FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEES

(AADPAC and DSaRM)

Monday, December 17, 2018

8:01 a.m. to 4:46 p.m.

Day 1

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. BROWN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you've not already done so. I would also like to identify the FDA press contact, Ms. Lyndsay Meyer.

Lyndsay, if you could raise your hand. I'm not seeing Lyndsay yet this morning.

My name's Ray Brown, and I'll be chairing today's meeting. I'll now call the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We'll start by going around the table and introducing ourselves. We'll start to my left with the FDA.

DR. THROCKMORTON: Good morning. I'm Doug Throckmorton. I'm the deputy director for regulatory programs, Center for Drug Evaluation and Research, FDA.

DR. HERTZ: Good morning. I'm Sharon Hertz. I am the director for the Division of Anesthesia, Analgesia, and Addiction products in CDER.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology in CDER.

DR. SECORA: Good morning. My name is Alex Secora. I'm a reviewer in the Division of Epidemiology, CDER.

DR. AMIRSHAHI: Good morning. I'm Maryann Amirshahi. I'm an emergency physician at Medstar Washington Hospital Center here in D.C.

DR. DASGUPTA: Good morning. My name Nabarun Dasgupta, and I'm a pharmacoepidemiologist at the University of North Carolina, Chapel Hill.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist at Rutgers University.

DR. BOUDREAU: Good morning. Denise Boudreau. I'm a pharmacoepidemiologist at the Kaiser Permanente Washington and also University of Washington.

DR. MEISEL: Steve Meisel, director of medication safety, Fairview Health Services in Minneapolis.

DR. BESCO: Good morning. Kelly Besco, medication safety officer for the OhioHealth healthcare system in Columbus, Ohio.

DR. SHOBEN: I'm Abby Shoben, and I'm a biostatistician at The Ohio State University.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, pharmacoepidemiologist, Harvard Chan School of Public Health.

LCDR SHEPHERD: Jennifer Shepherd, FDA. I'm the designated federal officer for this meeting.

DR. BROWN: I'm Ray Brown. I'm a pediatric anesthesiologist at the University of Kentucky.

DR. ZACHAROFF: Good morning. I'm Kevin Zacharoff. My expertise is in anesthesiology and pain medicine, and I come from the Stony Brook School of Medicine in New York.

DR. McCANN: Hello. Mary Ellen McCann, I'm a pediatric anesthesiologist at Boston Children's Hospital and Harvard Medical School.

DR. BATEMAN: Brian Bateman, anesthesiologist at Brigham and Women's Hospital, Harvard Medical School.

DR. GOUDRA: Basavana Goudra, anesthesiologist at Penn Medicine, Philadelphia.

MS. ROBOTTI: Hi. Suzanne Robotti. I'm the president of MedShadow Foundation and the executive director of DES Action USA.

MS. NEWMAN: Sabrina Newman, patient representative, advocate for the National Fibromyalgia and Chronic Pain Association out of New Albany, Indiana. Thank you.

DR. CICCARONE: Good morning, everybody. Dan Ciccarone, professor of Family and Community Medicine, University California, San Francisco.

DR. KREBS: Hi. Erin Krebs, general internist at the Minneapolis VA and University of Minnesota.

DR. PISARIK: Paul Pisarik, urgent care physician at St. John Health Systems in Tulsa, Oklahoma.

DR. GARCIA-BUNUEL: Good morning.

Martin Garcia-Bunuel. I'm a primary care physician, the deputy chief of staff, and director of quality safety improvement at the VA Maryland Healthcare System.

DR. MACHER: Jeff Macher, professor of strategy economics and policy in the McDonough School of Business at Georgetown University in D.C.

DR. BALLOU: Jordan Ballou. I'm a clinical assistant professor of pharmacy practice with the University of Mississippi, specializing in community pharmacy practice.

DR. BRAND: Paul Brand. I'm a community pharmacist in Florence, Montana and a clinical pharmacist.

DR. FAUL: Mark Faul, senior health scientist, Centers for Disease Control and Prevention.

DR. HERRING: Hello. Good morning. I'm Joe Herring. I'm a neurologist and associate vice-president of clinical neuroscience at Merck and the industry representative to the AADPAC. Thank you.

DR. BROWN: Welcome to all our panelists. We appreciate you being here today.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be fair and open for a discussion of these issues and that individuals can express all of their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We're aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from

discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Now, I'll pass it to Lieutenant Commander Jennifer Shepherd, who'll read the conflict of interest statement.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential

financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves input and advice on strategies to increase the availability of naloxone products intended for use in the community. The committees will be asked to consider various options for increasing access to naloxone, weighing logistical economic and harm reduction aspects, and whether naloxone should be co-prescribed with all or some opioid prescriptions to reduce the risk of overdose death.

Because of the potential significant costs and burdens that may be associated with naloxone co-prescribing -- for example, economic costs to consumers and health systems, adjusting to manufacturing, volume growth, drug shortages -- the

committees will also be asked to consider the potential burdens that may be associated with naloxone co-prescribing for all or some prescription opioid patients.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Herring is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Herring's role at this meeting is to represent industry, in general, and not any particular company.

Dr. Herring is employed by Merck and Company.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following guest speakers have reported interests, which are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Phillip Coffin has acknowledged he is a co-investigator on the CDC prescription drug overdose prevention for states award for California, which includes training medical providers to conduct academic detailing on opioid stewardship, including the prescription of naloxone.

Dr. Peter Davidson has acknowledged he is a pro bono advisory board member for Lifedose [ph], a 501(c)(3) organization, formed to explore the possibility of acquiring FDA approval to develop and manufacture a generic naloxone formulation to ensure low cost access to naloxone for community-based organizations serving people who

use drugs. At this time, Lifedose does not have any products in development or application in process.

Dr. Joanna Katzman has acknowledged she is the principal investigator on a grant from Adapt Pharma given to the Department of Neurosurgery at the University of New Mexico to evaluate opioid overdose education and opioid treatment programs throughout New Mexico. The project period runs from July 2018 through June 2019. Dr. Katzman has not yet received any money from Adapt Pharma for this grant.

Dr. Alexander Walley has acknowledged he is involved in several government-funded studies through the Centers for Disease Control and Prevention, the National Institutes of Health, National Institute on Drug Abuse, and the Office of National Drug Control Policy. These studies focus on opioid-related topics such as opioid overdose, naloxone access, opioid use disorder, chronic opioid therapy, and opioid dependence in HIV-infected persons.

Mr. Tim Ingram has acknowledged he has 100 shares of Pfizer common stock.

As guest speakers, Doctors Kaufmann, Davidson, Katzman, Walley, Ingram, and Wermeling will not participate in committee deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships they may have regarding a topic that could be affected by the committee's discussions. Thank you.

DR. BROWN: Dr. Lloyd, if you could introduce yourself?

DR. LLOYD: Josh Lloyd, deputy director in DAAAP, FDA.

DR. BROWN: We will now proceed with the FDA's introductory remarks from Dr. Sharon Hertz.

FDA Opening Remarks - Sharon Hertz

DR. HERTZ: Good morning, Dr. Brown, members of the Anesthetic and Analgesic Drug Products Advisory Committee, and members of the Drug Safety and Risk Management Advisory Committee, invited guests.

Today we are here to discuss naloxone, one prong of the FDA's multipronged approach to addressing the morbidity and mortality from opioids. We are working to reduce the ongoing problem of overdose and death associated with the use of opioid analgesics to manage pain with the misuse of opioid analgesics, including behaviors such as taking more than directed, and with the abuse of opioid analgesics for the positive reinforcing effects, along with the abuse of illicit opioids.

Naloxone was first approved for use in 1971. Until 2014, it was only commercially available as a solution for injection. Naloxone is an opioid

antagonist that reverses the action of opioid agonists, such as morphine or heroin, by competing for and blocking the opioid receptor on cell membranes. It is short acting, and its effects can resolve while the opioid agonist is still present, necessitating re-dosing in some circumstances.

For successful intervention, to save a life and avoid any lasting effects from an opioid overdose, naloxone must be administered before permanent injury has occurred from hypoxia or anoxia. With an overdose of an opioid sufficient to cause a complete cessation of breathing, that means within minutes. In order for rapid reversal of an overdose with naloxone, naloxone must be present where overdoses can occur.

The first product specifically intended for use in the community was approved in -- I have here 2015, but I think it might have been 2014. But many organizations and local municipalities across the U.S. have developed programs for making naloxone available in the community, generally relying on the off-label use of commercially

available naloxone, solutions in pre-packaged kits using a syringe and nasal atomizer device or a syringe and needle. These programs generally provide training on how to recognize an overdose and how to use the kit.

Commercial products for use in the community may be easier for an untrained individual to administer in some situations. To facilitate bringing these newer formulations to market, the agency has held public meetings in 2012 and 2015 and has established an approach whereby sponsors can compare their product to approve naloxone in a pharmacokinetic study, and based on those results, may not need any additional clinical testing.

An additional public meeting and advisory committee was held in 2016 to further discuss the target dose for these products.

There are currently two naloxone products currently approved specifically for use in the community, an autoinjector and a nasal spray, and you'll hear more about these products shortly. We've required that approved products be suitable

for use in all patients, regardless of age, and that the package have at least 2 doses. And that's in case of either a delay in obtaining medical care, more definitive medical care, or in the chance that there might be a mistake from a layperson in a very frantic setting.

In spite of efforts by the agency to facilitate new naloxone products, and in spite of the efforts of numerous community-based programs to provide naloxone kits, overdose deaths continue to rise. The rate of increase is alarming due to the toxicity of certain currently available illicit opioids.

Much greater availability of naloxone is needed, but there have been some barriers. As you'll hear, cost is one barrier. The cost for the first naloxone autoinjector is now over $4,000, originating at approximately 600 for a package of two.

The average retail cost of the first nasal spray is approximately 150 per dose or 300 per package. Development of generics for newer

products must traverse a landscape of more than 30 patents. Even the retail cost for generic naloxone solution has increased from less than $2 in 2005 to approximately 40 in 2018.

Availability, in general, is another factor. You'll see estimates of the size of different populations who could benefit from access to naloxone, and some well exceed existing manufacturing capability.

There is still a great need to educate prescribers about the risk of accidental or intentional overdose among fully compliant patients and members of their households. Similarly, it can be difficult for prescribers to identify situations where there is risk for misuse or abuse of opioid analgesics.

There are a number of societal factors that are active in both promoting and limiting access. The large number of states with standing orders and other programs for access to naloxone at the pharmacy present a great opportunity, but support for these programs may not be consistent within

municipalities.

Just last week -- I'm going to assume many people here may have heard about a report of a denial for life insurance for a nurse trying to have naloxone available not because she had any history of abuse, but because she wanted to have it available in case she needed to use it to help provide somebody else in the community.

It's now known if policies by insurance will become a significant disincentive, but I think this is one example of just how complex this issue has become.

We're going to ask you to discuss the most relevant strategies for increasing access to naloxone in the community, considering different populations, potential costs, barriers to implementation, and relative benefits of different approaches.

In particular, we are interested in hearing your thoughts about whether naloxone should be co-prescribed with all or some opioid prescriptions, taking into consideration the costs

and burdens that may be associated with some form of co-prescribing.

To help you in your deliberations, we will hear from industry, including the recent announcement of a new generic from one of the innovators; agency presentations will provide additional regulatory background and current patterns of drug utilization and analysis of a model to estimate the health system costs of different target cohorts for prescribing; and we have a number of our guest speakers who will be providing us with both their experience as well as some of the data out there on the use of naloxone for reversal of overdose in the community.

Thank you, again, for taking time from your busy schedules. I know we have you here on a regular basis, many of you, and we are aware that's a commitment, and we appreciate it.

DR. BROWN: Thank you, Dr. Hertz.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To

ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicants and industry non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interests in a sponsor, including equity interests in those based upon the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of the presentation, it will not preclude you from speaking.

We're now going to proceed with the presentations from industry beginning with Mr. Kramer.

Industry Presentation - Robert Kramer

MR. KRAMER: Good morning. My name is Bob Kramer, and I serve as president of Emergent BioSolutions. Mr. Chairman, in response to your last question, I and my colleagues, we have no interest or financial conflict, just to be clear.

Let me start by thanking the FDA and the advisory committees for convening this important meeting to explore ways to expand naloxone access in the community by co-prescribing naloxone. We appreciate the invitation to participate in the meeting and hope to share information with you that will help you in your deliberations.

Turning to slide 2, you can see we have a lot of ground to cover, and I'd first like to provide a summary of our recommendations. First, we support the implementation of naloxone co-prescribing, targeting high-risk opioid prescriptions. We recommend the FDA implement opioid label amendments and associated regulatory measures to ensure a clear and consistent co-prescription approach. We believe this step

could rapidly accelerate adoption of co-prescribing naloxone targeted at the highest risk opioid prescriptions.

Secondly, we believe the economic supply and logistical burdens of such measures are manageable, and we are confident in our ability to support these initiatives.

Also, we're aware of one estimate of the cost of co-prescribing naloxone to the healthcare system, which was included in the FDA briefing documents. This estimate is much inflated from our estimate, as it includes a per-dose cost of naloxone that is significantly higher than the dose cost for Narcan nasal spray, and I'll point to these differences as we go through in my presentation.

The end result, however, just to be clear, is that a fully implemented co-prescription program targeting opioid prescriptions associated with the highest risk of opioid overdose would cost an estimated $150 million per year as opposed to the $64 billion number included in the report.

So just to reiterate, 150 million per year, not the $64-billion number that was in the report. These are stark differences, and they need to be understood in the backdrop of the conversation over the next few days.

On slide 3, I want to highlight a few points about Emergent BioSolutions quickly, if you're not familiar with our company. We're a 20-year-old U.S. publicly traded company that focuses in on a life sciences base. Our focus is on working with governments to be better prepared to address public health threats, whether they be accidental, intentional, or naturally occurring.

We have a portfolio of 11 marketed products that include vaccines for the protection against anthrax, smallpox, cholera, and typhoid, plus a portfolio of therapeutic treatments for protection against anthrax and botulism, and in addition, a drug/device combination portfolio that addresses nerve agents and chemical warfare agents.

We have over 1600 employees around the world, 19 different locations, many of which are

manufacturing locations that support our supply chain capability. We believe we can support increasing access to Narcan with our core competencies and experience providing preparedness solutions for public health threats.

The good news on slide 4 is that naloxone distribution is growing, albeit from a very low base. This chart shows the volume of naloxone prescribed by brand and by quarter. The chart represents what's happening in terms of individuals obtaining naloxone from traditional distribution channels like pharmacies. It does not, to be clear, include naloxone that's distributed to public health purchasers such as state health departments or police, where most of our units are distributed.

Narcan today has a 96 percent market share in the retail prescription market of naloxone products used in the community. Our blended average cost per carton of 2 doses to Medicaid, Medicare, VA, and commercial insurers is about $100. This cost has not increased since launch in

early 2016, and this is one fact that is the largest difference between our estimates and the ones included in the briefing document you may have referred to, which blended the cost of Narcan with another brand that costs over $4,000.

Looking at the slide, the growth over time has been driven by Narcan nasal spray. We believe the key factors underpinning this relative expansion are, first, ease of access of pharmacies, affordability, increase in awareness, as well as state-driven initiatives.

Narcan nasal spray, just as a reminder, is intended for community use. So it can be readily administered by non-medically trained persons. It's intended as an emergency treatment and importantly as a bridge to medical care. Each device delivers a single, fixed dose of 4 milligrams of naloxone in a very small, 100-microliter spray. It's supplied in a carton with two devices, and the shelf life provides two years of coverage.

Two points I want to emphasize. First,

Narcan nasal spray as the leading community use product is supporting the public health goal of expanded access today. Secondly, while naloxone expansion is heading in the right direction, as we'll cover in later slides, the levels of naloxone distributed relative to the elevated risk of opioid overdose remains grossly inadequate.

As the advisory committee members are aware, Emergent coordinated a briefing document on its behalf and on behalf of two other support sponsors presenting here today. I want to highlight just a few key messages from that briefing document.

The first point is that prescription opioids continue to play a key role in this crisis. The role is both direct as a cause of death and indirect as a gateway to the use of illicit opioids. The lost opportunity to intervene is significant.

A recent study by CDC of over 11,000 opioid overdose deaths across 11 states reported that about 40 percent of deaths are witnessed, but naloxone was rarely administered in these settings.

This is an enormous lost opportunity to dramatically impact mortality from this crisis. We believe working with healthcare providers and workers who prescribe and dispense opioids is critical to addressing this crisis.

The second point that I want to emphasize is that co-prescribing is widely endorsed, but adoption has been low. Simply put, we know that certain opioid prescriptions are associated with a higher risk of opioid overdose. We also know that almost all opioid stakeholders endorse co-prescribing naloxone with higher risk opioid prescriptions, but the levels of naloxone prescriptions being filled are not anywhere close to the number of opioid prescriptions being filled.

Just to put some simple numbers on it, there were just eight naloxone prescriptions in 2017 for 1,000 prescriptions of opioids, with more than 50 MMEs. This is despite the CDC recommendation of co-prescribing naloxone in its guideline for prescribing opioids for chronic pain issued in 2016. It's despite the Surgeon General naloxone

advisory issued earlier this year, which also calls for naloxone prescribing, and despite countless medical societies, associations, and agencies with the same call to action.

The key message from sponsors is that as a matter of opioid safety, we recommend that the committee and the FDA consider intervening with regulatory measures such as opioid label changes incorporating co-prescription to accelerate the adoption of this widely endorsed risk mitigation strategy.

In preparing for the meeting, we engaged IQVIA, which is a leading provider of patient prescription data, to try and identify how many Americans received opioid prescriptions that fell within the CDC definition of higher-risk opioids. Specifically, these criteria included those filling opioid prescriptions with daily doses of 50 MME or greater, concurrent use of opioids and benzodiazepines, and those filling a prescription for the opioid dependency treatment, buprenorphine.

Over a two-year period, a total of

97 million Americans filled at least one prescription, and 35 percent of these, or 34 million Americans, filled at least one prescription that fell within the definition of higher risk as defined by CDC. It's a huge number of individuals who are at an elevated risk of opioid overdose based on opioid prescriptions they fill. Indeed, if you look at just the last year alone, it's 20 million.

The conclusion here is that independent patient data claims from IQVIA, which identified actual patients for two years ending September of 2018, indicates 34 million unique patients filled at least one prescription that met CDC's higher overdose risk criteria.

Our recommendation is to focus regulatory measures on the opioid prescriptions associated with the highest risk of opioid overdose. This is also a key difference from the FDA economist universal coverage assumption that led to this $64 billion number.

On slide 7, when we then looked at what

portion of the 34 million Americans had also filled a Narcan prescription, the numbers were pretty surprising. Overall, the number was just 1.3 percent. This ranged from 0.8 percent of those on a daily opioid dose of 50 MME or up and 5.7 of those filling a buprenorphine prescription.

What this tells us is that over the last two years, a staggering 34 million Americans filled prescriptions that CDC identified as being associated with a higher risk of opioid overdose, but just 1.3 percent of these individuals have filled a prescription for Narcan. To us, this underscores the urgent need for FDA to intervene.

It also begs the question of what would happen if FDA did intervene. Fortunately, we have some excellent proxies for the potential impact. Starting in March of 2017, five states have implemented regulations, generally via the state medical board or society, urging co-prescription of naloxone alongside higher risk opioid prescriptions.

To be clear, this is not a mandate on

patients to have naloxone, it's a requirement for healthcare providers that prescribe naloxone or offer naloxone prescription to individuals taking higher risk opioid prescriptions. These states are Virginia, Vermont, Arizona, Rhode Island, and Florida. Two additional states, Washington and California, will implement similar regulations between now and January of 2019. These states generally use the CDC guideline for higher-risk prescription criteria. However, most states use the daily opioid threshold of greater than 50 MME.

The impact of these states' regulatory interventions was immediate and significant. These states have an adoption rate of up to seven-fold the national rate. As the chart shows, once the regulations are implemented in the states, you get an immediate spike in demand.

This data show that when co-prescription is required, adoption, as measured by filled prescriptions, will be 8 to 10 percent of those at-risk populations. This is another key variable that varies greatly from the assumptions laid out

in the economist's report.

The compliance rate could be lower because, as a reminder, the requirement is only to offer or provide a prescription. It then becomes the patient's choice and responsibility as to whether they fill the prescription and take it to the pharmacist.

While this state action level or level of action is positive, it does lead to an inconsistent picture across the nation. You have states that require co-prescribing and some that do not. You have states that require co-prescribing, and even when they do, the thresholds and the criteria may differ. This leads to confusion and inconsistent risk opioid mitigation.

Using these states' experience as a proxy, we estimate that if FDA intervene to stimulate adoption of co-prescribing naloxone alongside opioid prescriptions considered higher risk based on CDC criteria, an additional 3 million cartons of Narcan would be distributed over a two-year period with about 2 million occurring in the first year

post-implementation. While this is far from perfect in achieving coverage, it would represent a step-wise change in access to naloxone.

I want to address how we at Emergent are prepared and equipped to address the resulting increase in demand. First, we've already committed significant capital to expand capacity, and this will yield a doubling of our capacity in the next 12 months versus 2018. It will also allow us to reach 20 million devices or 10 million cartons during 2020.

The net point here is that we have current initiatives underway to support continued expansion of our capacity and expect to be able to manage the anticipated demand change from a regulatory intervention.

I also want to spend a few minutes to describe enabling factors that are already in place to support expanded naloxone access and some of the remaining challenges.

First, pharmacy access without a personal prescription is permitted in all 50 states, and

leading pharmacy chains have already adopted this. In fact, many have gone even further with pharmacists intervening to counsel opioid recipients on opioid risks and, indeed, raising awareness of naloxone availability with in-store campaigns.

Second, we'll cover the costs in greater detail on the next slide, but I want to flag that broad health insurance coverage at affordable, out-of-pocket costs to individuals and payer systems is critical to minimizing the financial barrier to access. We believe we have made significant progress on this front.

Third, awareness and stigma remain, in our view, as the greatest challenge. We believe the engagement of many stakeholders, including clinicians and pharmacists, in raising awareness of opioid risks and the potential role of naloxone in mitigating these risks is critically important. The initiatives we're discussing today are tremendously important in this regard.

Finally, we would respectfully caution

against a rush to an over-the-counter solution for this current crisis. For over-the-counter medications to succeed in expanding access, we believe conditions need to be in place.

First, there must be a dramatic increase in awareness and education to drive patient action. Today, awareness is very low, and this will take some time to build.

Second, we believe retaining the engagement of healthcare providers, rather than bypassing them, is critically important, as the issue concerns opioid safety, as well as access to naloxone.

Third, we will need to ensure that a system is in place to defray the out-of-pocket costs of an OTC drug for individuals so as not to create a barrier to access. Because OTC drugs are not required to be covered by health insurers, the vast majority of individuals would have a higher out-of-pocket cost than they have today.

We do not believe that OTC would improve the unique pharmacy access situation that exists for

naloxone today, and we reiterate that an expanded co-prescription program could facilitate physician-patient discussions about benefits and availability of naloxone and therefore increase awareness.

On slide 12, affordability of Narcan is central to what we do, and I want to provide the FDA, ADCOM members, and attendees with the facts today on Narcan nasal spray cost.

Since its launch in 2016, Narcan has been available at a discounted price of no more than $37.50 per dose, or $75 for a carton of two, to all public health purchasers, not-for-profits, police, EMS, 340Bs, Medicaid, and on the federal supply schedule. That represents a 40 percent discount off the list price. The price has never increased. The majority of our volume is at the $37.50 price or less per dose.

For individuals with health insurance, 97 percent of covered lives have access to Narcan nasal spray, and the co-pays on dispense prescriptions are very affordable with 77 percent

being less than $11 and 43 percent of these less than $1. The co-pay averaged over one period of time was $17.65. We continue to work with payers to try and reduce or eliminate the co-pay, and several insurers have taken this step with us.

The main point I want to make here is that we understand the importance of affordability and remain committed to maintaining it.

On slide 13, in closing, we recommended the FDA require that opioid labels be amended to address targeted naloxone co-prescribing via either a box warning or in addition to the indication statement. We propose language such as: prescribe community use naloxone to patients prescribed daily opioid dose of 50 MMEs or greater; patients concurrently prescribed any opioid dose or benzodiazepines; or patients with a substance use disorder.

We recommended the communication plan to healthcare providers be amended and that the blueprint for opioid training under REMS, which has already been updated to reflect naloxone

prescribing, be consistent.

With these actions taken, we estimate that the cost to health systems, based on 3-million incremental Narcan nasal spray units over two years, would be about $300 million or just 2 and a half percent of the annual spent on opioids. This is before taking into account any other potential savings from a reduction in opioid-related harms, such as those observed in Dr. Coffin's co-prescribing study pilot in San Francisco or the Veterans Affairs' experience.

In summary, we believe FDA regulatory action is warranted because co-prescription, as a risk mitigation strategy, has not yet been sufficiently adopted. We believe the logistical, economic, and supply burdens are reasonable and manageable. And the good news is the cost to the healthcare system of introducing the targeted co-prescribing that we recommend runs about $150 million per year, which is in stark contrast to the $64-billion estimate you may hear later today.

I urge the committee to base its decisions

on these facts, and ultimately, lives are at stake, and these risks can be mitigated with sensible targeted naloxone co-prescribing. Thank you very much.

Industry Presentation - Dean Mariano

DR. MARIANO: Good morning. I'm Dean Mariano, senior director of clinical development and medical affairs at Insys Therapeutics. I'm an anesthesiologist with additional board certifications in pain management and addiction medicine. I joined Insys in 2017 and maintain a small pain addiction consulting practice in Connecticut.

I'm the immediate past-president of the Connecticut Pain Society and the former chairman of the Connecticut State Medical Society's task force on opioids. I'm still an adjunct assistant professor at the Quinnipiac University Frank H. Netter MD School of Medicine.

I now come to the co-prescribing of naloxone with opioids from two perspectives, that of a clinician who has co-prescribed and that of

industry.

Deaths from opioid overdoses is a growing epidemic in the United States with deaths involving opioid analgesics having more than a five-fold increase in the U.S. since 1999. More than 49,000 Americans died from opioid overdoses in 2017. That's more than 115 people per day. At least half of all opioid overdoses involved a prescription opioid.

Overdose deaths increase for men and women, people ages 15 and older, all races and ethnicities, and across all levels of urbanization. Prescription opioids have added to this growing number of overdose deaths.

Prescription opioids continue to contribute to the opioid overdose epidemic in the United States. When looking at overdose deaths from prescription opioids, the CDC analyzes the following: natural opioids, which include pain medications like morphine and codeine; semisynthetic opioids such as oxycodone, hydrocodone, hydromorphone, and oxymorphone; and

methadone, a synthetic opioid used to treat pain and opioid use disorder.

Current information reported about overdose deaths does not distinguish pharmaceutical fentanyl from a illegally manufactured fentanyl. The CDC Injury Center separates synthetic opioids other than methadone from prescription opioid death calculations. The most common drugs involved in prescription opioid overdose deaths include oxycodone, hydrocodone, morphine, and methadone.

The federal government has a strategy to help with the opioid crisis. In 2017, the Department of Health and Human Services launched a five-point opioid strategy:

Strengthen public health surveillance, promote healthy evidence-based methods of pain management. HHS issued over 800 million in grants in 2017 to support treatment, prevention, and recovery while making it easier for states to receive waivers to treat through their Medicaid programs.

HHS supports cutting-edge research on pain

and addiction, including a new NIH public/private partnership. And finally, HHS works to better target the availability of life-saving overdose reversing drugs. The President's 2019 budget includes $74 million in new investments to support this goal.

The Surgeon General of the United States has echoed similar sentiment. In April 2018, Dr. Adams released an advisory on naloxone and opioid overdose, emphasizing the importance of the overdose-reversing drug naloxone for patients currently taking high doses of opioids as prescribed for pain, as well as for other at-risk populations.

He also has developed a postcard for the American population. The postcard has five key points to address what you can do to prevent opioid misuse: talk about it; be safe; understand pain; know addiction; and the last point, be prepared, is what I'm going to focus on. It reads, "Many opioid overdoses occur at home. Having naloxone could mean saving a life. Know where to get it and how

to use it."

Access to naloxone is improving. All 50 states allow medical providers to prescribe naloxone to patients who are at risk for an opioid overdose, including those in outpatient treatment for opioid misuse or who take high doses of prescription opioids for medical conditions. However, many individuals who at most risk for an opioid overdose do not have regular contact with healthcare professionals and would benefit from alternative means to obtain naloxone.

Naloxone access laws make naloxone easier to obtain by expanding how the medication can be distributed beyond traditional prescriptions, including statewide protocols, standing orders, and dispense without prescription.

The additional naloxone access laws and public-provider awareness has helped more at-risk populations obtain naloxone. With state naloxone access laws changing, the dispensing of naloxone from U.S. pharmacies increased at a rapid pace starting around the second quarter of 2015.

Where does naloxone fit in to response to an opioid overdose? Naloxone is an important part of the solution but is not the only component in responding to an opioid overdose. Recognizing signs of an opioid overdose, trying to arouse the person, calling 911, and performing rescue breathing and/or chest compressions are all part of a potentially successful opioid reversal. Patients, family, friends, caregivers, and others need to understand all the steps to help.

Naloxone for overdose treatment is part of opioid class labeling. Even when opioids are prescribed appropriately, there is still a risk of opioid-induced life-threatening respiratory depression. It should be noted that a vast majority of these prescriptions are dispensed in an outpatient setting, and patients may take their first dose while at home.

Class labeling states naloxone is a specific antidote against respiratory depression. Typically, the one way we know about respiratory depression in an outpatient setting is if they

present at the emergency department.

Labels are not the only source supporting co-prescribing of naloxone. The CDC guideline for prescribing opioids for chronic pain supports co-prescribing. Recommendation number 8 states, clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone in situations such as history of overdose, history of substance use disorder, higher opioid doses greater or equal to 50 morphine milligram equivalents per day, or concurrent benzodiazepine use.

Naloxone can help save a life from an opioid overdose but administering it is necessary. A study published in 2018 on pharmaceutical opioid overdose deaths in the presence of a witness looked at fatal opioid overdoses where there was evidence that witnesses had noted symptoms consistent with overdose and the outcomes. The results showed that we need patients, family, friends, caregivers, and others to develop an understanding on how to respond to an opioid overdose.

Out of the 587 deaths, 21 percent were witnessed, most occurring at the decedent's home, and 88 percent were co-prescribed other CNS depressants, especially benzodiazepines. Symptoms of overdoses were noted but not acted upon 70 percent of the time.

These findings support the administration of education and/or naloxone to partners in family members of people who use pharmaceutical opioids in order to reduce overdose deaths. Today, educational support is available and more organizations are getting involved.

Guidelines are being adopted in educational materials even in the absence of mandated guideline-based indications for naloxone co-prescribing. Some of the reasons to prescribe naloxone include: higher-dosed opioid prescriptions during opioid rotation because of incomplete cross tolerance; sleep apnea and other respiratory conditions; known or suspected alcohol use; current benzodiazepine, other sedative prescriptions, or antidepressant use; request from

patient and caregiver; and difficulty with accessing emergency medical services.

Even without EMS access issue, time is of the essence. EMS is not the sole solution in the response to an opioid overdose. Average time for an EMS unit to arrive on scene was 7 minutes nationally, response time increased to more than 14 minutes in rural settings, and nearly 1 in 10 callers wait up to 30 minutes. This is important because with lack of oxygen, permanent brain damage can occur after 4 minutes. This is a concern since most of the naloxone is being administered by EMS.

The National Emergency Medical Service Information System verifies that a majority of naloxone administration is done after EMS arrives. Greater than 78 percent of the time, this occurred out of the over 170,000 activations since January 2016 in over 3,600 EMS agencies throughout 43 states and territories. Only 6 percent of the time naloxone was administered prior to EMS arrival for all suspected opioid-related overdoses.

There is support the co-prescribing of naloxone with prescriptions could have a positive benefit. Co-prescribing is supported through research funded by the National Institute of Drug Abuse. The study evaluated the feasibility and effect of implementing a naloxone prescription to primary care patients prescribed opioids long-term for chronic pain. The study is the first to demonstrate clinical benefit of reducing opioid-related emergency department visits.

759 out of the 1,985 patients receiving chronic opioids were prescribed naloxone. Patients prescribed higher doses of opioids or had an opioid-related emergency department visit in the past 12 months were more likely to be co-prescribed. There were also no net change over time in opioid doses among those who received naloxone and those who did not.

When naloxone was co-prescribed with chronic opioids for pain, there were 47 percent fewer opioid-related emergency department visits after six months and 63 percent fewer after one year.

The study concluded, when advised to offer naloxone to all patients receiving opioids, providers may prioritize those with established risk factors. Co-prescribing may also have ancillary benefits, including patients become more aware of the hazards and engage in efforts to improve medication safety.

What do patients think about being offered a co-prescription of naloxone? This study focused on the patient's attitude towards the co-prescribing and their experience with naloxone. The study suspect that the term "overdose" may not capture all opioid-poisoning events, thus asked separately whether the patient had an experienced an overdose and a bad reaction from opioid use.

