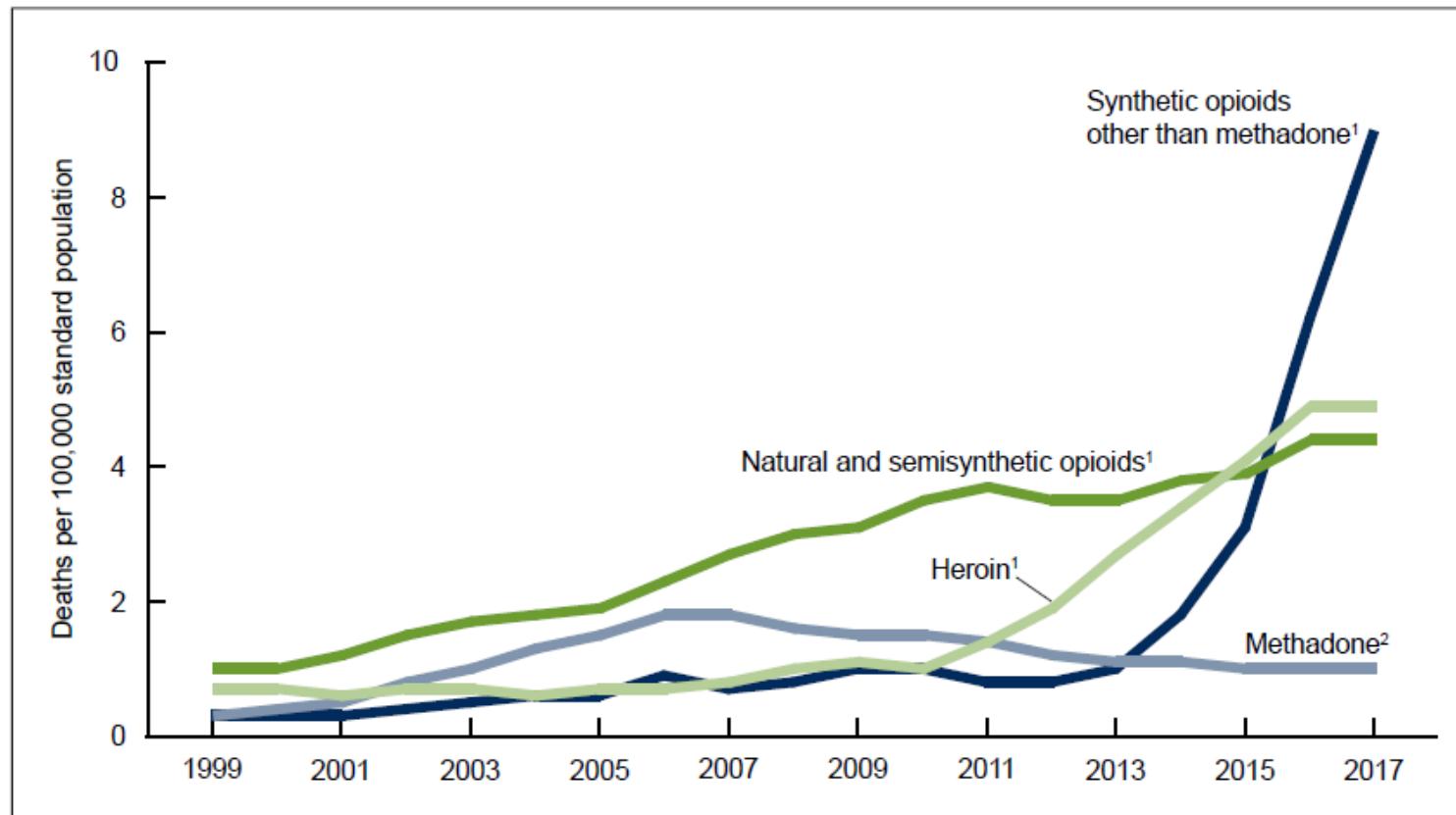
December 17-18, 2018: Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Opioid Overdose and Death is a Public Health Crisis



- US is experiencing a devastating public health crisis associated with the use, misuse, and abuse of illicit and/or prescription opioids
 - 2 million with a substance use disorder involving prescription pain relievers
 - 591,000 with a substance use disorder involving heroin
- Characterized by life-threatening respiratory and central nervous system depression
- Recent data show marked increase in the number of opioid-related overdose deaths driven by heroin and synthetic opioids other than methadone

Age-adjusted Drug Overdose Death Rates by Opioid Category 1999-2017



<https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf>

Initial Approval of Naloxone

- Approved in 1971 as Narcan
 - Solution labeled for intravenous (IV), intramuscular (IM), or subcutaneous (SC) use
 - Indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids
 - Also indicated for the diagnosis of suspected or known acute opioid over dosage
 - Earlier formulations of naloxone and its generic equivalents are not optimized for use by non-medical professionals

Newer Naloxone Products Approved for Community Use

- Evzio (naloxone auto-injector)
 - Approved April 2014
 - Prefilled single-use auto-injectors
 - Labeled for IM or SQ
 - A 2-mg dose
 - Average retail price \$4,641 for a package containing 2 units



Newer Naloxone Products Approved for Community Use

- Narcan Nasal Spray
 - Approved November 2015
 - A single-use device
 - Labeled for intranasal use
 - A 4-mg dose of naloxone in a 0.1 ml spray
 - Average retail price \$142 for a package containing 2 units



Newer Naloxone Products

Approved for Community Use

- Approved Indication
 - The emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
 - Intended for immediate administration as emergency therapy in settings where opioids may be present
 - Not a substitute for emergency medical care

Off-Label Naloxone Use in Community

- Provided in a kit containing:
 - Naloxone for injection (2 mg/2 ml)
 - In a prefilled syringe
 - Mucosal atomizer device
- Half of the volume (~1 ml) is sprayed into each nostril
- Unapproved route for the approved parenteral product
- Average invoice price \$29
 - Increase of 244% from 2006 to 2017
 - Rosenberg *et al*, Addictive Behavior, 2018



<http://www.providencejournal.com/article/20140215/SPECIAL-REPORTS/302159991>



<http://www.medpagetoday.com/publichealthpolicy/publichealth/52118>

Increasing Access to Naloxone

- Naloxone saves lives
 - Blocks the effects of opioids
 - Reverses the life-threatening effects of an opioid overdose
 - Timely administration is necessary
- “Promoting use of overdose-reversing drugs” is one of the five priorities to combat the opioid crisis by Department of Health and Human Services
- The Commissioner of the FDA, Scott Gottlieb, MD, specifically noted that the Agency is focused on increasing the use and access to the potentially life-saving antidote naloxone

Initiatives to Increase Access to Naloxone

- Individual prescriptions from healthcare provider in more traditional healthcare settings, such as pain clinics and opioid treatment programs
- Without individual prescriptions through community-based programs, offering overdose education and naloxone distribution outside of traditional health care setting
- Direct access from pharmacies under programs such as statewide naloxone standing orders or collaborative practice agreements

FDA Efforts to Increase Access

- Facilitating the development and approval of new naloxone products for use in the community
- Fostering the development of naloxone products for over-the-counter use as a means to increase its availability in the community
- Additional actions to be considered, including revision of the labeling for opioid-containing drug products:
 - to inform prescribers about the existence of naloxone products
 - to advise prescribers to consider co-prescribing naloxone
 - to recommend co-prescription of naloxone

Possible Strategies for Co-Prescription of Naloxone

- All patients prescribed an opioid analgesic drug product
 - Benefits include:
 - Places naloxone in all households with prescribed opioid medications
 - May help prescribers and patients understand the importance of proper use and storage
 - Available for accidental or other exposures by other members in the household
 - Does not reach all persons at risk for opioid overdose

Possible Strategies for Co-prescription of Naloxone

- High risk groups prescribed opioid analgesics
 - Concurrent prescriptions for other CNS depressants
 - Pain management requiring higher doses of opioid analgesics or with chronic pain managed with opioid analgesics
 - History of opioid-related emergency department visit, prior overdose
 - A personal or family history of substance use disorder

Possible Strategies for Co-prescription of Naloxone

- High risk groups who do not receive opioids analgesic prescriptions
 - Patients using medication assisted treatment for opioid use disorder
 - Prior history of opioid use disorder
 - Prior history of opioid abuse
 - Recent release from criminal justice system with a history of opioid abuse or opioid use disorder

Costs of Naloxone Co-prescription

- Ideally, naloxone is available to all patients who are prescribed opioids in the event of an overdose of the patient or other member of the household
- Healthcare resources are limited
 - Retail price of the approved naloxone products for community use can be high (as much as \$142 for one product, \$4641 for another, both in a package containing 2 units)
 - Cost of co-prescription can be substantial (depending on the assumptions made)

