FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Wednesday, October 5, 2016

8:00 a.m. to 5:09 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

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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)

P R O C E E D I N G S

(8:00 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, Michael Felberbaum, who should be in the back. There's Michael.

I'd like to welcome the members of the panel to this joint meeting. Today, we're going to discuss naloxone and its use in reducing death and disability associated with opioid use. These conversations are important in light of our current public health crisis, and the agency will use the data that they've received from us today to inform public policy in the future.

The information that will be presented is from the agency and from industry. Questions and statements about information presented here should bear in mind that the motivations of the meeting

are not about one specific product necessarily, but should reflect on the important but general questions posed by Dr. Hertz and the FDA.

My name is Raeford Brown. I'm the chairperson of the Anesthetic and Analgesic Drug Products Advisory Committee, and I'll be chairing this 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 introduce ourselves. Let's start down on my right.

DR. WOODS: Good morning. My name is Mark Woods. I am the clinical coordinator and residency program director in the pharmacy department at Saint Luke's Hospital in Kansas City, Missouri.

DR. WARHOLAK: Hello. My name is Terry Warholak, and I am an associate professor at the University of Arizona College of Pharmacy. I'm a pharmacist by training, and I have a PhD in outcomes. And my specialty is quality and safety.

DR. VINKS: Good morning. My name is Xander

Vinks. I'm a professor of pediatrics and pharmacology at the University of Cincinnati and also the clinical director of clinical division of clinical pharmacology at Cincinnati Children's Hospital. And I am a pediatric clinical pharmacologist and a pharmacometrician.

DR. PARKER: I'm Ruth Parker, professor of medicine, pediatrics, and public health at Emory University in Atlanta. I do a lot of work in health literacy and how to align content with people's ability to understand and navigate it.

DR. MEURER: I'm Will Meurer. I'm an associate professor of emergency medicine and neurology at the University of Michigan in Ann Arbor, and I actively practice emergency medicine.

DR. HUDAK: Good morning, Mark Hudak, neonatologist, professor and chairman of pediatrics at University of Florida College of Medicine in Jacksonville.

DR. HIGGINS: Jennifer Higgins. I'm the consumer rep to AADPAC.

MS. BERNEY: Barbara Berney, patient

representative.

DR. DAVIS: Jonathan Davis. I'm a professor of pediatrics at Tufts University in Boston. I chair the neonatal advisory committee in the Office of Pediatric Therapeutics here at FDA.

DR. STURMER: Good morning. Til Sturmer. I'm a professor of epidemiology at the University of North Carolina, Chapel Hill.

DR. McCANN: Hello. My name is Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's.

DR. EMALA: Charles Emala, professor and vice-chair for research, Department of Anesthesiology, Columbia University, New York.

DR. GALINKIN: I'm Jeff Galinkin. I'm a professor of pediatrics and anesthesiology at the University of Colorado. I'm a pediatric anesthesiologist, and I also do palliative care.

DR. CRAIG: David Craig. I'm a clinical pharmacy specialist at Moffitt Cancer Center in Tampa, Florida, and mostly do cancer pain and supportive medicine.

DR. GUPTA: Good morning. Dr. Anita Gupta. I'm vice-chair and associate professor of the Division of Pain Medicine at Drexel University in Philadelphia.

DR. BROWN: Once again, I'm Rae Brown. I'm a professor of anesthesiology and pediatrics at the University of Kentucky and a practicing pediatric anesthesiologist.

LCDR SHEPHERD: Good morning. I'm Jennifer Shepherd, designated federal officer.

DR. WALCO: Good morning. Gary Walco, professor of anesthesiology, pediatrics, and psychiatry at the University of Washington and director of the Pain Medicine Service at Seattle Children's.

DR. WINTERSTEIN: Good morning. I'm Almut Winterstein. I'm professor and chair of pharmaceutical outcomes and policy at the University of Florida.

DR. BATEMAN: Good morning. Brian Bateman. I'm an anesthesiologist at the Massachusetts General Hospital and associate professor of

anesthesia at Harvard Medical School.

DR. SHOBEN: I'm Abby Shoben. I'm an associate professor of biostatistics at the Ohio State University.

DR. HARRALSON: Art Harralson. I'm an associate dean for research at Shenandoah in the George Washington University here in D.C.

DR. ZUPPA: Good morning. I'm Athena Zuppa. I am associate professor at the University of Pennsylvania. I'm a pediatric intensivist at the Children's Hospital of Philadelphia, and I direct the Center for Clinical Pharmacology there.

DR. BEAUDOIN: Good morning. My name is Francesca Beaudoin. I'm an assistant professor of emergency medicine at Brown University. I'm a practicing emergency physician and a clinical researcher with a focus on substance abuse.

DR. BRENT: Good morning. I'm Jeffrey Brent. I'm a distinguished clinical professor of medicine and emergency medicine at the University of Colorado. I am a medical toxicologist by subspecialty, and my primary interest is in the

intensive care management of acutely-poisoned patients.

DR. FUCHS: Good morning. I'm Susan Fuchs, professor of pediatrics at Feinberg School of Medicine of Northwestern University and also a pediatric emergency medicine physician at Lurie Children's Hospital, and my interest is emergency medical services for children.

DR. MAXWELL: Good morning. I'm Jane Maxwell. I'm a research professor at the University of Texas in Austin, and my specialty is epidemiology, particularly of substance abuse.

DR. NELSON: Good morning. Lewis Nelson. I'm the chair of emergency medicine at Rutgers New Jersey Medical School in Newark, New Jersey, and I'm a medical toxicologist at the New Jersey Poison Center.

DR. WU: Good morning. My name is Victor Wu. I'm vice president for clinical transformation at Evolent Health and an assistant professor for internal medicine at George Washington University School of Medicine.

LCDR CHAI: Good morning. My name is Lieutenant Commander Grace Chai, and I'm the deputy director for drug utilization in the Division of Epidemiology II for FDA.

DR. LLOYD: Good morning. Josh Lloyd, clinical team leader in Division of Anesthesia, Analgesia, and Addiction Products.

DR. HERTZ: Sharon Hertz, division director, same division.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for public health initiatives in the Office of Surveillance and Epidemiology at FDA.

DR. BROWN: Dr. Herring?

DR. HERRING: Good morning. I'm Joe Herring. I'm the executive director of clinical neuroscience at Merck and industry representative to the AADPAC.

DR. BROWN: Welcome again to everyone.

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 a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle 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 are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the 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 will 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 the 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 these committees 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 these committees' compliance with the 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 the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized 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 discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interests 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 discussion of naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages and the role of having multiple doses available in this setting.

The committees will also be asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision if multiple doses are available.

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. Joseph 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.

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 committees of any financial relationships that they may regarding the topic

that could be affected by the committees' discussions. Thank you.

DR. BROWN: We will now proceed with the FDA's opening remarks from Dr. Joshua Lloyd.

FDA Introductory Remarks – Joshua Lloyd

DR. LLOYD: Good morning. Dr. Brown, members of the Anesthesia and Analgesia Drug Products and the Drug Safety and Risk Management Advisory committees, and invited guests, thank you for joining us for this general matters meeting to discuss the development of naloxone products intended for use in the community.

As you are well aware, the opioid overdose epidemic is a public health crisis in the United States, and it's associated with significant morbidity and mortality due to life-threatening CNS and respiratory depression.

Naloxone has been and continues to be a critical component in addressing this epidemic. We at FDA have supported and undertaken a wide variety of activities to expand the use of naloxone in the community to directly impact this crisis and save

lives.

Expanded access to naloxone in the community is one component of the commissioner's opioids action plan, which outlines FDA's plan for addressing this epidemic.

Naloxone use in the community has traditionally consisted of supplying kits that involve off-label administration of commercially available parenteral products. These kits include a syringe and a mucosal atomizer device to allow for intranasal delivery or, less frequently, a syringe and a needle to allow for intramuscular injection and are often accompanied by training.

We have developed a regulatory approach for approval of new naloxone products for use in the community, given the ethical and logistical challenges associated with studying new products in this setting, which you will hear more on later.

Namely, new products are required to demonstrate comparable or greater exposure to naloxone, particularly in the critical early moments after administration of the drug, as

compared to those levels achieved with Narcan, which was approved to reverse the effects of opioids in 1971.

Generally, the standard comparator has been 0.4 milligrams of naloxone intramuscular. We now have two products that have met this standard, Evzio, approved in 2014, and Narcan Nasal Spray, approved in 2015. These products are specifically approved for use in the community along with instructions for use and require no additional training.

Subsequent to these approvals, various stakeholders have expressed concern that the dose may be too high over fears of precipitating an acute withdrawal syndrome. And other stakeholders have expressed concern that the dose may be too low due to the possibility of failure to adequately reverse an opioid overdose in a timely fashion in a setting where additional supportive measures and medical expertise may not be immediately available, particularly when highly potent opioids are involved.

This morning, you will hear presentations from the agency about the activities we have undertaken in support of expanding access to naloxone in the community, including the regulatory approach we developed for studying in establishing the safety and effectiveness of these products, as well as the clinical issues surrounding these products in both pediatrics and adults.

You'll also hear about the utilization of naloxone products. Dr. Faul from the CDC will present recent findings regarding the need for multiple doses of naloxone to reverse opioid overdose in several areas of the country.

Today, you will be asked to discuss whether the current minimum standard for approval is adequate, and if higher doses are recommended, how to weigh the need for efficacy against the risk of precipitating an acute withdrawal syndrome.