Ninety percent of the 60 patients studied never previously received a naloxone prescription; 82 percent successfully filled the prescription and 97 percent believed that patient prescribed opioids for pain should be offered naloxone.

Most patients had a positive or neutral response to being offered naloxone. Positive reactions included improved relationship with

clinician, appreciated the offer, and community benefits.

Thirty-seven percent reported safer opioid use behaviors, including improvements in opioid dosing, timing of opioid use, decrease in polysubstance use, proper opioid storage, not using opioids alone, an increased knowledge about opioids and opioid overdose.

No negative behavior changes were identified. Thirty-seven percent had personally experienced an opioid-poisoning event, 5 percent reported that the prescription naloxone was used on them, and 77 percent of participants estimated that the risk of an opioid overdose as low.

The conclusion from this study was primary care patients on opioids found it acceptable to receive a prescription of naloxone. The prescription reached patients who did not have access to naloxone, and having naloxone may be associated with beneficial change in opioid use behaviors.

Other studies have looked at the community

benefits of naloxone. In this study by Katzman et al., which she'll be speaking later today, is the first large scale prospective study to report community benefits of naloxone when provided in an opioid treatment program setting. The study measured the opioid overdose reversal rate with take-home naloxone among participants with a diagnosis of opioid use disorder in an opioid treatment program setting.

At intake, 44 percent of the 244 participants overdosed at least once and 87 percent witnessed an overdose. At the 3-month visit, 13 percent successfully reversed an opioid overdose on 38 community members. One study participant overdosed and was reversed by EMS. Eighty-seven percent of the reversed were family or friends of the study participants.

How many doses of naloxone did it take to successfully reverse an opioid overdose? Of the 38 reported overdose reversals, 50 percent required 1 dose of naloxone, 45 percent required 2 doses of naloxone, and 5 percent required 3 doses of

naloxone. The third dose was delivered by EMS or a study participant with an extra dose. All reported overdose reversals were successful, and all involved injected heroin. It is not known if community members would have survived without the naloxone.

EMS data shows a significant population requires more than 1 dose of naloxone for reversal of an opioid-related overdose. Looking at the National Emergency Medical Services Information Systems statistics, it takes 1.34 doses of naloxone on average out of the more than 170,000 activations since 2016; 74 percent required one dose, and almost 26 percent of the patients required 2 to 4 doses of naloxone for reversal of an opioid-related overdose. The National Institute of Health is fostering partnerships to address this concern.

The National Institute of Health public/private partnerships is part of the Health and Human Services five-point opioid strategy. One of the focus areas under enhanced medications for opioid use disorder and to prevent or reverse

overdoses is to develop more potent or longer-lasting opioid antagonists. Insys Development Company anticipates an NDA filing of its 8-milligram per actuation naloxone nasal spray formulation with a unique first in class PK profile the first quarter of 2019.

In conclusion, co-prescribing naloxone may have positive impact on unintentional opioid overdose deaths. It is difficult to predict who on chronic opioid therapy will experience opioid-induced respiratory depression associated fatalities.

A study by Takeda et al. states if naloxone is co-prescribed in a universal precautions manner for all patients receiving chronic opioid therapy, it may have a significant impact on intentional and unintentional overdose opioid deaths. Thank you.

Industry Presentation - Charles Argoff

DR. ARGOFF: Good morning. I'm Charles Argoff. I'm a neurologist by training, professor of neurology at Albany Medical College. I'm also subspecialty certified and board certified

in pain management. I direct our pain management fellowship, which is kind of unusual as a neurologist to be in that position, but I am. I am director of our company as a pain center, and it's a pleasure to be, and thank you for the opportunity to speak. I was asked by kaléo to speak this morning.

The agenda for my presentation includes discussing the role of naloxone in the opioid overdose public health crisis. I will add to what's been said already that this is a complicated term and sometimes an offensive term when you're the person who is the patient, who is experiencing great relief from opioid medications and functioning, and you're made to believe that you are part of an epidemic.

I think as we think about the use of naloxone, it's really important to think of what you would want your mother to be told when she was prescribed warfarin and what measures would be taken routinely as part of being on warfarin to ensure safe use.

If we acknowledge that opioid therapy is part of the treatment paradigm for chronic pain for some people -- the CDC guideline doesn't say never prescribe opioids -- it is a guidance for us to use them as safely as possible. And we need to think about that as we think about the subject we're here today and tomorrow about, the role of naloxone.

That leads to a second part of the agenda, which is expanded access to naloxone. Are we going to at the end of the day have a risk factor? You are all familiar on this committee with opioid risk tools, and you know that one that comes to mind, it's not a perfect tool, is the ORT, opioid risk tool, which some can score zero on. But zero doesn't mean no risk. Zero means low risk.

So everyone who is prescribed and using an opioid for medical purposes, before we get into opioid use disorder and illicit drug use, is at risk of an unintentional event.

Are we going to take a risk factor approach? Do we have uniform agreement about that, or are we going to take the universal precautions approach;

and then how can we implement all this?

We are responding. Everyone in this room, everyone who may be listening in is responding to a very dynamic public health crisis. I mention some comments about prescribing opioids. I am a clinician. If I wasn't here today, I probably would have 20 to 30 people on my schedule. I prescribe opioid therapy to those people who are appropriate candidates. And I am concerned about unintentional consequences.

I also have developed and spoken in this very room about the potential benefits of the very REMS programs that were put into place with the blueprint that was developed for trying to prevent harm from the use of long-acting, extended release opioids, and I'm very familiar with the modifications that have been made.

So prescribing opioids inherent to such is safety, safe and appropriate use. Co-prescribing naloxone can be part of that. We know that people suffer from opioid use disorders; we know that. People, and their families, and family members need

to be aware and educated about the role of naloxone and trained in the use of naloxone in overdose.

Certainly, those individuals who are using illicitly heroin and/or are using other illicit drugs, including fentanyl, which we are all too familiar with the rising concerns of that particular substance and how it's being used and laced in other medicines, these individuals need to be in a position where naloxone can be helpful to them. That means it needs to be available.

I made some of these points already, but I want to emphasize this point. Numerous publications have emphasized the role of chronic opioid therapy in certain individuals. Those of us who actually maintain a clinical practice actually see patients for whom chronic opioid therapy is part of their effective regimen.

It's been estimated by some that 5 to 8 million U.S. adults regularly use opioid therapy as part of their chronic pain treatment. This is even in the face of a 25 percent decline in the total number of opioid prescriptions dispensed between

the years 2012 to 2017; increasingly recognized, and there are new treatments being developed for this, and we still recognize that opioid use disorder is not uncommon to the estimated 2.1 million people who are 12 years or older diagnosed of opioid use disorder in 2017.

These are individuals who have a high rate of relapse, and there's a crucial need to expand evidence-based treatments for this group; that these are at-risk groups.

It's not as if there aren't numerous recommendations for expanded access. CDC guideline, public health service, numerous professional organizations, EMA, Federation of State Medical Boards, CDC, there's not disagreement in general that naloxone and opioid overdose education should be readily accessible to individuals likely to witness a life-threatening opioid overdose. This has been mentioned by our previous speakers. And when you think about take-home naloxone, we think about considerations for a risk-based versus universal prescribing. I

mentioned this point earlier.

If you think about risk-based -- I know this is not the kind of -- I'm just going to be a little bit unorthodox. Raise your hand in this room if you can always predict who's going to be at risk. No one can do that. Everyone is at risk if they're prescribed an opioid, and everyone is at risk if they're using for illicit purposes.

The cons of using a risk-based, take-home naloxone program is that you may miss people. The pros of a universal take-home naloxone approach is that your reach is a broader population; there's less targeting and stigma. I gave you an example of when you treatment somebody with insulin, for example, for diabetes, there are certain patient education and family education strategies that you incorporate as part of best practice.

Shouldn't best practice for opioid therapy be incorporating what happens if things go south and you need to use an opioid reversal agent? Shouldn't that be part of what we do? Isn't that what's part of a risk mitigation strategy program

in the real world?

So a universal take-home naloxone program would reach a broader population. There would be less targeting and stigma if this became a fluent discussion with people when they're prescribed opioids for chronic approaches, and it may lead to a more efficient strategy at the level of the healthcare provider office.

The cons, and there have been people who have commented upon this already, is the increased pharmaceutical costs and the more potential for inappropriate administration. I think that it's for you to decide during today, and tomorrow, and other times what's in the best interest from a public health point of view.

If you remember just two slides ago, I had a slide with many different organizations that have made recommendations. These are the recommendations from different organizations. You can see the AMA has its own. The CDC has some overlap. Some are different.

Is there anyone here who wouldn't see how

confusing this might be? Which recommendation are you reading and in what setting do you prescribe or make sure naloxone is available? And I think one of these studies have already been addressed, the Opioid Use Disorder study. Drs. Takeda and Katzman have demonstrated an opioid use disorder that there is evidence that take-home naloxone can help prevent opioid overdose deaths.

Drs. Takeda and Katzman published a study looking at a universal precautions approach in chronic pain. In each of these studies, using and adopting a universal precautions approach gave important evidence that take-home naloxone, at least in the opioid use disorder study, can help prevent opioid overdose deaths in targeted populations. And in the chronic pain study, actually, people didn't use naloxone. It was given only to high-risk patients, but that in and of itself, by having it available was an important measure.

I want to come back to this point. The goals of any -- I think it's important to look at

this picture in a view of chronic pain being a chronic disease state and opioid use disorder being a chronic condition as well. The goals of any long-term chronic disease, like diabetes, or asthma, or others, are to maximize the benefits while managing the risk of treatment and progression of disease. We all know only too well that everything that we do from a treatment point of view has risks.

Individualized treatment for these conditions, they can certainly drain resources, and optimal management of these and other conditions also involve other individuals. When we look at this with respect to chronic pain and using chronic opioid therapy in chronic pain, part of going forward needs to involve the assessment of the risks, the acknowledgement of the risks, the use of all available measures to reduce risk, and involving family, friends, and other care providers in the management of chronic pain and the risks associated with certain treatments, in this case chronic opioid therapy.

With any chronic condition, we know that relapse of some degree is expected. We know that we are not curing people with chronic pain, and so it may be that individuals would be on chronic opioid therapy for an unknown period of time, and we need to manage the risks.

Recommendations, just in conclusion, naloxone should be an integral component of treatment for patients who are on chronic opioid therapy for chronic pain or the diagnosis of opioid use disorder. Healthcare providers, pharmacists, and patients should be educated on naloxone as a life-saving emergency intervention for opioid overdose.

It's already been made mention of multiple times, somewhat overlapping perhaps but also an entirely separate group of people who misuse or abuse opioids, who are currently in treatment, and those who are not in treatment, access to naloxone for these populations have to be increased as well so that harm reduction can occur. Concerned family members and friends in all populations need to be

involved and trained as well.

Thank you for your attention and listening to me, and it's my pleasure to ask Omar Khalil from kaléo to come up.

Industry Presentation - Omar Khalil

MR. KHALIL: Good morning. Committee members and distinguished guests, my name is Omar Khalil, general manager of Neurology & Addiction with kaléo. On behalf of the entire kaléo team, I want to thank you for inviting us to participate in today's meeting.

We are here because we all agree that more needs to be done to improve access to naloxone in this country. As a company focused on patients, we believe today's discussions represent a very important step in addressing that challenge.

I would also like to thank Dr. Charles Argoff for sharing his observations as a clinician on the frontlines treating patients and observing the real-world challenges in managing the chronic diseases of pain and opioid use disorder. Now, I would like to share some of kaléo's observations in

this field.

kaléo first started to see the signs of the opioid overdose crisis around a decade ago when one of our founders witnessed a woman admitted to the ER following an accidental overdose after wearing more than a dozen fentanyl patches.

Once she was revived with naloxone, she claimed her doctor never told her to remove one patch before she put on another. And while we can never verify the truth of that statement, discussions with other ER physicians that day indicated that overdoses were an increasingly common occurrence.

In 2011, we met with the FDA to discuss the need for a take-home naloxone. As we explored this need, it became clear that despite the availability of generic naloxone, opioid overdose mortality numbers continued to climb and that a large number of the overdose deaths were occurring in the home.

Based on our experience working with the healthcare community, we determined there was a need for additional naloxone delivery options for

people who were not medically trained. Our company invested more than $80 million to develop and launch Evzio in 2014. This became the first take-home naloxone product approved by the FDA for use by non-medically trained individuals. It was designed to be easy to use. It is the only naloxone product with voice guidance, which even reminds the user to call 911 following administration.

Testing was conducted related to the rigors of the use outside of the hospital, including exposure to extreme temperatures, crushing forces, and liquid ingress. As part of the development effort, we invested in a state-of-the-art robotic production line that conducts over 100 automated quality checks on each device, ensuring streamlined and consistent quality production.

In 2016, kaléo participated in the FDA advisory committee meeting to discuss the proper dosing of naloxone, given the growing availability of synthetic fentanyl. In 2017, kaléo launched a 2-milligram version of Evzio. Over the past four

years, we've also stepped in to assist first responders and harm reduction groups, despite the fact that Evzio was not initially developed to serve that segment of the market.

To-date, we have donated approximately 350,000 autoinjectors. And according to voluntary third-party reports, our donations have been used to help save more than 5,500 lives, a fact about which we are extraordinarily proud.

In regard to access, kaléo has also witnessed how an extremely complex and challenging healthcare system has impeded access to this important, potentially life-saving medication. In short, our healthcare distribution system was applying old models to address a new and complex problem.

We believe strongly that barriers to patient access will not help save patient lives or costs to the healthcare system. As results of these obstacles, kaléo faced an existential decision to either stop providing Evzio or launch a new access program built with the commitment that eligible

commercially-insured patients could receive Evzio at no cost to them and without significant delay, regardless of whether their insurance company blocked access or applied a high-dollar co-pay.

While kaléo has received significant criticism as a result of this approach, what many don't recognize is the impact we've had on patients. In the first year, fewer than 5,000 Evzio prescriptions were filled under a traditional model. When we eliminated those barriers and launched this new access program, in the second year, more than 66,000 prescriptions were filled.

In the vast majority of those commercial prescriptions, kaléo was the entity that paid for product. We also address the unfortunate but common feelings of shame and stigma, a hindrance for some patients, by shipping Evzio directly to their home.

While our patient-focused program has improved access for some, we recognize that it has its limits. As a company founded by patients for patients, we refuse to accept the solution that

doesn't address the needs of more of those who are at risk. And while we have removed the barrier of cost for many, we recognize that approach could have an impact on certain payers and does not provide an adequate solution for patients with government insurance.

This is why we recently announced that we are launching an authorized generic for Evzio at a list price of $178 per carton and are working to lower the price of the branded product to that same level as well. We are working closely with the major payers to negotiate unrestricted coverage for the authorized generic for Evzio and have been encouraged by their initial positive response.

We have also lowered our price for first responders, government agencies, other professional rescue or public health-focused organizations to $178 per carton, or $89 per dose, with additional discounts available as well. We have already started filling orders under this program.

As we consider other barriers and obstacles to increasing access to naloxone, I won't cover the

ground that Dr. Argoff and the others have already discussed. However, I do want to point out the importance that education plays in addressing this problem. While we are all taking steps in the right direction, we still hear too many stories of patients who are unaware or aren't prepared to acknowledge the risks of opioid use, physicians who feel their patients don't need take-home naloxone, or pharmacists who don't know how to counsel a patient in need.

A critical factor of any successful naloxone distribution program has been the education provided to the patient by an appropriate trusted healthcare provider. We believe the best way to address this crisis rests in the relationship between the healthcare provider, the pharmacist, and the patient. We know that when physicians have candid conversations with patients about the use of opioids to address chronic pain, they reduce the risk of an accidental overdose.

We know when pharmacists effectively communicate to their customers the importance of

filling their naloxone prescription, they increase patient education and the likelihood of filling that prescription. We also know, based on our discussions with harm reduction groups, that each time they save a life with naloxone, they are given another opportunity to convince a person suffering from the illness of addiction to seek treatment.

We understand that one idea under consideration is the development of an over-the-counter naloxone product. We believe there are two different dynamics that should be considered as it relates to over-the-counter naloxone.

The first is the availability and sale of naloxone directly to patients without a prescription through retail channels. We are concerned that approach may actually reduce access to naloxone in the near term. While we may reach a point in the future when that option is viable, our experience suggests we are not there yet.

Based on our experience, the likelihood that a patient will self-identify as at risk and then go

to the pharmacy to pick up an over-the-counter naloxone is still low. Years after many states have issued standing orders for take-home naloxone, we still don't see significant uptake by patients.

Another major challenge is affordability for patients. Keep in mind, an over-the-counter solution generally puts the entire burden of cost on the patient, which we have already seen as a barrier to access. We know that patient abandonment increases as patient out-of-pocket expenses also increase.

With naloxone. given the challenges regarding awareness and education that we have already discussed, the threshold for out-of-pocket expenses is very low. Currently, even when the cost to the patient is zero dollars, we see roughly 30 to 40 percent of patients who never follow through on filling their Evzio prescription. Those percentages naturally jump higher when there is even a small co-pay.

Conversely, the second dynamic to consider when discussing over-the-counter naloxone is the

regulatory burden for organizations looking to distribute naloxone broadly or for use on their own premises. We know that many organizations have taken an active role in distributing naloxone directly to patients in need, or making it available in locations where there may be a risk for overdose.

The fact that naloxone is categorized as a prescription medication increases the regulatory burden that these organizations must go through to do so compliantly.

We fully support finding a means to treat naloxone in these situations similarly to other over-the-counter medications as we believe this will increase access to naloxone for this segment of the community.

Lastly, I want to spend a few moments addressing our investment in manufacturing and quality. Currently, we operate two state-of-the-art automated autoinjector manufacturing lines based here in the United States, one of which is dedicated to Evzio. Our

manufacturing process has been designed to meet FDA's strict CGMP device performance reliability requirements.

As I mentioned previously, during the manufacturing process, we conducted over 100 automated quality checks on each device produced. With our current capacity, we have the potential to product single-digit millions of units each year, and we are also planning on initiating capacity expansion activities in 2019 to prepare for expected demand growth in future years.

In closing, I would like to stress kaléo's eagerness to be part of the solution. We have heard far too many stories of loved ones who have been lost in this opioid overdose health crisis, but we have also witnessed the relief and gratitude on the faces of mothers and fathers who described rescuing their sons and daughters from the brink of death, thanks to naloxone.

Let us all be reminded that the work in front of us is about saving lives, and there can be no higher calling than that. Thank you.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for industry from the panel?

(No response.)

DR. BROWN: If not, I have one. Several of the speakers spoke to -- and Mr. Omar, I think you did just a few minutes ago -- the regulatory burden associated with the dispensation of naloxone. I think that's one thing that the panelists are going to want to speak of over and over again over the next two days.

On the other hand, if you take the approach that you take away all the regulatory burden or a substantial portion of it and make it an over-the-counter drug, nobody seems to be interested in that.

Could you address that?

MR. KHALIL: I can certainly share my perspective, and then I think the other sponsors certainly can share their own perspective. Our perspective on over-the-counter is really twofold. The concern with making it available without a

prescription through retail pharmacies, again without the awareness and education that is needed, given where we are today with naloxone, the likelihood of patients going into pharmacies, purchasing naloxone directly without the interaction with a healthcare provider, we are concerned in the near term that that would limit access and limit the availability of naloxone.

On the flipside, for organizations who are looking to distribute naloxone, currently, because it is a prescription medication, they would need to have a medical director available, have certain licenses based on which state they are in, in order to be able to do that compliantly.

Those are the burdens that we would see. If there was a way to overcome those burdens and make it easier for those organizations to distribute naloxone, that would help address the needs of increasing access to those members of the community while maintaining the ability for patients, and physicians, and pharmacists to have that interaction that will increase access in the

prescription market.

MR. KRAMER: Thank you, Mr. Chairman. I would simply reiterate some of the points I made in my talking points around this issue, which is for OTC to work effectively, there needs to be significantly increased awareness and education for these patient populations.

We need to make sure that by putting an OTC mechanism in place, it does not create any economic barrier to the very people who need these products by creating cost that are much higher than they are today. We continue to focus on awareness, education, and affordability before, I think, it makes a lot of sense to actively pursue this OTC process. Thank you.

DR. BROWN: Thank you. For future speakers, if you could just mention your name because we're transcribing all of this, and it makes it difficult for the transcriber to understand who's actually speaking.

Dr. Brand?

DR. BRAND: Thank you, Mr. Chair.

I guess my question is to Dr. Kramer. In conjunction with the public health, the consistent and constant public health message regarding the risk of opioid overdose, I'm looking at your slide that said 40 percent of the overdose deaths involve prescription opioids, which means, of course, 60 percent are involved with illicit opioids.

Would you be opposed to over-the-counter Narcan, considering that the majority of the people who need Narcan, to use Narcan, are not necessarily the patients since they typically are unconscious but are people who can't get a prescription for it; say, an onlooker, or a caregiver, or a first responder who need to have access to it and need to have the education how to use it?

The other portion, there was a slide that said 70.4 percent of the witnesses took no action. So that's why I say an over-the-counter program with public education as to what to do, would you be opposed to that?

Thank you, Mr. Chair.

MR. KRAMER: Sure. Thank you for the

question. And just for clarity, I'm not a doctor, but appreciate the edition.

I think for that issue, we have to look at the fact that we're trying to deal with both populations of people who are affected with opioid overdoses, both the prescription occurrence, as well as illicit drug users and how we deal with that.

So the key for us is increasing the overall awareness. I think at some point in time, it may be appropriate, and OTC might be the best tool for that. But right now, we've got to overcome some significant barriers around awareness and education, while not making it a disincentive to the very people who need access to this product by unintentional causes of price increases and economic issues.

DR. BROWN: For the transcriber, that was Mr. Robert Kramer, president and chief operating officer of Adapt Pharma.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I'm

sorry, Mr. Kramer, another question for you.

On your slide number 8, you give statistics on five states implemented regulations requiring naloxone prescribed with higher risk opioids -- or I should say I have two questions.

Did I miss it? Did you tell us, what was the morbidity on this? Were lives saved? What as the outcome?

MR. KRAMER: This is again, Bob Kramer. I don't know that we have the data, or I have it with me now, but we're certainly glad to look at that and provide that to you. I just don't have it right now.

MS. ROBOTTI: Yes. It would be a wonderful way to see if expanded naloxone distribution actually has an outcome favorable.

Second question, also, Mr. Kramer, in your presentation, I believe you mentioned that there's a two-year expiration date on your form of naloxone. I do not know how expiration dates are set. Is there judgment involved in that? That seems very short, and a lot of naloxone that might

potentially be still useable would expire and be lost.

What flexibility is there -- and that might actually be an FDA question -- in expiration dates of all forms of Narcan, of naloxone?

MR. KRAMER: For ours, I can only speak that we have stability data that supports the two-year shelf life. We continue to monitor the overall stability of that product in the device. We're certainly open to looking at extension of dating, if you will, but it has to be supported by firm data. I'm sure FDA would agree with that.

MS. ROBOTTI: You would be the source of that data?

MR. KRAMER: Yes, we would.

MS. ROBOTTI: Thank you.

MR. KRAMER: Again, this is Bob Kramer answering. Sorry, Mr. Chair.

DR. BROWN: Dr. Goudra?

DR. GOUDRA: Basavana Goudra for Penn, anesthesia. Two questions; one, I think it is Dean Mariano who said that there is evidence -- well,

you were citing one of the studies, which mentioned 63 percent or 64 percent decreased hospitalization.

My question is -- I mean I was kind of intrigued with this. I thought anybody who would get naloxone is depressed enough in terms of respiratory standpoint, and considering naloxone as short half-life, they still end up hospital anyway. So how did they end up with 63 percent decreased hospitalization?

The second question, maybe Dr. Robotti already talked about it, is there any data to suggest that co-prescription of naloxone has actually decreased mortality?

DR. MARIANO: To answer the question, the study looked at the reduction in emergency department visits related to opioid-related visits. There was a 63 percent reduction in opioid-related emergency department visits while giving naloxone at home, which they estimated that by giving people naloxone at home, it actually raised the possibility that they provided -- it affected the patients' behavior with respect to opioids.

So it reduced the amount of people coming into the ER for opioid-related ER visits. They're postulating that it reduced opioid risk behaviors, that it wasn't about admissions into the hospital itself, what that study focused on. That was co-prescribing supported.

So fair? So they're looking at that it hopefully has added to reducing opioid risk behaviors at home that led to reductions in ER visits. Thank you.

DR. BROWN: That was Dean Mariano, senior director of clinical development, medical affairs, Insys.

Our next question, from Dr. Pisarik?

DR. PISARIK: Paul Pisarik. I have a question. In those five states that had naloxone co-prescribing, is it too early to see if there's been a reduction in the mortality rate from opioid overdosing?

MR. KRAMER: This is Bob Kramer. Again, thanks for the question. It is a bit too early to see that, so we continue to follow the data, but

it's too early to tell right now.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: This question is for Mr. Kramer. I'm not sure I fully followed the points being made around over the counter. You brought up two points: the need for patient awareness -- and I guess that would imply that patients would need to self-identify as being at risk and then choose to purchase the product.

Just because the product is available over the counter doesn't mean that it can't be prescribed. Omeprazole is available over the counter, and physicians prescribe PPIs all the time.

Couldn't there be a model where physicians routinely prescribe this, but for patients who recognize that they might be at risk or their family members might be at risk, that they would be able to buy it over the counter?

The second point you made was that if it moved to an over-the-counter model, it would drive up cost. I'm not sure I fully appreciate the

interrelationship of those two.

MR. KRAMER: Thanks. This is Bob Kramer again. I think the answer to your first question is really a question for the regulators, for FDA, whether a prescription would still be required or be appropriate if it were, in fact, offered OTC.

On the second question, what we're trying to do is to ensure that the patient, and clinician, and physician conversation occurs. And to the point on cost, our perspective is that, I think, we should be very careful to ensure that by making products like these naloxone products OTC, that it doesn't have unintentional consequences of making the product more expensive to the very people who need it.

We have seen that happen, and we just want to make sure that that doesn't happen because, again, many OTC products are not covered by health insurance programs. The burden will fall to the patient, which could further create a barrier to them accessing the very product that they need and at the time that they need it.

DR. BROWN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I have two questions that are actually a follow-up to Dr. Brown's questions before. It's about getting the naloxone to the right place, in the hands of the right people that are going to use it. I think it's for Dr. Kramer as well, but maybe anybody can answer.

Again, the use of prescription opioids in the context of a party in teenage years, one of them having an overdose, that would be prescription opioid. But I wonder if you can expand on the overdoses that you attribute to prescription opioids.

Which ones are in the context of use of opioids for that intentions versus use of prescription opioids for not the intention that they were prescribed? How are you going to get naloxone to the prescription opioids in those situations?

In the same context, very nicely somebody said that we want to have naloxone in the hands of those that are likely to witness an overdose. How

are you planning to get naloxone to those people? Is there going to be like a buddy system or family members being always involved in the co-prescription? Because otherwise, the person passing out is not going to be using it.

MR. KRAMER: Again, Bob Kramer with Emergent. I think on the first question, we just don't have the data to adequately respond to your question.

I think in the second question around how do we ensure that naloxone products are available in and around the patients who are using higher-risk opioids, our point is to make sure that whether it's Narcan or any other naloxone product, is to get that in the home and get that around the -- again, some of the colleagues talked earlier today about the caregivers, the mothers, the fathers, again, the people who are surrounding these folks who are on higher-risk opioids, is to get the product there so they can deploy it when they need to, because we have all heard how timely administration of naloxone is critically important.

DR. BROWN: We're going to keep a continuous rolling list of clarifying questions, but we're going to move on now to the FDA presentations. We'll get to everybody's questions at a later time.

We'll now proceed with the FDA's presentation by Dr. Jiang.

FDA Presentation - Timothy Jiang

DR. JIANG: Good morning. My name is Timothy Jiang. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. The topic of my presentation today is Clinical and Regulatory Overview of Naloxone Products Intended for Use in the Community.

The United States is experiencing a devastating public health crisis associated with the use, misuse, and abuse of both illicit and prescribing opioids. The crisis has taken a staggering toll with an estimated 2 million Americans having a substance use disorder involving prescribing pain relievers and close to 600,000 having a substance use disorder involving heroin.

Opioid overdose is characterized by

life-threatening respiratory and central nervous system depression that may lead to irreversible hypoxic brain injury. Opioid overdose is an emergency and requires immediate treatment. In recent years, there has been a marked increased in the number of opioid-related overdose deaths driven by heroin and synthetic opioids other than methadone.

The figure from November 2018, National Center for Health statistical data brief, shows the age-adjusted rates of drug overdose death by categories in the United States from 1999 to 2017. The four categories are synthetic opioids other than methadone, which include fentanyl, fentanyl analogues, and tramadol in dark blue; heroin in light green; natural and semisynthetic opioids, which include morphine, codeine, hydrocodone, and oxycodone in dark green; and methadone in light blue.

According to the definition of the data brief, drug overdose deaths include death resulting from unintentional or intentional overdose of a

drug, being given the wrong drug, taking a drug in error, or taking a drug inadvertently.

The key finding from the age-adjusted rate of drug overdose deaths involving synthetic opioids other than methadone increase by 45 percent from 2016 to 2017. Other key findings include rates of drug overdose deaths continue to rise.

In 2017, the age-adjusted rate of drug overdose deaths was 3.6 times of the rate of 1999. The rates of drug overdose involving heroin, natural or semisynthetic opioids, and methadone were the same in 2016 and 2017.

Naloxone is a small molecule, mu opioid receptor antagonist. It was initially approved in the United States in 1971 with the trade name of Narcan. Narcan, as originally approved, is an injectable naloxone product that can be dispersed by intravenous, intramuscular, or subcutaneous routes of administration.

It's indicated for the complete or partial reversal of opioid depression, including respiratory depression induced by natural or

synthetic opioids. Narcan is also indicated for the diagnosis of suspected or known acute opioid overdosage.

Earlier formulations of naloxone and its generic equivalents are not optimized for use by non-medical professionals, although as I will present in my subsequent slides, some unapproved kits include these products for use in the community.

Two naloxone products intended for use in the community have been approved for use in both adult and pediatric patients. Evzio was initially approved in April 2014 and is a prefilled, single-use autoinjector for intramuscular or subcutaneous use that is currently available as a 2-milligram dose of naloxone hydrochloride per injection. Evzio's average retail price is $4641 for a package of two units in the event repeat administration is required.

Narcan nasal spray was initially approved in November 2015. It's currently available as a single-use device with a 4-milligram dose of

naloxone in a 0.1 mL spray. Its average retail price is $142 for a package of two units.

The indication for the newer naloxone products was modified to indicate the products are intended for use in any situation where opioids may be present, in addition to the use in emergent treatment for known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

Additionally, as I referred earlier, improvised naloxone products are being used in some community settings to reverse opioid overdose. One such product is supplied as a kit consisting of injectable 2-milligram in 2-mL naloxone in a prefilled syringe with a mucosal atomizer device to allow for intranasal delivery.

Half of the volume, 1 cc, is sprayed into one nostril, and the remaining volume, 1 cc, is sprayed into the other nostril. The injectable product that is being used in this kit is not approved for intranasal use.

The average invoice price for the naloxone

product in this kit is $29. It is noted the price has increased by 244 percent from 2006 to 2017 based on a recent publication by my colleagues in CDER's economics staff. Other products are supplied as kits containing naloxone intended for subcutaneous or intramuscular injection.

In many cases, life-threatening respiratory depression due to opioid can be successfully reversed by timely administration of naloxone, a drug that blocks the effects of opioids. The utility of naloxone in saving lives is reflected in the endorsement by the Department of Health and Human Services where "promoting use of overdose-reversing drugs" is one of the five priorities to combat the opioid crisis.

The commissioner of FDA, Dr. Scott Gottlieb, specifically noted that the agency is focused on increasing the use and access to the potentially life-saving antidote naloxone. There are existing initiatives to increase naloxone availability by various distribution programs outside the realm of FDA.

Naloxone is currently available through individual prescriptions from healthcare providers in more traditional healthcare settings, such as pain clinics and opioid treatment programs. Naloxone is also available without individual prescriptions through community-based programs offering overdose education and naloxone distribution outside of traditional healthcare settings.

In addition, naloxone is available by direct access from pharmacies under programs such as statewide naloxone standing orders or collaborative practice agreements. You will hear presentation on this topic by my colleague from the Division of Epidemiology in the Office of Surveillance and Epidemiology, as well as by several guest speakers.

As noted in the prior public meetings pertaining to naloxone products, FDA is committed to increasing availability of naloxone products intended for use in the community. FDA has been facilitating the development and approval of new naloxone products for use in the community by

non-medically trained persons and is working to foster the development of naloxone products for over-the-counter use as a means to increase its availability in the community.

You will hear a presentation by my colleague from the Division of Nonprescription Products this afternoon. The agency could also consider additional actions, including revisions of label for some or all opioid-containing drug products to inform prescribers about the existence of naloxone products, or to advise prescribers to consider co-prescribing naloxone, or to more strongly recommend co-prescription of naloxone.