Considerations for Naloxone Co-prescribing

- Substantial and growing percentage of opioid-related deaths are associated with the use of illicit opioids
 - Co-prescription of naloxone may not reach a large proportion of individuals at risk for an opioid overdose death
- In order for reversal of an opioid overdose to be successful, it must be administered soon enough to prevent irreversible anoxic injury to the brain
 - In some cases, this means the overdose would need to be witnessed for naloxone to be administered early enough to rescue the patient

Conclusion

- FDA is committed to increase access to naloxone for community use by additional actions
 - FDA is seeking advice on how best to meet this goal



Drug Utilization of Naloxone

December 17-18, 2018: Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

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US Food and Drug Administration

Naloxone Distribution: Unique and Complex



- Pathways:
 - Settings
 - Wholesale, direct sales, donations
 - Inpatient, outpatient, community
 - Variable dispensation requirements
 - Harm Reduction, Opioid Education and Naloxone Distribution (OEND)
 - Administration
 - Inpatient, emergency medical services (EMS), police
 - Bystanders
- Formulations/Routes of Administration:
 - Nasal, Injectable

Outline



- Naloxone Availability
 - Proprietary Data Sources
 - Sales Distribution
 - Retail Prescriptions
 - Other Data Sources
 - Donations and Direct Sales
 - Publications and Distribution Programs
 - Summary

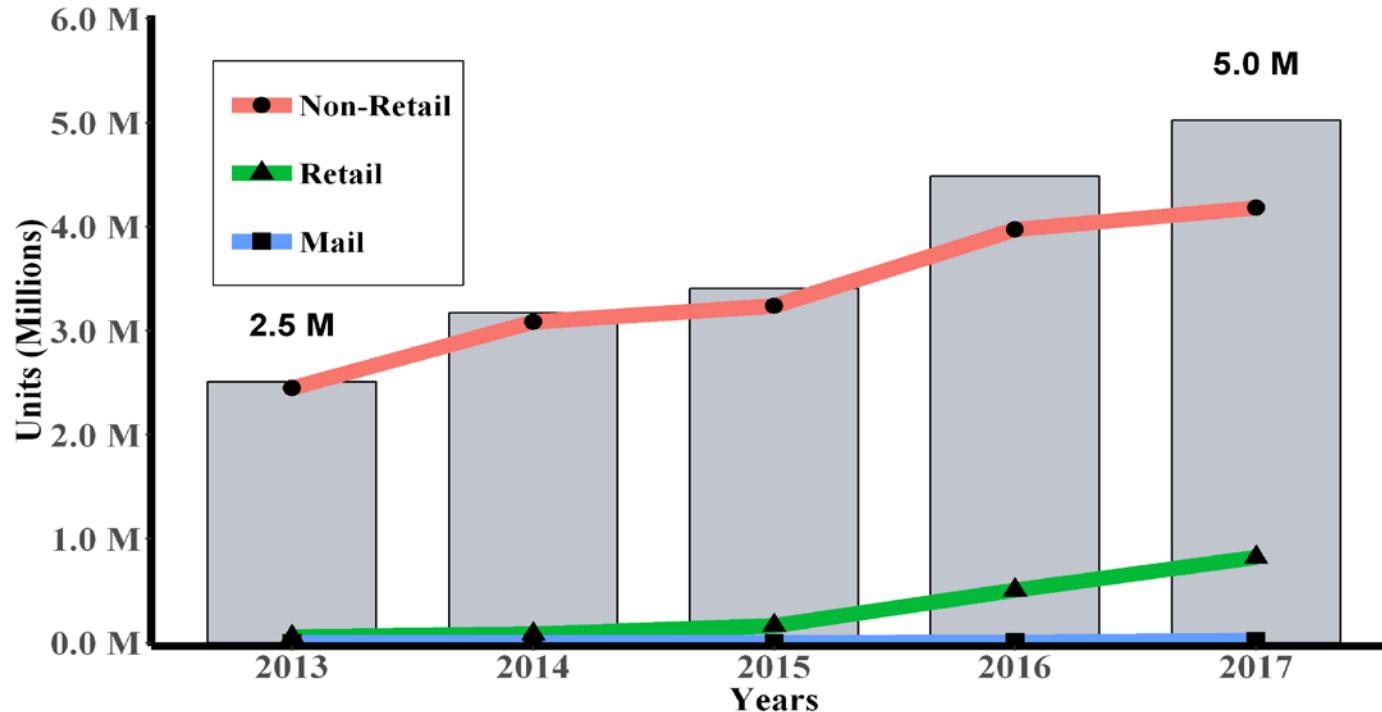
Proprietary Data Source: Sales Distribution Data

- IQVIA, National Sales Perspectives
- National estimates of the volume of drug products sold from manufacturers to settings of care
 - Non-federal hospitals
 - Retail pharmacies
 - Clinics
 - “Other settings”
- Measures naloxone products distributed through traditional channels of distribution
 - Primarily captures sales through wholesalers and distributors
 - Does not capture donations and some direct sales from manufacturers
- Products measured in units sold (e.g., vial, ampule, syringe, device)

Sales by Setting: All Formulations



Nationally estimated number of naloxone units (auto-injector, nasal spray and injection formulation) sold from manufacturers to various U.S. channels of distribution

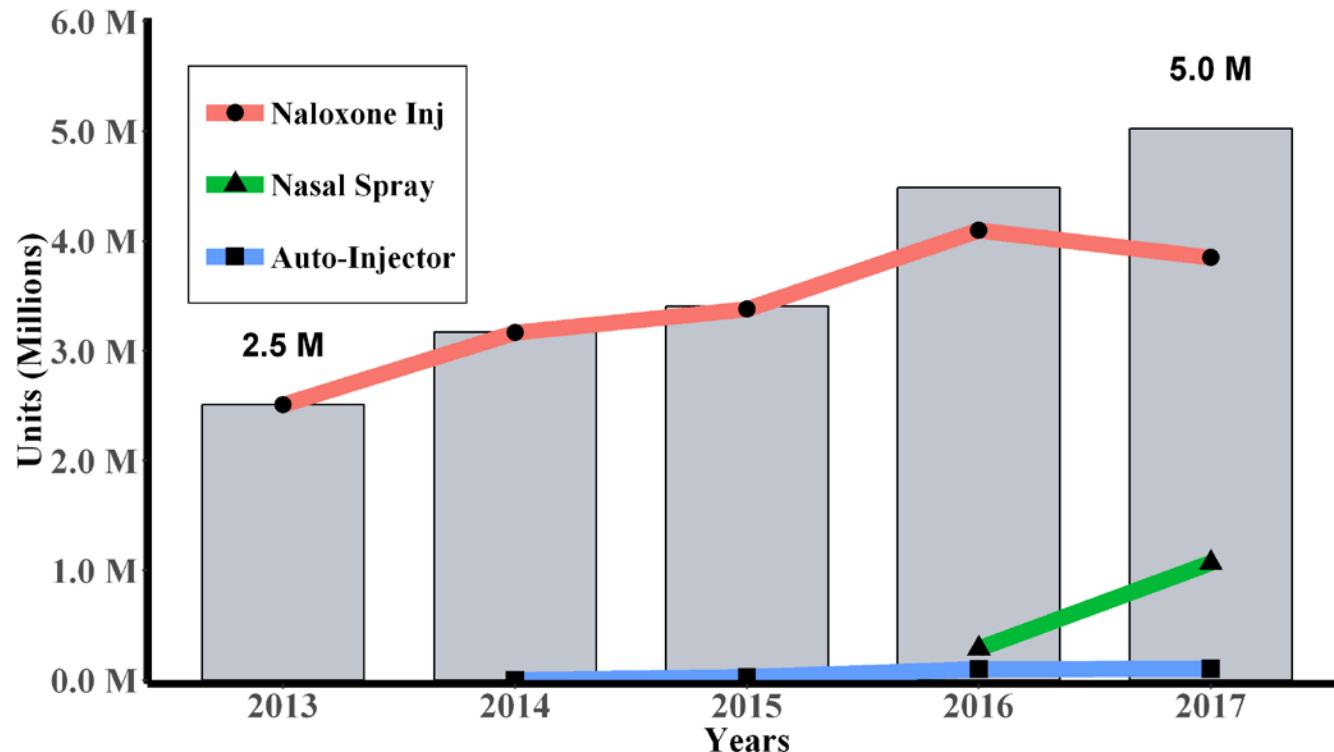


Source: IQVIA, National Sales Perspective (NSP). 2013-2017. Data Extracted October 2018.

Non-retail channels: non-federal hospitals, federal facilities, long-term care, HMOs, clinics, home health, and miscellaneous (including prisons and universities).