We will also ask you for advice about naloxone dosing for pediatric patients and how to integrate that into these programs. Also, as more products are under development and seek marketing

approval, we will ask your advice on whether there's a benefit in having different doses of naloxone available and how a clinician can determine which product or dose to prescribe.

Additionally, we will seek your advice about the utility of products that require assembly by the person administering the drug or more than basic instructions for use.

Your advice and recommendations will be essential in assisting us as we move forward with the development of community use of naloxone products in an effort to further expand access to this life-saving drug. We are grateful that you have agreed to join us and look forward to this extremely important discussion. Thank you.

DR. BROWN: Thank you, Dr. Lloyd.

We're now going to begin with industry presentations, beginning with Adapt Pharma Operations, Limited.

Industry Presentation - Seamus Mulligan

MR. MULLIGAN: Good morning, ladies and gentlemen. Adapt Pharma, as the sponsor for the

only FDA-approved naloxone nasal product, Narcan Nasal Spray, is pleased to be here today.

My name is Seamus Mulligan. I'm a pharmacist, and I'm also CEO of Adapt Pharma. Adapt Pharma's sole focus is the development and distribution of Narcan Nasal Spray. We have no other business activities. We are focused solely on Narcan Nasal Spray.

I am joined here today by several of my colleagues, as well as experts in the field of pharmacology and anesthesiology, Dr. Pesco Koplowitz and Dr. Joe Pergolizzi. But interestingly, I'm also joined by Chief Joe Ryan, who oversees the naloxone distribution program for 620 law enforcement officers in Delaware County, Pennsylvania.

They have successfully deployed Narcan Nasal Spray since April of this year, and Joe can give you some real-world experience on the use of Narcan Nasal Spray and address some of the questions regarding adverse events and efficacy as they see it in the real world.

During our brief presentation, I'm going to review Narcan Nasal Spray, summarize the current situation as we see it, and provide you with our dosing recommendations and suggestions together with support for those suggestions, including some data on field experience with Narcan Nasal Spray since launch.

Let me first start by briefly describing the product. Narcan Nasal Spray, 4 milligram, was developed with input from the National Institutes of Drug Abuse and was approved by FDA under priority review in less than 14 weeks last year.

The approval occurred in the fourth quarter of 2015. The launch of the product occurred in quarter 1 of this year. So it's been on the market now seven months, and it's been rapidly adopted. Over 360,000 doses have been distributed across the nation to a wide variety of organizations and entities, including the VA, law enforcement, community organizations, and retail pharmacies. The product continues to grow rapidly.

Now, just to give you a look at the profile

of the product, I know some of you have read it in the background briefing materials, but there's no harm to repeat it, it's 4 milligrams of naloxone contained in 100 microliters or 0.1 of a mL. The product is single use. It is a needle-free nasal delivery system.

The product is supplied pre-filled. It's ready to use. It requires no priming, no assembly, or no training. Importantly, it is non-titratable. An actuation of the device provides for delivery of the full dose. The product is also supplied blister-packed with two devices per carton. The devices are individually blistered, not co-blistered.

Turning now to the product and how it works, it's very simple. The slide here illustrates just a picture of the product. You simply place the nozzle in the nostril and click to actuate delivery of the 4 milligrams. We developed this unique product to support easy and affordable access to a broad range of caregivers or witnesses in the community.

So the product looks like this, just to give you an actual illustration of it in action. The device you see pictured on the slide is a physical version of the device. That's the size of it. You'll see it like that. You insert this barrel into the nostril, and then that's 100 microliters actively delivered. That, by the way, is a placebo.

It's simple and easy to use, and even in stressful situations, like this is for me, I'm able to actuate and deliver the product. So it's important to have a product that can be used in such an easy fashion.

Now, I know it's not the aim of today's meeting, but you can't talk naloxone without talking about price. I mentioned earlier we designed the system to be easy and affordable.

In terms of affordability, when the product was approved, we announced at the time of approval a public interest price of 37.50 per dose or $75 per carton of 2 doses. And this price is available to all first responders, law enforcement, and

community organizations across the nation.

It is available regardless of size. The smallest state county and health board or police force can get the same price as the largest city organizations, and that is important. They come direct.

Narcan also has extensive insurance coverage because as we seek to broaden use in the community, insurance coverage is a barrier, and we have worked hard to ensure that the broadest coverage is available. Today, we have I think approximately 88 to 90 percent of all insured lives in the United States covered for Narcan Nasal Spray, and of those, 46 percent have a zero co-pay, so price is not a barrier to access. And in that regard, 78 percent have a co-pay of $10 or less if they have insurance.

We also work with CVS and Walgreens to partner for distributions to allow access and price for people who walk in off the street to buy the product. So it's important to manage all groups to afford ease of access and price. And I'm pleased

to announce today that Medi-Cal has agreed to cover Narcan Nasal Spray at a $0 co-pay. And that provides for unrestricted access to Medi-Cal's 13 million beneficiaries.

Now, that's giving you some background on the product, how it works, the physical attributes of it. Here are some of the more scientific attributes of it, the pharmacokinetic properties. And I list here some of the data from the pivotal studies, which were conducted in conjunction with NIDA and which form part of our NDA.

If you look at the graphs on the right, you show the naloxone plasma levels and concentrations at various time points, over a 4-hour period post-dosing of 1 and 2 doses of Narcan Nasal Spray, 4 milligram. And this is compared to the 0.4-milligram naloxone intramuscular injection, which is the lower black line.

For me, the key points are, you can see the rapid absorption achieved for the Narcan Nasal Spray and the dose proportionality of the product. In addition, one Narcan Nasal Spray delivers total

naloxone exposure of approximately 5 times that achieved with the 0.4-milligram injection of naloxone.

The relative bioavailability was 47 percent compared to the IM injection, and this is very different to the low bioavailability of the improvised nasal device, which is reported at anywhere from 5 to 20 percent with wide variability. So Narcan Nasal Spray, 4 milligrams, should fall within the top end of the currently-approved safe and effective dose range, which is 0.4 to 2 mg by injection.

Finally, I would also note that the variability, which is important when you're looking at physiological differences as well on nasal products, for Narcan Nasal Spray was low and similar to the injection.

I'm going to break the data out a little bit differently and look at the critical early time points. This table here shows that Narcan Nasal Spray achieves plasma concentrations of between 3.5- and 6-fold, that of the 0.4-mg IM injection at

a period of between 2.5 minutes and 20 minutes post-dose. So this is just the multiplier, the fold higher increase that the Narcan Nasal Spray, 0.4 milligram is over the IM injection. We also think that the high levels of naloxone concentration at these early time points are critical for opioid overdose reversal.

Turning now to the situation as we would see it, naloxone is well established, having been approved since 1971, and we know that in a clinical setting, reflecting the long-established dosing guidance, it is recommended that clinicians administer an initial dose in the range of 0.4 mg to 2 mg by injection, with subsequent titration of up to 10 mg.

But let us think about the community setting, which is why we're here today. According to CDC's WONDER database, 76 percent of overdose deaths happen in the community, and 70 percent of those community deaths are at a decedent's home. And per the WHO summary report, these overdoses are most likely witnessed by a family member or friend.

So in this setting, the primary goal is emergency treatment of opioid overdose as a bridge to medical care. But because of a lack of medical equipment and expertise at that point in the home, a different approach to dosing is needed. Simply, it's not practical in the community to support a clinical-based dose titration approach.

So in the absence of a better alternative, what has happened today? We've heard earlier from the agency. But there are multiple naloxone products, including non-FDA-approved improvised nasal versions in use in the community. The result can be a wide range of pharmacokinetic profiles, depending on how they're applied, which can lead to confusion and critically potentially different reversal rates in the community setting.

An adequate reversal dose for a given overdose event depends on multiple factors, not least of which is the type and dose of opioid involved and the person's opioid use history, or indeed the individual's physiological condition.

Now, this is critical in our view in the

community setting because you do not know these factors in advance. Now, a witness or a caregiver who is faced with an overdose on an unresponsive person cannot predict the appropriate initial naloxone dose needed.

So the important point here is that in a high-stress situation in the community, you do not normally have access to medical expertise and equipment to support a clinical titration dosing strategy.

So if a titration strategy is not possible, that leaves you with the obvious question. What fixed initial dose in the known safe and effective dose range would provide the greatest confidence of a consistently adequate dose and minimize the key risks of delivering too little naloxone too late?

So our dosing suggestions for community use and the rationale, I lay out in this slide. We have four clear suggestions for community-use naloxone products.

First, the naloxone products should provide for rapid onset because every second counts. The

delivery system should be as simple as possible to use without instructions or training beyond the supplied instructions for use, and a backup dose should be supplied.

But critically, because of the multiple unknowns in an overdose event, we suggest targeting an initial dose that gives the greatest confidence of delivering a consistently adequate exposure to naloxone.

In our view, it is simple. The prudent approach for all community-use naloxone products is to achieve plasma exposure that approximates the high end of the currently-approved initial dose range, and that is 2 mg by injection.

This ad comes at a particularly important time because consider this. We are trying to activate as potential first responders more and more people in the community who may not be medically trained. So it is different from before. We are trying to activate many more people to be familiar with and comfortable to use naloxone.

Collectively, we must insure that we provide

them with the right tool, and that that tool will deliver a consistently adequate initial exposure as a bridge to medical care. Anything more complicated just increases the likelihood of failure to reverse the overdose and recover the individual.