There are several possible strategies for co-prescription of naloxone. Co-prescription naloxone concurrently with opioids could be considered for all patients.

The benefits of this strategy include that it places naloxone in all households with prescribed opioid medications. It may help prescriber and patients understand the importance of proper use and storage. It is available for

accidental or other exposures by other members in the household. However, this strategy does not reach all persons at risk for opioid overdose.

Alternatively, co-prescription of naloxone concurrently with opioids could be considered for only some patients at higher risk for overdose. The higher-risk groups include individuals with concurrent prescription for other central nervous system depressants; individuals with pain management require higher doses of opioid analgesics or with chronic pain managed with opioid analgesics; individuals with a history of opioid-related emergency department visits or prior overdose; and individuals with a personal or family history of substance use disorder.

Additionally, prescription of naloxone could also be considered for high-risk groups who do not even receive an opioid analgesic prescription in the first place. This group includes patients using medication-assisted treatment for opioid use disorder; individuals with prior history of opioid use disorder; individuals with prior history of

opioid abuse; and individuals with recent release from criminal justice system with a history of opioid abuse or opioid use disorder.

You will hear a presentation on this top by my colleague from CDER's economic staff and by several guest speakers.

Ideally, all patients who are prescribed opioids also would have naloxone available for use in the event of overdose of the patient or other member of the household. Unfortunately, healthcare resource are limited and the retail price of approved naloxone products for community use can be high as I discussed earlier.

CDER's economic staff has conducted analysis to assess the potential costs of requiring co-prescribing and concluded that cost of co-prescription can be substantial, depending on the assumptions made. The issue will be discussed further during the course of this morning.

When discussing whether naloxone co-prescribing should be targeted to all or some patients prescribed opioids, as I discussed

earlier, a couple of additional considerations are worth noting.

While prescription opioids contributes to a substantial portion of overall opioid-related morbidity, recent data suggests that a substantial and growing percentage of opioid-related deaths are associated with use of illicit opioids. As a result, co-prescription of naloxone may not reach a large proportion of individuals at a risk for overdose deaths of opioids.

Additionally, in order for a reversal of an opioid overdose to be successful, it must be administered soon enough to prevent irreversible anoxic brain injury. In some cases, this means that overdose would need to be witnessed for naloxone administration to be early enough to rescue the patients.

In conclusion, the agency is committed to increase access of naloxone in the community by additional actions. How best to meet this commitment is a topic for discussion today and tomorrow, and we look forward to hearing your

suggestions and comments.

Thank you. I will invite my colleague, Dr. Mehta, to the podium.

FDA Presentation - Shekhar Mehta

DR. MEHTA: Good morning. My name is Shek Mehta. I am a drug utilization analyst here at the FDA. Today, I'll be presenting information on the drug utilization of naloxone. Before I begin, I would like to highlight some important characteristics with respect to the distribution and administration of naloxone.

The pathways for distributing naloxone are unique and complex. There are a variety of settings of care and types of administration that are associated with this rescue agent.

For example, naloxone can be administered to patients in inpatient or outpatient settings. It can be administered by healthcare providers, first responders, or by bystanders in the community. When naloxone is distributed through these various modalities, some distribution and use may be missed in the community and commonly utilized data sources

used in a research. Also, when naloxone is dispensed or distributed, we often don't know how many times it was administered, in what form, and to whom.

To further elucidate naloxone utilization and distribution, we turn to proprietary drug utilization data sources and published literature to better understand how and where naloxone is being used.

The goal of my presentation is to provide information and context on the availability and distribution of naloxone using a variety of different sources. First, I will describe information from proprietary drug utilization databases available to the FDA. This will include nationwide trends in U.S. sales distribution data and dispensed prescription data.

I will also present data from other sources such as those found in publications and from various distribution programs. Strengths and limitations of available data sources will be discussed throughout the presentation. I will

conclude with key findings of our analysis.

A proprietary database was used to provide sales distribution data sold from manufacturers to various channels of care. Although sales data do not reflect actual patient use, these data provide national trends in the distribution of naloxone. Of note, donations and some direct sales are not captured by this database.

Listed here are settings of care where naloxone is distributed. We have limited granularity of the exact facilities that comprise each distribution channel.

For example, distribution to EMS may be done through sales to the non-federal hospital setting when the hospitals stock ambulances. It can also be distributed through sales to other settings captured in the data source used, which does not have more specific information, but may include distribution to state and local governments that also supply police, EMS, and other first responders. Sales data were analyzed based on product formulation. One unit is considered one

administration of a vial or device.

First, we will look at naloxone sales by setting. This figure displays the nationally estimated number of naloxone units sold by manufacturers to major channels of distribution. Naloxone sales gradually doubled from 2.5 million units sold in 2013 to 5 million units sold in 2017.

In 2017, 83 percent of naloxone units sold were to non-retail settings, largely to hospitals and clinics, while 17 percent was to the retail channel. Although small, the retail channel had the largest percentage increase over the examined time.

This figure provides the nationally estimated number of naloxone units, by formulation sold from manufacturers to all settings of care. The majority of sales were for vials of naloxone. Sales for the nasal spray, as shown by the green line, and sales for the autoinjector, as shown by the blue line, were low but increasing.

Of note, these sales do not include donations or some direct sales from manufacturers.

The majority of these sales were to non-retail settings such as hospitals, as shown in the previous slide. Sales to the retail sector alone are shown next.

This figure shows sales distribution data but only for products sold to retail pharmacies. In contrast to patterns of overall sales, the small but increasing volume of sales to the retail setting were primarily for the nasal spray formulation, as shown by the green line.

Next, we will further examine the availability of naloxone intended for community use by focusing on the retail dispensing setting. Two additional proprietary databases containing prescription transaction data were used to examine retail prescription dispensing patterns.

With these databases, we are better able to understand the volume of prescription products dispensed directly from pharmacies to consumers. However, it is unknown who the intended use is and when or even if the naloxone is administered based on retail prescription data alone.

As we have seen from sales data, the outpatient retail setting represents a small proportion of total naloxone availability. However, it is an emerging setting where availability has grown rapidly.

This figure provides the nationally estimated number of naloxone prescriptions dispensed from U.S. retail pharmacies stratified by formulation. Similar to patterns in the sales data, prescriptions dispensed more than doubled from 134,000 prescriptions in 2016 to more than 330,000 prescriptions in 2017.

Over 70 percent of the prescriptions in 2017 were for the nasal spray formulation of naloxone. Of note, prescriptions were typically for two units of naloxone.

To provide further context of the prescription market, this figure provides the nationally estimated number of opioid analgesic prescriptions compared to naloxone prescriptions dispensed from retail pharmacies. The amount of opioid analgesic prescriptions dispensed far

surpasses the naloxone prescriptions dispensed from retail pharmacies by several orders of magnitude each year over the examined time period.

Note that in 2017, there were 336,000 prescriptions of naloxone dispensed while over 196 million opioid prescriptions were dispensed in that same year.

In order to provide context on the state-by-state variability, this figure provides a ratio of naloxone prescription per 1,000 opioid analgesic prescriptions dispensed by state in 2016 compared to 2017. Although very low, the ratio of naloxone prescriptions to opioid analgesic prescriptions dispensed appears to have increased in some states such as Virginia and Vermont.

Although the impact on dispensing was not formally studied, Virginia and Vermont were among the states that implemented standing order or collaborative practice agreements in 2016. Note that these data do not indicate concurrent or co-prescribing of naloxone to individual patients.

Although informative of nationwide trends

and patterns, the proprietary databases have limitations. The databases used do not capture distribution of drugs outside of the typical pharmaceutical supply chain, such as donations to community programs or direct sales. For example, first responders such as police and EMS may not receive naloxone from usual supply chains.

Prescription-level data are based on prescriptions dispensed only from retail pharmacies. Naloxone may be prescribed and dispensed through a traditional prescription process. However, many states have standing order or collaborative practice agreements that expand the availability of naloxone to guardians and bystanders that may witness an overdose.

However, these data are not representative of all naloxone available to the community. In addition, not all dispensed naloxone is used, and the number of administrations per overdose event is unknown. Patients ultimately administered naloxone may not hold an actual prescription or be dispensed naloxone from a pharmacy.

To further elucidate naloxone utilization and distribution, we assessed other data sources such as reports from manufacturers and literature to better understand how and where naloxone is being distributed and used in the community.

Data on donated products and some direct sales are not fully captured in proprietary data sources, shown previously. In some years, large proportions of certain naloxone formulations were distributed through direct sales and donations as compared to available information captured in proprietary data sources.

This slide illustrates the complexity of the market, as well as potential gaps and knowledge, concerning the distribution of naloxone. Many distributors may have compassionate pricing and other distribution programs.

In our literature search, we identified many published studies on naloxone distribution where the methods of distribution were based on distribution models and target populations could be organized into three broad and potentially

overlapping categories.

First, there are prescribing programs that operate in traditional healthcare settings like primary care, pain clinics, or drug treatment programs. Standing orders or collaborative practice agreements are also methods utilized to enhance availability of naloxone through pharmacies. Data sources available to the agency generally capture naloxone dispensing through these settings.

The second group pertains to community-based harm reduction and overdose education and naloxone distribution programs that tend to use a diffuse network of organizations throughout a defined community for naloxone trainings. Some long-standing, well-known programs include the Chicago Recovery Alliance and Project Lazarus.

The makeup of the network of community-based organizations varies based on the program. These OEND programs primarily target high-risk groups, however, they also train and distribute naloxone to any person in need, including lower-risk people and

the friends and family of those at risk of overdose.

The third group overlaps somewhat with the second group. However, an important distinction is that the individuals receive a naloxone kit at a single point in time, often with inconsistent follow-up assessments for further naloxone dispensation.

Also, the target population here for take-home naloxone programs is specifically those with high, short-term risk of overdose and generally lack a long-term care plan after naloxone is provided. These types of recipients may include those recently released from incarceration or treated in the ER for opioid overdose.

Our proprietary databases often do not capture dispensing and distribution through community-based programs or take-home naloxone programs.

While the data are still somewhat limited in this area, we viewed this published work similar to other critical hypothesis-generating information on

the effects of naloxone use in the community. Overall, we learned that naloxone is distributed through several different models, many of which are outside of traditional healthcare settings.

Regardless of how naloxone is obtained, there are reports in the literature of administrations and overdose reversals, both among those who obtain the naloxone and their close contacts.

Naloxone prescribing programs in more traditional healthcare settings, such as in clinics or treatments centers, can be targeted based on one's perceived risk of overdose or can follow a universal precaution prescribing model, where every patient receiving an opioid is prescribed naloxone. The targeted approach appears to be more common than the universal precaution model.

Finally, we found no formal study comparing the effectiveness of overall public health benefit of any one specific distribution model.

Although there is much to learn from this burgeoning area of research, these data also have

some limitations. It is often unclear how community-based programs obtain naloxone and how much is distributed from those programs. The literature includes small descriptive surveys of convenient samples. Most data came from surveys often with short and inconsistent follow-up on subsequent naloxone administrations. Therefore, data on actual naloxone use and opioid overdose reversals may be an underestimate.

It is unclear whether findings from these studies are representative of other similar programs or programs in other geographic areas. Data on naloxone administrations generally relied on self-report without independent data verification. Often, these data were collected when participants return for additional naloxone.

Aside from data from the Veterans Affairs model, which is to be presented today, data on targeted or universal precaution prescribing models mostly came from small pilot initiatives with unclear generalizability to the total U.S. population. There is great value, however, in

understanding what can be learned from these many local experiences, and many of our guest speakers today will provide informative insight into this program.

National estimates of naloxone sales and prescription data show increasing trends in community availability of naloxone. However, more data are needed to fully characterize the unique and complex patterns of naloxone distribution, utilization, dosing, and effectiveness.

As some of the challenges discussed today illustrate, innovative and collaborative methods are needed to address issues associated with naloxone distribution to populations at risk. While there are limitations with these data, there is still a tremendous amount to be learned from the various naloxone distribution models in use.

Invited speakers will address the various types of naloxone distribution programs and their effectiveness in distributing naloxone in hopes to reduce events and mortality. Each type of program has its own unique strengths and limitations with

respect to increasing naloxone availability and preventing opioid overdose death. We look forward to hearing from our invited speakers and their experience on the frontlines of these efforts.

I'd just like to thank my colleagues who helped with the presentation. Thanks.

FDA Presentation - Matthew Rosenberg

MR. ROSENBERG: Good morning, everyone. My name is Matt Rosenberg. I'm from the economic staff here in the Center for Drug Evaluation and Research at FDA.

Before I get started, I just want to acknowledge the important challenge that we face here today, as well as tomorrow, in trying to figure out whether and how broadly to implement policies like naloxone co-prescribing or something similar.

The opioid crisis continues to have devastating societal impacts, and we want to do as much as possible, with the limited resources we have, to try to stem the tide. I believe that the economic model I'm about to present here can help

orient us in this space, even though, of course, it has limitations as any forecast of a novel policy would. But I think that it can at least help us get a sense of scale.

For instance, are we potentially looking at health system cost of millions of dollars per year, billions of dollars per year, or maybe even more?

Are there certain groups that we would want to target from the perspective of public health, both in terms of cost and benefits?

What steps could we take to tip the balance further in our favor, either by reducing cost or increasing benefits?

I hope I can persuade you by the end of this talk that our numbers can contribute to some useful evidence for you as you consider these questions over the next couple of days. So just very briefly before I move on, I want to thank colleagues of mine who have contributed to this work.

Now, as I'm going into the details, I just want to walk you through briefly why we think an economic model in particular is needed in this

space. The challenge with implementing these initiatives is that there's inevitably going to be some response by the marketplace as we increase demand for naloxone.

Suppose that the price per dose on the Y-axis here and the number of doses on the X-axis are at the point indicated by this circle. What happens if we're going to implement naloxone co-prescribing or some other sort of targeted prescribing initiative?

Well, first, let's consider what the total costs are under this sort of chart. You can see that the area between the circle and the axes, the price times the number of doses is what we would be concerned with here.

As we increase use of the drug, inevitably our circle shifts over the right because more people are using it. And of course, more people purchasing it, even at the same price, would increase cost to the health system.

But there's the second effect that we'd be concerned about, and that's really why the economic

model comes into play here. And that's the fact that increasing demand for a drug like naloxone is inevitably going to drive up its price, and we have seen from previous research, as my colleague highlighted, that prices of naloxone have been increasing over the last decade or two.

Keeping this in mind, we would think that as demand goes up, so would the price, and total cost would be higher than we would expect if we were only just expanding the access by itself.

With this in mind, I want to give you a sense of how we try to tackle this problem and why we see some larger numbers perhaps than others have been projecting in this space. We start out by assuming, as we have kind of had a discussion this morning, that co-prescribing is likely to be carried out with these community-use products, and particularly the FDA-approved ones like Evzio Autoinjector and Narcan Nasal Spray.

We then worked trying to estimate this cost for populations that are in the recent Surgeon General's advisory on opioid overdose and naloxone

use, and we assume that every available patient in this group is going to receive a co-prescription. Using various assumptions, we build out an economic model, and we estimate two types of costs for each patient population.

The first cost is for the new doses that are needed to expand access, and this includes the total spending on those doses, so the total cost of purchasing them and dispensing them in a pharmacy. For doses that were previously in use, we only focus on the higher spending because of the increase in the price, and we estimate these costs for when the policy is fully implemented.

What do I mean by this? The policy is initially implemented, and you can see there's some sort of ramp-up period. People are getting their first prescription as they get a prescription for an opioid for the first time or as they replenish the prescription that they previously had.

Eventually, we get somewhere approaching a steady state where people are periodically replacing doses as they expire or as they get new

prescriptions, but we're generally hovering around some sort of level of access here.

Our model focuses in on this steady-state period, so we're not worrying too much about the startup cost here, but of course, those would be something as well that we have to keep in mind if we were to implement this.

Before I show you our overall findings, I want to give you an example of how we estimate the annual cost of naloxone co-prescribing or targeted prescribing initiatives that fall under a similar category. For the next couple of slides, I'm going to focus here on what we're calling our all opioid analgesic population, which focuses on patients who are dispensed an opioid analgesic product in a retail pharmacy.

This is our largest population. This is kind of our universal precaution model that we're talking about, although, of course, it would still not include people who are on illicit opioids, but it at least gives a sense of how large some of these costs could be. And as we go down to look at

smaller populations, hopefully, it will start to make some sense of how we provided those numbers.

This group starts out with 58 million patients, which we estimated using 2017 data from IQVIA's total patient tracker database.

We divide this population into two separate groups. The first one here on the left are those patients who have been previously prescribed or co-prescribed naloxone with their opioid, and we estimate that this is 96.9 percent of patients, but we know we have probably over-estimated how many people are in this group.

Then we put everybody else on the right-hand side of all the patients who haven't previously been co-prescribed naloxone or haven't received it in several years, which means that the dose is probably expired, and they would need a co-prescription.

We're going to focus on how we arrived then at which patients are going to get their naloxone out of these two groups, keeping in mind that the group on the right-hand side is definitely going to

need naloxone because they either don't have their co-prescription, or they don't have any other doses available; whereas the one on the left is only going to need to replenish it if it's used up or expired.

This group on the left, we have a few categories that we divide it up into as we think about these sorts of considerations. Some patients don't need to replenish their doses because they're still going to be available. They're not used up or expired.

Some patients are going to use their dose to try to reverse an overdose maybe out in the community or elsewhere. Then the remaining patients who haven't used their dose, some of them are going to have it expired because just simply we have reached the shelf life and it has to be replaced.

We take these two groups and we assume only a 70-percent fill rate for the prescription, which is what we see for other sorts of emergency products like EpiPen or epinephrine autoinjector,

and then at 2 doses per prescription, we end up with this 46.7-million-dose number for the folks in the left-hand group that we started with. And you'll notice that some of these numbers are not going to quite multiply out as you expect simply because of rounding, so hopefully, that's nothing to be too concerned about.

The 2-million-group, the second group, this is going to be a much easier calculation. Since they don't have naloxone, we have to prescribe it to them. And in applying the same process as before, we end up with 2.8 million additional doses for this group.

How do we estimate the overall number of doses needed by the health system to meet the needs of a particular patient population? Well, we take the 46.7 million doses from the first group, add it to the 2.8 million doses from the second group, and then we subtract out doses that we estimate are already in use by the population.

Since we're looking at a very broad group here, we include everything, but for smaller

populations, we'd actually scale this down. For instance, if it was only half of the 58 million number, we would put only half a million doses in that subtraction. When we add that all up, we see that there would be 48 and a half million doses needed by the health system, in addition to what's being used now; and if you add on the 1 million or so doses already in use, that gets us closer to about 50 million doses altogether.

What do we do then with this number from the previous slide? Well, knowing that there's an increase in demand for the drug, we have to figure that there's going to be some sort of response here where prices for the drug are probably going to go up. But the question is, by how much?

We used an economic model here to work on this piece, and specifically what's called a constant elasticity supply and demand model. But don't worry if you aren't so familiar with the economics jargon because we're not going to spend too much time going through the technical details here. The general idea is similar to what you

think of in your ECON101 supply and demand curve.

We have a demand curve on the left here that's downward sloping. So that means that when the price of the drug goes up, fewer people want to use it. And then we have a supply curve that's upward sloping. So as the price goes up, a company would want to produce and sell more of the drug.

The intersection of these curves is the price of the drug when there's a lot of competition in the marketplace, and we term this here as the production cost, which is the additional cost of producing one more unit of the drug. That's the result from economic theory.

Suppose that we have co-prescribing, and we shift out the demand curve by some amount as shown by this new line. So what happens to the price? Well, you can see that the price is going to go up. The quantity is going to go up as well, maybe not entirely as much as the increase in demand, and the price is going to go up to some new numbers, as we see here.

It turns out there's actually a formula

within this kind of model you can use to estimate how much the price is going to go up with a certain set of assumptions. I'm not going to spend too much time going over it here, but the idea is that we'll try to apply this on the coming slides to estimate how much prices could increase.

Now, something we need to keep in mind though is that this idea of being at the production cost only occurs if we have a lot of competition in the marketplace. With lots of generic competition, we would be at the intersection of those curves in terms of price. But if we don't have competition, it's possible we could be higher.

To capture this possibility, we have created two separate scenarios. The first we call the with generics scenario. By this we mean that there's a lot of competition for both of the brand name products and the prices drop down to the estimated production cost.

This is effectively a lower bound because we know that obviously firms are in business to try turn a profit, and they're not going to want to

sell products at a loss.

We then have the without generics scenario here. This is the status quo. We only have branded products in the market, and prices are going to be a bit higher. So they're going to be more like the retail prices that you see in pharmacies rather than the production cost, which is going to be less. This is an upper bound, and we're going to talk somewhere later about how different levels of retail price might affect the estimates.

I'm going to start from the without generics scenario and work backwards because as you're going to see, we estimate the with generics scenario by scaling this one down. We use data from IQVIA's national prescription audit database to try to estimate the retail prices.

We take the exit pharmacy prices and market shares for the two products, and you'll notice that the number for Evzio Autoinjector is higher than the recently announced price because this is what it was a few weeks ago. We're going to talk some

more about what the implications of a lower price could mean later on, but for now, we're going to start out with this higher number.

We get an average retail price of $478.41 per dose when we take a weighted average by these market shares. We then use the formula from the previous couple of slides to try to estimate how much the change of demand affects prices. Based on the number of doses we calculate earlier, you can see that we're estimating a 4,689 percent increase in annual demand for community use naloxone products based on the assumptions we have made about this different groups, and that with our model, these increasing demands translates into a 2,347 percent increase in the price.

How high are prices going to go up with these kind of percentage increases? In the without generics scenario, we're starting with the retail price here. That was $478.41. Where do we go from there? Well, with this kind of percentage increase, the prices go over $11,000 per dose. In the with generics scenario, we scale these numbers

down by 89 percent to account for having 8 or more generic competitors for each product, which brings us to around $1300 per dose.

We then take these new prices, and we calculate the annual cost for each of the two patient groups I mentioned earlier within each patient population. This slide is going to focus on the with-generic scenario to illustrate the general process, but the without generics scenario is the same approach but just with higher prices.

In the groups that need new doses, we take the total purchase price and a dispensing cost of $3.94 per dose. For the doses that were already in use, we only take the increase in the price. When we add these all up, we get $63.9 billion per year for with-generics and $579.2 billion, as you can see in the title, without-generics.

On these next few slides, I'm going to show you what our results look like for many of the patient populations that we have tried to approximate based on the Surgeon General's advisory.

In this first table, you can see groups that we believe are more likely to interact with the health system and be impacted by a co-prescribing initiative in particular. You can see the first row includes the groups we just estimated. And as you go further down the table, we're looking at more and more targeted groups.

As we reduce the size of the patient population, of course, the costs are going to fall. In most cases though, they still are going to exceed a billion dollars per year in the without generics scenario. So that's our upper-end estimate.

On this slide, I'm presenting other sorts of groups that we don't believe are going to interact with the health system as much but that we may ideally want to reach with some sort of targeted prescribing approach. Now, of course, these costs are going to assume that we get the drug to all the patients in this group, although in practice, that's probably not going to be the case.

These findings are similar to what you saw

on the previous slide, although the groups are generally a bit smaller. For some of the more targeted populations in the last few rows, we have a better chance of getting under a billion dollars per year.

As we think about these results and what they mean, it's important to keep in mind that we're probably not going to be able to fully anticipate how all the different players in this market and elsewhere are going to respond to a policy like this. I'd like to highlight a few changes that we have recently heard about in naloxone market and how they might affect these cost estimates.

Just last week, we found out that Evzio Autoinjector is going to be available as an authorized generic at a list price of $178 for 2 doses. And obviously, in our earlier numbers, we used that higher price. So what are the implications, then, of plugging in a low price instead?

You can see I've replaced that price of

about $2,300 per dose with a lower value of $89 per dose. Obviously, the average retail price is going to fall. It's going to be something like $75 a dose. What implications does this have then for our overall cost?

Plugging in this new price drops things. Obviously, we're not at the without generics scenario at this lower price. We're down to $90.2 billion compared with something over $500 billion before, but we're still about 50 percent higher than the scenario with generics.

In our original findings, we also assume that only demand increases. But what happens -- we have heard some of these even this morning, that companies are planning to expand production capacity. We know this is going to shift out the supply curve simultaneously and offset some of the increases in price. How much do we expect cost to go down as this happens?

This chart shows how cost might decline relative to our original numbers if the supply curve simultaneously shifts out by certain amounts.

For instance, if the supply curve shifts out by a factor of 3 -- and keep in mind, this is not the same as increasing capacity by a factor of 3, but if this sort of thing happens, we would expect costs to drop to about 40 percent of what they were.

You can see that this effect is starting to level off, that it drops off to about an 80 percent decline, and then the effect of increasing supply starts to diminish.

How large are these annual numbers that we're looking at? I want to provide a few benchmarks that we can use to help us think about the scale of these results.

The highest selling drug in the U.S. in 2017, by revenue, had total sales of $16.9 billion. In several of our scenarios, naloxone would become the largest pharmaceutical market in the U.S. by dollars. In 2017, total U.S. pharmaceutical spending was $452.6 billion. So even in the scenario with the lower prices, in our larger patient populations, we're looking at increases in

spending of perhaps 20 percent or even more.

As we consider what we're going to do in terms of targeting patient populations, we have to consider the benefit side of the coin as well. We know that giving out naloxone has the potential to save lives or perhaps avoid serious injuries that could occur during overdose events.

These benefits are tricky to pin down, because as we have been finding out this morning and in our own research as well, it's hard to know what the overdose rates are in different populations and how we could save them or perhaps improve their situation using naloxone. But I have found a study that I think at least is helpful for beginning to think about these different benefits.

A Coffin and Sullivan study in 2013 looked at a population of people who use heroin and estimated that the drug would be cost-effective, giving out a kit of naloxone in a community setting at a price of up to $2,240 per dose.

How does this compare to our scenarios? Well, in the scenario with generic competition, as

well as at the lower prices that we saw for Evzio, it would actually be cost-effective in all of our patient populations. In the without-generic scenario, it would not be cost-effective until we reduce the patient population to 6.7 million patients or fewer. But as we think about this, there are several challenges to taking these sorts of numbers and using them to make decisions.

First, we know that people who use heroin are a higher-risk group, that we're looking at perhaps broader approaches with some of these patient populations that could target people who have different levels of risk, perhaps lower risk. And if that's the case, we would need to have an even smaller patient population, and perhaps some of the larger ones we have considered might not be cost-effective even with generics.

Then the second thing to keep in mind is that even if the policy is cost-effective, it's still very costly, which means that the health system may not have the resources to implement some of the larger patient populations even if they were

cost-effective groups.

Before I wrap up, I just want to highlight three of the main limitations of our model. First, we're relying on a set of assumptions, and we know that there is uncertainty about what the marketplace looks like and how people are going to respond to co-prescribing. This means that the range of potential cost is probably bigger than what we have shown here.

We have done some sensitivity analysis, and we have shown that, generally, for most of the assumptions, the order of magnitude isn't really changing much as we vary them within some reasonable ranges. but we know that there are things that we won't be able to anticipate, and the cost could be certainly a bit higher or lower than what we're showing here.

The next challenge is that we're assuming that everyone is getting the drug, and we know this is probably not going to be the case, and we have seen evidence this morning that that hasn't been the case. And even when you look at our economic

model, you'll see that an increase in price, of course, is going to imply a decline in quantity.

If we wanted to reach some of these other groups, we would have to have probably even higher prices than what we're seeing because we would have to shift ourselves kind of even further up in terms of demand than we are right now.

Generally speaking, our model is probably going to overestimate the costs that are actually incurred at a given patient population because some people are inevitably going to be turned away by the higher prices.

Finally, we don't account for production limits on naloxone. And I think we've heard this morning that production capacity is probably not going to be large enough for several years to hit some of these larger groups when we're talking about things like 50 million doses per year.

If this is the case, we're probably even underestimating how much this is going to cost, because when you approach capacity limits, prices go up even faster than they do when you're in a

situation where supply is more flexible.

As my presentation comes to a close, I want to leave you with just a few short perspectives on our results.

We have seen, of course, that in some cases, naloxone co-prescribing or targeted prescribing could have large annual health system costs, depending on which patients we go after. Our results though do hint at a few strategies that could help to tip this balance in our favor. The most obvious one is focusing on smaller groups of high-risk patients. And by doing this, we bring the cost down and probably increase the benefits.

We can also try to promote generic competition for these products or also consider expanding OTC availability, but we know that there are patents in place on a lot of these products, and it might be more challenging than it looks to get new things in the marketplace.

Of course, if production capacity is expanding simultaneously with demand, that would help to absorb some of the price increases and keep

the costs from being as high as our model suggests.

Thank you for your time this morning, and I'm happy to answer any questions you have about the work or otherwise. Thank you.

Clarifying Questions

DR. BROWN: Thank you very much. We'll now proceed with some clarifying questions for the FDA. Please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter.

Dr. Dasgupta?

DR. DASGUPTA: Hi. Thank you. I have a question for Dr. Mehta. It's a simple question. I feel like we haven't seen any numbers. We have seen what the branded numbers are. We have seen the numbers of industry and the IQVIA data. I still don't see any kind of relative comparison of how much naloxone is distributed through the harm-reduction programs, the OEND programs.

If the number of doses -- it looks like it's about a million a year go out in the branded products. But if the naloxone programs are

distributing a million, 2 million doses a year, our understanding of all these modeling is going to be very, very different, because that's all the liquid-injectable, or mostly the liquid-injectable, which is at a much lower price.

Can you give us some numbers on how to put these numbers that we saw this morning into context?

(Pause.)

DR. MEHTA: We actually don't have an estimate of the amount of drugs that's distributed through all these OEND programs and take-home naloxone programs, so it's very hard to ascertain that information just from the disparate and diffused networks of all of these different programs.

We have an idea of what's distributed through transaction information from our proprietary databases, but again, it's hard to kind of aggregate the information from very disparate and diffused networks of different programs.

Does that answer your question?

DR. DASGUPTA: It does. It just makes all my interpretation go out the window.

(Laughter.)

DR. BROWN: Dr. Besco?

DR. BESCO: Hi. Kelly Besco. I have a question for Dr. Jiang. You quoted a price of using the prefilled syringe with the mucosal atomizer device of $29, and I just wanted to clarify if that quoted price included the price of the atomizer device itself or just the prefilled syringe product?

DR. JIANG: It's the naloxone products only. It's based on a publication by my colleague, if you want to elaborate further, and has nothing to do with the device; products only, for one unit.

DR. BESCO: Do you have any idea how much the atomizer cost?

DR. JIANG: I have no idea. I was told during the preparation it cost a few bucks, but whoever wants to add on, please.

DR. BROWN: Dr. Ciccarone?

DR. CICCARONE: Hi. Dan Ciccarone here.

Question for Matthew Rosenberg. Thank you for your impressive analysis and presentation today. I'm trying to reconcile your numbers, which are impressively large, with those presented by industry this morning. And I know I'd really prefer to set up a debate here.

But if you could just give us your side, why are your estimates two to three orders of magnitude higher than what they were trying to tell us this morning?

MR. ROSENBERG: I think our numbers are a bit larger for a few reasons. We've shown some populations that are probably larger than what they're looking to estimate. I think the industry folks suggested that we target some smaller groups, which would also bring the number of patients down. So I think our model would probably agree that cost would be lower if we focused on those patient populations, but there are also some differences in how we have estimated things.

I believe in their model, they have just taken perhaps the current retail prices and

extrapolated them to all those doses, but in our model, we have tried to get a sense of how much they're going to go up. We've seen naloxone prices have gone up historically as people have been trying to expand access. There are, of course, other questions about what people should do or not; those are different questions. But we think that prices are probably going to rise, and that that has to be considered in these sorts of estimates.

DR. BROWN: Dr. McCann?

DR. McCANN: Mary Ellen McCann. My question is for Dr. Mehta. On slide 17, I think you said that there's not any efficacy studies looking to see whether you increase the amount of naloxone in the community, whether it makes a difference or not.

I was just wondering, could the FDA either encourage or compel states, like Virginia or Vermont, to conduct these efficacy studies? And if not, could the FDA do those studies themselves? Maybe this is for Sharon.

DR. MEHTA: Yes.

DR. STAFFA: This is Judy Staffa. I don't know that that's within our authority to require that. With regard to undertaking that, that would have to be something we would have to consider through some kind of collaborative relationship and acquiring funding for something like that.

DR. McCANN: All right. Thank you.

DR. BROWN: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. For Matt Rosenberg, I hope this isn't a naïve question, but your cost assumptions don't include the distribution of the individual injectables, which still is a percentage in the market on page 4 of the Emergent slides.

I would think the fact that it's an injectable would not be a deterrent for people to use it in populations potentially comfortable with using an injectable, and guardians would be highly motivated to learn how to, particularly if it's generic or extremely a lot less expensive.