Sales by Formulation: All Settings

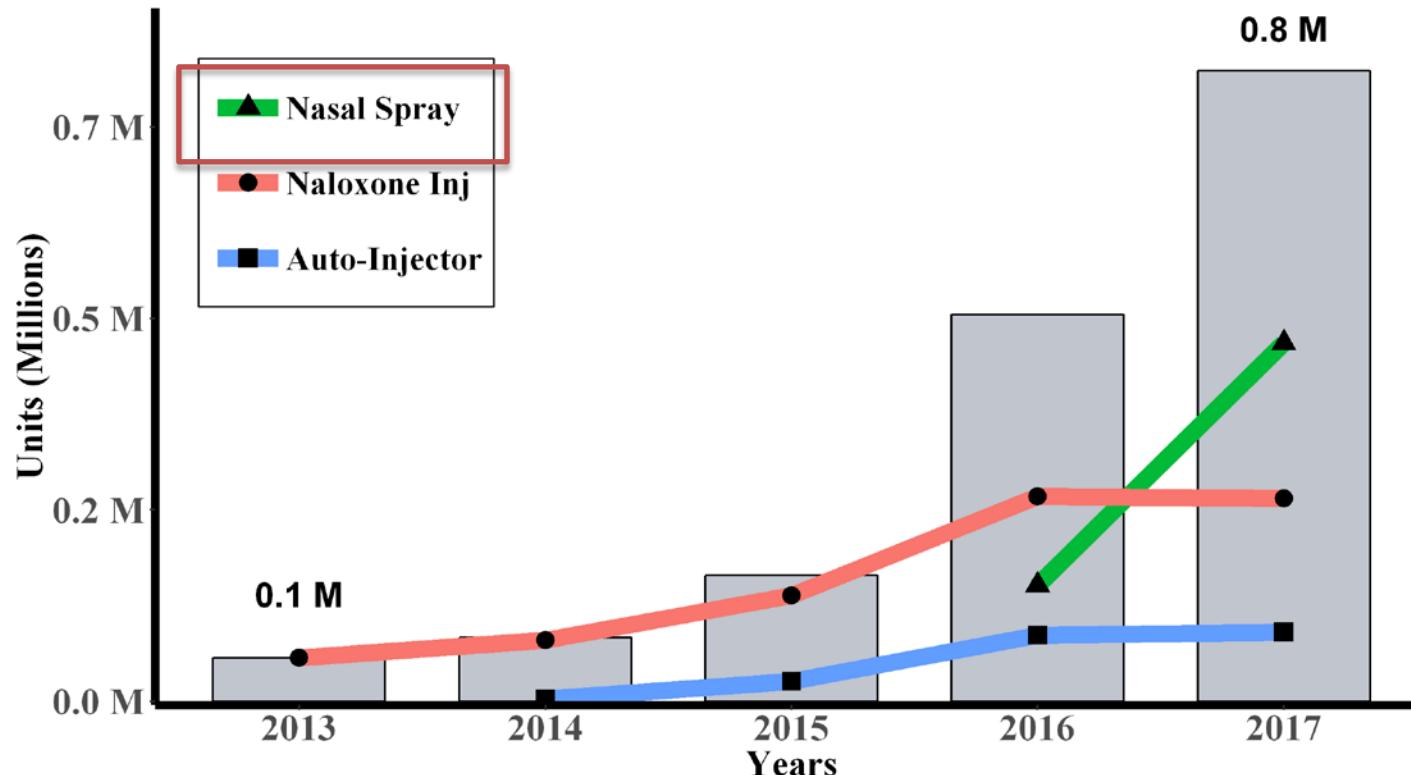
Nationally estimated number of naloxone units sold from manufacturers to U.S. channels of distribution, stratified by product formulation (auto-injector, nasal spray and injection formulation)



Sales by Formulation: Retail Pharmacies



Nationally estimated number of naloxone units sold from manufacturers to U.S. retail pharmacies, stratified by product formulation (auto-injector, nasal spray and injection formulation)



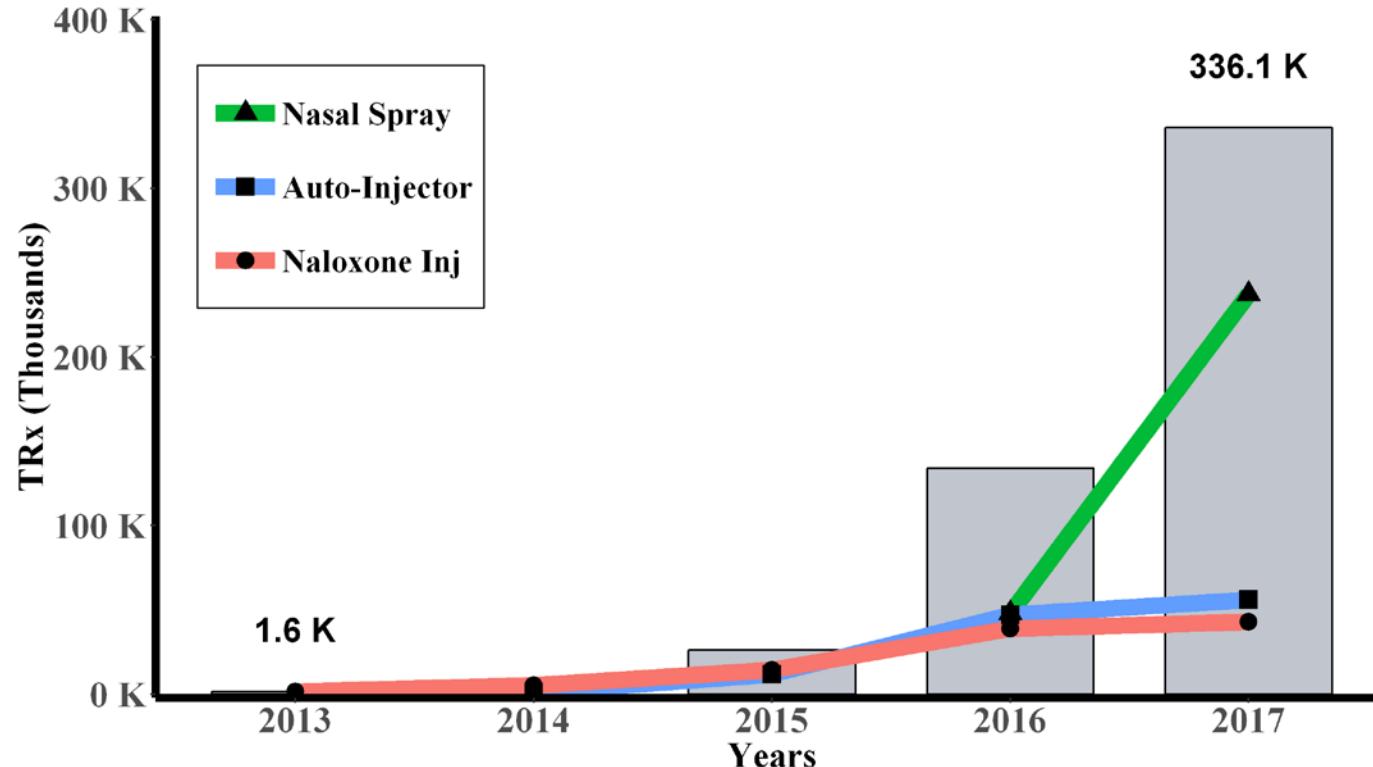
Retail Prescription Data

- IQVIA, National Prescription Audit (NPA) and Symphony Health's PHAST™ Prescription Monthly
- Provides national estimates of the number of prescriptions dispensed from U.S. outpatient retail pharmacies
 - Nationally and by state