I'd now like to briefly review our rationale for this recommendation or suggestions under two critical headings, firstly, the exceptionally favorable risk-benefit profile of naloxone, and secondly, the dramatic rise in overdoses from high-potency opioids.

Naloxone has been FDA approved for 45 years or more for the treatment of opioid overdose, and you all know it. It's remarkably effective if an adequate dose is delivered in time. It works by comparatively binding to opioid receptors and temporarily displacing the active opioid.

The literature would suggest that in healthy adult volunteers, 50 percent mean, that opioid receptor occupancy is achieved with 1 mg of naloxone administered by injection, but the

2-milligram provides for 80 percent receptor occupancy; 2 mg by injection is at the upper end of the recommended initial dose range.

Turning to the pediatric population, the American Academy of Pediatrics recommend a minimum dose of 2 milligram by injection in children weighing 20 kilos or 5 years old.

Now, not to argue, but lower doses have been used successfully to reverse opioid doses for many years. And while the success is unquestioned, the success rate is unknown, especially in the face of growing higher-potency opioids.

I want to share with you today the interim results of a recent study performed in Finland on Narcan Nasal Spray using C11 radio-labeled carfentanil. I believe it's especially important to reflect here today, given the emergence, the recent emergence of carfentanil, one of the most potent opioids in opioid overdose deaths.

I wouldn't normally want to present interim data, but it is important, especially when we're looking at the media narrative that is developing,

that naloxone does not antagonize carfentanil. You continually see it in the general media.

This data here shows that naloxone does. In an 8-person crossover, placebo-controlled PET study, using C11 carfentanil, performed in Finland, and comparing the impact of a commercially available Narcan Nasal Spray and a 2-milligram strength of naloxone nasal spray, the following conclusions were arrived at.

Firstly and important, given my comments about the media narrative that's developing, naloxone competitively antagonizes carfentanil. Secondly, the Narcan Nasal Spray, 4 milligram, displaced 88 percent of the C11 carfentanil, and the receptor displacement was faster for the 4 milligram.

Now, I believe this data supports the widely-accepted logic of greater naloxone exposure leading to greater effectiveness for naloxone and reflects the real-world experiences of many professionals using naloxone in medical settings today.

Turning to the safety of naloxone, the safety profile has been well characterized over many years. I should state here, for example, Narcan Nasal Spray is approved by FDA for use from 4 weeks old.

I list in the slides some of the warnings related to duration of efficacy: limited use in certain situations, possible cardiovascular events, especially those pre-existing cardiovascular issues. The understandable concern as it relates to neonates is by definition more likely to be managed in a medical setting and should not impact on community use.

I do want to spend, however, a few moments on the concern that naloxone may precipitate acute withdrawal symptoms in some opioid-dependent patients. Not all opioid-dependent patients experience these symptoms, and for those that do, the severity varies depending on those dose, and type, and degree of dependency.

The literature would suggest that the symptoms, while extremely unpleasant, are generally

transitory and non-life-threatening, and there is no evidence that acute withdrawal occurs in non-opioid-dependent persons, as you would expect.

Our recommendations are not designed to punish such patients where acute withdrawal occurs, to be clear on that, but it is to maximize the effectiveness of naloxone therapy in all populations contemplated under community settings.

Many overdoses are due to accidental or mistaken dosing or consumption, like the child or adolescent who consumes a parent's pain meds, or the grandparent who accidentally takes too many pills. They all deserve the best opportunity for reversal and recovery.

It's worth noting finally that in non-opioid-dependent patients, very high-potency doses of up to 90 mgs of naloxone have been well tolerated.

Now, in response to this outcome, Adapt commissioned an independent third party to perform a field survey to attempt to understand real-life experiences of Narcan Nasal Spray. Fifteen

entities who had received Narcan Nasal Spray were able to estimate they'd already achieved over 1400 reversals.

More importantly, though, for today's deliberations, 8 entities that captured verifiable outcomes data on 245 reversals were able to report a 99 percent reversal rate. Importantly as well, a review of detailed case reports for 196 reversals highlighted no adverse events in 62 percent of the reports.

The most common reported events were withdrawal, nausea, and irritability, which were consistent with known adverse events. No new safety concerns were identified.

Now, I would stress this was not a prospectively designed study in any shape or form, but it does give you comfort on effectiveness and adverse events related to this dosing regimen in the real world. And feel free to ask someone like Joe about how he finds the product, having switched to it.

We'll now move on to the second rationale

supporting our dosing suggestion, which relates to the dramatic rise in overdoses from high-potency opioids. We are at a critical turning point in this epidemic, which urgently requires us to consider the appropriate community naloxone dosing approach.

The epidemic has mutated, as you well know, into a more virulent fashion driven by high potency, rapid-onset opioids such as fentanyl and carfentanil, solely or in combination with other agents.

The trends are horrific. Some of this data here now is dated, but the CDC reported an 80 percent increase in deaths related to synthetic opioids in 2014 compared to the prior year. However, more recent state data shows this alarming trend has continued and multiplied.

For example, in the first half of this year alone, fentanyl and its analogues were implicated in 2 of every 3 opioid overdose deaths in Massachusetts, and a similar picture is emerging in communities across the country on a daily basis.

We have seen multiple direct warnings from CDC and DEA. The most recent was 10 days ago, I think, from DEA, warning of the dangers both to opioid users and to law enforcement from accidental contact or inhalation.

Clinical experience and literature would identify that these highly potent synthetic opioids like fentanyl require rapid and increased naloxone exposure. That is because fentanyl is multiple times more potent than other opioids such as morphine or heroin.

It's also highly lipophilic, exerting its peak respiratory depressive effects within 5 to 15 minutes, and many of you are very familiar with it. An even more aggressive impact is to be expected with carfentanil, which is a more potent agonist again. Accidental inhalation of just the drug dust can be sufficient to lead to an overdose.

Now, what complicates the matter further, however, is much of the fentanyl and carfentanil is illicitly manufactured and being covertly added to or substituted into illicit heroin, or pain pills,

or even cocaine. The impact, therefore, is, there is little dose controlled by the user or patient, and opioid users don't know what they are taking. The risk is clear cut. Lower doses of naloxone may deliver too little naloxone, too late.

We continue to see in multiple media reports, in CDC and DEA warnings, and in EMS state-level data, such as that from Massachusetts, and I expect we'll hear more later today, that these rapid-onset and high-potency opioids need multiple doses of the lower strength naloxone products. The most recent one was a media report, which indicated 14 doses required.

Now, not only does this increase the cost of therapy, but more acutely, the delay in administration threatens the actual ability to recover a person in time, and it also raises practical risks when talking to first responders, the practical risk that that responder may not have multiple improvise kit or auto-injectors available on hand.

So in conclusion, in a community setting, a

dosing approach is not viable. This is because there are multiple unknowns about an adequate dose, and there's a lack of medical expertise or equipment to support titration.

Therefore, an alternate fixed initial dose approach is required when used in a community setting as a bridge to medical care. The question, therefore, is whether we should target naloxone exposure at the low or high end of the initial approved dose range.

Adapt's view is that exposure at the high end of the known safe and effective initial dose range, which is 2 milligrams by injection, is supported by naloxone's favorable risk-benefit profile. And moreover, it is required by the dramatic rise in overdoses from high-potency opioids.

So whether it's for the safety of first responders, or someone who accidentally overdosed on their pain meds, or a person who chronically uses opioids, the bottom line is that the new face of the epidemic needs new naloxone tools.

That naloxone delivery system should support safe and easy use and allow reliable and rapid administration of a non-titratable dose. And as we've said earlier, a backup dose should always be provided.

Finally, we urge FDA to issue guidance to provide clarity on the appropriate dose for community use and to address the dangerous misconceptions in the general public that naloxone may not work against certain opioids when we know it is about adequate dose and time to deliver. The status quo risks a situation for some persons of too little naloxone, too late. Thank you very much.

DR. BROWN: Thank you very much. We'll now move to Amphastar Pharmaceuticals.

Industry Presentation - Jason Shandell

MR. SHANDELL: Good morning. I'm Jason Shandell, the president of Amphastar Pharmaceuticals. Amphastar is the parent company of IMS, which has been making naloxone in a pre-filled syringe for over 30 years. We are

honored to be here today at the FDA to present our views regarding the use of intranasal naloxone in the community.

Opioid overdose has become a serious epidemic in this country. We believe that expanded use of naloxone is an important part of the solution to this tragic problem. For many years, first responders have been successfully administering our naloxone intranasally to reverse opioid overdoses.

Today's presentation will focus on our views regarding the safety and efficacy of intranasal naloxone. Following my introduction, my colleagues will discuss the historical use of our product intranasally and the development of our new intranasal product, which is currently under FDA review.

Overdose prevention programs distributing naloxone started back as far as 1996. Opioid overdose has become a major public health crisis. From 1999 to 2004, more than 165,000 people have died in the U.S. from overdoses related to

prescription opioids.

Intranasal naloxone is highly effective due to the large and highly vascularized area of the nasal airway, which allows for fast absorption. Reported clinical evidence and multi-state survey data regarding intranasal naloxone use demonstrate that intranasal administration is safe and highly effective for opioid overdose reversal.

This slide demonstrates that the nasal airway volume varies widely from 3.5 mL in neonates to over 55 mLs in adult males. This is an important factor to consider when formulating an intranasal naloxone product.