MR. ROSENBERG: Yes. So as you mentioned, those formulations are much less expensive than the

ones we we're looking at here. And our model would imply, of course, that if we were to substitute for those formulations instead, that cost would be quite a bit lower than what we have shown. There are trade-offs involved probably, in terms of how well the policy might work versus the cost, that if we give out these sorts of formulations, it may take more effort in terms of training or other sorts of things.

So I don't know how costly training is versus buying the more expensive version of the drug. There are probably differences in those costs. I agree with you that considering those sorts of options could also be a possibility if other safeguards were taken to make sure it would work as well.

DR. HERTZ: Hi. This is Sharon Hertz. I'd like to encourage you to ask the question of some of the later speakers, particularly about acceptance of nasal versus injectable, because I'm not sure that we know how acceptable that is, and they may have more experience.

DR. BROWN: Sharon, did you mean you don't know what -- what did you mean by that specifically?

DR. HERTZ: About the off-label use of the Prenolol in a kit, I believe is what you are asking us about, right? The current generic injectable naloxone and how we could factor that in? And you had mentioned, Suzanne, you thought that the cost would be lower if people just use that injectable.

MS. ROBOTTI: As an injectable, not with the kit on top of it.

DR. HERTZ: Just to sort of explore that a little bit later with some of our guests.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: I have a question that goes both to FDA and maybe to Mr. Kramer as well, and it's just maybe also an overall comment to maybe take one step back. I think we have, with the pricing, a lot of considerations. I think we'll probably talk much more about this, the three orders of magnitude difference in estimates that come from the population come from the estimate in

cost and increases in pricing. And we'll probably get somewhere closer but probably still have a lot of uncertainty at the end of the day.

I just want to raise the question, if we're thinking about the opioid epidemic as a public health emergency, one of the biggest crises the country has seen, whatever language you want to use, if you recognize that, are we really restricted to the context of the market pricing of drugs the way would discuss co-prescribing of a PPI for somebody with an NSAID and thinking about what would insurance cover in these circumstances?

My thinking was really triggered by just looking at the portfolio of Emergent that includes vaccines such as anthrax vaccine and so on. And maybe I'm completely off line here, but I don't think that in the case of an anthrax attack or epidemic, we would use that same approach.

I don't know how you -- I would assume there is bulk purchasing by the government that puts this in place for emergency scenarios. Wouldn't there be a scenario to put something in place for this

step, fixes the price at an acceptable level for both sides and deals with it in the context of an unusual emergency rather in the context of typical prescription drug pricing that we use for typical chronic conditions in the country?

DR. BROWN: Is this something we're going to discuss at a later point? I know we talked about it in the comment, or does somebody at the left-hand side have a comment about this?

MR. KRAMER: Thank you for the question. I think it's a really important question, and I have been kind of dying to jump in here.

In response to an earlier question about the significant difference in cost estimates, I would offer a couple of points. First of all, I don't think we have much disagreement or misunderstanding about the total number of high-risk opioid patients who need to be addressed with some type of naloxone products. Whether it's 58 million or 50 billion, I don't think that's a big difference.

I think the two major differences in our estimates are the following. First, there is an

adoption rate difference in what Mr. Rosenberg has in his model, which is, I believe, 70 percent, versus what the data show us in the five co-prescription states since implementation, it's closer to 10 percent. So that is a seven-fold increase by itself.

But the significant increase -- and I was trying to write some numbers down, as Mr. Rosenberg was going through his presentation, to project that there is going to be a 2,300 and something percent increase the cost of these naloxone products, and I'll just talk about Narcan, which is ours --

DR. BROWN: Mr. Kramer, could we speak to the FDA presentations right now and speak to the industry presentations in a few minutes? I want to get directly to Dr. Gerhard's question.

My question to the FDA was, is this something that we're going to talk about, that one of the speakers is going to talk about at a later point?

DR. HERTZ: This is Sharon Hertz. I think that we are not prepared to speak about that now,

going to that vaccine type model, but perhaps some of the speakers later on, the invited speakers, can address that.

DR. BROWN: Dr. Meisel?

DR. MEISEL: Steve Meisel. Questions for Dr. Mehta and perhaps some others. I have two questions, actually. One is, every good idea has got unintended consequences. I can envision a scenario where grandma is in hospice on narcotics and isn't doing very well, and a family member panics and has access to naloxone and administers it, and then creates a crisis of uncontrolled pain and other sorts of conditions, and similar scenarios along the way.

Are you aware of any situation where naloxone was given for purposes other than what we're talking about here, which is an overdose? And if so, what the outcomes may have been?

DR. MEHTA: Yes.

MR. SECORA: Hi. This is Alex Secora. I helped out with the review with Dr. Mehta. I'm not sure that in the published literature there were

reports of use outside of indication. There may be that situation that occurs, but there weren't reports that we can identify in our literature, no.

DR. MEISEL: Then my second question, and again, I'm not exactly sure who to refer this one to, we talk about kits of 2 doses because one dose can probably work and you might need a second dose, or maybe there's an error. But with some of the street drugs that are out there, 2 doses may not be enough. You might need to give 3 or 4 doses with these, with carfentanil and all sorts of things that are out there, high doses of fentanyl.

Have we modeled what might really be necessary in terms of cost for situations like that? This is probably a question for the economics folks. I think there would be some circumstances where 2 doses in a kit are maybe not enough, and how would we manage that?

MR. ROSENBERG: This is Matt Rosenberg from the economic group. We haven't looked at any specific modeling around that, but the more doses that we need, that's going to increase cost. Each

patient we're assuming is getting one prescription right now, but if they would need 4 doses, that would be 2 prescriptions.

DR. BROWN: We're going to take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or within a member of the audience. We're going to resume at 11:10.

(Whereupon, at 10:53 a.m., a recess was taken.)

DR. BROWN: We're now going to begin the invited speaker presentations with Captain Christopher Jones.

Speaker Presentation - Christopher Jones

CAPT JONES: Good morning. I have no conflict of interests to disclose.

Chris Jones from the CDC, and I wanted to start off this panel really talking about who are the risk populations. You have heard of some of this already, as people have referred to the CDC guidelines as SAMHSA Opioid Overdose Prevention Tool Kit was also included in one of the slides.

We've gone through an exercise within HHS to try to look at this, look at what we've recommended, and today, just talking through some of the populations to hopefully inform the conversations. I'm not going into the specific effectiveness for prescribing or co-prescribing naloxone to these populations. You'll hear from some of the other speakers around the effectiveness of different approaches.

Really, there are two buckets of individuals that we consider prescribing or co-prescribing naloxone for: those who are prescribed opioids for pain, and then I'll go through different groups here; and then individuals who are at high risk who may not be prescribed opioids for pain.

A distinction, people often when they say co-prescribing, it's sort of in the context of analgesics being prescribed for pain, co-prescribing naloxone. But I don't think we can discount the importance of prescribing or equipping individuals who are at high risk who are not prescribed opioid analgesics.

Within the opioids prescribed for pain, there are four subgroups here: people who are prescribed opioid doses, 50 morphine milligram equivalents per day or higher, that's consistent with the CDC guideline, which you have already heard, and it's consistent with the SAMHSA Opioid Overdose Prevention Tool Kit as well; people who are co-prescribed benzodiazepines regardless of the opioid dose; people who have respiratory conditions, such as COPD or obstructive sleep apnea, again, regardless of the opioid dose; and then individuals who have substance use disorder, excessive alcohol use, or mental disorder, again, regardless of the opioid dose. And I'll talk to some of the data to support these recommendations in just a minute.

Individuals who are not prescribed opioids for pain, and some of these are quite obvious but I think really incredibly important high-risk populations: individuals who are using heroin or synthetic opioids or misusing prescription opioids; individuals who are using other illicit drugs, and

I'll talk about that more in a minute, such as methamphetamine or cocaine, where the supply may be contaminated with illicit synthetic opioids; individuals who are receiving treatment for opioid use disorder, including medication-assisted treatment; and individuals who are released from incarceration or other controlled settings who have a history of opioid misuse due to a loss of tolerance.

Looking at the individuals who are prescribed opioids for pain, patients receiving opioid doses of 50 MME or higher, you can see here just two different studies. There is a variety of literature to support a dose-response relationship.

People have chosen different thresholds, somewhat arbitrarily in the literature. People have not always used the same definitions. But this looks at risk of non-fatal -- that should be opioid overdose, not opioid dose -- and then one for fatal from Tennessee. But you can see here a pretty consistent finding of as the MME per day increases, the risk for overdose increases.

When we look at MMEs for acute or chronic pain -- so there also have been some question of should we focus on people who are prescribed opioids chronically for pain? Amy Bohnert's paper, looking at overdose deaths in the VA population did look at both, people who had an acute pain diagnosis and people who had a chronic pain diagnosis.

These are just the overdose death rates by grouping of MME. You can see here, again, a dose-response relationship by the categories that she chose, both for acute pain, as well as those with chronic pain.

Opioids and benzodiazepines, this is Dr. Dasgupta's paper, so I apologize for presenting information that you have researched. This, again, goes to supporting the role of benzodiazepines in overdose deaths. We have seen in the national mortality data that opioids and benzodiazepines are commonly implicated in overdose deaths, that benzodiazepines are some of the most common substances that are listed on death certificates

for overdose deaths involving opioids.

I think this speaks to really the importance. You can see here the line that has the open circles, or individuals who died from an overdose involving opioids that had also received a benzodiazepine, looks very different than those who did not. And even the MME relationship is different; so not surprising, given the pharmacology of the substances, but, again, a pretty substantial risk population.

When we look at other comorbidities, I think these have been less well teased out as far as guideline recommendations. The two states that you have heard about today, Virginia and Vermont, their recommendations around co-prescribing are largely based on MME or opioids plus benzodiazepines. They don't really go into other comorbidities.

These are, again, from two different studies that looked at overdose risk. I have just highlighted, again, COPD, which I mentioned earlier, substance use disorder, different mental disorders, depression, bipolar, schizophrenia,

anxiety, and then of course, benzodiazepines on the right. Then on the second study, again, the magnitude of the odds ratios or hazard ratios are slightly different but a consistent signal of increase in risk; for mood disorders, pretty broadly defined; again, opioid use disorder, other use disorders, and then benzodiazepine use as well. And these models control for MME, so their risk is above and beyond what might be adjusted for the MME.

Moving to other populations who are not prescribed opioids -- and again, I think there's room here. Even as this is really confusing on co-prescribing, again, there are regulatory actions that could be taken to address the expansion of naloxone among these populations.

The issue with fentanyl and illicit synthetic opioids has really broaden the risk pool for individuals who might benefit from naloxone. We've seen in the last couple years clusters of overdoses where people thought they were using one particular substance, whether that'd be counterfeit

benzodiazepine pressed tablets, or opioids to look like commonly abused prescription opioids, or even cocaine or methamphetamine, where individuals have been exposed to illicit fentanyl.

For those individuals who are obviously not using opioids on a regular basis and think they're using a stimulant of some sort, they would be at incredibly high risk for respiratory depression associated with opioids because they have no tolerance.

This has really expanded the population of people who are at risk for overdose. We did an analysis of data through 2016 in the mortality data. In 2016, 40 percent of deaths that involve cocaine also involves synthetic opioids. You can see for psychostimulants and benzodiazepines, it's been a pretty clear pattern of increase in the last few years. The 2017 data came out a couple of weeks ago. We haven't had a chance to look at that, but no doubt, you'll see that synthetic opioids are contributing to the deaths involving other substances.

We see that this really parallels what DEA is seeing in their NFLIS data or essentially their seizure case data where we see fentanyl exhibits, but we also see fentanyl plus heroin, fentanyl and cocaine, fentanyl, cocaine, and heroin that are showing up in the DEA data, fentanyl and other substances.

Again, I think we have to sort of think more broadly than just people who might be knowingly using opioids when we're thinking about who's at risk and who might benefit from expanded access to naloxone.

This just shows, again, sort of the unpredictability in the illicit drug supply. In 2013, acetylfentanyl showed up in Rhode Island and other Northeastern states. We saw fentanyl, carfentanil, but there are a number of different analogues that are showing up. And as we take measures to control these illicit substances, additional analogues are showing up. Some of them are more or less potent than fentanyl, but it really lends to some unpredictability and people

being able to protect themselves and mitigate risk for overdose.

The last group is people who are leaving incarceration. This is from Ingrid Binswanger's work looking at individuals who are released from incarceration in Washington State, showing the substantially increased risk for overdose in the first couple of weeks following a release from incarceration; again, another population, to me, a low-hanging fruit population of if you're leaving, you should be given naloxone.

Thinking about other people who might have been in more controlled settings, so people who are receiving treatment at a residential treatment facility for opioid use disorder who are then integrating back into the community, and they have been using substances. They've been in a controlled environment, and those people are also at an incredibly high risk due to lack of tolerance or loss of tolerance.

That is it for me. I was told to keep it brief, so hopefully, that was very brief. But I

hope that it will help inform the conversation in thinking about how do we target at-risk populations and how do we account for the changing illicit drug supply as we think about what regulatory levers to pull as we try to address this issue.

DR. BROWN: Thank you, Dr. Jones.

Our next speaker, Alexander Walley, associate professor of medicine at Boston University.

Guest Speaker Presentation - Alexander Walley

DR. WALLEY: Hi. Thank you. I'm happy to be here and present to the FDA. I'm glad you're looking at this topic. I'm going to focus on naloxone dispensing via retail pharmacies.

My experience with naloxone I think is first as a care provider. I'm a primary care provider and prescribe buprenorphine and naltrexone for opioid use disorder. I also prescribe chronic opioid therapy for some patients with chronic pain. I worked in a methadone maintenance program where there's a lot of people with opioid use disorder.

I've also spent time at the Massachusetts

Department of Public Health since 2007, where I have been the medical director of the Opioid Overdose Prevention Program and write the standing order for Massachusetts that allows that program to distribute naloxone, as well as the statewide pharmacy naloxone standing order.

I'm going to talk about the promise of pharmacy-based naloxone rescue kits, the barriers of pharmacy-based naloxone rescue kits, and some opportunities. But before we go there, I just want to mention and acknowledge Dan Bigg, who we lost this year. I guess you could call this OTV naloxone, out-the-van naloxone.

This is his Chicago Recovery Alliance van where he distrusted naloxone since the early 2000s, late 1990s. There's discussion about unintended consequences, which I think has come up. We have a lot of experience with community distribution of naloxone, and there aren't a lot of unintended consequences. In fact, I can't think of any unintended consequences in my experience with naloxone.

The one unintended consequence we've seen develop, which we didn't expect, is really the rise in the cost. I'm really heartened that FDA is accounting for cost now because I have been to other FDA meetings about naloxone, where we actually couldn't address the issues of cost. I think that is a really major driver around the public health issue.

Really, on the basis of the work in the community, naloxone has been mainstreamed. Many professional organizations, World Health Organization, our National Drug Control Strategy, has recognized the role that naloxone rescue can play in addressing the overdose crisis. Most notably, I think the Surgeon General's announcement in April really was a call to action, which I think specifically shines a light on pharmacy-based naloxone.

Along with federal leadership, at the state level, there's been really innovative regulatory and legal -- a movement essentially to make naloxone more available in pharmacies. State laws

nationwide have drastically increased patients' ease of access to naloxone through pharmacies. The great majority of states now allow naloxone to be distributed without a prescription via standing orders under collaborative practice agreements or pharmacist prescribing authority.

People not at risk themselves for overdose have access to naloxone via third-party distribution in many states. There's immunity of pharmacists from liability for furnishing naloxone in many states. In some states, there's actually mandated insurance coverage so that insurance companies cover it.

There's a great resource here. PDAPS.org, which really tracks naloxone-related loss. However, despite all of that, there has been slow adoption at the pharmacy. There are three studies. In Indiana, two and a half years after the rollout of pharmacy-based naloxone, only 58 percent of pharmacies stocked naloxone and 50 percent of pharmacists who were surveyed were not comfortable dispensing naloxone specifically to people who

injected opioids.

In New York, three years after opening up of access there, the New York Times did a survey of New York City pharmacies, and only 37.5 percent of the pharmacies stocked naloxone and/or were willing to dispense it.

California, two years after its liberalizing of naloxone, making it more available in retail pharmacies, 24 percent of the pharmacies surveyed dispense naloxone without a prescription. Fifty percent were stocking it and 60 percent were willing to bill insurance for naloxone. So there are gaps there despite the movement, the legal and regulatory movement.

Just looking at my own state, Massachusetts, this is a study done by my colleague, Tom Stopka. In 2015, 97 percent of Massachusetts pharmacies were selling syringes at that time, but only 45 percent were selling naloxone.

This is a qualitative study that I think gets at the conundrum that pharmacists and people who go to pharmacies face that was led by my

colleague Traci Green, which you'll hear from tomorrow. These are perspectives of people with chronic pain, substance use disorder, caregivers, and pharmacists in Massachusetts and Rhode Island.

There's fear about consequences from obtaining pharmacy naloxone from patients. I think that if you go to the pharmacists and bring it up that you are interested in getting Narcan, automatically red flags go up in that pharmacist's mind. Why do you want Narcan? Do you think you're going to overdose? Then all of a sudden, there you are, the criminal again.

Some pharmacists are concerned about offending patients. I think for me, it might ruin a relationship even knowing the background of somebody. But you don't want to step over those boundaries, where you would ruin a relationship. Then they will go and talk to their friends, "Oh, she thinks I'm an addict."

So you basically have this hesitancy on both sides, on the provider side and on the patient side, of offending the other person by talking

about overdose and talking about naloxone.

There is some good news. One of my favorite quotes from this study was, "You can take the stigma away by making it as common as, do you want fries with that?"

Others have had good experiences. "He asked me if I knew how to use it, and I said, yeah, and that was it. So I mean I think it should be that easy because there are some people who will give you a hard time, you know."

This concept out of opt-out offering of naloxone was considered a promising strategy by both patients and providers. If it was up to me, every single opiate prescription that was being filled would also be dispensed with Narcan. If the patients aren't using them or their families aren't using, it would help, I think, to overcome and reduce the stigma that Narcan is only for heroin.

Some opportunities, as I think has already been mentioned or I pointed out, naloxone has been available through community-based programs really sparsely throughout the U.S., like concentrated in

some areas but really needed in far more areas through harm reduction programs. Just in 2013, which was really way before the opening up of pharmacy access of naloxone, there were over 130,000 doses that were documented distributed in a study in MMWR. In 2017 alone, through our community-based distribution system, so outside the pharmacy in Massachusetts, we distributed over 60,000 doses.

Dr. Jones' study, which I put up the main graphic here, shows this increase in naloxone distribution through pharmacies where you see that they're finally starting to be a player in this. And we saw even more recent data I think in one of the earlier presentations that shows substantial increases in 2016, 2017, and 2018. So we're now really seeing exponential growth in distribution of naloxone through pharmacies.

Some of those states, I think, that were relatively early adopters, we're starting to see increases in uptake. In Texas, there was a project that looked and showed that 69 percent of the

pharmacies were stocking and willing to dispense standing order naloxone; 80 percent were willing to dispense to a third party; and 50 percent were willing to bill insurance for third party. I think that's progress.

In Massachusetts, we recently worked on a study that did a random buying of naloxone in 20 selected pharmacies in the state, and there were 79 percent of the pharmacies where there was a successful purchase. So I think there's progress in the right direction.

This has been a vision, because pharmacies are the healthcare locations that are most widely distributed in communities, that there's a lot of promise for lots of different populations.

Here's a study that was just published this year from North Dakota, where a pilot was done where they implemented an opt-out pilot, meaning do you want fries with that situation. In three North Dakota retail pharmacies where the pharmacists had prescribing authority, 16 percent of patients with a morphine mL equivalent dose of greater than 50

were offered naloxone in this one-month pilot. It took 5 to 10 minutes of the pharmacist's time per prescription. The co-pay was typically less than $10.

They found that training for the pharmacists and the technicians could improve intake; and one of the needs identified was having at the pharmacy an automatic morphine mL equivalent calculator that could facilitate eligibility determination.

There are lots of ways that pharmacies could be involved, including the traditional, where you go in as a consumer, you purchase it, and you walk out. Others include the prescriber writing a prescription. We have seen these partnerships develop between pharmacies and addiction treatment facilities, or social service organizations, or even harm reduction agencies, where the pharmacy can procure the naloxone on behalf of those and ideally be able to bill insurance. So there's limited cost out of pocket to the patient.

There's been the development of publicly-funded, through SAMHSA and AHRQ, resources

to educate providers, pharmacists, and patients. Here are two websites that provide lots of resources that are able to support distribution of naloxone through pharmacies.

Here are examples of some public service posters that have been developed at the prevent-protect.org website to promote naloxone distribution in pharmacies.

One issue I just wanted to mention is that pharmacies are now venues where overdoses happen. Pharmacies generally have bathrooms. There's people that are at high risk that go there. This is one of the resources that has been developed at one of those sites. It turns out also, pharmacists are trained in CPR and they, themselves, are important people to train on how to respond to overdoses.

I really appreciate having this opportunity, and I look forward to any comments or questions. Thank you.

DR. BROWN: Thank you.

Our next speaker is Dr. Phillip Coffin,

director of Substance Use Research, San Francisco, Department of Public Health.

Guest Speaker Presentation - Phillip Coffin

DR. COFFIN: Good morning, or afternoon. I have been tasked with talking about co-prescribing from clinics, and I've opted to largely focus on work that we conducted in San Francisco. As I understand, there are several different speakers on this topic.

The major study, which has been referred to and which I believe, to my knowledge, is the only study of co-prescribing that has any sort of outcome or outcome-ish data, was called the Naloxone for Opioid Safety Evaluation.

This was a NIDA-funded R21 that we conducted from 2013 to 2015 in San Francisco among safety net clinics at the San Francisco Department of Public Health. These are clinics that only accept publicly-insured patients, either Medicare or Medi-Cal, or uninsured patients, or Healthy SF patients.

These clinics, as you'll see in some of the

data, there's a lot of substance use disorders among patients, many patients in the clinics. What we did in this setting, we went around to each clinic and trained them in how to prescribe naloxone. Our recommendation was that you offer it to anyone who's prescribed an opioid. That was sort of the universal precautions-type approach that's being talked about.

We supported the staff. We presented at various staff meetings and things like that. We had a clinic champion at the clinics who would set up the things on how to prescribe it. At that point in time, what we were recommending prescribing was that off-label jerry-rigged nasal device that has been discussed before.

Thus, we had to have atomizers in the clinic that were given to patients, along with patient information sheets because the pharmacies, when dispensing that product, didn't have any patient information to go with it. So it was a very complicated way of prescribing naloxone from a clinic setting.

We also assisted with pharmacies because each time a pharmacy would receive such a prescription, they wouldn't know what to do with it, and the prescriber would get a message, or a call, or a message back that they couldn't do it. Then they would contact us, and we would contact the pharmacy. So over the course of this project, we got about 60 or 70 pharmacies around the city dispensing naloxone in this manner.

In terms of our data analysis, we did a chart abstraction of about 3,000 patients that ended up about 2,000 that were eligible for this, Patients were on long-term opioid therapy. We did interviews with patients, and we did surveys of providers along with a few other things.

This is an example of the type of a brochure that we provided to patients. This is one side of it. The other side had more information about naloxone.

Going through some of the data -- you've already some of these data, so I'll try not to just present the same stuff you have already heard.

I'll try to add to it a little bit. We are about 2,000 patients. This is your basic demographics. As you can see, if you look down towards the bottom, there's a lot of emergency department visits in this population. There are some patients in this two-year period who maybe had 2 [00], 3 [00], 400 emergency department visits.

The opioid-related number of visits, opioid-related was defined a little bit broadly. It was people who were in the emergency department for a reason that the attending physician in the emergency department determined to be due to either a side effect of opioids or seeking opioids. There were not too many opioid over-sedation visits, which is a slightly broader definition of an opioid overdose visit. We had 59 deaths during this study period, and 5 were from opioid poisoning, so we were not powered to detect any mortality benefit.

As I mentioned before, this was a high-risk population. Many of them were on quite a few opioids. Almost 10 percent were on over 400 morphine milligram equivalents. And the

highest dose was 4.2 grams of morphine equivalent opioids. We excluded methadone and buprenorphine from this analysis -- excluded methadone and buprenorphine that were prescribed for agonist maintenance treatment. If they were prescribed for pain, then we included them.

As was mentioned before, younger people tended to be prescribed naloxone more, the higher-dosed people and people who had an opioid-related ED visit in the 12 months prior to the initiation of the program. So even though we recommended it for everybody, prescribers, in general, were self-selecting patients that may be were at higher risk.

In terms of the outcome data -- and again, I think this is the only sort of health-related outcome data that we have for co-prescribing specifically. You'll forgive me. I'm not a biostatistician, and this was an extremely complex analysis. However, it was a Poisson or regression analysis that controlled for our demographics, morphine equivalent dosing, an ED visit for

opioid-related reasons in the preceding 12 months prior to the study, secular trends with a cubic spline, and lots of other fancy things.

What we found in this was that people who got naloxone had fewer opioid-related ED visits relative to people who didn't get naloxone over the course of the study in the follow-up period.

Again, this is in a population that has ED visits that are opioid-related at a rate of 7 per 1000 person years, so it's a pretty high rate of people coming to the ED for opioid-related reasons. And in that context, our number needed to treat would have been 29 patients to 1 opioid-related emergency department visit in the following year.

In trying to explain these data, I look at Alex Walley's paper from Massachusetts, which is really the best data on outcomes from naloxone distribution, which is where almost all of our data on naloxone are. They're from the distribution programs, not from co-prescribing programs.

The data from the distribution programs show a reduced rate of opioid overdose mortality in

communities that distributed naloxone compared to communities that didn't. In those data, they didn't see any difference in emergency department visits. Now, this is a population level dataset, so it might just be you don't see a difference in emergency department visits because you're keeping alive more high-risk people, so you end up kind of equalizing your emergency department visits; you don't really know.

In trying to figure out why we saw this reduction in opioid-related emergency department visits, a previous speaker this morning cited reasons that I also usually cite, which is possibly this provision of naloxone and the ensuing discussion with the provider because the --

As I'll show in a little bit, in a moment, there was a lot of really great discussions with providers that came with these naloxone prescriptions. It was a good way at the time to introduce the idea of opioid stewardship in a non-antagonistic way with patients. A lot of providers came to us and said that it really made

it easier to talk about opioid risks when they started it with offering naloxone because that wasn't about taking away their opioids; it was about making their medications safer.

We did interviews with patients who were offered naloxone, 60 interviews, 10 patients at each clinic. Our demographics were strikingly similar to the overall population. And as was mentioned before, a lot of them had witnessed an overdose. Only 10 percent had previously gotten take-home naloxone from our distribution program in the city.

Thirty-seven percent had a history of an overdose or a bad reaction, and this was actually a fascinating finding because only 20 percent said they had ever had an overdose. When we asked them if they had had any other bad reaction, an additional 17 percent reported a bad reaction, which they described as having fallen asleep, stopped breathing, or couldn't be woken up without assistance.

So it was something we considered an

overdose, but they didn't call it an overdose because they were taking their medications. As was mentioned, they had a low perceived risk of overdose. In general, they wanted naloxone in the future, almost all of them, and felt that it should be available.

These data were also presented on this page. A couple of patients felt that the prescription was unnecessary, or they felt judged by their provider, or they felt scared. In the course of this project, we pretty quickly realized that some patients could feel really offended by the presentation of this, and some providers were reluctant to offer it to patients because they didn't want to offend them.

So some of our recommendations were to -- this is part of the reason we used the universal precautions-type approach, was because if we risk scored patients by their overdose risk and then offer them naloxone, we felt that providers might be reluctant to prescribe them an opioid that they may actually legitimately truly need, and

naloxone at the same time; felt that that might raise medical, legal concerns for providers.

We wanted to take away that risk evaluation piece of it and just make it universal. We also wanted providers to be able to honestly say we're offering this to everybody who is prescribed opioids. We also felt that opioids in somebody's house was a risk, not just to them but potentially to other people who come in contact with those opioids, sort of the risky drugs, not risky patients model.

When we did that -- which started a little bit into the program when we really kind of started advising providers on how to approach patients with one of those approaches being, I'm not so concerned about you; you have been doing fine on your medications for a long time, but you got a lot of opioids in the house, and I know you have a grandkid, and somebody can accidentally get into these. I just want to make sure there's naloxone with your medications.

This is not my research. This is out of New

York. In the studies of naloxone, we haven't found any concerns about compensatory risk behavior for people who get naloxone. So I don't think there are really any particular risks in that domain. The other risk, which was mentioned earlier by a panelist, was the concern that a patient, for example, on hospice getting opioids might be administered naloxone by a family member that is worried.

I used to worry about that happening, and then I started speaking with hospice providers about it and learned that hospice providers have been giving their the patient's families naloxone for 20 years. That's already been well established. I don't know if they have had adverse reactions in that setting.

PCPs really accepted the program. They liked it. Almost all of them prescribed naloxone and wanted to do it in the future. A fair number felt that they might prescribe less opioids in the context of offering naloxone, but most felt that it wouldn't affect their prescribing. Frankly, to sum

up all these risks, these concerns that they note, the major concern was that it was a pain to prescribe that jerry-rigged nasal device.

One of the providers said, "I expected the decrease in deaths from overdose. I hadn't thought about how the act of prescribing has opened other important conversations." Another said, "The conversation about naloxone has changed the dynamic between discussions of harms and benefits."

We also did a systematic review of naloxone co-prescribing. We looked at 17 papers. The interest in prescribing naloxone obviously increased over time, not a surprise there. Most studies did implement universal prescribing, and they provided patients with take-home materials from clinics. Most of these were done earlier with the earlier devices.

This is my image of Dan Bigg because we should all have one. This was another study we did out of San Francisco. This was actually looking at the distribution program. The distribution program doesn't just provide naloxone to people who use

drugs, but also to family, and friends, et cetera, and a lot of other communities.

In that program, we were able to link initial fills of naloxone with refills of naloxone, and we found that the people who are most likely to use their naloxone to reverse an overdose were people who used heroin, people who used methamphetamine, and people who had previously witnessed an overdose.

This is to say if our resources are limited, it is really clear and obvious that our priorities should be on distributing naloxone. Most of the people who get naloxone through a distribution program; many of them are not accessing the healthcare system in a way that many other people do.

Getting people free or extremely low cost, essentially being able to hand out for free naloxone from distribution programs is the most important, and most powerful, and most well-studied avenue of intervention in this domain.

Another area which I think we really need to

focus on and hasn't been addressed sufficiently is the fact that, unfortunately, we have a problem in opioid use disorder treatment, which is the mortality, particularly at the end of any treatment program, any treatment program, but more so treatment programs that are not based on medications.

While it would be wonderful to improve these treatment programs so that it didn't lead to increases in mortality, I think a critical short-term way to ameliorate this problem is by ensuring that people have naloxone whenever they leave a treatment program.

In summary, this is a feasible, acceptable intervention even with crazy, complicated devices. The term "overdose" is problematic. We've searched for a new term and haven't been able to find one. This has been a problematic term since Edward Becker did papers in 1972 on the topic. We have not been able to fix that.

Naloxone co-prescribing might positively influence opioid use behaviors, patient-provider

relationships, and the frequency of opioid-related ED visits. And I say "might" because this was not a randomized trial. This is not DSaRM FDA approval data. The low threshold distribution models totally remain the most powerful way to expand access, and that's what most of the data are based on.

I will also note my cost-effectiveness paper from 2013 was mentioned, and that paper, again, was based on the distribution model of providing naloxone to people who use drugs and not on the co-prescribing model.

My estimate of the cost-effectiveness for the co-prescribing model, it would be a substantially lower cost of naloxone because the impact of naloxone in people who are at lower risk for overdose is going to be less substantial. The use of it, to reverse an overdose, is going to be less common in that scenario. Thank you.

Clarifying Questions

DR. BROWN: Thank you, Dr. Coffin, and thank you to all the speakers.

Are there any clarifying questions for any of the speakers by members of the panel?

Dr. Bateman?

DR. BATEMAN: Thank you. This question is for Dr. Coffin.

I'm interested in your data showing, really, a rather dramatic decrease in the risk of opioid-related emergency department visits after the implementation of naloxone. The way we sort of expect this medication to be used is people have an overdose, someone is around them, they reverse them, and then they call 911.

Your data would almost suggest that people are having overdoses in the community, getting reversed, and never showing up in an emergency department. I'm just wondering if you can comment on that. Did you hear stories like that, and what is your interpretation?

DR. COFFIN: We did not hear stories like that. The number of emergency department visits for overdose or opioid over-sedation was not high in the study to begin with. The vast majority of

overdoses that occur in San Francisco, and in most communities, frankly, the majority of them don't reach medical attention to begin with.

I would imagine that patients who are prescribed opioids would be more likely to get medical attention in the event of an overdose than somebody who is using heroin or street opioids.

I don't think this was directly related to overdose events. I think the findings that we saw, which included all opioid-related emergency department visits, if they're real -- and again, this is not randomized trial data, so I don't know if they're real. But if they are real, I suspect they're related to the way people are using opioids and the way they're addressing their opioid use.

Perhaps it led some people to go to the ED less to request more opioid medications. Perhaps it led people to watch their opioid use more carefully and have fewer falls. I'm not sure. I don't really know.