Naloxone Prescriptions Dispensed

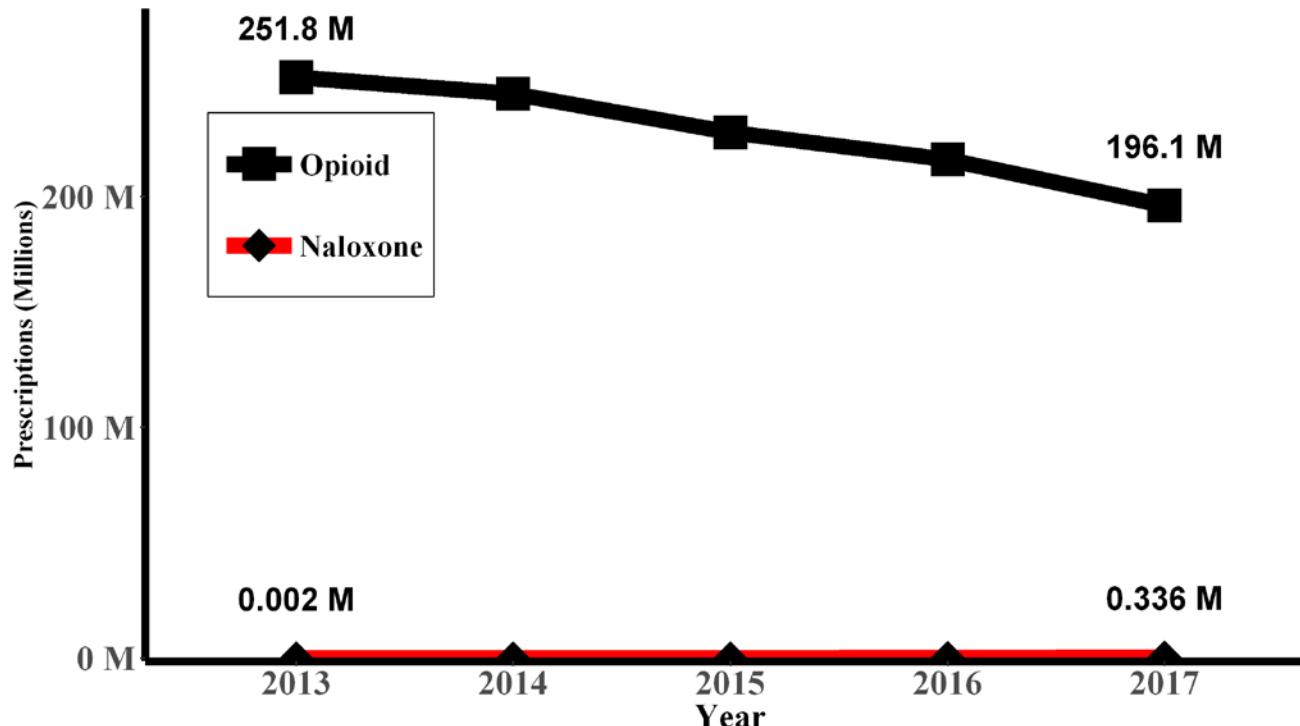


Nationally estimated number of naloxone prescriptions, stratified by product formulation (auto injector, nasal spray and injection), dispensed from U.S. outpatient retail pharmacies



Naloxone and Opioid Analgesic Prescriptions

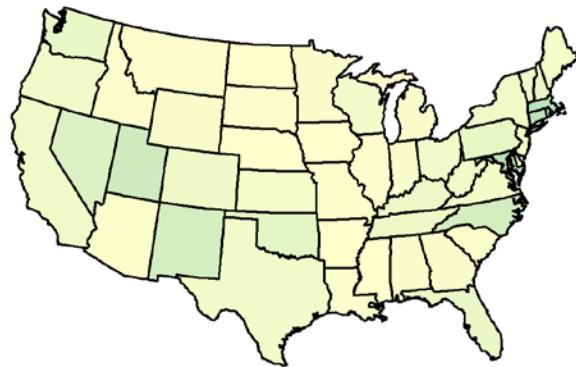
Nationally estimated number of naloxone prescriptions (all formulations) and opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies



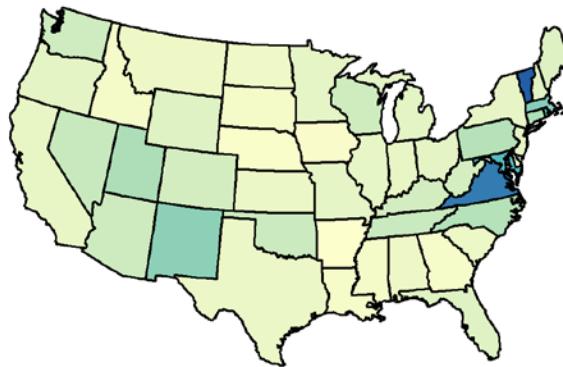
Ratio of Naloxone Rx per 1,000 Opioid Analgesic Rx by State

Nationally Estimated Number of Naloxone Prescriptions per 1,000 Opioid Analgesic Prescriptions
Dispensed from U.S. Outpatient Retail Pharmacies in 2016 and 2017 (48 contiguous)

2016



2017



Naloxone

per 1,000 Opioid



2.5 5.0 7.5 10.0

Proprietary Database Limitations

- Sales distribution data are not all-inclusive
 - Distribution outside of typical supply chains (e.g., donations) or outside of traditional settings (e.g., first responders) not captured
- Prescription data are not a direct estimate of total use:
 - Recipient of dispensed prescription may not be ultimate recipient of naloxone during overdose event (e.g., guardian)
 - Not all naloxone sold is dispensed, and not all dispensed is used; administered dose unknown
- May underestimate real-world utilization

Outline



- Naloxone Availability
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 - Other Data Sources
 - Donations and Direct Sales
 - Publications and Distribution Programs
 - Summary

Other Distribution Pathways



- Donations and Direct Sales
 - Evzio Auto-Injector
 - Approximately 30,000 two-unit packages distributed annually as donations, 2014 – 2018
 - Narcan Nasal Spray
 - Over 250,000 two-unit packages distributed in total between November 2015 – November 2018

Kaleo Inc. Annual Report: Distribution Data. Food and Drug Administration. Permission received November 2018.

Adapt Pharma. Annual Report: Distribution Data. Food and Drug Administration. Permission received November 2018.

Literature And Other Sources

- Prescribing programs in health care settings
 - Primary care, pain clinics, pharmacies, or treatment programs
- Community-based programs outside of traditional healthcare settings
 - Harm Reduction
 - OEND
- “Take-home” naloxone programs
 - Recently incarcerated, recent overdose, those who inject drugs

Literature Summary



- Distribution both within and outside of traditional health care settings
- Reports of community-use naloxone administrations and opioid overdose reversals
 - Naloxone recipients and close contacts
- Both targeted and “universal precaution” models exist
- No formal comparative effectiveness studies

Published Data Limitations



- Community-based programs
 - Convenience samples
 - Inconsistent follow-up
 - Self-reported administrations, without independent data verification
 - Unclear generalizability
- Small pilot initiatives on prescribing models in health care settings

Summary



- National trends of naloxone sales and more granular utilization data show increasing trends in the community availability of naloxone
- Many programs to make naloxone available at the local or community level
- Innovative and collaborative methods are needed to better understand national patterns of naloxone distribution, utilization, dosing, and effectiveness





Nonprescription Model Drug Facts Label Project

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December 17-18, 2018: Joint Meeting of the Anesthetic and Analgesic Drug Products
Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Outline

- Why Nonprescription (OTC) Naloxone
- Overview of Consumer Behavior Studies for Nonprescription Drugs
- Developing the Drug Facts Label (DFL) for OTC Naloxone
- Label Comprehension Study (LCS): Refining and Testing the DFL
- Current Status and Next Steps

Why OTC Naloxone?

- Existing expanded access programs (such as pharmacy standing order programs) are a significant tool, but more is needed – not everyone can/wants to obtain the product through a healthcare professional
- Surgeon General's 2018 Advisory

U.S. Surgeon General Advisory

“I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, **knowing how to use naloxone and keeping it within reach can save a life.**”

Development Programs for Nonprescription Drugs

- Often rely on safety and efficacy established for the prescription product
- New studies may be required if proposing a new indication or a new patient population for the OTC market
- Need to “translate” key elements of the prescription label into consumer-friendly terms
- Consumer studies needed to evaluate the “OTC-ness” of product

Drug Facts Label

FDA

Drug Facts

Active ingredient (in each tablet)

Chlorpheniramine maleate 2 mg.....Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings

Ask a doctor before use if you have

- glaucoma
- a breathing problem such as emphysema or chronic bronchitis
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product

- drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over

take 2 tablets every 4 to 6 hours;
not more than 12 tablets in 24 hours

children 6 years to under 12 years

take 1 tablet every 4 to 6 hours;
not more than 6 tablets in 24 hours

children under 6 years

ask a doctor

Drug Facts (continued)

Other information ■ store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

OTC Consumer Studies

Label Comprehension Study

- Understanding the key label messages

Self-Selection Study

- Choosing the right product for “me”

Actual Use Study

- Using according to labeled directions

Human Factors Study

- Interacting with the product

FDA Proposed an Innovative Approach:



- To develop a model DFL that could be understood by all potential consumers who might use OTC naloxone
- To iteratively refine the DFL and evaluate consumer comprehension through a contract with established consumer research firms with expertise in conducting label comprehension studies and interviewing substance abuse populations
- To conduct an independent review of the resulting data

FDA Proposed an Innovative Approach (cont'd):



- If study is successful, Sponsors can adapt the model DFL to their naloxone product
- Sponsors would only need to add information specific to their particular device and assess through human factors
- Label comprehension was the key study to be conducted – self-selection and actual use are likely not needed

Label Comprehension Studies

- Identify communication objectives (most important concepts that need to be understood by consumer)
- Construct a questionnaire that targets communication objectives in an unbiased way
- Enroll a geographically and demographically diverse population

Literacy Considerations

- Average reading level in the U.S. estimated at 8th grade
- Drug Facts Label should be written at a 4th- 8th grade reading level
- Limited literacy subjects should consist of consumers with 4th-8th grade reading skills, as assessed by validated instruments