Compared to naloxone injection via intramuscular, reformulated intranasal naloxone should provide for safety and efficacy. With respect to efficacy, quick onset is a must. There should be comparable or higher partial-time naloxone concentration as compared to the 0.4-mg intramuscular dose. In terms of the safety, there should be same or less total systemic exposure as compared to the 2-mg intramuscular.

In addition, intranasal naloxone should provide for the ease of use for both medical professionals and laypersons, as demonstrated in human factors studies. Additionally, there should be no introduction of meaningful side effects such as local irritation or acute withdrawal syndrome, known as AWS.

Finally, we recommend administration into one nostril with a second unit that is readily available if needed. I will now turn the presentation over to my colleague, Tony Marrs, who will discuss actual use data from two overdose prevention programs. Thank you.

Industry Presentation - Tony Marrs

MR. MARRS: Hello. My name is Tony Marrs. I'm the vice president of clinical operations at Amphastar Pharmaceuticals. Today, I'm going to be discussing our examination of intranasal off-label use of IMS naloxone injection in two overdose prevention programs.

As part of our evaluation, we performed a retrospective case study using two programs from

two states, New York and New Jersey. These were done using the IMS naloxone injection in a 2-milligram-per-2-mL configuration.

It was used off label intranasally. The rescues were performed by first responders, primarily police officers and firefighters in a community setting. We used data from the two state agencies listed here.

In this evaluation, we were given case reports from about 1700 treated victims of which nearly 1400 had complete records and were considered as the opioid overdose population, of which I'll be describing in the subsequent slides.

In this population, the average age was 31 years, 70 percent were male, and the majority were Caucasian. When we looked at the number of units used for treatment, we found that 98 percent of reversal attempts were performed with 1 or 2 units.

There were significant findings when we looked at victim survival rate. The overall survival rate was 93.9 percent; 84 percent of the

victims responded within 5 minutes; 98 percent of the victims required only 1 or 2 units to reverse, using an average of 1.4 units for their rescue attempts. We also looked at cases in which fentanyl was used. In these 8 cases, we found a 100 percent survival rate using 1 or 2 units of naloxone.

The majority of victims were 18 to 64 years with pediatric victims having 100 percent survival. There was little variation in survival rates based on race. Similarly, we see high survival rates for gender between the two categories. As stated earlier and shown here, the majority of victims were reversed with the administration of 1 or 2 units of naloxone.

When we look at severity, we see that victims with the most severe initial status, defined as not breathing and not having a pulse, had an 80 percent survival rate. Those deemed very severe with no breathing or no pulse had almost a 97 percent survival rate. Victims with slow breathing and/or a slow pulse had the highest

survival rate, 100 percent. When analyzed by state, New Jersey and New York had similarly high survival rates.

In conclusion, we found the following. There was a high overdose reversal rate of 93.9 percent. We found that reversal is very quick with 84 percent of victims responding within 5 minutes. For the number of units used, we find that 98 percent of victims received 1 or 2 units. Therefore, we believe a 2-unit kit is necessary and appropriate.

The use of intranasal naloxone, 2 milligram per 2 mL, was found to be safe and effective. Now, I'll turn it over to my colleague, Dr. Robert Cormack.

Industry Presentation – Robert Cormack

DR. CORMACK: Thank you, Tony.

Good morning, everyone. I am the senior director of regulatory affairs at Amphastar, and today, I will present our thoughts on development of intranasal naloxone products for use in the community.

A successful intranasal naloxone product for use in the community setting should have the following features. Any naloxone product, not just intranasal ones, should be emergency-ready in that the first responder or bystander can quickly unpack and administer the drug in an easy and rapid manner.

It is important that the drug product be stable at extreme temperatures, as it is expected to be sometimes stored, or carried, or deployed in hot or cold conditions. The solution should be sterile and ideally preservative free.

Intranasal products should require only a single nostril for dosing. The other nostril can be utilized should a second dose of naloxone be warranted, hence desirability of a 2-unit kit.

Finally, the intranasal solution should be deliverable to the victim in a variety of head/neck positions, minimizing the need to specially position the victim.

As we know, FDA requires that the proposed product must achieve two criteria, one, comparable

or higher naloxone concentration at the Tmax of the reference product, which is naloxone, 0.4 milligrams, by IM; and two, there should be no delay in the onset of action of the proposed product as compared to the reference product.

In this slide, the curves in blue represent the plasma naloxone concentration of intranasal delivery, and the curves in red represent the plasma naloxone concentration of the reference product, 0.4 milligrams, via intramuscular administration.

In these two figures, t-star represents the Tmax for the reference product, namely the purple dot. And t-prime represents the time when intranasal naloxone achieves the Cmax of the reference product. That would be the green dot.

The left figure depicts the efficacy assessment. The shaded area represents the partial area under the curve, AUC, zero to t-star, as shown here. The partial AUC of intranasal naloxone in this case is greater than that of the reference product, meeting FDA criterion 1.

The right figure depicts the onset time assessment. As shown here, t-prime is at the left of t-star, meaning a quicker onset time for intranasal delivery, thus meeting FDA criterion number 2.

In summary, to meet the efficacy evaluation for approval, we have, one, for efficacy comparable or higher naloxone exposure from zero to t-star, characterized by AUC zero to t-star. It should be expected that the following equations are satisfied.

The partial AUC for the proposed naloxone intranasal product should be statistically greater than that for IMS' current product, administered by IN, which is further statistically greater than that for the reference listed drug, 0.4 milligrams, by IM.

Two, for onset, the onset time of intranasal naloxone, which is characterized by t-prime, is not delayed. It should be expected that the following equations are satisfied.

The onset time characterized by t-prime for

the proposed naloxone intranasal product should be demonstrated to be statistically less than that for IMS' current product, administered by IN, which is further statistically less than that for the reference drug, the 0.4 milligrams by intramuscular.

The statistical analyses used in both assessments should be based on standard bioequivalent methodologies.

Having the above discussion in mind, we can further summarize the intranasal development into the optimal dose zone, which can be represented by the green area in this figure.

The lower and upper curves represent the currently approved doses and delivery, IM 0.4 milligrams, and IM 2 milligrams naloxone, respectively. The safety and efficacy profile of these two doses have a proven track record of actual use for almost half a century.

The gray area under the lower curve represents the area in which the exposure has an insufficient efficacy, and the red area beyond the

upper curve represents the area where the exposure may be too high, resulting in more side effects, such as AWS. Any proposed product PK profile should be within the green suitable exposure zone.

In addition to efficacy, any new intranasal naloxone product requires evaluation of safety. Naloxone injection has a strong safety profile with few side effects. However, based on our current knowledge and experience with the drug, systemic exposure exceeding that of the highest injection dose available, 2 milligrams IM, may cause unwanted and unknown effects.

Since clinical experience with intranasal delivery of naloxone is still relatively limited, safety studies should be conducted and volunteers to test for local tolerability of the formulation, for example, a nasal and oropharyngeal mucosal examination.

Additionally, self-assessment by symptoms by subjects will be part of the safety program. It is our belief that such safety evaluations and possibly more must be conducted with high-dose

formulations of naloxone.

Another important safety consideration for high-dose formulations of naloxone is the possible emergence of acute withdrawal syndrome, or AWS as presented earlier. AWS or "dope sick" occurs when the effects of opioids are abruptly reversed, as in the case of an administration of an antagonist such as naloxone to opioid overdose victims.

AWS is associated with body aches, fever, irritability, and tachycardia, among others, as described in the labeling, as well as in several published articles. Vomiting has also been commonly reported.

Moreover, with too high of an initial dose of naloxone, there is a possible risk of physical injury to the first responder or bystander from a revived, often combative victim. This outcome may possibly affect a willingness to perform future rescue administration with naloxone.

Finally, in my last slide, I want to remind every one of you of the importance of performing human factors studies to aid in the optimization of

labeling as well as design the device for proposed intranasal naloxone product. The study should be designed with the intended users in mind. These include first responders such as EMTs and police, as well as non-medically trained laypersons and adolescents.

The study should be conducted in a stressful testing environment to simulate real-life conditions. Finally, the resulting labeling from the human factors study should be validated to ensure proper understanding and use of the product by the intended user population.

With that, I will conclude Amphastar's presentation. Thank you very much for your attention.

DR. BROWN: Thank you very much. We are now going to move ahead to Insys Therapeutics, Incorporated.

Industry Presentation - Steve Sherman

MR. SHERMAN: Good morning. Dr. Brown, members of the committee, thank you for allowing me the opportunity to speak for you today. As a

disclosure, I'm a full-time employee of Insys Therapeutics, and the statements I make represent our company's thoughts.

Insys Therapeutics, actually, if you've never heard of us, is an innovative company, where we're really passionate about making a difference in people's lives by addressing unmet medical needs. And one of the unmet medical needs and why I'm here today is to talk about the opioid overdose situation in the United States that really results from the misuse and abuse of opioids, be they illicit opioids like heroin or prescription drug opioids.

The current situation is there is really two routes of administration, and that kind of is limiting the use. The two routes are IV or intranasal, and we think that there's potential solutions for that. Also, I'm going to address the dose, the onset. And unfortunately, opioid overdoses aren't limited to just adults; they happen in kids.

As mentioned previously, naloxone was first

approved in 1971. It was IV, IM, and subcutaneous, but the IV is really the recommended route. And many patients who need naloxone happen to be injection drug users. So in an emergency situation, it's kind of hard to find a vein for intravenous injection.