DR. BATEMAN: So that would almost suggest that maybe the counseling is more important than

the medication.

DR. COFFIN: In that scenario, I think so. I think the interaction with their provider and the discussion around opioid safety was powerful, and I do believe that providing naloxone enhanced that interaction substantially.

DR. BROWN: Dr. McCann?

DR. McCANN: Mary Ellen McCann. This is for Dr. Walley. My question is about online pharmacies. Are any of them dispensing these Narcan products and do you have any data about that?

DR. WALLEY: No, but I think that is an important idea to think about. I didn't mention, but it was on one of my slides, mobile pharmacy. In Massachusetts, we're trying to allow for pharmacists to go to, say, community meetings. We found that the demand for naloxone at community meetings has really taxed our state-funded program. Because we're a universal healthcare state, we could have a mobile pharmacy out of, say, for example, a community meeting and have a pharmacist

distributing naloxone, billing people's insurance there.

We have done that on a handful of occasions. I think that's a promising model. The logistics of setting that up have been more complicated than we expected.

Then this idea of a mobile online distribution is interesting. In Massachusetts, the definition of a prescription requires a face-to-face interaction between a provider and a patient. We have gotten around that with naloxone, but we haven't extended it to try and do online pharmacy yet.

I see all over the billboards for erectile dysfunction medications being able to be distributed through online pharmacies now, so every time I walk by one, I'm like, we should do that for naloxone.

DR. McCANN: Thank you.

DR. BROWN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: It was the same question. Thank you.

DR. BROWN: Dr. Krebs?

DR. KREBS: This is a question for Dr. Coffin, but others can comment as well and if they have an answer. You mentioned you tried to find another term other than overdose that works better. I think this is really important because we aren't really talking about distinct populations here. We're talking about a drug-using population for whom overdose makes a lot of sense as a familiar concept. And we've applied that word to users of prescription medications, but that's not a term we normally use, so it implies misuse for many patients.

I'm curious about what other terms you have tried, bad reaction, poisoning, toxicity. Have you tried those and found they're not satisfactory?

DR. COFFIN: Yes. Poisoning or toxicity are not patient-level words, really. The term "overdose," I think you're right. And it's not only problematic for patients, it's problematic for a lot of providers. Providers, also, when they hear overdose, they assume the person is using

heroin or took their whole bottle of pills as opposed to had an accidental opioid-induced or over-sedation event basically, or respiratory suppression event.

The term that we tend to use clinically is "bad reaction" especially for a bad reaction where you stop breathing or can't be woken up without help. It's similar to the reaction that we use in some research studies, or the definition we use in some research studies. But I haven't found that magical word that can totally replace overdose.

DR. BROWN: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. My question is for Dr. Walley. You had presented data, and I believe it was North Dakota, that it would take about 5 to 10 minutes of a pharmacist intervention for each co-prescription. Having worked prior in a retail pharmacy, if we implement co-prescribing on a large scale, this could be tremendously burdensome to a retail pharmacist who's already tasked with prior authorizations, counseling patients, filling prescriptions.

Do you have any suggestions how we can perhaps streamline this and make this less burdensome that we can implement it on a larger scale?

DR. WALLEY: Yes. I think that 5 to 10 minutes should be taken in context of a pilot study with 3 enthusiastic pharmacies. And these were actually independent pharmacies, which I don't think were under the same time pressure that the typical retail, say, for example, chain pharmacy is under.

There's substantial work being done right now in federally-funded studies with collaborations with retail pharmacists, looking at how to streamline that process. There's a lot of public education that's going on as well.

I don't think 5 to 10 minutes is what's needed. I think as we learn more, we're going to be able to get that down to a lot less than that, like any other medication transaction that occurs with the pharmacy.

It's not really that complicated when it

comes down to it. And it's really right in line with what pharmacists should be talking to patients about, if we're talking about a co-prescribing situation. So the pharmacist really should be talking to the patient about the risks of the primary opioid or the other sedating psychoactive medication, and then it's a natural discussion to talk about the role of naloxone after that.

So I think it fits in nicely to what pharmacists should be doing, but exactly what that script is, I think we'll be finding out soon, efficient ways to deliver that.

DR. BROWN: Dr. Ciccarone?

DR. CICCARONE: Question for Dr. Coffin. Thank you so much for your impressive body of work over the years on this topic. I'm curious more about the study on co-prescribing. The intent was for it to be universal, and yet, it was interpreted, if I heard you correctly, as targeted.

Walk me through the pros and cons, then, since one of the decisions here is going to be around co-prescribing universal versus targeted. I

think you're still on the side of universal. Can you justify that a little bit or correct me if I'm wrong?

DR. COFFIN: I'm not sure what side I'm on.

(Laughter.)

DR. COFFIN: Were I on the other side of this curtain, I would be seriously thinking about how to vote.

The intent was universal for the reasons that I described. The implementation, of course, was not, just as vaccinations, or mammographies, et cetera, like we intend them to be universal for the audience that they're intended for, however they're implemented at a much lower rate.

In general, historically, preventive interventions like this might be implemented to 15 percent of the population. We felt pretty good that we got it to about 38 percent of the population we had recommended.

Some of the people who got it when I looked at the dose that people were on, some of the people were people who are on low-dose codeine with

Tylenol, one pill a day. That would certainly, in my mind, probably be a low-risk population. And there were patients who were on a gram a day, who didn't get naloxone co-prescribed, which would have been definitely a population that I would have thought.

In my practice since that study, as was disclosed at the beginning, I do academic detailing of -- I train providers in academic detailing to go out and talk to other providers about opioid safety, opioid stewardship, and that does include naloxone.

Our guidance in that program for indications for naloxone, it evolves a little bit, but historically, it's been anyone who uses illicit opioids, who uses street opioids. Now, I would broaden that to anyone who uses street drugs of any kind, anyone who may witness an overdose, of course.

In terms of the people who are prescribed opioids, we decided to rely upon the CDC recommendations. I like that the CDC

recommendations included dose threshold because that dose threshold can be irrespective of the provider's perceived risk of the patient to overdose, and it can address the issue of having a bunch of opioids in the house.

Having some Tylenol, acetaminophen, and codeine in the house, probably the likelihood that your kid is going to accidentally overdose on that is pretty low. It's a pretty low-dose drug, but having hundreds of milligrams of morphine in the house all the time, the risk of that resulting in an accident or exposure to somebody else is pretty substantial. So I have relied upon the CDC recommendations in my work since that study.

DR. BROWN: Dr. Brand?

DR. BRAND: My question was for Dr. Walley. One of your slides, you listed that 50 percent of pharmacists didn't want to bill insurance for a third-party prescription. As a retail pharmacist, I'm thinking that if you bill their insurance for a prescription that ultimately is to be used on someone else, does that constitute insurance fraud,

or how do you get around that?

DR. WALLEY: Right. I'm just going to repeat that because I think that's a really important question and an issue when it comes to implementing third-party prescribing.

The issue is that when either through a standing order or a direct prescription, say, that I write or a prescription that goes to somebody under a standing order where I don't actually have a relationship with that person, if the naloxone is not to be used on them when they overdose, that's what we call third-party prescriptions.

There are laws in most states that allow for that. That's not typically permitted -- that's not recognized as a prescription, that type of mechanism, except for naloxone in a lot of states. So it is a legitimate prescription in most states, and it can be done. Then the issue is, what's the insurance's view on it?

This is a big area of concern. I'm confident that in Massachusetts, it's okay. It's not insurance fraud. We've gone to multiple

insurers to discuss this with them. Mass Health, which is our Medicaid program, is aware of it and has issued a guidance to pharmacists that has basically encouraged them to bill Mass Health in this situation. There aren't any suits that have been brought to challenge this as insurance fraud.

So that all being said, it would be great to get clarity from CMS, or the individual state insurance authorities, or the individual insurers themselves to recognize that this is in the public health interest, and it shouldn't be insurance fraud.

This is an advantage to the programs that don't go through insurance, through the public health programs, right, because in that case, there really is not question of this. But I think if we're going to respond to the public health crisis through this preventative measure, it needs to involve people who aren't they, themselves, at risk. And in order to do that, somebody is going to have to pay for it, and it's expensive per unit cost. So I think insurance is an important payer,

basically.

DR. BROWN: Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn Medicine. Two questions; I guess, either Dr. Coffin or Dr. Walley both can take it.

Is it likely or is there any evidence to suggest that co-prescription of naloxone is going to change the prescription patterns, prescription habits of clinicians in terms of opioid prescription? Will they get more comfortable in prescribing that?

The second question is, can it encourage more abuse from the patient's perspective, knowing that they're probably safer now to abuse them?

DR. COFFIN: The first question was -- sorry, could you repeat the first question?

DR. GOUDRA: The prescription patterns of the patients.

DR. COFFIN: Yes. In our study, we didn't find any impact on opioid prescribing for patients who got naloxone versus those who didn't in the analysis that we did for Annals of Internal

Medicine.

In our initial analysis of that, we did find a reduction in opioid-prescribing among those who got naloxone compared to those who didn't. However, that wasn't accepted by the Annals of Internal Medicine statistician.

I still have some concern about the final version that showed no impact. I'm not sure which one was right, so I don't know is the answer there.

Our interviews with providers suggested that about a quarter of providers would reduce their dose if they thought they had reduce their opioid-prescribing if they were prescribing naloxone, whereas about 7 percent thought they might increase their prescribing of opioids. But most felt that it wouldn't affect their prescribing of opioids.

Then in terms of encouraging or worsening somebody's opioid use behaviors, what's been demonstrated in the literature beginning with studies in 2004 and with a study that I mentioned in my slides, we now have several studies that show

no compensatory use or risks with naloxone prescribing. While it is conceivable, and I'm sure somebody out there has decided to use a ton of opioids because they have naloxone, I'd be shocked if that never, ever happened.

We don't hear about it in the distribution programs or the co-prescribing programs, and the rigorous data on the subject has suggested the opposite instead.

DR. BROWN: Dr. Dasgupta?

DR. DASGUPTA: A question for Captain Jones, please. The use of the opioid thresholds, 50 milligrams or 190, whatever number it is, seems to be like a consistent potential model for how co-prescribing might work with naloxone.

In the implementation of the CDC guidelines, on a national level, have you seen a level of comfortableness at the pharmacy or clinic level in calculating those MMEs, and how much uncertainty is there in that? Because if we make that as a gate into naloxone co-prescribing, I'm afraid that there's a lot of fluidity in how that number is

calculated to make that such an important gate.

CAPT JONES: I think this is a current topic of discussion. As part of the guideline process, CDC did issue a calculator, but it's for a subset of opioids, not for all possible opioids. And it probably, if you look at the IQVIA data, would account for the vast majority of prescriptions that are dispensed. So some of the lower utilization opioids, they did vet in the same way. And some of the MME conversion factors that have been used from CDC, and CMS, and others are based on Michael von Korff's original work, and some are extrapolated from what's in labels.

There's an issue of using MMEs for surveillance versus clinical care. I think we've tried to say on our broader list of MMEs, this is really a surveillance tool versus the more vetted smaller subset, which we feel went through the process of review as part of the guideline.

So I think it is really important, and there's lots of questions around how do you treat buprenorphine, how do you treat methadone given its

tricky pharmacokinetics.

I think from an FDA perspective, if it were to be a threshold that were put in place, I think more conversations would need to occur where consensus is out there that we agree that if we say 50 MMEs is the place to do it, that we all agree of what 50 MME is. I think that's really, really important.

Then figuring out, as new products come on the market, how do we account for that; how is that incorporated into these things; and do you have to convene a group to then come to consensus? So I think there are logistical issues that have to be worked out, but it's a really important question.

DR. BROWN: We had some questions from earlier this morning.

Dr. Krebs, did you have some questions or a question for our industry representatives?

DR. KREBS: Yes. I might as well come back to it, although I think I might have answered it to myself, but I'm not actually sure if I have made the right interpretation.

This is going to back to the assumptions behind the cost calculations, actually. This is for Mr. Kramer and the Emergent presentation, and it's looking at the states that are requiring co-prescribing.

My understanding is that these five states required physicians to prescribe naloxone with some threshold of higher risk opioids. Then it looks like 8 to 10 percent of patients meeting that threshold of higher-risk opioids filled the prescription. And other numbers we've seen have assumed something like 70 to 80 percent of patients who get a prescription fill it.

So my question is, the gap between 8 to 10 percent and 70 to 80 percent, is that the physician adherence to the requirement that they prescribe? Is it that 10 percent of patients prescribed Narcan fill it, or is it that 80 percent of patients who receive a prescription fill it, but most of these patients aren't actually getting a prescription? Does that make sense?

MR. KRAMER: It does. Again, this is

Bob Kramer with Emergent BioSolutions. I appreciate the opportunity to come back and clarify some things.

Our experience with these five states has been that the adoption rate, in terms of the number of prescriptions that ended up being converted, or adopted, and filled, is in that 8 to 10 percent range. And I think it is a significant difference between what the other model shows or assumes, which is a 70 percent conversion or adoption model. That was the one difference.

The other, as I was starting to say, is really on price and the inflation factor for naloxone products that we have assumed versus perhaps was in the model.

Just to be really clear, and I can only speak for our product, Narcan, it's been on the market for three years. We have never had a price increase. It's $37.50 per dose. That's what we sell it to the public interest market. I think this is a real contrast that the committee should weigh in terms of what is a theoretical behavior of

pricing versus what's actually occurred. We have had no price increases for three years. We have no plans to increase prices.

Just as a business model, Emergent, we have been in this space dealing with public health threats. And as one of your committee members, Mr. Gerhard commented, we've sold tens, if not hundreds of millions of doses, of vaccines and therapeutic products over the last 20 years, and we have never experienced that kind of pricing behavior on our products.

The pricing behavior is typically in a consumer price index type of range of maybe a 3 or a 4 percent per year price increase, not the 2,300 and something percent price increase that was included in the model.

DR. HERTZ: Hi. This is Sharon Hertz. So am I hearing you say that unlike others in the industry, you are committing not to increase the price of your product over some time period?

MR. KRAMER: Again, this is Bob Kramer. What I'm saying is that we have not increased the

price for Narcan for three years and have no plans to do so.

DR. HERTZ: For how long?

MR. KRAMER: As a company, our approach to pricing products, whether it's a vaccine, or a therapeutic, or in this case, naloxone device, is to make sure that we and our customers agree on a long-term price so that as an industry, we can make the necessary investments in research, and development, and capacity expansion to be the reliable partner to governments to provide these medical countermeasures.

DR. HERTZ: So how long will you maintain the current price?

MR. KRAMER: I'm not going to commit today that we will never increase the price. All I'm telling you is that for 20 years of history for Emergent, we have never increased prices to the magnitude that was described in that model. At best, it's been the long consumer price index, measures of 3 to 4 percent per year.

DR. BROWN: Dr. Zacharoff?

DR. KREBS: I just wanted to make sure I understood. It was 10 percent of patients who received a prescription actually filled it. Do you know how many of these patients received a prescription, or you only know the fill?

MR. KRAMER: I believe we only know the fill or the conversion.

DR. KREBS: So the adherence gap could be on the prescriber side or on the patient side; we're not sure?

MR. KRAMER: It could be.

DR. KREBBS: Okay. Thank you.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. I have two questions for Dr. Mariano, one with respect to your presentation, slide number 13, where you talked about the fact that between the period of 2011 and 2013, you quoted a study that showed 587 deaths.

If I understood that slide correctly, 79 percent of the deaths were not witnessed, which seems to me to mean that if there was nobody there

witnessing the arrest, that there might have been a situation where there was no opportunity to give naloxone.

The other thing that this slide said -- you had the slide a second ago, slide 13 -- 72 percent of these patients, I'm presuming these are all patients, not people using opioids illicitly, were co-prescribed benzodiazepines, and then 88 percent of them were co-prescribed other CNS depressants.

My take-home message seemed to be that one way to radically improve safety -- I mean we can't guarantee there's going to be a witness, so we can leave that 79 percent of unwitnessed deaths alone for a minute. But one really important message that I took away from this slide was that co-prescribing benzodiazepines and other CNS depressants is really dangerous if you're prescribing opioids.

I wanted to know what your thoughts are with respect to the idea that we co-prescribe naloxone when in actuality, it's the co-prescribing of other medications that's creating the high-risk

situation.

DR. MARIANO: Speaking personally, as someone who's been a pain physician for over 20 years in this space, we know, based on all the data that we have had for years, that when you added benzodiazepines and opioids together, you get like a five-fold increase in risk of a death related to co-prescribing those two together versus having opioids alone. The CDC dataset stated that for years.

There is definitely issues when you're looking at adding respiratory depressant medications together, including your CNS depressants, and alcohol, and everything else with opioid medications.

When we look at adding naloxone to the mix when we're prescribing opioids, is it the naloxone itself that's going to help with the reversal? Combined together is enough to push them over the edge. If we can reverse one of the true attributes of causing that respiratory-depressant event to possibly bring them back from the brink of apnea,

by reversing the opioid component, that might be enough to reverse them.

The other factor is by prescribing naloxone, what some of the studies have shown is it has reduced the amount of polysubstance use just by having the dialogues, just having the education, and having the discussions with patients.

I'm not saying they're going to say that using naloxone or something like that is going to change an overdose related to a benzodiazepine because it's not. I think it's hoping that we're going to start looking at better education, a better look at how we're utilizing opioids with other substances, and how naloxone fits into that whole package of making the patient more -- a safer environment in general.

If that even helps having the discussions and having the talks about polysubstance use, and maybe reducing that, or saying, hey, you know, we can't continue going down this road, I'm going to prescribe you naloxone; however, we have to address X, Y, and Z on top of it because these are risks,

I'm hoping it helps.

DR. ZACHAROFF: Thank you. One more quick question. On slide 21 of your slides, the last bullet says community benefits, that patients when surveyed, even though it's a small group of patients, their positive reactions included those three things. The last one was community benefits. And I'm wondering what community benefits is referring to.

DR. MARIANO: Dr. Coffin could probably actually chime in better than I can for this since this was his study. But what I took from the article when I read it -- and it was an excellent article by the way -- I took the community benefits, again, the education, the understanding of it, recognizing opioid overdose, maybe being able to use it in the community if you do recognize it because a lot of these people do have friends who are utilizing medications. It was those types of factors.

Dr. Coffin, I know I'm not trying to throw this on you, but would you agree or disagree?

DR. COFFIN: Yes.. Basically, people said that having naloxone, they could use it in their community. Most of these people lived in communities with high rates of substance use.

DR. ZACHAROFF: So we're talking about people actually having it for the sake of carrying it around with them or having it available to administer to someone in the community in the event that there was a need for it?

DR. COFFIN: That was one of the positive reactions to being offered naloxone in clinic, yes.

DR. ZACHAROFF: Okay. Thank you very much.

DR. BROWN: Dr. Ciccarone? Dr. McCann?

DR. McCANN: Hi. This is for Dr. Kramer. Dr. McCann. My questions is on slide 8.

My question is, if you can trust the internet, I looked up the mortality rate from opioid deaths in Virginia in 2016, before the co-prescribing was instituted, and it was 1130 deaths. Then another Googled article said that the death rate actually went up 30 percent in 2017, probably fueled by fentanyl on the street rather

than prescriptions.

You earlier said that it was too early to determine whether co-prescribing actually decreased opioid deaths. Do you have a time frame of when it would actually be measurable?

MR. KRAMER: Again, this is Bob Kramer with Emergent. I'm not aware of a widely accepted time frame, but on your earlier point, I think the study time for when that data was collected and when the program was implemented in that particular state was a little bit later, perhaps second quarter of 2017. So there may be a little bit of a disconnect between those sets of data that you were referring to.

DR. McCANN: Thank you.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. I just wanted to make one comment when we think about what the total anticipated demand would be, to be careful to consider this kind of lack of compliance or whether the fill rate is 10 percent or whether it's 70 percent, because if it were after some

implementation, 10 percent, we would have to have another meeting to figure out how we get it to 70, or 80, or 100 percent.

If we considered that a certain population at a certain level of risk should have the drug, and then only 10 percent would fill it, there's a problem there. However, obviously, finding what is the right level of risk population from a universal approach to some subset of that is a different question.

Then obviously, it's also the fill rate is not independent of the price. If you'd make it free, presumably, you'll get that rate up much higher. So I think we come back down to the issue that price is really the critical consideration of how we get some handle in the several orders of magnitudes, different, and whether there might be out-of-the-box approaches to deal with this differently than for regular prescription drugs.

DR. BROWN: If there are no other clarifying questions, we're going to now break for lunch. We're going to reconvene again in this room in one

hour, about 1:30.

Please take any personal belongings you may want with you at that time. Committee members, please remember there should be no discussion of the meeting during lunch, amongst yourselves, with the press or with any members of the audience.

(Whereupon, at 12:24 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

DR. BROWN: If we could come back to our agenda, we're going to proceed now with the presentation from our invited speaker, Dr. Elizabeth Oliva.

Speaker Presentation - Elizabeth Oliva

DR. OLIVA: Thanks for inviting us to present on some of the work we have been doing in the VA. We last spoke with you three years ago, and a lot has happened. I'm going to try and get through as much as I can. There are slides, though, and addendum slides as well, so lots of information.

I just want to acknowledge the many people in the village that really helped us get our program up and running. A lot of the people in the community are here to today, so we really are standing on the shoulders of giants. So I really appreciate all of my community partners and their continual support. I call them my brain trust.

There's been a lot of talk today about

naloxone distribution, and one of the things I do like to talk about and really emphasize -- and I think Phillip Coffin did get and touch upon this -- is there's really a tremendous amount and a tremendous opportunity in the opioid overdose educational piece, the OE part of OEND.

We can give out millions of naloxone prescriptions, but if people don't know how to recognize an overdose, they're not going to be able to use it, so that life-saving potential will not become realized. More importantly, we actually would prefer if people prevented these to begin with, so really, teaching patients who probably this might be the first time that a provider talks with them about the risk for overdose.

Regardless of which patient population you're talking about, patients with OUD, it may be the first time a person tells them about what their risk is and how they can mitigate that, including not using alone, being sure to cut your dose in half; really harm reduction that's been in place in communities, but bringing it into healthcare system

implementation.

Again, with patient-prescribed opioids, there's a lot we can do also because, again, they may have had opioids for years, decades, and they may not have recognized what are some of the things that can put them at risk of an overdose.

In our educational materials, we target two patient populations: patients with opioid use disorder and patient-prescribed opioids. And similar to previous speakers, we are expanding some of that to just patients with substances use disorders, given that a number of patients using some of these other drugs that may be laced with fentanyl are also at risk of overdose.

In terms of what VA has been doing broadly, naloxone and OEND is just one part of our broad strategy. We work very closely with partners across the system to really try to hit this from as many different ways as we can, given that we have a closed healthcare system where we can really work and work together to ensure these risk factors get addressed.

In 2014, we did establish a national program. People out there are in healthcare systems, and we did write up a paper that really talked about how we got that up and running. I'm always happy to talk with people as they're standing up their programs and pay it forward.

There's been a lot of support for this. We had an undersecretary for health information letter in 2014 that really helped set the stage. Even besides that -- and you'll see some of our original kits -- Pharmacy Benefits Management has just been an amazing supporter of this initiative and recognized very early on that we needed something like this.

Since the inception, PBM has been providing funding for naloxone to be dispensed to VA patients without the medical center incurring the cost of naloxone, and not only that, there's been recent legislation that has eliminated co-payments for patients getting naloxone, as well as getting education on naloxone. Really, there should be no barriers to this within the VA system.

We also have clinical guidance, our recommendations for issuing document that really talks about -- sorry, I meant to highlight in red the third sentence in our recommendations, which is offering naloxone rescue to veterans prescribed, or using opioids who are increased risk for opioid overdose, or whose provider deems, based on their clinical judgment, that the veteran has an indication for ready naloxone availability. We have basically empowered our providers to give it to anyone they think needs it.

Here's the evolution of the kits within VA. We had originally started with an intranasal kit, with the mucosal atomizer that have been described earlier, as well as the intramuscular naloxone kit. And as soon as formulations were available that were for laypersons, we switched those out. So we now carry the nasal spray, as well as the autoinjector.

There's a tremendous amount of technical assistance within VA. We have a SharePoint. We have videos that are available via YouTube. These

videos are also incorporated into our standardized training and note templates within the VA. We have an amazing academic detailing program, which I'll show you has evidence of really helping us get this program up and running. They offer a tremendous amount of one-on-one, face-to-face provider training. They've funded to make sure that all of our brochures are available within the clinic.

It's amazing that even just printing out a trifold brochure can be a barrier for people. We get those trifold brochures paid for and can be stocked and professionally printed in every clinic that requests them. They also fund DVDs that have these OEND videos on a DVD for patients as well to be stocked in the local clinics as well.

You will see we have a number of panel management tools that actually help people identify patients at risk for overdoes. I'll show what some of those look like. We have a lot of training that we have developed that is available actually externally as well.

Here's what the academic detailing OEND

SharePoint looks like. This is really modeled on like an Amazon style, one-stop shop for providers that goes over the provider materials, and it has patient materials. What you'll see -- I'm not sure if you'll be able to see from the back -- essentially, there's a thing that says order. People can use this as a way of ordering.

All of our patient ed is both in English and Spanish. So again, this is a one-stop shop. It has the links to the videos. It also has our data tools, our ways of identifying patients at risk of overdose. So these are all, again, one-click for anyone who's interested and has access to patient level data, and can access these reports.

Patient education is not complicated. I learned this very well from Eliza Wheeler when she first trained me on training people on OEND. We actually just have a trifold brochure, which goes over -- again, remember, there are three tenets: how to prevent, recognize, and respond to an overdose.

I'll show you both versions. This is the

one for patients with an opioid use disorder: choose before you use, this is the prevention information. The front part again, all about prevention; back part is how to recognize, and then how to respond to an overdose, so signs of an overdose and how to respond.

Same thing with our patient brochure for patient-prescribed opioids, you'll see that that education has to be a little bit tailored, given that they're prescribed opioids; so that prevention information, again, in the front and recognition and response on the back.

To date, we have given naloxone to a -- well, it's actually over -- I think it's over 160 today. I want to say the last time we spoke to you, about three and a half years ago, we were only at 5400. I want to just say given the tremendous amount we've grown in three and a half years, it really is a testament to how you can move a system and how you can get people onboard prescribing naloxone.

Here is what it looks like. We are

obviously still in the early stages of implementation when you think about an S-shape implementation curve. We are still growing. Thankfully, it's linear, so we're hoping to continue on. But you'll see the top left-hand side is patients with a naloxone fill; bottom left, number of prescribers. We are up to 17,000 prescribers, over 17,000 to date.

Top right, opioid plus benzos, this is what percent of patients, 26 percent, we've gotten to in the previous year; bottom right, percent of patients with OUD who have gotten a naloxone fill.

When people are implementing, I try to break it up into key implementation considerations: provider education, patient identification, then you educate the patient, and then it's really important to tie in post-overdose care.

As I mentioned, we have a tremendous amount of provider education. We have an in-person through academic detailing. We have web-based. We also have a national monthly call. We're probably about 2 to 4 facilities who will present on how

they're implementing OEND. So we have quite a number of examples, that I'm happy to share with the advisory committee if they're interested, of different ways in which people have gotten this up and running in their facilities. The big thing is to, again, address stigma and misperceptions, particularly around risk compensation, which could be a barrier.

As you can see academic detailing is a published paper that showed that providers who did get academic detailing had 7 times greater prescribing of naloxone compared to those who did not get academic detailing.

In terms of patient identification, this is one of our risk dashboards. I just want to mention that right here, it's not hyperlinked. But essentially, once you open up this report, it'll list your facility, and it'll have a hyperlink on that far right-hand column number, patients with no fill. So it will automatically list all the patients in your facility that have not had a fill.

What you'll see right now is that based on

RIOSORD, one of the predictive risk models, you can kind of see risk-based prescribing happening in general, that the patients with the highest risk class 8 or over, 54 percent of them have gotten naloxone. When you get down to 5 to 7, it's 43 percent, and then 22 percent.

Nationally, in terms of opioids plus benzos, we're about 32 percent total. I'll just, again, give you these examples. For patients with OUD, we're at 23 percent, and 35 percent of those with a possible overdose who have gotten naloxone. So again, these reports were meant to give people actionable list of patients that they can reach out to.

We have another tool. This is actually being mandated nationally for very high-risk patients to get an interdisciplinary team review. The VA stratification tool for opioid risk mitigation is based on a predictive risk model to identify patients at risk for overdose or suicide who are prescribed opioids.

What it does, it identifies patients as very

high, high, medium, or low risk. It lists why they're at risk. So it says "relevant diagnoses" right next to the risk, and it will tell you exactly what is placing them at risk. And then it has risk mitigation strategies, and naloxone you'll see is one of the risk mitigation strategies, and then it has care team and follow-up information.

We also have another tool -- we have many tools in VA, so the issue is more just making sure we're supporting people depending on what type of tool they use. This one is used typically in primary care. It's the Opioid Therapy Risk Report, and it will list when naloxone has been dispensed, and essentially it has also what the morphine equivalent has been in the past 12 months, as well as pain scores and such.

They have developed a really cool clinic huddle tool that can be used to show people's appointments that day, and it'll list any patients who you may want to consider naloxone for. This can be used, and it has like every surgery -- every clinic available on VA, they will be able to get a

list of patients and potentially ones that might need naloxone.

One of the things I want to really highlight is really try to move beyond -- this is MEDD and opioids to address the opioids crisis. There have been multiple risk models, predictive risk models, that have essentially said that comorbidities account for more risk compared to opioids across multiple risk models. don't have time to go into that. The slides are in the addendum slides, but I just want people to take a step back and think.

If you a have patient that has a medical condition, pain, overlapping mental health substance use disorder, and let's say they have opioids, you take those opioids away, you still have all these other things that put them at risk for an overdose or suicide. So maybe they're not going to overdose on those opioids, but maybe they'll overdose on one of the other medications you're prescribing.

The idea is to really think about taking a patient-centered approach that addresses

comorbidities for all patients regardless of MEDD threshold, or naloxone-prescribing, or opioids are no longer part of the patient's treatment plan because opioids, again, are maybe a third of the risk, a really small portion of the risk when you look at the overarching assessment of risk factors.

This is an example of why MEDD is not going to probably help from a population-based perspective. Eighty percent of patients who die of an overdose or suicide in VA were under 90 MEDD. And almost 4 out of every 5, again, who died, 80 percent, were under that 90 MEDD threshold. Almost 3 out of 4 of all deaths were among patients with mental health or substance use disorder.

I tell people, you don't need a fancy risk calculator. If you have a patient-prescribed opioids who has a mental health or substance use disorder condition, you should think about prescribing naloxone.

Here's what our store model looks like. Again, there was a question that was raised about opioids and benzos. I have in the addendum slides

something that might be of interest to the committee, that basically prescribing of other sedating pain meds, like SNRIs, TCAs, and anti-convulsants actually had greater risk when combined with opioids and benzos. You want to put that on your guys' radar as something to think about as well. But this will just show you just, again, medical, psychiatric, and other types of comorbidities that can impact risk.

We have a lot of patient education that has been happening. I'm happy to go into more, but really, the key issue is really increasing awareness and figuring out who you're reaching out to, and different ways to make sure they get educated.

There's post-overdose care. Again, there's some really concerning studies coming out suggesting that patients who have a non-fatal overdose are at really high risk of an overdose in the following year. So I think it's really important to improve care post-overdose, so we have a national standardized note template that walks

people through and that will basically generate a cover sheet reminder, if the treatment provider isn't the one completing it, that lets them know that there is a possible overdose.

I'm going to be wrapping up; I know I'm at time. Healthcare system considerations, this is just one tool in our clinical armamentarium. It's not a panacea and it's not just about naloxone. There are numerous ways in which you can get this up and running. When you're doing it from a healthcare system approach, coordinating across program offices is critical.

Again, patient identification, just generally patient-prescribed opioids, as well as those with opioid use disorder. But I think the one reason why we have been able to move as quickly is just really emphasizing to providers it's a few minutes of training that could save a life. It's not complicated, it's not rocket science, it's a trifold brochure, you can do this.

Clinical consideration is really making sure we integrate medication-assisted treatment. I talk

about life-saving naloxone and life-transforming medication-assisted treatment. I think that we can do more to really help link folks together. Again, post-overdose care is a critical juncture. Again, considering comorbidities and any history of opioid use, I think we are all onboard about patients with a history of past illicit use.

I think that the field is moving more towards thinking about patients who maybe have been using for a chronic period of time who may have risk factors, who even if they're no longer being prescribed opioids may still be at risk, and still need that, and still need pain management treatment. There's a lot more we can do in that space.

Some relevant considerations for the committee, patient refusal of naloxone, there are some addendum slides talking about how patients can be really bad at risk perception. It's really important for us, if we say, oh, would you like this? They'll probably say, no, I don't need it; even though there's one study that said that

basically, patients at super high risk, 70 percent of them thought they were below the average risk of an average American. So there's a lot more we can do.