Unique Challenges Faced in Developing an OTC Naloxone DFL

- One person has to administer to a nonresponsive other person
- “Call 911” as part of Directions is unprecedented for a DFL
- Necessary to stay with person until help arrives to prevent death by relapse
- Multiple doses at timed intervals could be required

Challenges Faced in Developing an OTC Naloxone DFL (cont'd)

- Used in an emergency situation – highly stressful
- Cannot assume prior training by learned intermediary – assumption must be that person is reading the label for first time.
- Conciseness is critical – FDA decided that DFL had to be significantly simplified to its key elements

Developing the DFL for Naloxone



Interdisciplinary project team (e.g., medical officers, labeling experts, social scientists):

- Analyzed the Rx label and conducted literature review to incorporate most important clinical elements
- Consulted with internal and external substance abuse experts
- Determined what is currently happening out in the field with naloxone distribution programs to identify recurring themes and best practices

Developing the DFL for Naloxone (cont'd)

- Synthesized this information to determine the key elements for inclusion in label
- Sought input from internal communication experts about best ways to design DFL to optimize its use in an emergency situation
- Resulting DFL is accompanied by adjacent pictograms – a first for nonprescription products

Label Comprehension Studies – Best Practices



- Iterative approach allows for the label to evolve in real time, as rapid feedback is gathered from participants in a series of one-on-one interviews
- Pilot study is conducted to test revisions to the label and assess recruitment methods, data collection tools, and sample sizing
- Pivotal study is conducted incorporating changes as a result of the pilot testing

Testing the DFL



Testing divided into 3 tasks

- Task 1: To obtain rapid feedback about the model DFL from potential end users of OTC naloxone by conducting unstructured cognitive interviews (n=36 participants)
- Task 2: To evaluate label comprehension, recruitment methods, interviewing techniques, data collection tools, and appropriate sample size through a pilot LCS study (n=36 participants)
- Task 3: To evaluate label comprehension through a pivotal LCS study (n=710 participants)

Testing the DFL – Key Target Populations

- Adults who use prescription opioids and associates
- Adults who use heroin/fentanyl and associates
- Adolescent all-comers
- Adult all-comers

Primary Endpoints

- Check for suspected overdose
- Give the first dose
- Call 911 immediately
- Repeat doses every few minutes until fully awake or until emergency personnel arrive
- Stay with the person until the ambulance arrives
- Check for suspected overdose AND give the first dose of this medicine AND call 911 immediately (composite endpoint)

Primary Endpoints (cont'd)

- Product use: for the treatment of opioid overdose
- Signs of overdose – “if you think someone used an opioid, and the person does not wake up or is not breathing well, these are signs of an overdose”

Secondary Endpoints



- It is safe to keep giving doses
- Give another dose if the person becomes very sleepy again
- Some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry

Research Locations – Pivotal Study



- Individuals who use prescription opioids and/or heroin and/or fentanyl, and associates:
 - CBOs in Chicago, Charleston (WVA), San Francisco, Raleigh-Durham.
- All-comers (adults and adolescents):
 - Tampa, Dallas, Los Angeles, Indianapolis, Raleigh, New York

Current Status

- Contractor has completed the study and it is currently undergoing FDA independent review

Next Steps

- When review is complete, the DFL and results of study will be made available to the public
- If label is successful, industry can adapt it to their product
- If it is not successful, the lessons learned from the process will still be valuable to Sponsors looking to develop a DFL for naloxone
- Could expedite consumer behavior testing process and allow for a faster OTC transition for naloxone

Thanks to the many
people at FDA who
have worked on this
project!



Estimates of the Annual Health System Costs of Naloxone Co-Prescribing



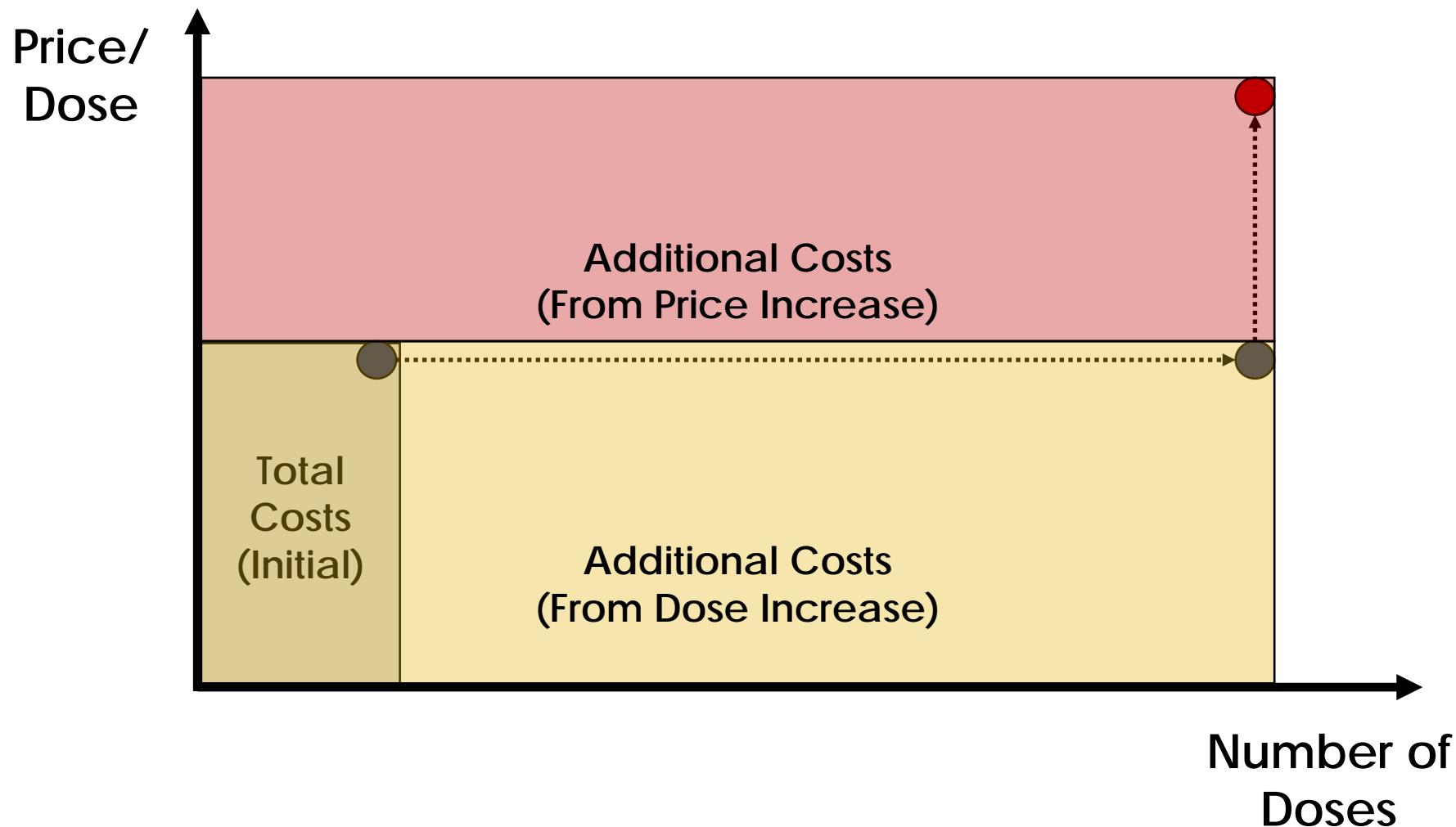
Disclaimer/Acknowledgements

This presentation reflects the work of the author and does not represent FDA's views or policies

Thank you to CDER colleagues who contributed to and provided feedback on this work:

- Office of Surveillance and Epidemiology
- Office of Regulatory Policy

Naloxone Co-Prescribing May Increase Health Spending in **Two** Ways



Overall Model Setup



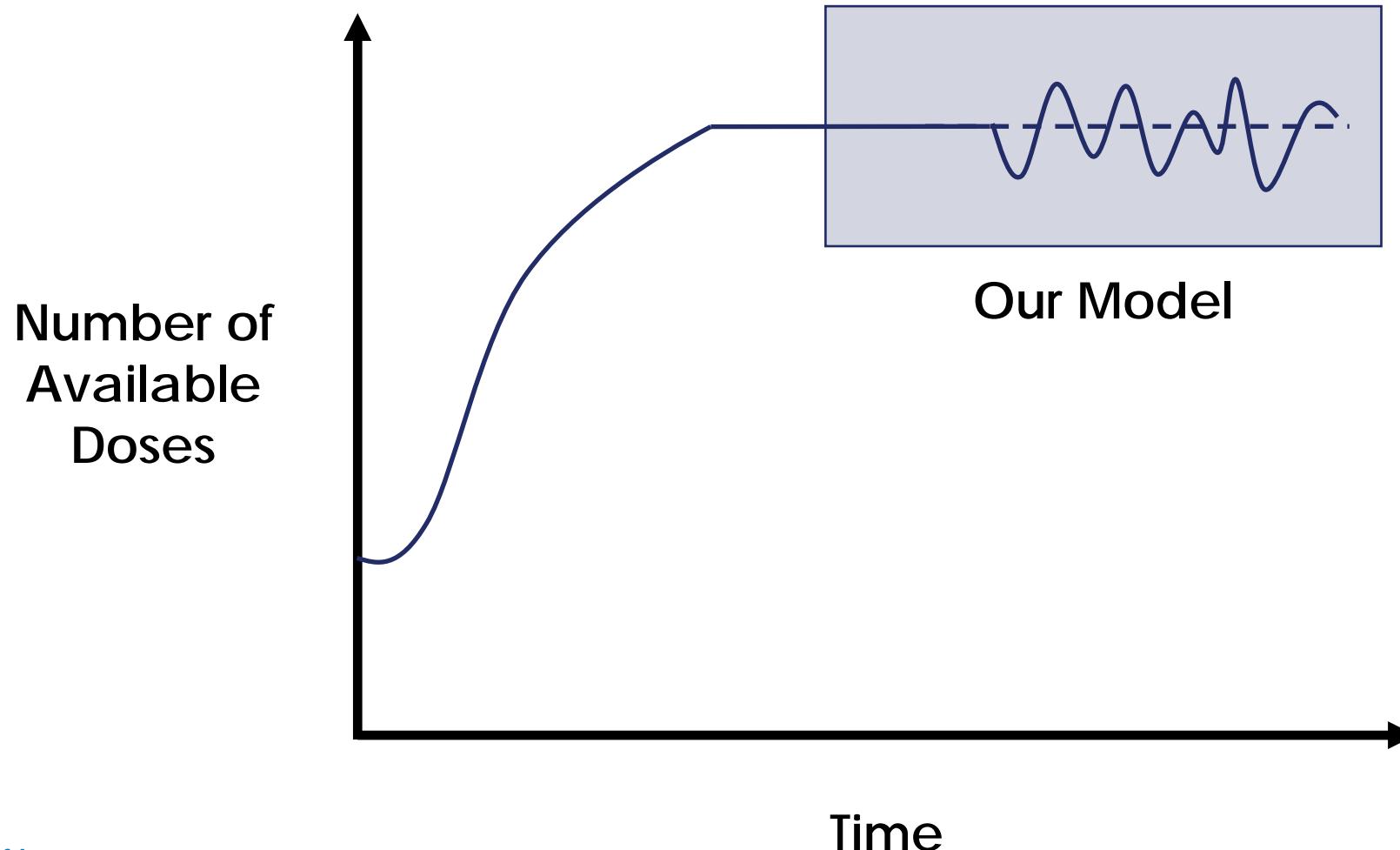
Assume that co-prescribing will be carried out with approved community-use products
(Evzio Auto-Injector and Narcan Nasal Spray)



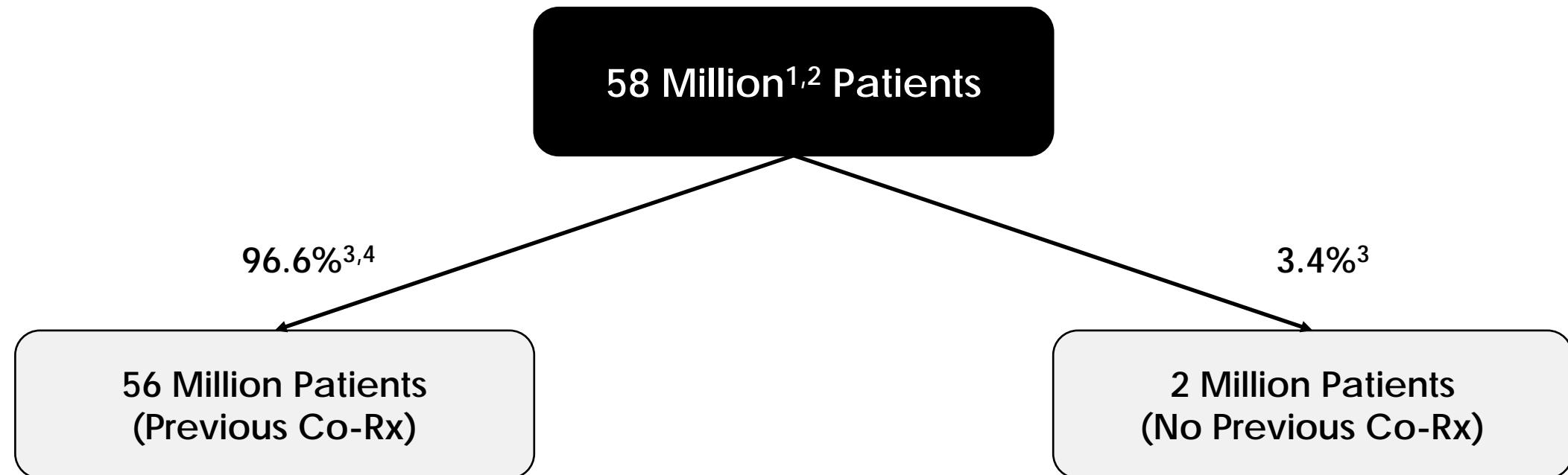
Calculate costs separately for newly needed and previously purchased doses

- ✓ New Doses: Total Spending
(total purchase price + dispensing costs)
- ✓ Previous Doses: Increased Spending
(higher purchase price)

We Assume Naloxone Co-Prescribing is Already Fully Implemented



Example Cost Estimate: All Opioid Analgesic Rx



¹IQVIA. Total Patient Tracker. 2017. Extracted: October 2018.

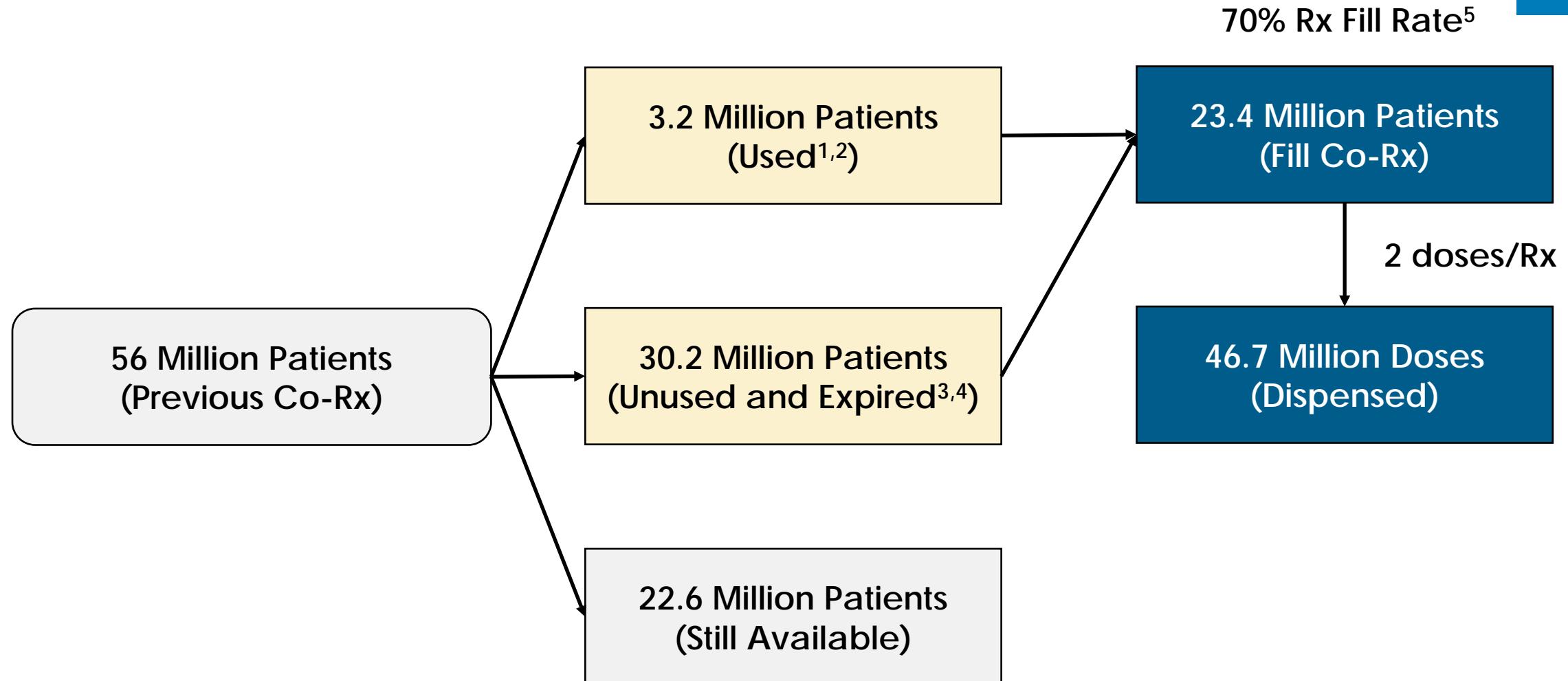
²Defined as patients dispensed an opioid analgesic product in a retail pharmacy

³Substance Abuse and Mental Health Services Administration. Slides Based on 2017 NSDUH Annual National Report. 2018.