Moreover, 80 percent of those who are chronic drug users, injection drug users, are either hep C or HIV positive, which means, for the first responders who are giving IV, there's an increased risk of needle stick infections.

So we think we need to expand access to naloxone through lay-friendly devices that allow people the closest to opioid overdose: -- friends, family, and first responders, police. And as mentioned recently, the FDA did recently approve an intranasal device, and we think that's a huge step forward in the expansion of access to naloxone.

However, I hope it's not the last step forward because in 2005, Bardan, et al. did a study and looked at intranasal naloxone administration. And 17 percent of the subjects who received

intranasal naloxone were unresponsive to the intranasal naloxone. However, they did respond to an IV administration of naloxone. So it wasn't that they were unresponsive to the drug. They were unresponsive to the method of administration.

When they looked at those 17 percent of patients, they found that some of them had epistaxis, some of them had severe nasal mucus, some of them had nasal trauma, and some of them had septal abnormalities. A lot of opioid abusers don't all inject. You can get a big rush from heroin and opioids intranasally. And if you're a chronic nasal opioid abuser, your nasal passages are pretty much shot.

For those of you who don't live in Arizona, I was reminded this morning when I went for a run, the people on the east coast, and the Midwest, and wherever else, can get nasal congestion due to colds, or allergies, or the flu. So we believe that other easy-to-use, non-invasive, even less expensive alternatives are still needed.

A group looked at 112 different routes of

administration for a drug listed by the FDA, which is an amazing fact, and they considered three viable non-injectable routes for emergency delivery of naloxone by laypeople, and those three happen to be buccal, nasal, and sublingual administration.

It so happens that we have a device that you can administer naloxone sublingually, and we think that, as mentioned earlier, death by opioid overdose is by severe respiratory depression, and it can be prevented by a timely administration of naloxone.

An amazing thing about naloxone, until the patient actually dies, if you administer naloxone, you're going to bring the person back, and that's an incredible upside for a drug. The most important thing is to act right away.

A barrier to greater community use, as we've heard, is a suitable and optimized needle-free drug delivery system. And unless the patient takes a massive IV dose and dies right away, generally, you can reverse the opioid overdose between 1 to 3 hours. Now, with the new opioids, that might not

be true, but you have some time.

So for a finite -- and I'm going to re-emphasize, for a finite set of the population, we think sublingual administration could be used. And when you ask, what's that finite population, it's the population who hasn't passed out yet, so if they're unconscious, sorry, you can't. Unless they are responsive to an outside stimulus like a loud noise or general shake, if you can get them to open their mouth and lift up their tongue, you can spray under their tongue, and the administration works. And we think that's a suitable alternative in those situations.

This is a very easy-to-use device, fingers on each side, thumb on the trigger. Open your mouth, lift up your tongue, and fire away. So it's a single-use device. It requires no priming.

When we looked at it in a PK study, we actually found that the sublingual route resulted in levels that were higher than the IM dose of 0.4 milligrams at 2, 4, 6, 8, 10 minutes, all the way through 60 minutes. And the ratios for our

8-milligram dose administered sublingually were 1- to 3-fold higher, from 2 minutes to 3 hours, compared to the 0.4-milligram IM dose, and both treatments were generally well tolerated.

A picture is worth a thousand words. You can see the 8-milligram naloxone spray. It's higher from 2 minutes through 1 hour. And if you're talking about longer-acting opioids, we think that that is important.

Additionally, I was asked to talk about the dose and onset. We've mentioned that treatment must begin as early as possible, and the recommended doses are 0.4 to 2 milligrams, and you can repeat that dose up to a total of 10 milligrams.

Also, in the literature, we've looked at doses not for opioid overdose, but for spinal cord injuries. Bracken, et al. used some pretty high doses. They used by 5.4 milligrams per kilogram boluses, and then a 4 mg per kg-hour infusion. And they've been administered without any reported untoward events.

As mentioned earlier, the dose and the route produced variable intensity of AEs, the major AEs being withdrawal symptoms. And if you use an IV dose or higher doses, you're going to produce more AEs and more withdrawal symptoms, but withdrawal symptoms are generally transient because naloxone has a relatively short half-life.

Those generally last between 30 and 60 minutes. And between the patient dying and experiencing withdrawal symptoms, I'm sorry, the risk-benefit ratio is highly in the benefit.

I know that a lot of people would like to do clinical studies in naloxone get the optimal dose, but because of the high safety margins and the recommended doses, we think that it's relatively unwarranted and unethical to conduct clinical studies.

I'm sorry. I skipped a slide. Then as I mentioned, opioid overdose doesn't just occur just in adults; it occurs in pediatrics. But with neonates, at least the American Academy of Pediatrics notes that there's really insufficient

evidence to use naloxone for a newborn with respiratory depression during exposure to internal opioid use. But if chemical studies are not feasible in adults, we think that they're not feasible in kids. And we believe that the dose in pediatrics should be -- for single-use devices like this, or the intranasal device, or even the pre-filled syringe, we think that the adult dose should be suitable for children.

Our recommendations, then, are that sublingual and other alternative routes of administration should be considered for the delivery of naloxone. We think that demonstrated levels exceeding IM at 2 minutes should be required because time is of the essence.

Adult doses in single-use devices such as this and the intranasal devices should be acceptable in pediatrics. And finally, we think a device that could be used sublingually or turned on its side intranasally should be encouraged. And I thank you for your attention.

DR. BROWN: Thank you. We're going to move

along now to Kaleo Pharmaceuticals.

Industry Presentation - Eric Edwards

DR. EDWARDS: Good morning. I am Eric Edwards, vice president of Kaleo. On behalf of the entire Kaleo team, thank you for the opportunity to provide our perspective on this dynamic landscape and this important discussion. It's also great to see some of the pioneers in community-based overdose education and naloxone distribution who have joined us in the audience today.

These are the main areas we'll be reviewing with you today, including an overview of our company, the epidemic, use of naloxone in the community setting, and characteristics of different formulations with respect to dosing. We will end with a summary of Kaleo's position on FDA's discussion points.

Kaleo is a word that in ancient Greek means to have a calling or purpose. And we believe our calling is to provide innovative medical products that help empower patients and caregivers to confidently take control in potentially life-

threatening situations.

We are a privately-held pharmaceutical company focused on products specifically for use in the community setting by non-medical professionals that combine an established drug with a known safety and efficacy profile, a high-tech innovative delivery device, as well as a data dossier with the goal of achieving superior outcomes, all of this with quality at our core.

We have two FDA-approved products, the Auvi-Q, epinephrine auto injector, and Evzio, naloxone auto injector. And for us, success is all about the impact we are having in the community. It's about saving lives. To date, Evzio has helped us save over 1800 lives based on reports to Kaleo of its use in the community, which is now on average about 17 lives per week.

We're all here today because of this growing public health concern that has reached epidemic proportions along with the evolving and dynamic opioid landscape. In 2014, there were 47,055 deaths from drug poisoning, close to 19,000 of

these from prescription opioids. There are still twice as many deaths from prescription opioids as compared to heroin. However, it is clear that heroin related morbidity and mortality is growing at a faster rate.

Opioid emergencies do not discriminate. They impact all age groups, including young children, males and females, and all socioeconomic classes.

Finally, there continues to be new potent opioids that have been introduced as well as new prescription opioid formulations that require us to have this conversation today about current dosing recommendations.

We wanted to first begin, providing a summary of our positions. We will then move to providing supporting data. We now have 40 years of safety and efficacy data with the injectable IM subQ or intravenous route of administration and with an improved dose range of 0.4 milligrams to 2 milligrams.

The benefit far outweighs the risk when

being administered during a suspected opioid emergency characterized by life-threatening respiratory depression. The only potential exception is in neonates, who are opioid dependent as in this population.

Administration of naloxone may be life threatening if not recognized and properly treated. However, opioid-dependent neonates are typically born in a hospital or clinical setting in the vast majority of cases and are best managed in a clinical setting, where there is access to close monitoring and titratable naloxone.

Next, there should be a single approved dose of naloxone by route of administration. This helps to ensure that there will not be confusion around dosing protocols with clinicians or caregivers.

Specific to take-home naloxone for the community setting and understanding that in a panic-stricken opioid emergency, fast competent action must be taken. The potential for serious risks to patients may include concerns that, with multiple doses being approved, there may be a delay

in prescribing naloxone, or, even worse, hesitation in administering naloxone due to potential confusion, which may have a direct impact on patient outcomes.

Additionally, products must be readily accessible and used quickly and correctly by individuals, even without training in the community setting, or patients may not receive the timely treatment they need prior to emergency medical system arrival.

Consideration should be given to routes of administration where real-world efficacy has not been proven in certain clinical situations. For example, patients may be taking common medications or have nasal abnormalities such as deviated septums that may interfere with drug absorption, especially in that early critical time period while awaiting for an ambulance to arrive in a community setting.

These are the typical products that have been used in the community setting with naloxone. There are two FDA-approved products specifically

indicated for use wherever opioids may be present, such as in the community. These products that include the Evzio auto injector and Narcan pre-assembled nasal spray were designed and intended to be used by non-medical professionals. The last product is a combination kit that includes an approved glass cartridge with a separate mucosal atomization device that must be assembled prior to use.

I'd like to point your attention to the dosage form row, as one of our points today around standardization for routes of administration is to ensure consistency according to delivery.