Again, issues coming up, what about patients who live alone? I think we can still emphasize again that OE part of OEND and also, just again, strategies to decrease stigma. There's been a number of letter-based approaches. I think we really need to make sure we involve the provider and treatment team. We do not want to undermine that patient-provider relationship.

Again, that opt-in versus opt-out that was discussed earlier in terms of potential unintended consequences, we really need to think about that when we're developing these approaches. And I feel that whether or not you say that it isn't held against us, it still feels that way. So there are just a lot of things that we have learned that we are working on, kind of addressing within the VA.

We also have a Rapid naloxone initiative that just started in September where we're trying

to get VA police as well as AED cabinets equipped with naloxone, and there's some information about if folks are interested. I have a grant that actually just started December 1st that's going to be looking at probably what this committee would have liked, which is the effectiveness of a rescue medication and preventing opioid overdose mortality among veterans. That data might be in a year or two, but we are definitely going to be looking at that and looking at whether or not risk-based prescribing is impacting mortality. I also have a grant I just submitted to evaluate the new VHA Rapid Naloxone Initiative.

Sorry about going over time, but thank you for your time and attention.

DR. BROWN: Thank you very much.

We'll now continue with Dr. Joanna Katzman.

Guest Speaker Presentation - Joanna Katzman

DR. KATZMAN: Thank you so much. I'd like to thank the FDA for inviting me here. It's really an honor and a privilege. And I'd also like to thank some folks here that have really helped me

get excited about naloxone research, Dr. Fred Brason, Dr. Kim Wagner, and Dr. Peter Davidson who had helped me with some research along the way.

I'm from the University of New Mexico, and I recently stepped down from directing the University of Mexico Pain Center for six years, and now I'm the senior associate director of Project ECHO at the ECHO Institute. I started the ECHO pain and opioid management, ECHO, 10 years ago, and we now have 47 ECHO pain or ECHO opioid programs around the country, including the VA, the Department of Defense, and the Indian Health Service. I have a small grant with Adapt Pharma to survey programs across New Mexico, and as spoken earlier this morning, I haven't used any funds yet related to that.

I wanted to let you know that I'm going to be talking today about take-home naloxone and specifically about providing naloxone directly to the patient or client with or without a prescription, specifically for targeted populations at risk of opioid overdose.

New Mexico drug overdose rate is about 25.2 per 100,000. This was in 2016. As it still is higher than the U.S. national average of 19.8 per 100,000, as you can see, the curves are getting closer and closer together. In 2017, although not on this curve, the New Mexico rate has dropped even more to 24.7 per 100,000. The New Mexico rate, as you can tell, has fallen since 2014.

The improvement in New Mexico's ranking is also illustrated by these two side-by-side tables. On the left is the 2005 data with New Mexico ranking being number one in the country. On the right is the 2016 data with New Mexico being number 12 in the country. In 2017, New Mexico is not number 12 anymore; it's number 17, and we have dropped from 500 deaths to 385 deaths, down 4 percent.

I believe it's related to a number of things, most likely our naloxone distribution in the state, both community-prescribing and by targeted distribution to high-risk populations,

along with our concerted effort with mandated continuing medical education specific to pain, opioid overdose education, and naloxone prescribing to every clinician with prescriptive authority. Our rate in the state, as I mentioned, is 24.7 percent.

New Mexico has not seen the overdose deaths due to illicitly manufactured fentanyl. However, methamphetamine and benzodiazepines are frequently combined with opioid-related deaths in New Mexico. As a matter of fact, methamphetamine overdose in New Mexico are close to the top in the United States. We really are a state of breaking bad.

Although New Mexico continues to improve in U.S. rankings for drug overdose deaths and has no counties listed in the CDC 220, New Mexico continues to have the highest rates in the entire country for overdose, specifically Rio Arriba County and other counties as you can see staggered around the state. And I should mention that New Mexico is not new to the unintentional opioid overdose epidemic. As a matter of fact, New

Mexico, as previous slides have shown, since the 1990s and early 2000s, really is where the heroin epidemic first began in Northern New Mexico.

Now, naloxone distribution is also not new to New Mexico. It's really where most of the community prescribing and naloxone legislation really began. In 2001, we had early community dispensation distribution and legislation related to authority to administer. New Mexico was the first state to enact the Good Samaritan law.

In 2014, we had Medicaid coverage. In 2014, pharmacists had prescriptive authority, and most pharmacists in the state learned how to actually prescribe. In 2016, we had a naloxone standing order. And then in 2017, I helped work with legislators to enact the first of its kind, New Mexico House Bill 370, which mandates take-home naloxone for patients in all opioid treatment programs, inmates released with a diagnosis of opioid use disorder, and all law enforcement agencies.

Between 2014 and 2016, I was leading the

pain center at that time, and we wanted to study a universal precautions protocol for studying the effectiveness of giving naloxone as take-home to every patient who came in on an opioid analgesic no matter if we were prescribing the opioid or if they were getting an opioid from their primary care provider, but we were seeing them for chronic pain.

We realize that risk is fluid, so if they were on an opioid, no matter a small dose of Vicodin or a large dose of methadone, if they developed a respiratory illness, if they were using and we did not know it, we realize we wanted to see what would happen with their risk.

We also knew that we were taking care of their patients very effectively with controlled substance agreements, random pill counts, urine tox screen because our New Mexico Medical Board has a lot of rules and regulations. We also wanted to see if we could do this in a short amount of time with a streamline effect.

We enrolled 206 patients. Over two years, you can see our morphine equivalent dose. We had

one patient use the naloxone and no death was reported. We learned many things. We learned that the overdose education in naloxone distribution was very easy. We learned that we could use the take-home naloxone without disrupting the efficiencies in the clinic. And we learned that risk was fluid, and we could do this in our clinic with quite amount of ease with various providers. We then took this program to our addiction clinic.

What we did is we took this to our addiction clinic for patients with substance use disorder. Our addiction clinic has quite a high amount of female patients because we preferentially enrolled patients who are pregnant or just delivered a baby. Our study demographics, however, matched our opioid treatment program population.

We also found that even though we tried to get a companion present, most of the time, 90 percent of the time, the companion was not accompanying the patient when we were giving them overdose education in naloxone distribution.

We enrolled 244 patients at three months.

We retrospectively looked at these patients, and 15 of these 244 patients had received a prior naloxone prescription from our addiction clinic. When we asked these patients, none of them had gone to the pharmacy to pick up their naloxone prescription.

At six months, we had enrolled 287 patients. 251 patients had completed the 6-month follow-up of our study, which included every 3 months urine tox screens, questionnaires, follow-up visit questions, asking them had they used the naloxone, and if so, what was the context and so on.

Forty-four of the study patients had performed an overdose on a community member, on 65 patients in the community. As you can see, 35 study participants performed one overdose rescue; 9 study participants performed 2 overdose rescues; 2 study participants performed 3; and so on.

At six months, the results were such that 43 percent of the rescues involved 1 naloxone dose, 54 percent involved 2, and a small number involved more than 2, involved 3 because 911 was called or

in one of the instances, someone in the situation had a third dose.

911 was called 46 percent of the time, which is a usual in this opioid treatment program, and this is what we found in multiple cities around the country, is that 911 is usually called less 50 percent of the time. We also found that approximately 80 percent of the time, the person who was reversed was known to the reverser.

We also did a logistic regression analysis, and we wanted to know, of these 65 patients who were reversed, of the 65 patients who reversed other people in the community, who were they, what was special about these 65 patients out of the 251 patients who we enrolled?

Well, they were a younger population, between the ages of 18 to 44; they were Hispanic, but this did match population being studied. Significant odds were that they had witnessed a prior overdose before being enrolled into the study.

Odds 3 times were that they had been

reversed themselves before on naloxone. And interestingly, but not surprisingly, about 5 times the odds were that they two or more illicit medications in their tox screen and that many of them had missed a urine toxicology screening appointment.

At 12 months -- and this is unpublished but going to be published soon, and at one year, we have now enrolled over 402 study subjects; 332 study subjects completed the 12-month follow-up. This is prospective study. 79 out of the 332 reversed at least one community member. And we have had 115 reversals in the community.

If you go back to that original discussion point, that between 2016 and 2017, we have had 500 deaths in New Mexico, but in 2016 and in 2017, we dropped from 500 deaths to 385 deaths, dropping our ranking in New Mexico from number 12 in the country to number 17 in the country; we have 115 community reversals here. So I do think this shows some evidence that mandating naloxone in opioid treatment programs is making a difference or at

least a significant association.

Also, another interesting point here is that for whatever reason, and we have not written about this, enrolling patients or giving patients opioid overdose education and naloxone, and having them come back and talk to you about their naloxone, and did they reverse somebody in the community, and what was that like, we have an 83 percent retention rate at our opioid treatment program at the university. And now, we're going around the state and looking at all of our opioid treatment programs around New Mexico; 83 percent retention rate for opioid treatment program in on year is very high.

This is our 12-month follow-up. As I mentioned, 115 community overdose reversals, and I might mention not one patient in the opioid treatment program -- these were people in the community that. These were study subjects that reversed community members. No patient was reversed themselves. However, and this is a typo, study subjects came back. And that should be 85, not 8530. There were 85 study subjects that came

back requesting more kits. So there's a possibility that these are patients in the clinic, having been reversed by family members, requesting more naloxone.

It looks like 1 dose was given for 53 reversals, 2 doses were given for 60 reversals. It's about 50 percent needing 1 or 2 doses, and all were reversals were heroin related.

We're now looking at all the opioid treatment programs around New Mexico. We're surveying all the different people who work at the opioid treatment programs. There are barriers to writing prescriptions, providing take-home, and we're trying to figure out what are the barriers to providing take-home naloxone at opioid treatment programs.

It looks like it's affordability, it looks like it's time to educate patients, and it looks like it's patients not wanting to use it, and some of the directors at the opioid treatment programs are telling us that it's liability.

When they state that it's other barriers,

we're asking them why, and they're stating it's not their clinic policy, there's no naloxone dispense at the clinic. They're also stating that the staff are not educated on naloxone. And then we're also going to the clinics and providing the staff with opioid overdose education.

Finally, as you know, New Mexico, as I mentioned at the beginning, has a very, very significant harm reduction program and community education program. In the first six months of 2018, the New Mexico Department of Health dispensed over 2000 doses, 2060 doses to be exact. There were 845 reversals, so that's 41 percent of all naloxone doses dispensed used on an opioid reversal.

With this House Bill 370, with mandating naloxone at opioid treatment programs, with every inmate leaving jail who has an opioid use disorder, and as you know, that's a high-risk situation, and with policing, I think we're making a difference in New Mexico.

I think lessons learned in terms of

take-home naloxone so far is that it has been very successful in reversing community members if given to patients at opioid treatment programs, that targeted naloxone distributions through harm reduction programs, syringe exchange programs, and other keys sites critical for overdose education -- for overdose reversal, excuse me.

Correctional facilities are now providing take-home naloxone and opioid education. We do not have robust data readily available yet. And over 68 law enforcement agencies, including the Bureau of Indian Affairs, are abiding by this House Bill 370, but barriers still exist in mandating take-home naloxone to some of the opioid treatment programs throughout New Mexico. Thank you.

DR. BROWN: Thank you very much. We'll now continue with an invited speaker presentation from Dr. Daniel Wermeling.

Guest Speaker Presentation - Daniel Wermeling

DR. WERMELING: Good afternoon. I retired in March of this year, and one of the things I did was also have a mobile naloxone pharmacy on Friday

afternoons, and we still fulfilled full prescription requirements and had prescriptions filled. We did about 60 in 3 hours on Friday afternoons. What was important was that these are injection drug users, and we had 50 percent refill rates every week. So IDUs are really going to turn this over.

That's not why I have been asked to come today. Dr. Hertz wrote me a couple of times in the last six months to try to explain some of these things. First, I also started a company called AntiOp, and all of the assets, whether they were owned by me through the university or independently in the company, have been sold to other parties. I don't consult for any of the companies that are here or for anybody else.

I also have this in the context of a startup company in which there's no revenue, so keep that in context as we talk about cost. I have been involved with nasal spray development for 25 to 30 years, 11 INDs, and 1 NDA, which is for naloxone. So I'm not using anybody else's secrets

when I talk about this. It's meant to be a broad conceptual framework to think about how to do things in large buckets.

Now, we were partially successful. In 2009, I filed NHI grants and other things to get started on a naloxone nasal spray development. After about three or four years, I was able to partner with Indivior, and then we co-developed. It's the same Aptar mono-dose nasal spray as you have seen, but we had a lower naloxone concentration but the same total dose in a kit. We were using one sprayer per nostril instead of one sprayer per one naris.

Functionally, the only other change is that since I've done this for a long time, I knew that doing non-sterile products is cheaper than trying to make a sterile product. That's something else that's not well understood, is that these products are made under aseptic conditions to the same technical qualifications as an injection.

The second part is that when I first started this, there was only one machine in the country that could do 125-microliter -- think about that

volume -- 125 microliter fills at speed. You could do it at R&D scale but not at commercial speed. Then as I got farther along, another company did develop the equipment, but only one company actually had a pre-approval inspection for something that actually did reach the market.

We weren't successful with the NDA here, and the partner I had, Indivior, elected not to continue development, but they did make a commitment to France, so there was an authorization for temporary use until the NDA equivalent was filed. And in 2017, it was commercialized, and you'll see it's Nalscue, and basically, the cost there is on the internet, roughly 80 euros for a kit.

In trying to think about how to conceptualize this for the audience, I tried to put things in three big buckets. You have the research and development cost. And at least for me, as a nonrevenue company, that means it's somebody else's money, and there's a cost of money. And there's a time cost of money and a risk adjusted cost of

money. So that's an investment, and you're using a lot of contractors.

There's product manufacturing and distribution, and that tends to be the focus of a lot of discussions, like Lesley Stahl on CBS the other day saying naloxone costs 10 cents according to industry insiders. I can confirm that it's for the powder; it's not for the product.

Then you have the corporate institution itself. You have their own people who are involved with research and development, clinical development, nonclinical product development itself. And then you have to run a corporation. So these are all things that are running at one time. Product manufacturing and distribution is minuscule compared to the rest. So when we talk about cost, you have to include all costs. You don't get to just say, it's 10 cents.

Now, who's going to do this? Back in 2009 and '10, I remember Phil Skolnick saying to me at a meeting like this that there's not a business here. I said, "Yeah, I know, I kind of worry about that

because there's no understanding of what the market is in 2010," and there's no sense of volume or the standard of care. And so who's going to put money in this when there's no understanding of it at all?

Big companies aren't going to get involved with this because they don't know, and it's probably too small for them to even put capital in, versus startup and small and medium companies and generic companies, if somebody gets approved, they can come in. The difference, though, is that their marginal cost to do anything is higher than if you're a large company. They don't have scale. Think about that as a context also.

Large bucket, first cost to develop. Now, I don't know what Indivior's and my final cost were to do all of this -- that wasn't disclosed to me -- but I'm just going to use a round number. Let's say $25 million over five years. That may be a typical kind of 505(b)(2) development plan. And it's an at-risk investment. There's no guarantee for it, so those people have compensation expected for that at risk.

Now, to think about it here, when you look at $135 or $150 for a kit, think about the amortization of the cost into the per unit price. So you're just sort of doing some simple multiplication and division to try to see how much is allocated to any particular element of the buckets.

The other element is that this gets expensive the farther you go, and so it's an inverted pyramid. The early parts of this are relatively inexpensive, but to get through this and to prepare for launch, that's where things get expensive.

Then the FDA in previous meetings like this have explained what's required in the NDA, and so there's been excellent guidance for companies to do this. There's nonclinical summaries, clinical summaries for the active and whatever inactive ingredients you have, you have the pharmacokinetic studies, pediatrics, and human factors on can the product actually be activated properly.

Something else that's significant is the FDA

user fee. When I went online to explore what this was, and you can explain where you check your boxes are for where you are, it's about a 2 and a half million dollar expense, so that's not insignificant in and of itself. Then of course, you may be required to do other things post-approval.

Then you get to just the product itself. You're going to buy naloxone, which the cost is almost immaterial. You're going to choose a device. And as I said, I have worked with this Aptar mono device for 20, 25 years. It's the most elegant technology for nasal spray that I understand, but it's expensive.

When you do all of these things, you're doing a lot of chemistry work in the laboratory and making small scale production batches to try and understand if this is scalable or not. You have research and engineering and things that look like commercial scale batches for each one. Then you have compliance, quality assurance, and writing all of this up.

If you're looking like you're going to be

successful, then companies may take risks without the NDA approval letter and say we're going to make a batch and fully package it and have it ready for distribution. So now you may be investing significantly, at risk, waiting to see what the FDA says.

Now, when I go through big buckets of cost in this element, there are two things that I think are expensive that I question whether they're needed. One is that it's a sterile product. From my experience doing things that are preserved, antimicrobially preserved products are less expensive than doing sterile products.

The other thing, in 25 years, I have never seen nasal spray geometry be determinative of anything about systemic drug absorption. It's a testing technology looking for a use, and it's expensive.

Now, let's say, when we talk about production, you're going to make your first batch. This is your commercial batch; 250,000 units, the drug itself is nothing, but you're committing with

that decision perhaps 3 and a half million dollars for acquiring all the components, formulating the materials, and having aseptic production, so this is the clean room, bunny room kind of production, assembly and labeling. So this is all unique equipment that's met and designed just to handle this little device.

Then you have to commit for all of these batches you're doing chemistry test for years, so you're committing a million dollars for all the time points over two to three years. So it easily could be $50 [000] to $100,000 at time points for physical, chemical, microbiologic, and spray pattern physics. So you start multiplying numbers of batches times number of tests, and you can see this multiplies out to a big number really quickly.

Then you have retention samples. So your yield efficiency -- I just threw a number in. I'm not sure what anybody else's would be. But you have to take some units out for retention, and so they're no saleable units. So they're dedicated to QC testing for all these time points, stability

testing, and in case FDA wants any of them. So your effective yield is reduced.

Then you have to package it, so it goes into secondary, tertiary packaging, which you have all seen. Then you have to send it out. So you've got shipping, insurance, returns, rebates, and the wholesaler who takes perhaps 5 to 6 percent.

When you get to this scale with these kinds of dollars, it's not hard to see that the cost of goods is about 20 [dollars] to $30 per commercial package. And if you think about that in terms of what happens in retail, industry doesn't like to have cost of goods exceed 20 to 25 percent of transaction pricing, so this fits, to me, kind of a general trend.

Then it costs to distribute. It's not a free service. And for all the different vendors who provide materials or services, then they're in the chain, and they make a profit before you do. So you think about it as a value-added tax. It just keeps multiplying and goes up as you go along.

Finally, the final vendor then is the

pharmacy when they're ordering the drug and actually dispensing it. Other factors in here for distribution might be that it triggers a royalty payment, and that can easily be 5 to 10 percent of commercial sales for one of these products.

You still continue to pay FDA, so you have annual product strengths per year, and then you are committed to other kinds of things like medical information, you have to collect safety data, annual reports, lots of regulatory commitments as you go along.

Then of course, you have your company. Now, I learned from other failures that I've had to not own anything. My company owned three things: an iPad, a phone, and data, because that's all that FDA cares about is the data. So I learned not to own anything. But when you really get into at scale, you're going to own things, right? So you have buildings, and people, and insurance, IT systems, computing, your financial systems, all of these things, bankers, and cost of money.

If you're operating the company, then you

have all of these things and tons of attorneys. I must say, over the whole plan, I must have had ten different attorneys and spent hundreds of thousands of dollars a year just with that.

Circling back, do we have success? I think we could say from today's discussion that we're not where we want to be? One of the barriers has been described as cost. What we have, in my opinion, is a high cost/low volume environment, when actually, the business model has to flip if we're going to be successful. It has to go to a high volume/low cost type of model if we're going to succeed societally.

Are there ways that we can think about this? If you increase volume, I would differ a little bit with our economist earlier. There are different kinds of effects. There are multiple effects that take place at one time, and human behavior is hard to predict. But I threw out a thought experiment.

What if at the beginning of this in 2010, I said that another specification of the product, non-development, but just was to say, it can't cost at the transaction price more than $20? Then you

can start thinking about technologies that might fit that. And I had a really hard time trying to think about a technology that could go through all of this development process, have a corporation, and have a lower cost of goods for a product.

Yet, I still think about, I used this term, how do we make rain naloxone? We need to have this dropping from the skies. So I have a number of considerations that I hope may have some impact.

One is to do cheaper products. The cheapest thing I could think of, which is inelegant, it's nothing like an Aptar sprayer, but doing blow-fill-seal. There are multiple manufacturers all around the country. It's not technically hard. And you can get millions, and millions, and millions of these things without difficulty, yet it's a solution. Some companies actually have a nasal spray adapter on them, so you could get to something that's less expensive.

How many doses do you need? Who knows. You can extend shelf life, perhaps. We saw a 3-year shelf life with our product, but that's in

controlled circumstances. You don't know if it's been put in the window sill or if it's been in the trunk, all kinds of different ways that drugs can be treated.

Lastly, what would FDA accept? I mean, this is a step backwards, in a sense, of how they would look at things to use in an inelegant delivery system. On the other hand, you could say, we could put a half a mL of 20-milligram or 40-milligram per mL solution in there and deliver 20 milligrams to a patient. The efficiency I'm not as worried about. It's still going to get there.

FDA has some other things to help on the financial side of things. One is that there's called a priority review voucher. This is a way that for other kinds of diseases that FDA has provided incentives, also for rare pediatric things. If this is something that is really important to them, they could look at their own cost structure, about what it is that passes through to industry.

You could get rid of nasal spray geometry

because I think it's relatively worthless. You can improve preserve products, trim post-commitment studies, use nonsterile products, and eliminate the user fee of 2 and a half million dollars. These are significant dollars.

Three, so now you can look at OTC in development. I think we have heard that it can increase access, but it doesn't decrease cost. The cost is the cost. You're still including or encumbering, let's say, by the time you got FDA approval, $30 million in debt. Unless you had revenues, how do you pay for that? You had to get it from somebody.

It doesn't bend the cost curve necessarily except to take the pharmacy out of it; you're not doing wholesale distribution to a pharmacy, and a pharmacy having a dispensing fee. That's what's removed.

One of the consequences could be that you cut people off with insurance unless our rules change. So you could discuss whether cost is a real issue here or not.

Then lastly, I've heard about nonprofit. There are some companies who may get funding for development as a gift or a donation, but you still have these other operational costs. Somehow you have to pay for these things, and you have to generate enough sales and volume of units to generate a profit. Before you can forego one; you have to make one.

I would say so far, we haven't had enough volume, sales of naloxone-related products to generate big profits. In fact, I would guess we may not even have the cost covered yet.

The one that really strikes me, though, is sort of an economics 101 thing, and that is ability and willingness to pay. What we don't have is bulk purchasing. This is drip, by drip, by drip. So if you're going to do this drip, by drip, by drip, there is going to be a slow build-up of sales units, but we're using different kinds of terms to explain this. This discussion of 2 million units today, in my mind, is off by at least a factor of 10 and maybe 15. And we'll go through that.

What the companies need, they can commit if they have purchase orders. So somebody has to be able to step up and say, okay, we're going to buy, with this production schedule 10 million units. What would that price be if you were going to buy 10 million units? Would price go down? I bet you could bargain for a lower price if you were committing to that much.

Now, to commit to that much, I think about things in another way relative to distributional models, and that's for vaccines. We use a lot of catastrophic, healthcare, epidemiologic terminology when we discuss this crisis, but do we systematically then use methods or discuss methods that are equivalent to the type of crisis that we say?

For example, influenza vaccines and bioweapons, national defense kind of fit into this category. There are numbers of companies who are involved with this. What they have built in, in part, is partial-committed purchase orders. Federal, state, and local governments buy some of

our national vaccine production every year. In fact, that's 160 million doses each year that are made by these companies and distributed.

What's the cost of a flu vaccine? It's almost nothing, right? My insurance just covers it. It may have a small co-insurance, but it's not something that breaks the bank. Yet, if we contrast this, we have 70,000 flu deaths a year and we have 160 million units of flu vaccine prepared and administered each year. But we have 70,000 deaths due to overdose and 2 million units produced. Yet, we use the same kinds of terms epidemiologically about it, but we're not committing the same level of resources at it.

What we would we do, another thought experiment, if we had one of these issues comes here from Africa like Ebola or something else, and a company had a nasal vaccine? How would we handle that professionally, societally, financially?

I'm going to guess we're going to pull all the stops out. And I think that's what we did with a few other examples in the past. A lot of things

were done when a few individuals showed up here in the United States with one of these infectious disease matters. So what would it cost and how is it covered? Are we using, again, an imbalance of prioritization of resources for infectious disease-related matters versus this matter?

I think some of the cost issues can be addressed, but I think there has to be frank conversations amongst the stakeholders, and that is buying. We have to have buyers. My sense is we need about 25 million units a year to handle new prescriptions and maybe a 30 or 40 percent refill rate. I have seen larger numbers, but this is sort of my sense of it.

There are cheaper ways to do it in terms of the product, and that's one element of cost, but the others also still exist. And of course, this is just an educated opinion. I've been at this, but I wasn't successful in the sense of having the product approved here, but I was in another place. So I do have a sense of cost for these various products that I have worked on, including naloxone.

A few other slides that I put at the end is that we just don't have sufficient distribution to manage this. We're way too low, and so volumes have to pick up. Another factor here for the physician colleagues is that we don't have a standard of care. The physicians in my community would say, well, show me where this is in my guidelines, and of course it doesn't exist yet.

I remember that was one of the things I thought about many, many years ago, has the standard of care yet been adopted and how well is it articulated in being adopted? Is there an ability to pay?

We have some inconsistencies with insurance, and this doesn't really fit traditional healthcare models. In Kentucky, 50 percent of the people die from injecting fentanyl and half die from pills. It's hard to ignore one side. I know you're here for prescription opioids, but you've got two populations basically, and the phenomenon are different, and one has insurance and one may not have insurance.

I put together a slide of sort of a hypothetical build-up just so you could see where there may be allocations of cost and just some additional things that basically relate to volume, can we get enough units sold to satisfy all the different interests? Thank you.

Clarifying Questions

DR. BROWN: Thank you, Dr. Wermeling.

It's time for us to have some clarifying questions for the speakers that we have heard. Are there any clarifying questions for the invited speakers from the panel? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

If there's nobody else that's going to ask a question, I would like to ask Dr. Wermeling, 25 million doses of naloxone at scale, is that going to affect substantially the model that we saw this morning and the amount of government outflow of capital?

DR. WERMELING: Here's a way I can try to

explain it. I worked at UK for 40 years, and we're a member of the University of Health System Consortium. It's all the academic medical centers in the country. They have tremendous buying power.

Everybody doesn't pay the same for drugs, so the UK has an advantage, let's say, over my community hospital neighbors in that they can buy things at a price that the other can't. So volume speaks.

Now, I can't commit or say whether the other companies would be able to talk about how the cost curve bends, but if something came forward with a purchase order and said we want this many units, my guess it's negotiable.

DR. BROWN: Thank you. Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel from Fairview in Minneapolis. First, thanks to all three of these speakers for pretty remarkably effective and helpful presentations.

I have two questions. One is for Dr. Katzman. Just a point of clarity here, on slides 3 and 4, you talk about the ranking dropping

from number 1 down to number 12, and then you said number 17, I think, now. If I look at slide 3, your rates have actually gone up. The change here is the fact that other states have gone up faster than you have gone up, but it's not the fact that you're fallen.

Am I reading that correctly?

DR. KATZMAN: I think this is not on.

Sorry, Dr. Meisel. Right. Correct. As the U.S. national drug overdose mortality rates have gone up between 2013 and 2016, so has New Mexico. New Mexico's rates actually have fallen between 2014 and 2017, Dr. Meisel, but they're still higher than the U.S. national average, which is climbing up, but New Mexico is actually falling separately from that.

DR. MEISEL: Right. And the rest of the country is going up at a faster rate. Thank you. That was just my clarity for you.

I have a question for Dr. Wermeling. You put up a picture, and I don't remember what slide number, I won't worry with it, for naloxone in

these little pillow packs kinds of things, and you talk about the studies of nasal sprays, and maybe that's not all that helpful.

Are you suggesting -- those little things are just pillows of liquid; that you just kind of squirt up into somebody's nose and that would be effective?

DR. WERMELING: Sure.

DR. MEISEL: Do we have any data from anybody that that would actually would be effective?

DR. WERMELING: It's a function. The function is osmosis. So if you have a high concentration of drug on one side of the membrane, it's going to be absorbed. My sense is that although some of it may run away, if you put a little bit of methylcellulose in it, it'll adhere to the nasal cavity.

DR. MEISEL: But nobody has studied this per se, right? That's not commercially available, nobody has done that. Is that right? That's a postulate?

DR. WERMELING: No. We have done nasal solutions. If you look at other products like midazolam, for example, old studies, but nasal midazolam was first dripped in with a syringe.

DR. MEISEL: Okay. And then very, very quickly, you talked about the sterility. I can't seem to find it. Is Narcan nasal spray today manufactured sterile or is it just antiseptic? I can't seem to find that anywhere. Maybe the vendor can help us with that.

MR. KRAMER: This is Bob Kramer. Our product is not labeled sterile, so that's the differentiation.

DR. MEISEL: But it is manufactured sterile?

MR. KRAMER: It is, yes.

DR. MEISEL: Okay. Thank you.

DR. BROWN: Dr. Dasgupta?

DR. DASGUPTA: Dr. Katzman, can I trouble you to look at slide 16 from your deck one more time? Thank you for showing us these data. Of course, data catches our attention.

There are two things here that I think I

understand, but I would love for you to be able to put into context. In the right-hand side where it says, "study participants," there was only two with reported overdoses, and then all the other reversals were in the community, and those were not to the person who was in the clinic who it was prescribed to.

Do you think that's consistent with other programs? If you could help us put that into context. And similarly, on the left-hand side where 85 were lost, is that similar to what you see in other programs as well?

DR. KATZMAN: Thank you for the question. This is really the first prospective study like this of its kind, so I really can't answer that question, if it's similar to other studies. This is novel in that sense of being prospective. What I can tell you is that's a typo, and like you said, it's 85 that are lost or stolen.

So what we're hypothesizing is that we think perhaps it's the study participants that may have been coming in and requesting -- we took it as face

value. And, obviously, we gave them additional kits, and we think the majority probably really did lose it, but we're wondering if some perhaps were reversed themselves by family members or a friend. And we're wondering if some did reverse others in the community and just for whatever reason did not want to report it. But nonetheless, we think that the 115 was probably an underreport of how many people were reversed. Thank you.

DR. BROWN: Dr. Ciccarone?

DR. OLIVA: Sorry. This is Elizabeth Oliva. I wanted to add to that. We did have tracking of pilot reversals. We had 172. About two-thirds of that was actually used on somebody else. I think it's consistent with the UK data where they stopped that study, of giving it to people after incarceration, because essentially people were using it on the people on the control arm.

So I think in general, because it's kind of more a public health approach, the idea is that the person you're going to give it to is likely going to be using it on somebody else and just flooding

the system so that people have it available.

DR. DASGUPTA: So maybe all our focus on the patient characteristics up front is -- how would you feel about that?

DR. OLIVA: I think we're going to have to throw a multi-pronged approach at this, so I think some of the data is going to suggest there are definitely patients at risk, that it would be good to educate for a variety of reasons, not just because it might reduce.

There's a lot of opportunity from that patient care perspective, but in terms of probably a population-based perspective, I'd probably ask somebody like you what your thoughts are on that and how we might best be able to address that from an epi perspective.

DR. BROWN: Dr. Ciccarone?

DR. CICCARONE: Dr. Oliva, thank you so much for your leadership in this area. We've been talking a lot about pricing and volume. I'm hoping you could shed some light about what's going on in the VA. Obviously, you have a huge amount of

doses. Can you say something about pricing?

DR. OLIVA: Well, actually, probably I'm not the right person to talk to about pricing because that goes through Pharmacy Benefits Management's services. So they actually have all those numbers. I'm just in charge of implementing. think you can get those numbers from the federal supply schedule. I think we have pretty much the best pricing that's offered to anybody.

In terms of pricing -- I'm not sure if I mentioned it -- we do recommend nasal spray if it's clinically appropriate. We have both formulations available, but just for a cost consideration, we are recommending the nasal spray unless there's some issues where there might be some contraindications, and then people do have the autoinjector that they can prescribe.

DR. CICCARONE: Thank you. If I can squeeze in one more question.

Dr. Wermeling, regarding those blow-filled-seal packs, what dose concentration were you suggesting for those?

DR. WERMELING: A high one; 40-milligram per mL and put a half a mL in it. So you're going to get huge exposure. I don't know what it would be. You'd have to do the study. It'd probably be a dose ranging -- just like any other typical study, you would have to do a dose and volume ranging study, and then decide which one you want.

DR. CICCARONE: Thank you.

DR. BROWN: Dr. Macher?

DR. MACHER: This is also for Dr. Wermeling. I was wondering if you could dimensionalize. If we got rid of the sterility requirement, how much cost would decrease?

DR. WERMELING: So for production of the vial, 2 to 3 X.

DR. MACHER: Okay. And then if we went from a 2 dose to 1 dose but with a higher dosage, any idea there?