⁴Estimated as $100 \times (1 - \frac{\text{Rx Pain Reliever Initiations}}{58 \text{ million}})$

Total Doses: Previous Co-Rx

FDA



¹Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. (1545-861X (Electronic)).

²Fraction estimated as the number of overdose reversals divided by the number of vials distributed through take home naloxone programs in CY 2013

³North Carolina Harm Reduction Coalition. Naloxone 101. <http://www.nchrc.org/programs-and-services/naloxone-101/>. Accessed October 24, 2018.

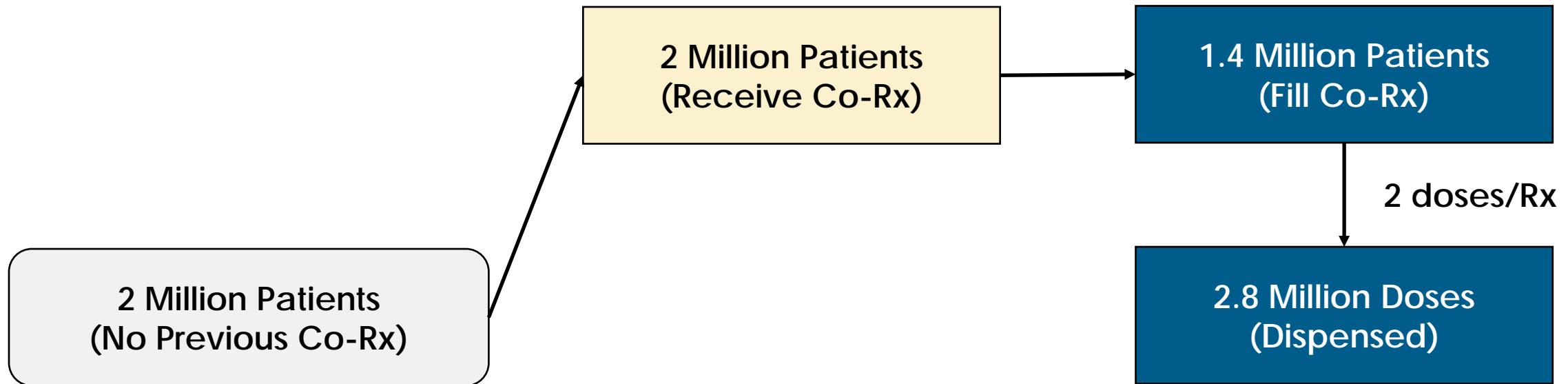
⁴Fraction estimated as (1-Use Rate) x $\frac{12}{\text{Shelf Life}}$

⁵Abrams EM, Singer AG, Lix L, Katz A, Yogendran M, Simons FER. Adherence with epinephrine autoinjector prescriptions in primary care. (1710-1484 (Print)).

Total Doses: No Previous Co-Rx



70% Rx Fill Rate¹



¹Abrams EM, Singer AG, Lix L, Katz A, Yogendran M, Simons FER. Adherence with epinephrine autoinjector prescriptions in primary care. (1710-1484 (Print)).

Total Doses: Overall

46.7 Million Doses (Previous Co-Rx)

+

2.8 Million Doses (No Previous Co-Rx)

-

1.0 Million Doses (Already in Use By Population^{1,2})

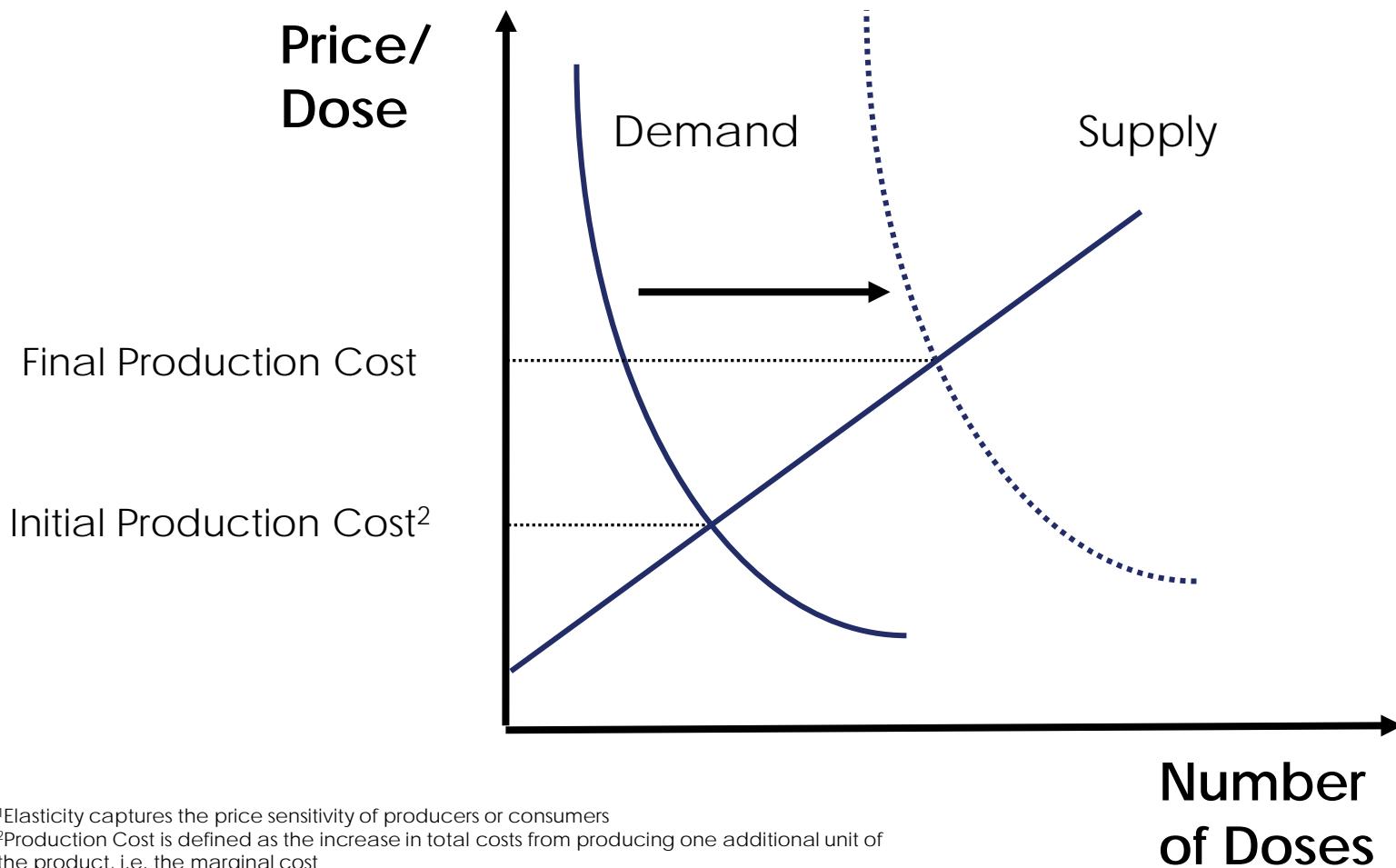
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48.5 Million Doses (Newly Needed)

¹IQVIA. National Prescription Audit. 2017. Extracted: February 2018.

²Defined as the number of patients divided by 58 million, multiplied by 1 million doses

We Use a Constant Elasticity¹ Supply and Demand Model to Estimate Price Increases



$$\frac{P}{P_0} = \frac{D}{D_0} \frac{1}{\epsilon_S - \epsilon_D}$$

P = Price

D = Demand

ϵ = Elasticity of Supply or Demand

¹Elasticity captures the price sensitivity of producers or consumers

²Production Cost is defined as the increase in total costs from producing one additional unit of the product, i.e. the marginal cost

Price Increases Depend On Generic Entry



WITH GENERICS

- Evzio + Narcan + Many Generics for Both
- $\$/\text{Dose}$ = Estimated Average Production Cost

WITHOUT GENERICS

- Evzio + Narcan
- $\$/\text{Dose}$ = Average Retail Price

We Calculate **Average Retail Price** Using Product Market Shares (Without Generics)



Product	Average Price/Dose	Market Share
Evzio Auto-Injector ¹	\$2,320.45	18.1%
Narcan Nasal Spray	\$71.12	81.9%

Source: IQVIA. National Prescription Audit. January 2017 to December 2017. Extracted: February 2018.