As you can see, there are significant differences in doses proposed by route of administration. Additionally, one challenge that currently exists is that inconsistency in the nasal route of administration with two different doses being used in the community setting for opioid overdose reversal.

Relating to the current community treatment algorithm, when managing opioid emergencies in the

community setting, there are three different phases as part of the treatment algorithm. We will focus on the caregiver/layperson portion here.

Early administration of take-home naloxone should occur with the goal of restoring and maintaining breathing followed by seeking emergency medical care and associated definitive emergency treatment.

This is important because the average response time in America for emergency medical services is 9.4 minutes. Cell death in the brain can occur from hypoxia in as little as 4 minutes; hence the need for rapid naloxone administration once an opioid emergency is suspected, particularly in an individual who's been found to be unresponsive.

Once EMS arrives, additional naloxone and advanced cardiac life-support measures can occur. Once a patient arrives at the hospital, the goal is to ensure appropriate reversal, monitor for renarcotization, and follow up based on the circumstances surrounding the events, whether

needing to contact the patient's physician to ensure their opioid regimen is adjusted in the case of a chronic pain patient who has had an opioid emergency or an accident or having the appropriate substance abuse disorder team follow up to ensure the patient receives timely and effective treatment.

I'd like to reiterate the safety profile of this small-molecule drug. First, there is no upper limit for incremental dosing in the approved take-home naloxone products for the community. As such, the FDA in the approved take-home naloxone products does not have an over-dosage section.

Due to its safety profile, an individual should administer naloxone every 2 to 3 minutes until breathing is restored while waiting for definitive emergency care to arrive. Safety has also been demonstrated at the maximum naloxone concentrations that are 5 to 25 times-fold higher than the current take-home naloxone products. Additionally, as a reminder, there is no pharmacologic action when a patient has no opioids

in their system.

Withdrawal that occurs following administration of naloxone, including at higher doses, is typically not life threatening as compared to the consequences of hypoxia if there is a delay in administration during a suspected opioid emergency. In fact, the FDA labeling for the take-home naloxone products have separated the warnings and precautions out into sections, first scenarios where opioid abstinence syndrome or withdrawal occurs in non-post-operative settings and withdrawal based on data from post-operative settings.

Some serious cardiovascular and pulmonary adverse effects have been noted in that post-operative setting, but a direct naloxone related cause and effect has not been identified.

Here, we state information on the pharmacokinetics of naloxone. I'm not going to go through all of these, but I'd like to focus on those variables that may impact outcomes in that community setting.

First, related to absorption, it's important to ensure naloxone is absorbed as fast as possible, attaching to opioid receptors quickly to ensure respiration is restored within that early critical phase of administration.

Secondly, as the half-life of naloxone is shorter than many opioids, there is a potential for renarcotization, necessitating emergency medical care follow-up and the potential for multiple doses of naloxone needing to be administered prior to further resuscitation taking place.

Finally, different products and associated delivery systems have different bioavailability, requiring different doses based on the route of administration. For example, as compared to the intravenous route of administration, the IM or subQ route has a bioavailability of approximately 36 percent, and the IN route has a bioavailability as compared to the intravenous route of anywhere between 5 and 17 percent.

This is why much higher doses are required with non-injectable routes of administration to

achieve comparable exposure. Our next couple of slides review some of these PK profiles and parameters in a little more detail.

These two figures represent two different pharmacokinetic studies conducted by Kaleo in 30 healthy volunteers on the left and 30 volunteers with chronic rhinitis on the right. The first point I will make is that when assessing the pharmacokinetics of naloxone in the context of products intended for use in the community setting, the most critical results are in that early time period, the first 10 minutes or so, where fast absorption will have an impact on outcomes while waiting for definitive emergency care.

The first study on your left was a comparative bioavailability study conducted as a requirement for Evzio to obtain FDA approval. In this study, Evzio was found to have comparable bioavailability to the standard, 0.4-milligram naloxone reference as administered by a vial, syringe, and needle with the exception of Evzio having a slightly higher peak plasma concentration.

On the right, a study was conducted in order to compare different routes of administration using the same naloxone dose, 2 milligrams, in patients with chronic rhinitis.

The results demonstrated a substantial difference exists in the relative bioavailability of intramuscularly administered naloxone as compared to intranasally administered naloxone. Additionally, when a common nasal decongestant and vasoconstrictor, oxymetazoline, better known by the brand name Afrin, was administered pre-intranasal naloxone treatment, the bioavailability was reduced by approximately half.

Importantly, the impact of the common vasoconstrictor on the bioavailability was most prominent in that early critical phase of absorption.

The next slide provides further data on this finding. So this slide shows different pharmacokinetic profiles across different administration routes, sorted in descending order by maximum systemic concentration.

Results in the top two rows demonstrate that naloxone can be safely administered at much higher doses as compared to those products currently used in the community setting. You can see in the Cmax and AUC columns, for example, just how much greater exposure there was with another naloxone study.

The second to last line that is in bold represents the current FDA-referenced threshold, a 0.4-milligram IM dose administered by syringe and needle, that is used as the standard for comparison of the approved take-home naloxone products intended for use in the community. As you can see, both Evzio and Narcan meet this minimum threshold.

As seen in the last row and discussed in that last PK figure slide, the addition of a vasoconstrictor prior to the administration of naloxone decreases naloxone peak concentration and overall exposure as compared to the reference standard, not meeting this minimum threshold required by the FDA.

So when we talk about important characteristics for naloxone products used in the

community setting, first, a product needs to be intuitive, easy to use during a panic-stricken opioid emergency. This is because a patient is likely to be unresponsive, and there is no guarantee that the layperson or caregiver may have ever received training on an naloxone product.

This is the reason why Evzio, similar to an automatic external defibrillator or AED, provides audible and visual instructions for use via prompts that assist in guiding a user through the correct administration steps.

There is also a trainer found in each carton that allows healthcare providers to train patients, and allows patients in turn when they receive their prescription to train others on how to respond during an accidental opioid emergency, increasing both the speed and competence in the use of the product.

Next, a product needs to be easily carried, portable, and ruggedly designed to withstand the community environment. Evzio was built not only as a pocket-sized product, but one that has been

tested in numerous environmental and durability studies to ensure accurate delivery of the dose will occur under real-world conditions.

All products for use in the community should provide a safe and efficacious dose. Evzio contains two single-use pre-filled auto injectors that include a retractable needle, where a user never sees a needle before, during, or after administration.

The needle retracts into place in less than a second. The product can be delivered through closing and has been tested to accurately deliver a dose through multiple clothing materials, including the seams of jeans.

Again, any take-home naloxone product should include product and labeling to prompt a user to seek emergency medical attention. Following the delivery of Evzio, voice prompts tell a user to do exactly that.

I'm not going to demonstrate the Evzio auto injector, so this is the trainer that comes in a carton, and it's also the trainer that's passed out

to help facilitate training in the community setting.

(Demonstration played.)

DR. EDWARDS: It will repeat the instruction until you do it correctly.

(Demonstration continued.)

DR. EDWARDS: It knows where you are in the process and will follow along with you.

(Demonstration continued.)

DR. EDWARDS: So you can imagine a panic-stricken emergency, and you're listening.

(Demonstration continued.)

DR. EDWARDS: I'm going to use my arm, but you would typically use the vastus lateralis or thigh.

(Demonstration continued.)

DR. EDWARDS: Evzio also provides instruction for use, the last instruction being to seek emergency medical attention.

DR. EDWARDS: Numerous human factors and usability studies were conducted to support the approval of Evzio, including multiple formative

studies in a design validation study as well as a labeling comprehension study.

Following approval, Kaleo also conducted two randomized, open-label, well-controlled crossover studies to evaluate the ability of volunteers to administer a clinically meaningful dose of naloxone by Evzio as compared to the off-label intranasal kits in a simulated opioid emergency, both before product training or any exposure to the product and after receiving one-on-one training by a nurse.

The results demonstrated that greater than 90 percent of volunteers, without ever being exposed to or trained on Evzio, could administer naloxone as compared to zero percent with the off-label intranasal kit.

Interestingly, even after one-on-one training with a nurse and verification of training by just demonstrating correct use, volunteers came back at least 7 days later and, for Evzio, were able to administer the product 100 percent of the time as compared to the intranasal kit, where approximately 50 percent on average between the two

studies were able to demonstrate success.

Any naloxone product for the community should have human factors studies that demonstrate users cannot only administer a dose without training, but also following training are able to retain the information on how to use the product, especially when called upon to act during a panic-stricken opioid emergency.

In closing, the changing landscape in data support using naloxone at any dose to reverse life-threatening respiratory depression in the community setting. Neonates are best treated in a clinical environment, whether that means a mobile emergency department, a.k.a. our ambulances, or in a hospital setting, where most cases of neonatal abstinence syndrome occur. There should be one dose approved per route of administration to avoid potential confusion, given the paucity of data at this time in the community.

In the community, products need to be easy to use and administered quickly, even without training. More work needs to be done to understand

the impact of real-world community situations on the absorption and associated outcomes based on different routes of administration, such as the impact of vasoconstrictors like cocaine on naloxone effectiveness or nasal pathology that may impact the deposition or absorption by this route of administration.

More detailed responses to each of these discussion points raised can be seen in the following slides. I'll wrap up by reminding everyone why we are here today. We are here today because this opioid epidemic continues to be a growing public health concern, and Kaleo is committed to continuing our efforts in helping to address and reduce opioid related morbidity and mortality in the United States.