DR. WERMELING: Well, you saw the price for a kit. That was an estimate. But yes, it gets less expensive, of course, if you don't have to put as many kits --

DR. MACHER: Together, yes.

DR. WERMELING: -- together. You can try to stitch together a story. If you had to make something that needed to be less expensive, and without being disparaging, and if you wanted to send it to a third-world country who didn't have a budget like the United States, then you'd say, okay, if I had to do that, what would I do? Another theoretical question.

DR. MACHER: Yes. Thank you.

DR. BROWN: Dr. Faul?

DR. FAUL: My question is for Dr. Katzman. With the number of reversals, what percentage of successful reversals of this program did exist that you think EMS can do? Do you see any differences between maybe EMS and take-home naloxone?

DR. KATZMAN: Thank you for your question. I'm not exactly sure what you're asking. But in this high-risk population, patients with opioid substance use disorder who might be also using other illicit substances with alcohol, perhaps benzodiazepines, this is a population that really

less than half the time is actually calling 911. This is such an important conference, but we're actually talking about such two different populations, and we want to capture it all.

The other thing is New Mexico is such an underserved state too, that part of the conversation not only is about take-home naloxone for high-risk populations like patients in opioid treatment programs; we want to cover it with all the policing agencies including Bureau of Indian Affairs because we've got 30 tribes in New Mexico and patients leaving all correctional facilities. But we also want to make sure that EMS is well equipped and know how to take care of patients who are overdosing and are trained, and first responders are trained, too.

So that's the important thing, especially in rural communities like New Mexico, like Appalachia and other rural and underserved communities. It's just as important for EMS.

Am I helping you with that question?

DR. FAUL: Yes. Thank you.

DR. BROWN: Are there any further clarifying questions for any of the presenters from the panel?

(No response.)

DR. BROWN: If not, we're going to take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break. We'll resume at about 3:05. Thank you.

(Whereupon, at 2:48, a recess was taken.)

DR. BROWN: We'll now continue with another invited speaker presentation from Dr. Joy Gamber.

Speaker Presentation - Joy Gamber

DR. GAMBER: Good afternoon. Thank you for inviting me to speak today. I'm Joy Gamber. I'm a mental health clinical pharmacist with the Dallas VA Medical Center. Today, I'm going to be discussing naloxone access laws, so legal regimes in place to promote access to the antidote.

As a note, this presentation is of my own research and opinion and does not reflect my employer. As an introduction, first, I'm going to review background on potential legal concerns

relating to naloxone and then discuss the purpose of legislation. Next, I'm going to compare statewide provisions and maybe highlight some differences and unique laws, and finally discuss clinical outcomes associated with legislation.

There can be mostly theoretical risks to prescribers and layperson administrators of naloxone, both criminal and civil. Criminal risk to prescribers could include aiding and abetting the unauthorized practice of medicine.

This is to suggest that by prescribing naloxone to a layperson for ultimate administration to an overdose victim, a prescriber could theoretically be considered as enabling the rendering of medical treatment by someone who is not a licensed healthcare provider, and this in violation of certain state criminal laws.

Also, prescribing naloxone to a patient with the understanding that its used would be on someone who doesn't have an established patient-provider relationship with the prescriber could violate certain state prescription drug laws.

Civil concerns are going to relate to incorrect naloxone use, or incorrect use of naloxone, or failure to use naloxone, which could cause physical injury to another, which could leave the prescriber vulnerable to medical malpractice. Professional sanctions might also be issued for nontherapeutic prescribing and, again, aiding and abetting the unauthorized practice of medicine.

Patients or layperson users of naloxone might fear criminal prosecution for possessing the antidote without a prescription being found at an overdose scene, in possession of controlled substances or a paraphernalia, or being found in violation of their probation or parole terms. And laypersons could be civilly prosecuted similarly for harms related to incorrect use or failure to use naloxone.

The main purpose of naloxone access laws is kind of inherent to their title. It's to improve access to the antidote. This is primarily done through a few provisions.

First, third-party prescribing, this is to a

person to whom is not a direct patient of the prescriber but to whom naloxone is given because they're potentially in a position to assist an overdose victim.

Distribution makes naloxone more widely available to persons without a patient-specific order or an established patient-provider relationship. This allows dispensing via the community programs or by pharmacies and go so far as establishing naloxone as kind of a pseudo over-the-counter product dispensed by way of protocol or a collaborative practice agreement.

Also, pharmacist prescriptive authority expands access by allowing pharmacists to prescribe the antidote to patients at risk for overdose who are encountered in community practice. Other aims of legislation are to encourage education and training of and by prescribers and distributors and also to establish legal immunity for prescribers, dispensers, and laypersons involved.

Good Samaritan laws are kind of beyond the scope of this talk, but they're another type of

protection that's afforded exclusively to laypersons. Their purpose is to encourage the activation of emergency response by providing legal immunity to persons who might otherwise incur charges at the scene of an overdose.

This is a bar graph that was created by the Network for Public Health Law, and it shows just the proliferation of the naloxone access and Good Samaritan laws over the states in the past several years.

The next several slides are going to give you a detailed look at the status and characteristics of naloxone access laws across the states. An X is going to delineate presence of a certain provision, and headings across the top starting from the left are in reference to, first of all, existence of a naloxone access law, criminal protections for the prescriber, civil protections for the prescriber, third-party prescribing, distribution, and finally, criminal and/or civil protections for the layperson administrator.

In the second column, you'll see superscripts on some of the X's, and this is going to indicate that there are additional provisions in place. An A is going to say that the law also contains protections for pharmacists or distributors; a B means the law also provides immunity from disciplinary or professional sanctions; and C indicates authorization of pharmacist prescriptive authority.

On this slide, you can see that, for example, Idaho lacks any provision for naloxone distribution and that most states provide pharmacist or dispenser protections, but only a couple authorized prescriptive authority beyond that of physicians. Kentucky provides no criminal or civil protections for prescribers, only professional immunity

Here, Minnesota lacks legislation explicitly permitting third-party prescribing. Maine provides an example, however, of very highly comprehensive naloxone access legislation. So they offer protections across the board, as well as pharmacist

prescriptive authority.

Distribution is not found in Nebraska's legislation as being explicitly permitted, while New Mexico and New York fail to protect prescribers from criminal or civil liability.

You're going to see asterisks under a couple of the columns for Oklahoma, and this is because legal protections here are somewhat vague. In general, immunity is provided kind of under an umbrella act that's actually titled the Good Samaritan Act. And likewise, with Utah, they do not include explicit protections for prescribers; instead only pharmacy laws and nursing laws will provide for exclusion from unlawful conduct.

Rhode Island provides no criminal or civil protection for prescribers, and South Dakota provides no legal protection for laypersons.

Finally, Virginia offers on civil protections for prescribers and lay administrators, while Wyoming's law is maximally comprehensive.

Even among states who contain the same provisions in their laws, there's a lot of

variability in the details. For example, civil and criminal protections may be provided outright or they could be contingent on mandatory education and training requirements. Another difference is in the definition of third party. Most states define this as a family, a caregiver, or other person in a position to assist an overdose victim. But here are some states that go so far as to say that any person may be provided with naloxone.

Finally, the method of distribution authorized varies widely across the states. It could be established by a standing order, a protocol, a collaborative practice agreement, or direct legislative authorization, and agreements can be developed by a physician, a public health department, a board of pharmacy, a board of medicine. And also, to whom and by whom distribution is permitted also varies widely, so from pharmacies, to community programs, to schools, to prisons.

There also might be training mandates, in the case of distribution, for the distributor

and/or for the recipient of naloxone. Actually, in recent years, a few states have gotten rid of these provisions probably to further improve access.

In review of each state's laws, I did a lot of reading through LexisNexis, and I found that some states have actually implemented a few unique provisions to further improve naloxone access, so I wanted to highlight some of those.

Several states do establish grant programs to fund overdose education and to purchase stocks of naloxone. States have also started to mandate that at least one form of naloxone be covered by prescription drug programs and/or Medicaid, or at a minimum, not require prior authorization for the prescriptions.

Other states are requiring syringe exchange programs and opioid treatment programs to educate patients on overdose response and naloxone use. A couple of states have come to establish co-prescribing guidelines. In Massachusetts, pharmacies located in areas that are considered high-risk for overdose are actually required to

maintain adequate supplies of naloxone on their shelves.

Nevada requires opioid informed consent documents to include information on naloxone, and New York requires pharmacies with 20 or more locations to offer naloxone distribution from that pharmacy. New York also provides detailed framework of operational requirements for opioid overdose prevention programs.

In Oklahoma, legislation permits naloxone to be dispensed by a pharmacist without any prescription or any protocol in place. This is kind of the closest thing that I have seen to making it a pseudo over-the-counter product. Oregon and Rhode Island have created legislation for electronic tracking of naloxone dispensing, likely for later analysis of outcome measures.

Finally, Utah, Vermont, and West Virginia have made provisions for overdose outreach and response pilot programs.

In summary, as of November of 2018, all 51 states currently contain naloxone access

legislation. More states offer civil protections than criminal protections for prescribers. All but one state permits third-party prescribing, and all but three allow for distribution.

Most protect a layperson from civil or criminal prosecution, and a small minority of states have extended prescriptive authority to pharmacists or go so far as to say that any person can possess the antidote.

As of July 2017, the majority of states have also passed Good Samaritan laws to protect laypersons from prosecution of certain crimes discovered upon emergency response at an overdose scene.

Now is just a brief look of recent literature that's evaluated the clinical impact of these legislative changes. From 2007 to 2016, this study found that access legislation, particularly that contained provisions for third-party prescribing and standing orders, increased naloxone dispensing by 78 prescriptions per state quarter. This was a 79 percent increase in outpatient retail

dispensing when compared to states without any legislation.

The author suggested other regulatory methods to increase access to naloxone would be to require that pharmacies stock naloxone, requiring naloxone to be co-prescribed to patients at risk for overdose, and requiring all payers to cover naloxone without prior authorization or other barriers.

During the same time period, this study also found that the presence of any access legislation, but especially standing order provisions, was associated with increased naloxone dispensing through Medicaid as well. This was by 33 prescriptions per state quarter.

Lambdin et al. evaluated the impact of naloxone access laws in stimulating implementation of OEND programs from year 2000 to 2014, and results show that state with a naloxone access law were 28 times more likely to also implement an OEND program.

Watson et al. examined the knowledge in

overdose response trends among laypersons who received naloxone kits in 20 Indiana counties, and results show that the majority of respondents not only had knowledge of Good Samaritan protections in that state but also were significantly more likely to have called 911 in response to an overdose versus those without knowledge of protections there.

McClellan et al. assessed opioid overdose mortality trends and non-medical opioid use in relation to naloxone access laws and Good Samaritan laws from year 2000 to 2014. They found a 14 and 15 percent lower incidents of opioid mortality in states with these protections and no increase in non-medical opioid use. The paper suggested that universal adoption of laws could have saved an additional 3,000 additional lives per year.

They found that with the exception of prescriber immunity, which was associated with the 23 percent reduction in death, there was no other statistically significant associations between the specific provisions of these laws and opioid

overdose deaths.

A working paper by Erfanian et al. also examined opioid overdose mortality rates in relation to the naloxone access laws from 1999 to 2014. However, the results here were more mixed. They actually found that some provisions seemed to decrease overdose death rates while others seemed to increase overdose death rates. Their overall conclusion was that there was no statistical evidence for naloxone access laws in reducing opioid death rates.

However, another working paper by Rees et al., which looked at the same time frame, found that adoption of naloxone access laws was associated with a 9 to 11 percent reduction in opioid-related deaths.

This effect seemed to be delayed by about two years, and it was especially strong for non-heroin-related deaths. Criminal protections for layperson possession of naloxone seemed the most robustly associated with reduction in deaths, and they found Good Samaritan laws were not

associated with reduction in deaths. This paper also did not find any evidence of increased recreational opioid use from the laws.

In summary, there are various legal concerns, which have been raised in regards to naloxone prescribing, dispensing, possession, and administration by laypersons. State-based legislation is not completely comprehensive nationwide, and provisions are highly nuanced. More could be done in the way of unique and creative provisions to help increase access.

Review of current literature suggests that naloxone access legislation increases dispensing in community pharmacies and to Medicaid-eligible patients and may also help establish community-based OEND programs for more widespread distribution.

While one review was unable to find a difference in mortality outcomes, two other studies suggest that these laws also reduce opioid overdose deaths without increasing non-medical opioid use.

Here are my references, and I just want to

thank you for your time and attention today.

DR. BROWN: Thank you. Our next speaker is Mr. Tim Ingram.

Guest Speaker Presentation - Timothy Ingram

MR. INGRAM: Good afternoon. My name is Tim Ingram. I'm a local public health commissioner for Hamilton County, Ohio, which Cincinnati is the county seat for. I would like to thank the Food and Drug Administration for inviting me here to present some preliminary findings of a very exciting project that has been underway for about 9 months, 15 months exactly, called the Narcan Distribution Collaborative.

The collaborative is actually composed of many individuals and entities. However, the principals are Dr. Shawn Ryan, who is the medical director for BrightView Health, a behavioral treatment facility; Dr. Michael Lyons, an emergency department physician, emergent medicine physician, who's also involved in the project; Adapt Pharma, now Emergent BioSolutions; the five healthcare systems of Greater Cincinnati, Bon Secours, Mercy,

TriHealth, University of Cincinnati Medical Center, and Christ Hospital, and Cincinnati Children's Hospital; Interact for Health and the Deaconess Foundations; and Hamilton County Heroin Coalition; and the Board of County Commissioners, the locally-elected body there.

The Narcan Distribution Collaborative is a local public health initiative developed by Dr. Ryan, Dr. Lyons, and myself to address the unacceptable number of overdose deaths in Hamilton County, and we asked the question: What would happen to the rates of overdose death if the community were to completely saturate with naloxone availability?

In reviewing some 2016 Center for Disease Control data, Ohio is second in the nation with the highest overdose rate of 39 individuals per 100,000 population. Hamilton County, the third most populated county located in Southwest Ohio, is a primary epicenter for opioid addiction in the state and is contributing to Ohio's high ranking.

You can see what our vision of the project

is, and, again, we were looking to saturate the community across all spectrums based on data that we have through our robust surveillance systems for drug overdoses.

This slide shows Hamilton County resident deaths due to unintentional drug overdoses from the years 2008 through 2017. The pink shaded area is the number of deaths due to all opioids. The green line depicts heroin deaths. The purple line is for fentanyl deaths. The black line is cocaine, and the blue line shows prescription opioid deaths.

In 2017, just like the rest of the country, drug overdose deaths set a record high for Hamilton County and of course the state of Ohio. There were 444 overdose deaths to Hamilton County residents in 2017, and 89 percent of those deaths involved an opioid of some kind.

A shift towards fentanyl, replacing heroin in the drug supply, is the primary driver of the increase in overdose deaths. Fentanyl and its analogues were more present than ever in 2017. About 72 percent deaths involved fentanyl or its

analogues, while less than half involved heroin. There were nearly twice as many overdose deaths involving cocaine in 2017 compared to the time period of 2015 throughout 2016.

Seventy-two percent of the overdose deaths involving cocaine also contained fentanyl, indicating that cocaine is being increasingly mixed with fentanyl. 2017 also had a high proportion of deaths involving pharmaceutical prescription opioids, 23 percent than in recent years.

The original goals and outcomes for the Narcan Distribution Collaborative are to rapidly and substantially increase the distribution of 12,500 cartons or 25,000 doses of Narcan throughout the community using data to drive where we should distribute it. It reduced by greater than 50 percent both the number of fatal opioid overdoses and those resulting in intensive care admission.

The outcome measures were the number of naloxone doses distributed, the number of naloxone doses administered, and the number and proportion

of opioid overdoses that result in death or ICU admission.

The results, again, we asked the question, what would happen with the rates of overdose deaths in Hamilton County if it were to be completely saturated with naloxone availability? The results that follow are for the time period of October 1, 2017 through September 30th of 2018, unless otherwise noted. So let's look at some of the results thus far.

First and foremost, the Narcan Distribution Collaborative is exceeding expectations in the amount of Narcan distributed. At the start of the project on October 1, 2017, we expected to distribute 12,500 Narcan cartons, or 25,000 doses, over two years. However, we have distributed all the Narcan allocated to us in less than 15 months. As a result of this success, the manufacturer, now Emergent BioSolutions, recently authorized an additional 6,000 cartons of Narcan, which will total 18,500 cartons, or 37,000 doses, for this project to be used in 2019.

This table details all Narcan dispensed in Hamilton County from October 1, 2017 through September 30, 2018, and the next slide includes the year prior to the beginning of the Narcan Distribution Collaborative project. This shows Narcan cartons and other naloxone distributed in Hamilton County since October 1, 2016. In the year prior to the start of the Narcan Distribution Collaborative project, 1,488 doses of naloxone were distributed to first responders and 2,020 doses were prescribed.

Take-home naloxone programs were rare in Hamilton County prior to the initiation of the Narcan distribution project.

As previously mentioned, the community distribution portion of the Narcan Distribution Collaborative has been very successful.

With Hamilton County public health staff moving doses more quickly than expected, we reassessed the criteria for distribution, and as a result, in July of 2018, as you notice on the graph here, we intentionally reduced our rate of

distribution to assure we were targeting the communities with their greatest needs and then knowing at some point, in 2019, there will be no more free Narcan available.

We wanted this pullback of free Narcan to be gradual instead of abrupt. This will also allow us some time to strategize and to seek a sustainable funding source to continue the distribution of Narcan. Nonetheless, this effort remains the largest Narcan distribution effort in the country.

This slide displays residential zip code locations for individuals distributed take-home Narcan cartons. Each carton of Narcan contains 2 doses. Of the 8,288 individuals, almost 8300 individuals, distributed take-home cartons, this map displays zip codes for 6,285 of them. There were some data provided that was returned that was incomplete, and of course there is a significant amount of homeless populations that's also receiving Narcan.

As of September 30, 2018, 11,117 take-home Narcan cartons have been distributed from various

sites throughout Hamilton County. We expected survey data to return from individuals provided 10,351 cartons of Narcan, but as of October 15, 2018, only individual level data has been received from 8,288 individuals as shown in table 2. Although there are still survey data outstanding, the level of data completion is encouraging and actually better than expected, given the very practical nature of this program.

Table 3 shows the types of sites where individuals obtained Narcan. This exchange project, often called the syringe exchange program, a comprehensive blood and born infection prevention program in Hamilton County and also ran by the public health system, is the most successful Narcan distribution site implemented by the collaborative. Over 1,850 cartons, or 7,000 doses, have been distributed directly to this population suffering from opioid use disorder.

A partnership with the Hamilton County Sheriff's Office utilizing the justice centers also has been a very successful site. Close to 3,000

doses, or 1500 cartons, have been distributed there, and we occupy that site weekly.

We have very good working relationships with law enforcement and the fire departments in Hamilton County. They began a program called Use One Leave One. When they revived somebody, they would leave a dose of Narcan with a family member that's on the street.

We also have something you have heard of that's been wrapped in different paper, but basically they're quick response teams, which are composed of generally a fire person or an EMS person along with a social worker who visits the home of somebody who had overdosed that they had just revived to see if they were ready to get into treatment. That's also a place where we provide Narcan to.

Table 4 shows who initiated or requested Narcan by dispensing location. Again, the syringe exchange program is where the most staff-initiated request occurred for Narcan, as you might expect, because we have a very trusting relationship, these

folks. Since January 1st, we have exchanged 300,000 syringes on this site, along with providing vaccinations, HIV testing, hepatitis C testing, as well as providing them Narcan, and also, if they're ready for treatment, we have access to treatment.

Self-request occurred most frequently at the justice center as inmates are being discharged from incarceration and they are met by family members. Hamilton County, public health staff, and others staff the jail on Saturdays of each week with a full display announcing Narcan, providing them training as family members or the inmates walk by.

This next table, as we review the survey data, talks about that most people requested Narcan for the purpose of having it available to revive a person they may be near or for themselves if they overdose. One-third of the respondents selected more than one reason for taking home Narcan.

Further analysis of the survey results provides information on the client's prior history of opioid usage and whether they had ever administered Narcan or naloxone. It is interesting

to note that 28 percent of individuals who had previously overdosed, 72 percent of this cohort had overdosed multiple times. Another observation reveals that most of Narcan distributed went to people who reported they had never overdosed on opioids.

The next three slides display outcomes from a Narcan Distribution Collaborative public health initiative thus far. But before I discuss these results, it's important for me to point out to you that there are other factors, including the Narcan Distribution Collaborative project, that are impacting these outcomes.

First, I'd like to mention treatment capacity in Hamilton County has increased along with evidence-based treatment protocols. We have treatment on-demand access and more providers are setting long-term goals for therapy and for medication-assisted treatment for those individuals who say I'm ready to address this illness.

Two, several healthcare systems -- we have five great healthcare systems in the Greater

Cincinnati Area -- are beginning to integrate the care of their patients with behavioral health providers of the community by opening access to patient's electronic health records in order to assure continuity of care.

Nonetheless, the Narcan Distribution Collaborative project has contributed to reducing ED visits by about 42 percent and emergency medical transport runs by 38 percent for all types of drug overdoses, just not opioids but all types of drug overdoses. And most importantly, the number of deaths due to opioid overdoses in Hamilton County have decreased by 31 percent when comparing the 8-month time period from February 2017 through September 2017 to the 8 months since the launch of the Narcan Distribution Collaborative, which began, again, on October 1, 2017. These results are through May of 2018. Good progress.

Looking at for a period of time in 2017, from January 2017 through May 2017, compared with the same time period in 2018, show similar results, 33 percent decrease.

In summary, opioid drug deaths have decreased by almost 31 percent over the last eight months compared with the pre-Narcan Distribution Collaborative project in Hamilton County, Ohio. Emergency department visits and EMS transport runs are decreased overall for all drug overdoses in 2018. It's important to note that no adverse health events have been reported to date as a result of administering Narcan and that the Narcan Distribution Collaborative work will continue into 2019.

The Hamilton County Board of Health, our local-elected officials, and our state-elected officials, and our congressional delegation, I might add, and other community leaders support the work of the Narcan Distribution Collaborative.

As health commissioner, I look forward to the continued success of the Narcan Distribution Collaborative in 2019 and beyond, or until such time opioid poisonings are no longer the leading cause of death for people under the age of 50. After all, this the work we do at in public health,

and the Narcan Distribution initiative is helping to prevent deaths. I thank you for your time. I bid you a good day.

DR. BROWN: Thank you very much.

Our next speaker is Dr. Peter Davidson.

Guest Speaker Presentation - Peter Davidson

DR. DAVIDSON: Good afternoon. The last speaker for the day. Thank you, all, for sticking it out. My name is Peter Davidson. I'm an associate professor in the Department of Medicine at the University of California, San Diego. I have been conducting research on overdose and overdose prevention since 1997, originally in Australia and since 2000 here in the United States.

As a simple disclosure, my sole economic connection with naloxone is that I'm currently receiving an RO1 from NIDA to study the impacts of law enforcement use of naloxone on drug user behavior.

A little bit of background for why we're all here in a way, when someone has an overdose, it's like any other medical emergency. The ideal

response we would like to see from people who are present at the scene is to call 911, and then if possible, do rescue breathing. That's what we'd actually like to people to do. And we know among illegal drug users, at least 85 percent of overdoses are witnessed, so this should be something that's possible.

However, though, we know from decades of research that there are really substantial barriers to calling 911 if you're present in an overdose. We know when we ask people what did you do at your last overdose, and if they didn't call 911, why not? That they say, I was terrified at the police attending.

Partly in response to that, we have introduced Good Samaritan laws in the last few years, but they are sort of a relatively limited efficiency. They protect people from simple possession of heroin and possession of needles and things like that, but they usually don't provide any protection from possessing drugs to the purpose of sales, which is often in the eyes of the

attending police.

They don't protect people from violation of probational parole. We know street-based drug users are on probational parole at any one time. So these laws don't protect quite as much as we would like them to.

On top of that, in the last three or four years, law enforcement has responded to the overdose epidemic by kind of doubling down. They're now frequently treating overdose deaths as homicide cases, which may mean that if you're present at an overdose, law enforcement could charge you with homicide if you were involved in the purchase of the drugs that led to that person's death.

We know from the research that less than 50 percent of overdose witnesses call 911. We're basically broken the 911 system as far as people who use drugs are concerned.

One of the community responses to this situation is to try and cut out the middleman, to actually provide naloxone directly to people who

use drugs to use in the event that they're present when someone overdoses.

Like needle exchange before it, a lot of these programs were started by people who use drugs and those who are very close to them back in the late 1990s. People just came up with creative ways of accessing naloxone, and distributing them in their community, and then using it on each other when people overdose.

Those of us in the research world, in the public health world followed along behind it, sort of, oh, this is happening; we really should study whether there's unintended effects of this and whether or not this should be made more available.

Across the next 10 to 15 years, a lot of research has been done on this topic. The initial earliest research found that naloxone distribution to people who use drugs is feasible. A bigger body of research found that naloxone use by people who use drugs is a safe thing to do, that there aren't unintended consequences, that people can use it successfully in the event of a medical emergency.

More recently, we have started to see the evidence emerging that distributing naloxone to people who use drugs is effective at reducing mortality and is also cost-effective.

My colleague, Alex Walley, published in 2013 one of the really big important papers showing that communities in Massachusetts that had naloxone distribution directly to drug users saw reductions in the rate of deaths compared to communities that didn't have it.

We also have research that says immediate use of naloxone at the scene, like as soon as people realize, oh, someone has overdosed, reduces associated morbidity. And this is becoming particularly important now that the drug supply is contaminated with fentanyl, and the response time available between when someone uses drugs and when they overdose is becoming much shorter.

Partly, as a consequence of all this research, community naloxone programs started to expand fairly rapidly in the mid-2000s. My colleague Eliza Wheeler and I, along with some

other colleagues, did a survey of every known naloxone program back in 2010, and at that time, there were about 188 sites distributing naloxone around the country.

When we repeated that survey in 2014, that had jumped to 644 sites. And by then, we were already saying to each other, basically, we can't replicate this research any further. We won't be able to do this in the future because this is expanding so rapidly that we could no longer keep track of every program that was doing this out in the community.

Just in that 2014 dataset, those programs that were included in that survey had reported training 152,000 people out there in the community on how to use naloxone, and those people had reported using naloxone to save the life of someone after an overdose over 26,000 times. And we know this is a really significant undercount because many of these programs don't actually collect data, so they weren't able to tell us how many people had trained or how many people had come back to tell

them that they'd use naloxone.

Sort of jumping to the present day, at least some of these programs -- there's a group called the OSNN group, and basically they act as kind of a shared clearing house for best practice for community distribution of naloxone and also act as kind of a purchasing club to purchase naloxone.

There's 89 programs involved in that purchasing club in 34 different states. In 2017, those programs bought 506,000 doses. This year, these numbers are a little out of date. I think they're up to 865,000 doses and may actually get to a million by the end of this year.

I want to emphasize something that I'm going to repeat a couple of times during this presentation. All of this is injectable naloxone. Injectable naloxone is far, far cheaper than nasal naloxone or the autoinjector. So this is the only thing that many small community programs can actually afford to distribute.

I also want to emphasize that just about all that research that I mentioned was done with the

injectable naloxone, and all that practicality and safety studies were done within injectable naloxone. Drug users know how to use needles. This is not really a problem.

In the last few years, we have seen community naloxone sort of expand beyond just people who use drugs to other people who might be present at an overdose, family and friends, the staff of community agencies that serve people who use drugs, and most prominently perhaps law enforcement. However, the data that we have on the use rates of naloxone in these different populations suggest very strongly that it's the people who use drugs who are the most likely to actually use naloxone.

This data was shared with me by a colleague, Caleb Banta-Green, at the University of Washington from the first two years of a SAMHSA-funded project. Basically, they're finding that of all the kits issued to opioid users, 21 percent of those kits actually are used to reverse an overdose, whereas only 3 percent of law enforcement

programs end up using naloxone.

We're seeing similar things in other programs around the country. I mentioned I have a NIDA RO1 looking at law enforcement use of naloxone in San Diego. Basically, in the first and most successful year of that program, we trained 700 officers, and they used naloxone 60 times in the next year.

At the same time, in the same community, a community-based program started only a year or two earlier by a mother who had lost her son to overdose, trained 1500 people, and 619 of those people used naloxone successfully in the community to reverse an overdose. That's 60 versus 600. One of those programs, the community program cost almost nothing. It was run by a single person. The police program, by comparison, cost tens of thousands of dollars.

In summary, the person who's most likely to witness an overdose is another person who uses drugs. If we want to facilitate distributing naloxone in the community to the place where we'll

all have the biggest impact, these are the programs that we really need to be supporting.

The three things I'd like to ask the FDA to consider doing, which would really facilitate community distribution of naloxone, one, and possibly the biggest one right at the moment, is to clarify that injectable naloxone is also approved for community distribution.

Several of the industry representatives earlier today mentioned that their products were approved for distribution in the community. This kind of language has led to considerable confusion amongst funders, in particular SAMHSA and the big state health departments, which are funded by SAMHSA block grants. The confusion is that, oh, if only the nasal Narcan or the autoinjector are approved for community distribution, that must mean that injectable naloxone distribution to the community is an off-label use.

It would be enormously helpful if you clarified that injectable naloxone is also suitable for use in the community in a medical emergency

because, again, injectable naloxone is far, far cheaper than these other formulations and is pretty much the only thing that little community programs can afford.

Many of these programs have annual budgets of less than $100,000 a year. $35 may not sound like much for a drug, but for these communities, it's a total showstopper.

Secondly, another thing the FDA may wish to consider is extending the shelf life of most of these products to five years or longer. Every product currently available on the market has a shelf life of two years, but the FDA and the Department of Defense's shelf life extension project set back in 2006 said the actual shelf life of naloxone is at least 60 months, and more recent research has suggested that it may be longer.

Having a product that expires two years after manufacture is a considerable logistic and economic burden to community naloxone programs, and it would be enormously helpful if that time frame could be extended to match the data.

Thirdly, it would be incredibly helpful if at least some products were made over the counter. Just about every state has naloxone access law, which facilities naloxone distribution under standing orders, either individual by program ones or entire statewide ones. But because naloxone is not an over-the-counter medication, every program needs an associate or a physician just to order the medication.

If you're some tiny program out in rural Nevada, finding a physician who's willing to collaborate with you on this can be incredibly difficult. So having at least some products that are available over the counter would really facilitate distributing naloxone in these environments.

I want to add a final ask, and that is that the FDA make use of the expertise that's available in the community. These programs have 20 years' experience distributing naloxone directly to people who use drugs. These community experts who are the people that the VA went to, to help get things

started, these are the experts that big programs, statewide programs, like New York and Massachusetts went to, to find out how do we even do this and how do we scale it to a state level.

I really encourage the FDA in any future meetings involving naloxone to explicitly invite some of these people with 20 years of expertise of doing this work. Thank you very much.

Clarifying Questions

DR. BROWN: Thank you, Dr. Davidson.

We're going to speak to the issue of clarifying questions for all of the speakers that we have heard today. We've had very many. They have given a lot of information, which has been just excellent, and I appreciate that the FDA brought these folks in so that we could have a more complete understanding of the problem.

However, some of them are not going to be here tomorrow, and if we will want to ask questions of them, please ask those questions today if you possibly can. So at this point, Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti.

Question for Tim Ingram. In your program, which is really interesting, did you do a financial evaluation on program success, meaning how much the Narcan cost or would cost if the county, city, or state was to pay for it, and how much there was in savings in missed ED and emergency room and EMS runs?

MR. INGRAM: We haven't done that cost analysis yet. We know that the contribution from Emergent BioSolutions, we know what the estimates were when they had originally donated the product to us.

We have average cost for ED admissions. Although we have five systems in town, they are somewhat variable. The range can be anywhere from 900 [dollars] to $1700, depending on which system is going in and what exactly is going on with that particular person that presented, but we have not done the economic analysis. We may do so, but it has not been discussed.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Mr. Ingram, before you sit

down, thanks so much for your wonderful presentation. Just a question, in case I missed it. I saw that you presented data about distribution of naloxone and then the results of the distribution. Did you present or is there any data about actual naloxone administration?

MR. INGRAM: For the cost of administration?

DR. ZACHAROFF: For administration of the naloxone?

MR. INGRAM: No. We have difficulty in that area because of the nature of the population to gain that data back. We have some data. Since this is really a take-home naloxone program, we do get good data from other naloxone that's been distributed to first responders, and we do have some data on this. But this focus is really basically putting Narcan and the family members or others, or the folks that are suffering from opioid use disorder themselves.

So we are really targeting the population using different avenues, based on the data that we collect actually 7 days a week on monitoring

emergent department visits and 911 dispatches. We monitor it 7 days a week.

DR. ZACHAROFF: So your presumption is based on the distribution --

MR. INGRAM: The reductions.

DR. ZACHAROFF: -- that it must be administered?

MR. INGRAM: We believe that because we're seeing reductions that I mentioned, and just not overdose death rates -- and I qualify that, that there are some other factors that are in play here clearly because there are multiple other people that are doing work in this area.