Average Retail Price = \$478.41/Dose

¹We exclude the 0.4 mg/0.4 mL formulation since it was discontinued during 2017 and had a different average price per dose

We Then Use The Fractional Change in Demand To Estimate Price Increases

Fractional Demand Change = 47.9 (4,689% Increase)

Fractional Price Change = 24.5 (2,347% Increase)

Without Generics
(Retail Price)

\$478.41 → \$11,707.95

With Generics
(Production Cost¹)

$\$11,707.95 \times 0.11 = \$1,287.87$

¹Based on an unpublished FDA analysis of IQVIA National Sales Perspective data of the median decline in generic price relative to the pre-generic brand price for drugs with 8 or more generic competitors

Total **Annual Costs** for All Opioid Analgesic Rx Estimated At **\$63.9 Billion - \$579.2 Billion**



New Doses (With Generics):

48.5 Million x (\$1,287.87 + \$3.94^{1,2}) = \$62.6 billion

Existing Doses (With Generics):

1.0 Million x (\$1,287.87 - \$52.63) = \$ 1.3 billion

Total (With Generics): = **\$63.9 billion**

¹Coalition for Community Pharmacy Action. The Cost of Dispensing Study. September 2015.

²Takes the payroll and prescription department costs per prescription and divides this number by 2 to convert it to a per-dose basis

Results: Patient Groups That Interact With the Health System



Population	# Patients (Millions)	Annual Cost w/ Generics (\$ Billions)	Annual Cost w/o Generics (\$ Billions)
All Opioid Analgesic Rx	58.0	63.9	579.2
High-Impact Chronic Pain	19.6	9.5	85.5
Rx Opioid Analgesics with CNS Depressants	3.5	0.6	5.3
Medication Assisted Treatment (MAT)	1.4	0.2	1.5
Opioid-Related ED Visit	0.8	0.1	0.7

Results: Patient Groups That Don't Interact With the Health System



Population	# Patients (Millions)	Annual Cost w/ Generics (\$ Billions)	Annual Cost w/o Generics (\$ Billions)
Misusing Opioids	11.4	3.8	34.0
Opioid Use Disorder	2.1	0.3	2.5
Recent Criminal Justice and Rx Opioid Misuse	0.9	0.1	0.8
Recent Criminal Justice and Heroin Use	0.4	<0.1	0.3
Recent Criminal Justice and Opioid Use Disorder	0.3	<0.1	0.2

Lower Product Prices Could Reduce These **Annual Costs**

FDA

Product	Average Price/Dose	Market Share
Evzio Auto-Injector ¹	\$89.00	18.1%
Narcan Nasal Spray	\$71.12	81.9%

Source: IQVIA. National Prescription Audit. January 2017 to December 2017. Extracted: February 2018.

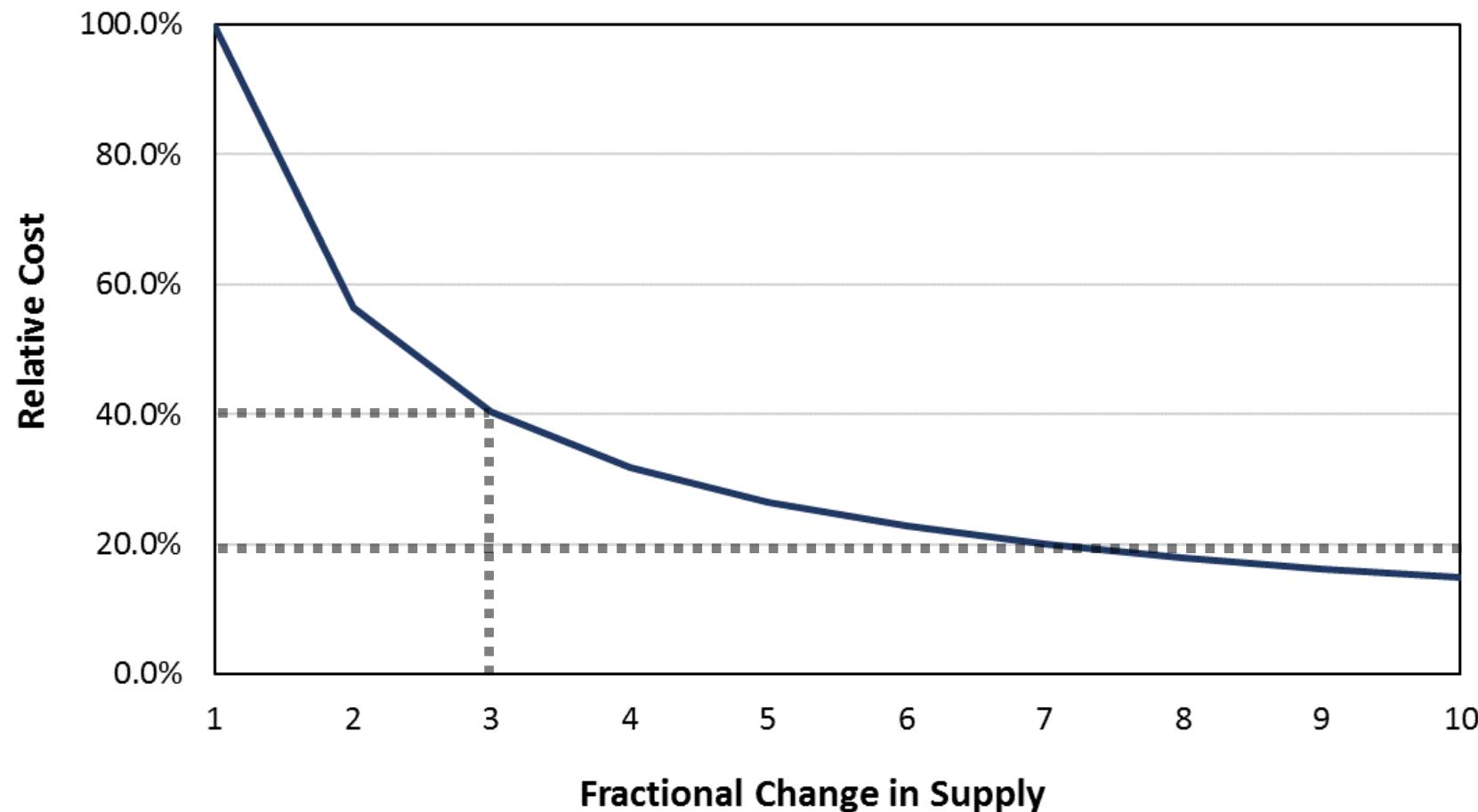
New Average Retail Price = \$74.36/Dose

New Estimated Annual Costs = \$90.2 Billion

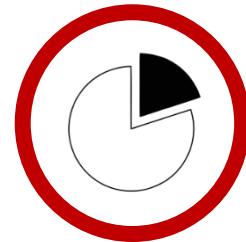
¹We exclude the 0.4 mg/0.4 mL formulation since it was discontinued during 2017 and had a different average price per dose

Increased Production Capacity Could Also Reduce These Costs

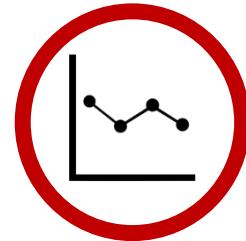
Change in Co-Prescribing Cost As Supply Expands



How Large Are These Potential Costs?



Highest Revenue Drug in US for 2017:
\$16.9 Billion^{1,2}



US Pharmaceutical Spending for 2017:
\$452.6 Billion¹

¹IQVIA. *Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022*. April 2018.

²These sales are for Humira (adalimumab).

What Might Be the Potential Benefits of Naloxone Co-Prescribing?

Coffin and Sullivan, 2013¹: Naloxone is cost-effective in **people who use heroin** up to **\$2,240/Dose**

With Generics Scenario: Always Cost-Effective

Without Generics Scenario: Only Cost-Effective For 6.7 Million Patients or Fewer

Key Question: Are our patients at higher or lower risk of overdose and death than people who use heroin?

¹Coffin P, Sullivan S. Cost-Effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal. Ann Intern Med: 158; 1-9. January 2013.

Our Model Has Three Main Limitations

- 1 The model inputs come with additional uncertainties that are not reflected in our ranges
- 2 The model assumes that the policy reaches all of the targeted patients
- 3 The model does not account for hard limits on naloxone production capacity

Strategies for Increasing the Public Health Benefits of Naloxone Co-Prescribing



All Opioid Analgesic Rx: \$63.9 Billion - \$580.8 Billion Per Year

How could we reduce these costs and/or increase the benefits?

- ✓ Focus on smaller groups of high-risk patients
- ✓ Increase generic competition or OTC availability
- ✓ Expand production capacity