Clarifying Questions

DR. BROWN: I'd like to thank our friends from industry for giving these excellent presentations today. We would like to begin to have some clarifying questions from members of the panel for the folks that have just given their

presentations.

When you ask your questions, please remember to state your name for the record. And if you are going to ask a question of a specific person, if you would ask that. And preferably, if there's particular slide that you're interested in, if you would give us the number of that slide, we'll be able to put that up.

If you have questions, if you will put your little tag up on its end, we'll be able to know that you want to ask a question. And I'm going to start with Dr. Higgins.

DR. HIGGINS: The first question is for Insys. Was there any study of the time differences to dose patients with respect to administration sublingually or intranasally? It seems like lifting a tongue and spraying would take longer, in my mind.

MR. SHERMAN: No. The only study we've done so far are PKs of sublingual and intranasal. And we didn't look at the time, but the administration time is -- and sublingually, actually, it's

absorbed within about 30 seconds.

DR. HIGGINS: The other question is for any of the presenters. Was there any data reviewed regarding availability of supplies of nasal naloxone? Where I live in western Massachusetts, many pharmacies do not have it in stock.

MR. MULLIGAN: Seamus Mulligan, Adapt Pharma. The supply is an issue and distribution across the nation because the supply chain is a little atypical than a normal pharmaceutical. You don't just sell to a wholesaler and have it pulled through a pharmacy.

You have all the community organizations, all the hospitals, all EMS, police forces. And they all buy their product from different organizations, so it's unusual and a lot of work is required to ensure nationwide supply.

But we've worked hard, apart from dealing with the first responder area and that's a different area, to make sure on the retail level by partnering with CVS and Walgreens. So it is in every CVS in the nation and in most Walgreens, as

well as other stores. And it's important to keep that effort up.

DR. BROWN: Dr. Emala?

DR. EMALA: Hi. Charles Emala. I had two questions from the presentation from Amphastar for Dr. Marrs and Dr. Cormack.

So on slide 11, for Dr. Marrs, there's survey information about the real use in the community. I'm particularly interested in the pediatric age group that's presented here as less than 18 years, and wonder if in this survey, or any other surveys, there's more real-world data on whether these products are being used in children, particularly in that 20-kilogram less than 5-year range, where we have some dosing suggestions, and particularly also whether we know if in the real world, usage in neonates is occurring.

MR. MARRS: Yes. Tony Marrs, Amphastar. Regarding the population of the off-label use of the data that we received, of this population, the youngest was 15 years old, of those 5.

In the total population, the youngest was 11

that we received data from. We're not aware of any other studies that looked at the neonate or younger population on this.

DR. EMALA: Thank you. My second question for Dr. Cormack from Amphastar is on slide 19. And it's mentioned or it states on the slide -- and I think this point was also mentioned by the gentleman from Insys -- that exposure may be too high, resulting in more side effects.

I'm wondering if that has actually been shown with a 0.4 versus 2-milligram dose or if that's an assumption, because I'm wondering if you're prone to withdrawal symptoms, if that's going to occur and that risk maxed out already at 0.4 milligrams.

So I'm just wondering if there's data to show that the risk of an opioid withdrawal is different at 0.4 versus 2.

DR. CORMACK: Right. I believe that hasn't been systematically evaluated, but from literature reports, the cases of acute withdrawal have appeared to come from the higher doses of naloxone.

Again, there's been no, to my knowledge, an evaluation of all the doses in relationship to the withdrawal syndrome, but most reports have been higher doses.

MR. SHANDELL: Yes. And I would like to just add, although there is no actual reported data, we have been in discussions with many first responders in the various states, they have expressed some concern in terms of the AWS and real-world situations where actual first responders have been physically injured due to the combative nature of the revived subject.

DR. BROWN: But these subjects were alive, correct?

MR. SHANDELL: Yes, yes. So definitely, one of the points we wanted to make, though, because of course -- one of the slides of one of the sponsors said, of course, you'd rather revive somebody, and AWS seems to be a minor issue compared to living.

What our concern and what we've talked to some of the first responders about is future administration. If somebody has been beaten up,

they may be more reluctant to administer next time. They may want to wait until they have backup. So it's really about the behavior of the first responder and the experiences that they have had.

DR. BROWN: Dr. Winterstein?

MR. MULLIGAN: Sorry. Chairman, could I add our perspective on that question regarding dose and the acute withdrawal syndrome?

DR. BROWN: Yes. I would appreciate it if you would, actually.

MR. MULLIGAN: Okay, sure, my colleague.

DR. PERGOLIZZI: Dr. Joe Pergolizzi, joint assistant professor, Johns Hopkins University School of Medicine. I draw your attention to a report out of the University of Kentucky, Dr. Wermeling, who did a very nice review of naloxone safety of opioid overdose, practical considerations for technology and expanded public access, published in 2015.

When he does a review of the various types of data that we currently have available for AWS, what we find is that the overall theme is that it's

more important to save a person's life, as was just mentioned, and that these types of situations for AWS in general are not life threatening.

He gives at least six or seven other types of publications with various dose ranges, all the way up to 8 milligrams, which show different types of prevalence; for violence, 15 percent out of 164 patients, in the patients by Biletz, vomiting, 4 percent.

When we look at confusion, hypertension, nausea, vomiting, and agitation, in the Buajordet paper in 2004 that he quotes, it's 8 percent. When we look at the Osterwalder paper in 1996, life threatening heroin addicts given up to 8 milligrams is 1 percent.

When we look at the Yealy paper in 1990, dose range between 0.4 to 8 milligrams given, what they said is general tonic seizures, 0.1 percent, vomiting 0.2 percent, and significant hypertension, 0.1 percent. Then again, when we look at the Kern paper, 2005, convulsions, 0.1 percent -- 1.1 percent to zero percent.

So when we look at the community epidemic that we have in the unfortunate situation where we're now having more exposure to high-dose, high-potent opioids with longer durations, it's clearly important that we use the right dose at the right time.

When we look at AWS, it's also equally as important to do as our colleagues at the University of Kentucky did and find if it's life threatening or not. It's more important to save a life and to provide a bridge for a medical service to come and address any potential AWS from that point on. Thank you.

DR. BROWN: I would like to ask you one more question since you mentioned that article. Could you find anywhere in the Wermeling article any discussion of cardiac arrest secondary to the administration of naloxone?

DR. PERGOLIZZI: I actually have numbers for cardiac arrest. So table 1, adverse effects of naloxone and reversal of opioid depressions, they mention that, in the approved package inserts,

cardiac arrest is mentioned. However, they don't give an actual incidence.

When we look at the table 3, adverse events associated with naloxone in the post-operative period, again, they mention cardiac arrest. They do not give a prevalence or incidence. They do give tachycardia. When we look at table 4 events, report an IM/IV naloxone administration of suspected opioid overdose, tachycardia has an event rate of 6 percent.

When we look at --

DR. BROWN: But no specifically --

DR. PERGOLIZZI: No specific.

DR. BROWN: I want to move on now, but specifically no discussion of the numbers on cardiac arrest?

DR. PERGOLIZZI: That's correct. And that's why the overall general statement and the conclusion is that these are non-life threatening in general.

DR. BROWN: Thank you very much.

DR. PERGOLIZZI: Thank you very much.

DR. BROWN: Can we move on to Dr. Winterstein?

DR. WINTERSTEIN: I have two questions. One is a follow-up question to this one. Real quick, is there data on the current standard -- and I realize there may not be a standard, but is there data on the current standard of the naloxone dose that's given by a medical professional?

So if there was an immediate emergency care service available, considering that the profile of opioids that are used have changed -- I saw one slide where there was reference to 0.4 to 2 milligrams. What's actually being used? And maybe the advisory committee members can chime in here. But that might be helpful.

So is there a standard that's currently used? Do people start with 0.4, or do they start with 2, or what do they start with?

DR. BROWN: Go for it.

DR. ZUPPA: I've actually looked at the CHOP formulary before I came down, and it says initial to start with 10 mgs per kilo, and if there's no

response, do 100 micrograms per kilo. So if you're a 10-kilo kid, you can get up to a milligram and then it maxes out at 2 milligrams per dose; IV, yes.

DR. EDWARDS: Eric Edwards with Kaleo. To address your question specifically, I think it's important that we do take into account setting, setting being the experience we have in the clinical environment, whether that's the emergency room or in a post-operative environment if you're an anesthesiologist, et cetera versus a community setting.

DR. BROWN: Thank you, sir.

Dr. Meurer?

DR. MEURER: I have a question for you, Dr. Edwards, and this will be related. Why didn't you pick 2 milligrams for the Evzio injector as opposed to 0.4 milligrams?

DR. EDWARDS: Yes. And it is related. Thank you. I was going to go on to say, based on observational data, as well as studies reported in the literature -- and we have 40 years of data in

that proven injectable route of administration, IM, subQ, IV, we know that the majority of patients treated with 0.4 milligrams by the IM or subQ route respond with that first dose. And for those who are non-responders, a second dose is usually available while awaiting definitive emergency care.

When Kaleo originally worked with the FDA to seek approval of the first take-home naloxone product for the community, we utilized this data to justify that 0.4-milligram dose, which falls within that reference product labeling of 0.4 milligrams to 2 milligrams.

DR. MEURER: I think, before, Mr. Chairman, you asked for the perspective of practitioners. When I was a resident in 2003, we would frequently use 0.4-milligram injection in the emergency department setting. And oftentimes, we'd just used like whatever's in the vial just because that's easier for the nurses.