One of the things we know that was a limitation was behavioral treatment access and having access when people are ready for treatment, getting them in treatment on that Saturday morning and not waiting 'til Monday. These things have changed.

The other thing that's been very difficult is the cultural shift that's occurring in our healthcare system. It's been a struggle given the

nature of the stigma that's attached with this population.

However, we are now starting to see, at least with two of the five systems in town -- as I mentioned, they're opening up their patient population records of people suffering opioid use disorders with the behavioral treatment providers and beginning to try to share lessons learned across the continuum.

We are looking at the results as one factor and knowing that we're having success. But I do not have data on administration.

DR. BROWN: Thank you. Dr. Meisel?

DR. MEISEL: Steve Meisel with Fairview in Minneapolis. Once again, compliments to these three speakers. I think, in retrospect, I would have paid to come here today as a seminar. This has been fascinating.

I had a question for Dr. Gamber, although maybe the agency can answer this as well. You talked about a compilation of 51 states and state laws on various aspects. Did the recently signed

SUPPORT Act, federal act, provide any clarity, any standardization in any of the elements that you described with liability, or Good Samaritan, or any of those kinds of pieces? Did the SUPPORT Act address any those elements, or was it silent?

DR. GAMBER: I'm actually not sure. I know just from my review of the legislation through November of this year that there is basically no standardization. Pretty much every single state kind of words things in their own ways. And even as far as researching to try to find if there's a naloxone access law in place, it could be under naloxone, it could be under opioid antagonist, it could be under opioid reversal antidote.

Like I said, the definitions of like third-party prescribing differ, distribution differs across the state. So to my knowledge, none of it has become very standardized. There are states that kind of go above and beyond, I believe, such as like New York that set out more defined, I guess, guidelines like for community programs or training requirements that maybe could be used as

like a standard. But between the states, there didn't seem to be much consistency in the language.

DR. MEISEL: Thank you.

Dr. Hertz, are you aware of any assessments of the new federal law that addressed of these pieces?

DR. HERTZ: My understanding of the elements in the SUPPORT Act -- and I have to preface that by saying my limited review of the parts that the division is trying to help work on, there are some aspects about naloxone, but I do not know that there's anything about state laws.

Prescribing authority is a state medical board function, so I don't know what kind of federal agency -- I don't know where that would come from on a federal level.

DR. MEISEL: That's fine. If there's nothing there, there's nothing there. Thank you.

DR. BROWN: Dr. Ciccarone?

DR. CICCARONE: Daniel Ciccarone, UCSF. I also want to echo kudos to all the speakers for excellent science and presentations. I really

appreciate it.

Commissioner Ingram, please, the finding of the 31 percent reduction in mortality is outstanding. I want to applaud you and your public health department for achieving that particularly during the fentanyl age.

One of the concerns that one reads about, both in the scientific literature, economic literature, media, is that naloxone may not be working as well as we want it to, either at a clinical level or in a public health level. There are even counterclaims that say that this is moral hazard; that naloxone distribution is leading to greater drug use and greater overdose.

What you're showing is that if you saturate, if you take an all-in approach, can we get opioid reduction? Because that would be my claim, that there isn't simply enough naloxone in many of these situations to face the synthetic, and the timing of your data, '17 and current 2018.

I just have one simply question for you.

MR. INGRAM: Thank you.

DR. CICCARONE: You're welcome. One of the goals was to saturate, and I see a peak. Somewhere earlier this spring, maybe early summer, you reached about 1800 doses per month. I don't know if that's doses or cartons. And then there was this tapering.

I'm wondering even at 1800 for your county, do you feel like it could have even gone higher?

MR. INGRAM: We purposely began to reduce the amount we were putting in the streets, if you will, and in different populations starting in July because we were concerned -- because we were so successful in getting it out, we were really concerned about what would happen if all of a sudden this free Narcan disappeared from the population that was used to getting it?

So we abruptly began to slow down the supply. And we were actually using data even before. This is a data-driven project. So what we thought we would do is we know the treatment providers in our community had the funding through other grants and so forth, that they were now

getting Narcan and naloxone.

One of the first places that we began to pull back on how much we were giving was actually in the treatment providers themselves while we tried to convince the healthcare systems that when they are seeing a patient who is presented at the emergency department, and most of them come through the emergency department, that when they put them back out on the streets, that they were also prescribing or providing them with Narcan. And initially, we began to see them with that, trying to teach them that they could actually bill for it.

So we believe -- but I do want to tell you that we have some news coming out of Emergent BioSolutions that they may up our supply based on some of the results. So we will move to more of a complete saturation model than just limiting it to certain areas.

What we're really trying to do here is change the culture of how healthcare looks at this issue in our community and to make sure that we have better integration between the behavioral

health system, which in Ohio, the mental health system in Ohio -- maybe unlike several other states; I don't know -- is that the mental health boards can't provide any direct services. They are brokers of money, if you will, and they had to provide it out to the many not-for-profits that provide those services.

So they're all out there. First what we had to do is convince them that they need to use evidence, medication-assisted treatment, protocols, and then begin to change the healthcare system's culture saying, look, we need to begin to look at this no different than another disease, as you've heard.

So this has been a journey for the last several years. And I can tell you, when you said the words, "moral failing," believe me, there are still folks in our community that don't feel that we are doing the right thing.

I will tell you that 98 percent of the monies that are being used in this project have all been privately raised. There are no public

dollars, very little, except for me standing here and some other dollars have went into this. So we did that purposely and deliberately because we knew that that taxpayers in the community were going to be very critical because we have folks that still see this as a moral failing and not as an illness, which it is.

So we continue to work. I can tell you with these types of results coming and the political will, it's gaining in Hamilton County because of the success we're having. So we're very optimistic that when we finish this project at the end of 2019, or perhaps now into 2020, that we will have a sustainable funding stream, given perhaps something else that may occur with the state pharmacy boards and the medical boards in Ohio, as well as what you may do here, because this will not go away overnight.

So thank you for your comment. I hope I answered the question, but I allowed myself to give another slide or two.

(Laughter.)

DR. BROWN: Dr. Dasgupta?

DR. DASGUPTA: Commissioner Ingram, again, please.

(Laughter.)

DR. DASGUPTA: Slide 7 from your deck, if you don't mind. This is what you get from giving a great presentation. Slide 7, you have a line there for prescriptions. Would you mind explaining? Is that co-prescriptions?

MR. INGRAM: No. No, those would be single prescriptions. Ohio, in 20- -- I don't know the exact year, I might have to ask my legal counsel that gave an excellent presentation here, on when Ohio passed that you could get naloxone without a prescription. I think it was in 2016.

Those are individuals who have walked into a pharmacy and requested naloxone, went through the training, and then got a dose, and paid for it.

DR. DASGUPTA: How do you get those data from the pharmacies?

MR. INGRAM: We're getting it from -- the University of Cincinnati, Dr. Lyons is our

principal investigator. He's pulling this data from different data sources that are available to us.

DR. DASGUPTA: Okay. And then when you say treatment providers, is that drug substance abuse treatment providers?

MR. INGRAM: Yes.

DR. DASGUPTA: Okay.

MR. INGRAM: Yes, it'd be substance use disorder treatment providers or behavioral treatment providers in the Greater Cincinnati area.

DR. DASGUPTA: Okay. Thank you.

Dr. Davidson, the naloxone kit that you showed us, we couldn't see it from over here. Would it be appropriate to pass it around for us to take a look, get a real sense of what it is?

DR. DAVIDSON: Yes. I can pass it around. It consists of 2 doses of naloxone, 2 needles, and then information packet stored in a needle disposal container.

Oh. We can't? Apparently, we can't pass it around. Sorry.

(Laughter.)

DR. BROWN: Dr. McCann?

DR. McCANN: Mary Ellen McCann. This is for Commissioner Ingram again. You probably mentioned it, and I just blanked out. On slide 15 when you talked about the remarkable decrease in morality and emergency room visits, do you have any data about how much illegal drugs were coming into that county, Hamilton County, during the study period as opposed to before the study period?

MR. INGRAM: Could you just repeat that question again? How many drugs did you say?

DR. McCANN: Illegal drugs or basically -- I don't think this is the reason for your remarkable results, but one possibility would be that there were no illegal drugs getting into Hamilton County.

MR. INGRAM: No. There are illegal drugs getting into Hamilton County.

DR. McCANN: Right.

MR. INGRAM: I will tell you, this is a public health initiative, and I talked about the other two variables that could be contributing to

this reduction. Also, there's a lot of work going on by law enforcement in our community and the Drug Enforcement Agency.

I don't know why Ohio became the epicenter, not just for the state but almost for the country, it seemed like. You were hearing about Ohio, and I can still remember when I was standing next to the corner in 2016 when carfentanil hit the streets for the first time, we didn't even know what it was. And then in August of that year, we had 128 overdoses in one week and lots of deaths.

So we still have a problem. And if there was a lady or a gentleman standing up here in law enforcement, they would tell you there's still a huge problem with illicit drugs hitting the streets of Hamilton County and Greater Cincinnati. And although they're doing a great job, they're trying to reduce the supply on the streets, it's still there.

DR. McCANN: So the question is, do they feel that they've reduced it a little bit or that more drug is just flooding the county?

MR. INGRAM: I will speak anecdotally based on the work I've done with our partners in blue because we work closely with them. They tell me that it's become more difficult than ever because of the fentanyl composition, because fentanyl, it takes so little to cause so much harm and so much damage. And it's easy to be shipped, hidden, and so forth. They said I think it's ever harder because of fentanyl.

Fentanyl has now become the drug of choice. We don't have a heroin problem in our community anymore. We have a fentanyl problem.

DR. McCANN: Thank you.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: This is also for Commissioner Ingram. On slide 13, you showed the data on the people who were getting these take-home cartons. And I was really struck by the fact that it's 40 percent across the row, and it's really almost 50 percent of the people you have data on had administered Narcan before.

My question is, that was surprising, and do

you have more information about that? And then how much do you think this was just an easy way for them to get a refresher kit of Narcan versus reaching new people?

MR. INGRAM: If I understood the question, and please correct me if I didn't, in the "no" column, obviously -- you're talking about the no category or the yes category?

DR. SHOBEN: The yes category.

MR. INGRAM: Yes category?

DR. SHOBEN: Yes.

MR. INGRAM: Almost 40 percent had administered Narcan, and then we were looking -- this is survey data, obviously. We're collecting. As we give out a carton of Narcan, we hand them the form, and we ask them to fill out the form.

We do training -- it's very easy. We have a very small brochure, and it's basically peel, place, push. It's three piece. And if they have any difficulty, we'll even show them exactly how to do it on one that's already been injected.

What was your other question, ma'am? I'm sorry.

DR. SHOBEN: That seems really high to me, that you had so many people who said they'd administered Narcan before getting a package from you? I guess, where are they getting it from, and how much is this reaching new people versus people who had previously had access to naloxone?

MR. INGRAM: This doesn't mean that they hadn't had Narcan before.

DR. SHOBEN: Sure.

MR. INGRAM: This is just the ones that were coming through the different distribution sites that I showed earlier. I know I'm not answering your question. Go ahead.

DR. SHOBEN: If you think about -- in my mind, the real test of how well this is flooding the market with naloxone work, ideally, obviously, not real world, but ideally, you would go somewhere where naloxone had never been available before and get a baseline of this is what the rate of what opioid-related deaths is, and then flood the market

with naloxone and see what it does.

This data suggested -- not that you haven't had fantastic results, but suggests that naloxone had been in the community before such that 40 percent of your participants had previously administered Narcan.

How much are you reaching new people versus just refreshing what was already in the community?

MR. INGRAM: Well, obviously, the no column is people that have not -- I mean, that tells the people that we're reaching for the first time. And I would tell you that we stood up the -- we call it the exchange project, which is the syringe exchange program -- a mobile unit, like a big RV with comprehensive services on it.

When we stood that up as a public health project in Hamilton County on January of 2018, we moved it specifically into those communities with the highest drug overdose death -- not just death but the highest overall drug overdose rates in our area. We went exactly to where the worst areas were.

I don't know how else to answer your question at this point. Thank you.

DR. SHOBEN: Thank you.

DR. BROWN: Dr. Macher?

DR. MACHER: I might suggest to Mr. Ingram he just wait until he doesn't have a question from someone, but I'm going to ask you another question. And I'm imagining the next question might be for you as well.

In looking at the data, most of the kits went to Hamilton County, but some of them went to your neighboring counties in Indiana and in Kentucky. And I'm wondering if there is either information you shared with your counterpoints in the counties as to whether they saw a direct reduction in ED visits and in drug overdoses, either directly because the kits you're supplying, or indirectly because of the social networks of the individuals you're providing kits to?

MR. INGRAM: Very good question. We have regional data too, which I didn't present today. And I did that deliberately because I wanted to

focus on just Hamilton County, Ohio, given that there will be some overlap based on that zip code information.

We have Narcan being distributed up in the Butler County, which is the second largest county in the Southwest Ohio area, next to Hamilton County, and they're seeing some reductions, too. But again, I would qualify that, that it's not just the Narcan Distribution Collaborative but because we also are trying to affect system change, but we know Narcan is helpful.

Also, we're seeing similar results in Clermont County too, which is the first county east of Hamilton County. But I specifically tailored this presentation to just give the data, the results on Hamilton County, Ohio. We are doing some regional work here.

I presume that when we finally publish this work in its final format, later in 2019 or early 2020, we'll be talking about the entire region. Thank you.

DR. BROWN: Dr. Pisarik?

DR. PISARIK: Paul Pisarik for Commissioner Ingram again. The naloxone that you'd been distributing is at no cost to participants; is that correct?

MR. INGRAM: That's correct.

DR. PISARIK: Do you think if naloxone were over the counter at a reasonable cost, that would make a difference also in your program? Would it help, like at the area more?

MR. INGRAM: If we charged, do you think it would --

DR. PISARIK: No. If naloxone was over the counter at a reasonable cost to the participants, do you think that would help to blanket the area even more?

MR. INGRAM: That's a good question. I thought about that a little bit because Ohio did kind of change -- well, Ohio did change the laws in 2016 to where you no longer had to have a physician's prescription to get naloxone.

In a sense, it's not over the counter, but in a sense, it almost is, if I can say that,

because you can walk in and get one. But, of course, the problem we have, and we've heard from various speakers, is there's that stigma that's attached, and that judgment that's occurring, and people somewhat are reluctant to do so, even still today.

I don't know. I really don't know. I'm so focused right now on just trying to make sure that we're putting the Narcan and also preventing the secondary infections that are occurring in our community because we are also starting to see an increase in HIV in the injectable drug use population, and I think that's a trend that's starting in the country. We're really focused on making sure that this doesn't get out of hand.

I would do anything that I could come back here and say, five years from now, that drug overdoses are no longer the leading cause death for people under the age of 50.

DR. PISARIK: Thank you.

DR. BROWN: Dr. Meisel?

DR. MEISEL: A question for the

commissioner. Again, I think you might as well just stand there. I just want to clarify -- first of all, again, congratulations for some outstanding work. The population that you're talking about are people, by and large, with opioid use disorder, right? We're not talking about anybody that gets prescribed OxyContin for chronic pain or those kinds of folks that we may be thinking about today in terms of do we have recommendations for co-prescribing, that sort of thing.

This is a very different population that you're describing; is that right?

MR. INGRAM: Yes, you're right. Predominantly, the people we are giving that, the syringe exchange program is our most successful distribution site, we know those folks are injecting opioids because they're coming on for lots of other reasons, not just for the Narcan.

But I will say to you that we also know that there are folks coming to some of the other locations who perhaps are fighting prescription drug problems, too. But if I had to say what would

be the majority of the population, it is probably the folks that, for one reason or another, can no longer get their prescription drugs that they used to, and they have turned to the other opioids, illicit opioids. That's probably the population we're reaching the most right now.

DR. BROWN: We're going to proceed now with our last presentation of the day from Dr. Barbara Cohen from the FDA.

FDA Presentation - Barbara Cohen

MS. COHEN: Thank you. Good afternoon. I'm Barbara Cohen, a social scientist with the Division of Nonprescription Drug Products, and I'm here this afternoon to talk about the Nonprescription Model Drug Facts Label Project, which I have led under the direction of Dr. Karen Mahoney, the deputy director of our division.

Here's an overview of what I'm going to discuss today. First, why OTC naloxone? Second, to put this project in context, I'll provide a general overview of the types of consumer behavior studies, including label comprehension studies that

companies may be asked to conduct when they're seeking to introduce a new therapeutic category into the OTC marketplace.

I'll provide insights into the process and challenges we at FDA faced in developing the model Drug Facts Label, or DFL, for OTC naloxone. And I'll talk about the rigorous label comprehension testing that we conducted to evaluate this model DFL. Finally, I'll conclude by discussing the current status of the study, as well as next steps.

Why OTC naloxone? Well, the goal quite simply is to make naloxone broadly available on store shelves for anyone to purchase, like any other nonprescription drug product.

Although naloxone availability has been significantly expanded in recent years through programs like, for example, standing prescription orders and others we have been hearing about today, still, these can require people to interact with a healthcare professional such as a pharmacist before they obtain the product. And it's believed that this can serve as a significant barrier for many

individuals, for example, the U.S. Surgeon General Advisory, and we talked about that earlier today.

When industry sponsors are embarking on development programs for Rx to OTC switches that would represent a new therapeutic OTC category, often they are able to rely on the safety and efficacy for the prescription product, although new clinical studies may be required, if proposing a new indication or a new patient population.

At any rate, what's always necessary is to translate key elements of the prescription label into consumer-friendly terms for the DFL with potential consumer studies needed to evaluate the OTC-ness of the product.

In terms of the differences, just to refresh all of our memories between a prescription label and an OTC Drug Facts Label, here's a prescription label. Keep in mind that this is intended for a healthcare provider audience and as such has many pages of text. By contrast, the OTC label intended for consumers with very little real estate available.

Here are the types of consumer behavior studies that we might ask the sponsor conduct, and here is what they assess. Label comprehension studies evaluate whether consumers can understand the key label messages. Self-selection studies evaluate whether consumers are able to choose the appropriate product for themselves personally, given their specific medical conditions and other medication usage.

Actual use studies seek to understand whether consumers can take a product home and use it according to the label directions. And human factor studies assess how consumers actually prepare a product for use and administer the product.

FDA had engaged with potential naloxone OTC companies in a 2015 public scientific workshop, exploring naloxone uptake and use, held in collaboration with NIDA, CDC, SAMHSA, and HRSA. We explained the typical development program that might be utilized for an Rx to OTC switch of a product that could lead to a new OTC therapeutic

category.

The feedback subsequently received was that some sponsors perceived the need to do these studies as a barrier to development. That feedback led FDA to initiate this project. We proposed an innovative approach. We decided on the goal of developing a model DFL that could be understood by all potential individuals who might use naloxone, and then rigorously refining and testing that DFL through qualitative and quantitative label comprehension research, conducted through a competitive contract by experienced consumer research firms, also with expertise in conducting studies with substance abuse populations. FDA would then conduct an independent review of the data.

We further decided that if successfully tested, this model DFL could serve as a template by which a sponsor could add information specific to their specific product or device, and then assess through human factors the comprehension of that product-specific information.

After further consideration of multiple factors, such as the circumstances of use and practicality of study conduct, we decided that the label comprehension study in this instance was the key study to be conducted, and that self-selection and actual use studies were likely not needed.

I'm just going to spend a minute further discussing what's involved generally with label comp studies before moving to the specifics of this project.

Typically, the first step after development of a draft label is to identify key communication objectives, the most important concepts on that label that need to be understood by the consumer.

Questionnaires should be constructed in a way that targets these communication objectives in an unbiased manner. And it's also important to us to enroll a demographically diverse population, particularly with regard to limited literacy individuals since the average reading level in the United States is estimated at the 8th grade.

We're ideally looking for Drug Facts Labels

to be written at a 4th to 8th grade reading level, and in the testing, limited literacy subjects should be incorporated as assessed by validated instruments.

Here are the unique challenges faced in developing an OTC naloxone Drug Facts Label. There are always challenges that companies face when reducing a full Rx-prescribing information down to the key essentials of the DFL as I just presented.

However, OTC naloxone represented a particularly unique situation. Unlike any other OTC drug, it's intended to be administered by one person to another in a situation where one person is unresponsive and every second counts. Furthermore, the person administering the product also needs to call 911 and stay with the unresponsive person to prevent death by relapse, as well as to continue to dose at 2 to 3-minute intervals if the person is not revived.

Obviously, this is all taking place in a highly stressful emergency situation in which it can't be assumed that the person administering the

product ever was trained or read the instructions even in advance before it became necessary to administer naloxone. In other words, we had to assume that the person was reading the label for the very the first time, to be conservative.

In light of these unprecedented circumstances, FDA made the decision to significantly simplify the label by distilling it to its key elements.

To address these challenges, we -- and here, I want to emphasize that we had a whole project team comprised of medical officers, social scientists, labeling experts, and the other relevant disciplines -- analyzed the Rx label and conducted a literature review to incorporate the elements of most clinical importance.

We also solicited input from the addiction treatment community, including naloxone distribution programs, as well as both internal and external substance abuse experts. The goal there was to identify recurring themes and best practices so as to determine the most critical elements for

inclusion in the DFL.

At the same time, we also sought input from our internal communication experts about the best ways to present this information. The resulting DFL was accompanied by adjacent pictograms, a first for nonprescription products.

I should also note that 2 product forms of naloxone were available at the time this study was initiated; that is the nasal spray and autoinjector. Proposed model labels were developed for each, identical except for a placeholder section that described administration, and in the subsequent testing, the labels were rotated.

Now, I'll discuss the process of testing the DFL. Simultaneous to the development of the model DFL, we crafted a statement of work that was based on the fundamental principles outlined in our label comprehension guidance, as well as additional best practices.

To optimize results, an iterative design is utilized in the formative stage. The label can evolve in real time as feedback is continuously

gathered from participants. In this case, we conducted one-on-one interviews to gain valuable feedback on a label. We further built on these best practices by then conducting a pilot study based on the revised draft, where we assessed recruitment methods, data collection tools, and appropriate sample size for the pivotal based on the thresholds we were aiming to achieve.

Finally, after findings from the pilot study were assessed, we proceeded with the pivotal study. Here, regarding the pivotal study, I also want to acknowledge the tremendous contributions of our statistical team, who was involved particularly with the pivotal quantitative study all the way from the development of the statement of work initially, through the creation of the statistical analysis plan, and culminating with the rigorous independent review of the pivotal study dataset.

Just aligning with what I said before, here's how the study was divided into the three tasks.

Task 1 was to conduct unstructured cognitive

interviews so as to obtain rapid feedback about the model DFL from potential end users. There were 36 participants interviewed in this task.

Task 2 was to evaluate the label comprehension recruitment methods, interviewing techniques, data collection tools, and appropriate sample size through pilot study, again involving 36 participants. And finally, task 3 was to evaluate the label through a pivotal quantitative study with 710 participants.

Now, I'm going to discuss the key target populations because another of our best practices is that the study population include all subjects who could potentially use, in this case, OTC naloxone, and be large enough to provide a reliable demonstration of key communication objectives.

We wanted to include a significant number of those who used opioids, both prescription opioids and heroin and/or fentanyl, as well as family members and friends, who I refer to on this slides as associates. These associates did not use opioids themselves but who might be called upon to

administer the drug.

We also wanted to include adults and adolescents who were, in a sense, all comers. In other words, they were recruited for this study through typical research databases, having nothing to do specifically with opioid use. This is because anyone needs to be able to pick up a label and understand it, not just those who are knowledgeable about or connected in some way with the therapeutic category. An opioid-naïve person today may have the need to administer the drug tomorrow.

Here are the 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; and a composite endpoint, check for suspected overdose, and give the first of the medicine, and call 911.

Product use is for the treatment opioid overdose. And the signs of the overdose are 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.

These are the secondary endpoints. It's 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.

As I mentioned earlier, a well-designed study involves a geographically-diverse population, so I just wanted to touch on the locations for the pivotal study.

For individuals who used opioids, community-based organizations and substance abuse centers, treatment centers in Chicago; Charleston; West Virginia; San Francisco; and Raleigh-Durham, and for adults and adolescent all comers, marketing research sites in Tampa; Dallas; Los Angeles; Indianapolis; Raleigh; and New York City.

Additionally, in the iterative phase of the project in tasks 1 and 2, the pilot study, research was conducted in other locations with high rates of

opioid abuse such as Columbus, Ohio and Baltimore, Maryland.

The current status of the study is that it's been completed by the contractor, and currently, the report and dataset are undergoing a thorough review by an independent team of FDA reviewers. As far as next steps go, once the review is finished, the results will be released publicly.

If the Drug Facts Label has been determined to achieve sufficient comprehension, industry may adapt it to their products. If it is not successful, the lessons learned from this process will still be valuable to sponsors looking to develop a DFL for naloxone OTC.

In any event, the study will hopefully serve to significantly expedite the consumer behavior testing program and allow for a faster OTC transition for naloxone.

Thank you. And I just want to acknowledge all of the many, many people at FDA, in so many different divisions and areas of the agency, who have worked on this project.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for the speaker? Dr. Besco?

DR. BESCO: Kelly Besco. I'm not sure the correct way to frame this question. In thinking about these products moving out from behind the pharmacy counter, I postulate that there may be a high degree of theft that would occur, and I'm just wondering how prior to making such a change in availability, how we might measure or better predict the theft potential of these products.

DR. MAHONEY: This is Karen Mahoney, deputy director, Division of Nonprescription Products. That's not a question that we have specifically considered. We do know that retail pharmacies as well as other retailers have theft prevention programs in place, but that's not a question that we specifically considered, but it's something to take back.

DR. BROWN: Ms. Robotti.

MS. ROBOTTI: You mentioned that you developed this label with only two of the three

naloxone products available. You did not consider developing a label for the injectable.

Is that so? Is there a reason why that was?

DR. MAHONEY: Karen Mahoney again. Although the labels have placeholders in place for two currently available community use of naloxone products, we would welcome programs for any kind of naloxone product.

The portion of the model DFL that included just a pictogram basically and very basic instructions for a specific type of product, that actually was not part of the testing. When a sponsor wants to come in for an OTC naloxone product, if the rest of the label is successful, what they'll do is they'll plug their device-specific information into that section and do limited retesting in a human factor's protocol. So any kind of naloxone product would be welcomed.

MS. ROBOTTI: So the manufacturer, whose name I do not know, of the injectable form of naloxone, they were not invited today, and they would have to come and apply for one of these

labels and to become OTC?

DR. MAHONEY: We have reached out to multiple naloxone manufacturers and IND holders, not just the current NDA holders, to welcome them to come in and talk to us about a naloxone OTC development program. Although you've heard today that the approved NDA holders don't see OTC naloxone as the way to go, that's not been the case across the board, and we have had lots of interest. So we see that as a positive.

DR. HERTZ: This is Sharon Hertz.

DR. MAHONEY: Did I answer your question, or is there further?

MS. ROBOTTI: You did. I just kind of feel they're underrepresented today and that they --

DR. HERTZ: This is Sharon Hertz.

MS. ROBOTTI: Hi.

DR. HERTZ: We invited anyone that we were aware of who had any interest that we could tell in developing a naloxone product. The ones who came are the ones who came, but nobody was excluded. Everybody was offered the opportunity.

DR. MAHONEY: Yes. I just want to emphasize again that we have reached out broadly to anyone who's interested in -- publicly, again today. We welcome it. Just send a meeting request to us, and we will respond. We haven't turned down any meetings, and we won't.

DR. BROWN: Dr. Ciccarone?

DR. CICCARONE: I appreciate this conversation and the labeling project. If someone could just spell out to me, what, at this moment, are the barriers to having an OTC naloxone product? The labeling, I see as one. Congratulations on that. What are the other things? Getting a company to move forward, I think I'm hearing is another?

DR. MAHONEY: Karen Mahoney. We have been listening closely to see what people perceive as the barriers. As Ms. Cohen mentioned, the need to perform a consumer behavior study was one thing that was mentioned as a barrier. So we decided to take that barrier away, and we found some funding, and we were able to do the study.

A potential sponsor of an OTC naloxone product would need to come in and meet with us about their development program. That would most definitely be very beneficial for them because they could get our feedback and help.

We've been holding those meetings with a very high priority. Then they would need to put together a package that would support the development of their program and send it in as an application. If a sponsor does that, it would have a very high priority in our review process.

DR. HERTZ: This is Sharon Hertz. There's not really a barrier. I mean we have a path to getting products approved. What we need is somebody who wants to go OTC, take advantage of the fact that the division has done all of this work. That's what we need. We need someone to come in.

DR. BROWN: Dr. Meisel?

DR. MEISEL: Steve Meisel, Fairview. This is less of a question, just more of a suggestion, and it's probably something that you haven't thought of.

There is a risk, I think, if this product were over the counter, that doesn't exist when it's used by healthcare providers, or with the assistance of healthcare providers, or dispensed by healthcare providers. And that is the risk of nomenclature confusion.

Naloxone and Naproxen, off the tongue, sound alike. I could easily see somebody who doesn't fully hear correctly think, I'm going to have to go get some of this stuff. And they go to the shelf, and they're familiar with Naproxen. They pick some Naproxen solution, and when some crisis happens, they try to stick it up somebody's nose.

That sounds absurd. For everybody in this room, it is absurd. But I have seen more preposterous things happen out there, and I can almost guarantee you that would.

So as we consider whether or not to make this product over the counter, I would encourage the OTC division to be cognizant of this risk and to think about strategies to ensure that people don't make mistakes by that kind of nomenclature

confusion.

DR. MAHONEY: Thank you for that. Our Division of Medication Error Prevention and Analysis was involved in our development of the model Drug Facts Label, and they have been very helpful. We expect their continued involvement as we go along. It's a very good point, and it's actually something that is considered for any drug that comes forward for approval.

DR. BROWN: Dr. Besco?

DR. BESCO: Yes. Kelly Besco, Ohio Health. I reside in Ohio, and I'm just starting to think to myself, I wonder how many people in my family know that there are standing order programs available for naloxone, that they could go in their pharmacy to obtain naloxone.

I'm just wondering if there have been any studies about patient and community knowledge about the existence of standing-order programs. I guess that might be a panelist question or even for FDA. I'm just thinking, moving to OTC is a big move, so I'm wondering just about general knowledge of the

public about these standing-order programs.

DR. BROWN: Are there any other clarifying questions for these past presenters or for any of the presenters today? Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. Just one quick question for FDA of what you see the role of the over-the-counter product or the over-the-counter status for this product, because at least in my thinking and kind of what I heard, the population that we are missing with potential co-prescribing type programs, all the illicit drug use, I don't think would be the people taking advantage of an over-the-counter product unless it is incredibly heavily subsidized, which just the switch to over-the-counter wouldn't achieve.

Therefore, you'd probably get most interest of maybe parents of teenagers that are well off, that kind of -- but those people could probably also be relatively easily targeted by kind of standing-order programs. Then it's just kind of a question, does it lower the administrative barriers and maybe address some states where those programs

don't exist?

I think by looking at these things separately, I think the financial barrier is probably still the largest, and it doesn't go away with over-the-counter status.

That's maybe more a comment than a question, but I'm not sure whether you have given this some thought of what you'd achieve or what the goal of an over-the-counter status product would be.

DR. STAFFA: This is Judy Staffa. I think what we were trying to do was to tee up -- as we consider co-prescribing as a strategy, we wanted to tee up all the different strategies that we knew were going on out in the community and that we knew were going on internally at FDA.

We wanted you to hear of every idea we have heard of or thought of as a context in which to consider co-prescribing. So to my knowledge, we're interested in hearing your thoughts about exactly what you just asked us.

DR. MAHONEY: This is Karen Mahoney. The potential anonymity of OTC availability could be

another reason that it could increase uptake of naloxone widely. Right now, there's still the requirement for some kind of healthcare professional, a contact, for almost every kind of access to naloxone.

Another question that has been brought up a lot has been whether or not overall cost would go up if naloxone became available OTC. There are obviously many, many factors that go into pricing. We do have some experience with the switch of other products from prescription to nonprescription. And in general, with those, overall healthcare system costs have gone down.

One specific question is what would happen to the cost for individual insured persons, and we don't have an answer for that. We do know that in the nonprescription world, there is a price point above which the consumer generally will not go and that companies have generally priced the product with that in mind.

Those are just a couple of things that are potentially relevant to the cost question. We

don't know. I don't want to mislead anyone and tell you that we know definitively what would happen to cost. But we do have some experience with what's happened with other products.

DR. BROWN: Any other questions?

(No response.)

DR. BROWN: Dr. Hertz, do you have any comments before we leave today?

DR. HERTZ: Mostly just that I'm looking forward to the discussion tomorrow.

Adjournment

DR. BROWN: The meeting for today is now adjourned. We kindly ask that all attendees dispose of any trash or recycling and to take all of your personal belongings with you.

Panel members, please remember that there should be no discussion of the meeting topic amongst yourselves or with any member of the audience. We'll reconvene at 8 a.m., in the morning.

(Whereupon, at 4:46 p.m., the meeting was adjourned.)