However, frequently now, since there are also 2-milligram vials, frequently I and others in emergency care would start with a 2-milligram vial

when administering in the emergency department, although in many cases, people have had it administered in the pre-hospital setting before. And each EMS agency will vary regarding whether they stock the 0.4's or the 2's.

And unfortunately, the dosing data in the NEMSIS database that's referenced in some of our material is frequently missing, so I don't know if there's good data on how much of each type is available or used and deployed at most EMS agencies.

DR. PERGOLIZZI: Comments. Again, Dr. Pergolizzi. The WHO in 2014 produced a very extensive document on community management of opioid overdose. In there, I think it recognizes the fact that, a majority of time when these people -- they're not subjects, normal, healthy volunteers -- they're not patients who we may have an understanding of their comorbidity or what other poly-rational pharmacy they may be on; these are people.

Most of the time, these people are going to

be encountered by a family member at home. That's what the WHO's report showed. So we have to take into account the fact that we're not going to be able to do what we do in a hospital setting or even when a "first responder" who has some training in this, we are not going to be able to titrate to effect.

When we look at the current data in the unfortunate abuse of carfentanil, fentanyl, buprenorphine, we have to respect the fact that we have a limited window of time and opportunity to be able to reverse this and avoid a life-threatening situation.

So it's critically important during that point in time that we have a standardized reproducible way of providing an amount of naloxone to save that person's life.

I draw attention to Albert de Haan's paper on buprenorphine. Buprenorphine is a very interesting compound, very potent partial agonist or pan-ag opioid receptor activity. We know it has a bell-shaped type curve. And here, if you look at

the dose response of buprenorphine, it's a 2-milligram dose that you're going to need in order to provide correction of respiratory depression. So it's important that we have the right dose at the right time.

DR. BROWN: Thank you. I'm just going to ask that you sit down now. And for future reference, we've asked the members of the panel to only get up and speak when called upon by the chair. And I would appreciate our friends from industry doing likewise.

The next person on the list, Dr. Fuchs?

DR. FUCHS: Susan Fuchs. This is for Dr. Edwards and references slide 3, so the Kaleo presentation. In this slide, you show two products that are FDA-approved, both your Narcan as well as the Auvi-Q. The Auvi-Q has been recalled completely from the U.S. market due to problems about inaccurate dosing delivery.

Are you afraid of that happening with your similar product?

DR. EDWARDS: No. Kaleo is confident that

the issue with Auvi-Q was isolated to that particular product.

DR. FUCHS: Thank you.

DR. BROWN: Dr. Hudak?

DR. HUDAK: Yes. I was struck by the difference in efficacy on the intranasal naloxone presented on slide 13 by Mr. Marrs and on the off-label intranasal naloxone kit presented on slide 13 by Dr. Edwards.

I was wondering, in one case, you had nearly a very high efficacy rate with intranasal injection. I'm not sure who administered these, whether these were EMS providers or people in the community, and contrast that with a zero percent effective administration for an off-label kit, which may be different than this particular use here and a very low 50 percent after-training, one-week success rate.

So I'm wondering if someone can comment on that.

MR. MARRS: Tony Marrs, Amphastar. Regarding my slide, as seen here, these were done

in a community setting by first responders, police officers, firefighters, and so the efficacy data there is what was reported by them.

DR. EDWARDS: I'll just comment that that is the significant difference, trained first responders used to responding to emergency situations versus caregivers or laypersons who had not previously had exposure to the product and were trained for the very first time with an assessment of that retaining of the training, coming back one week later in a simulated opioid emergency environment.

DR. BROWN: Dr. Nelson?

DR. NELSON: Thanks. With respect to the comments of Dr. Meurer and the others that asked, I would just say that, over the past 5 to 10 years in the emergency department, I think we've been scaling back the dose of naloxone we've been recommending to prevent opioid withdrawal.

Now, I realize that's intravenous, and it doesn't apply to the community, and this is perhaps a discussion we could have later. But apropos to

that, I would ask Adapt and Amphastar, if you have data on the intranasal dosing at half or a quarter of the dosing you currently recommend and what the PK, the pharmacokinetics, of that dose would look like in terms of Tmax and Cmax.

MR. MULLIGAN: Seamus Mulligan, Adapt Pharma. Yes, we have data on a 2-milligram presentation of the product. In the development, as I mentioned at the outset of my comments, we developed the naloxone nasal spray, Narcan product, in conjunction with the National Institutes of Drug Abuse and evaluated a 2-milligram and 4-milligram version.

So we have pharmacokinetic data. As you saw in the data I presented, there was dose proportionality between the 4 and 2 doses. There's similar dose proportionality on the downside to the 2-milligram product.

DR. NELSON: So if I can just follow up real quickly, do you have a slide that shows that, the PK, what the Cmax or Tmax would be just for comparison?

MR. MULLIGAN: No. I don't have it with me, but I think actually FDA has it and may show it later.

DR. BROWN: Dr. McCann?

DR. McCANN: Mary Ellen McCann, Boston Children's. This is for Dr. Edwards, slide 13. I guess I would like to know a little bit more about who the untrained users or volunteers were, what their characteristics are, or were.

DR. EDWARDS: As discussed, these were two studies that were open-label randomized crossover studies. This was conducted in an age range of 18 to 64 years. There were 15 males and 26 females, a total of 41 subjects in the first study.

In addition, the second study included 33 subjects: 6 laypersons, 16 pharmacists, and 11 pharmacy technicians, 16 males and 17 females with an age range of 20 to 66 years of age.

DR. McCANN: So you don't really know too much about their educational levels, other than that some of them are pharm assistants, correct?

DR. EDWARDS: We did collect information

relating to their educational background, I just do not have that information with me at this time.

DR. McCANN: Thank you.

DR. BROWN: Dr. Davis?

DR. DAVIS: Yes. John Davis. I guess I wanted to ask the panel, since we're also in the middle of a second epidemic, which is the obesity epidemic in the United States, with some states reporting up to 30 or 40 percent of their population being obese, with many individuals being morbidly obese, I was curious, with all this dosing data, if this is all done in nice, normal-weight individuals, or if there's any experience that anyone has in dosing people who weigh 300 or 400 pounds? That's the first question.

DR. BROWN: Is that a question specifically for any member of industry?

DR. DAVIS: Correct.

DR. BROWN: Do you have someone that you would choose to ask that question?

DR. DAVIS: I think, if we're talking about dosing and they're all talking about dosing, I'd be

curious if anyone had any data on patients who were overweight or obese versus normal weight.

DR. BROWN: So is there anyone from the industry panel that has any such data?

MR. MULLIGAN: No. All our work was performed in normal, healthy volunteers, not obese patients.

DR. DAVIS: Great. That answers the question. The second question is, obviously, with an intranasal route, there are lots of people, and we saw very limited data on if patients had rhinitis or if they had URIs, colds, or even if they are using intranasal cocaine or other drugs, and what the impact that would be on nasal administration.

MR. MULLIGAN: Again, I think I'll just refer to my earlier comments. Seamus Mulligan, Adapt. Our studies were performed in normal healthies. We did not evaluate different other physiological conditions. However, the delivery of a concentrated dose, 4 milligram in 100 microliters, I think provides a safety margin

for any other underlying condition. But our studies were performed in normal healthies.

DR. DAVIS: Can I just ask you how you came to the 0.1-milliliter dose versus, I guess, the other product has a 2-mL dose, which is significantly larger volume.

MR. MULLIGAN: One of the rules of nasal drug delivery -- there's a rule of five, that the drug should be able to deliver less than a certain amount, a small volume. And the volume 1 of those rules is, for nasal drug delivery, typically, a volume of effective delivery is between 100 and 250 microliters of spray. Anything more than that is probably lost down the pharynx.

DR. BROWN: Dr. Parker?

DR. PARKER: Ruth Parker. Emory University. Mine is not to anyone in particular, but whether or not anyone has information on the shelf life of the product varying by the formulation for which it would be intended, intranasal versus subQ versus sublingual versus IM, whether or not the formulation would impact its shelf life, stability.

DR. GERST: Hi. This is Diane Gerst. I'm the vice president of quality and regulatory for Amphastar Pharmaceuticals. Our ongoing stability trials have shown that the product is very stable.

We have an ongoing program at 40 degrees C over shelf life, and so far the results are very promising. We're looking at both potency as well as impurities. And that's for our proposed intranasal product.

DR. BROWN: Dr. Sturmer?

DR. STURMER: Thank you. This is a question for Adapt Pharma, slide number 16, where you mentioned the 99 percent reversal rate based on 8 entities. Are there any robust data showing that you have a 5-milligram intranasal has a better reversal rate than the off-label 2-milligram intranasal?

MR. MULLIGAN: No. There isn't any additional data. We sought this data out when we heard of this outcome by commissioning a third party. We do not have comparative data.

However, this is real field-use data. For

example, Chief Ryan, who is with us here today, he switched all of his offices, 620, right over to Narcan. So there's an example of someone who's found the efficacy has been maintained and less dosing required. But as a direct head-to-head field comparison, there is none, no data available that I'm aware of.

DR. STURMER: I have a very quick follow-up question. Are there any data on repeat use of the 4-milligram intranasal dose in illicit drug users?

MR. MULLIGAN: Not at this point. We have no data on repeated using. We hear anecdotal data on people who repeat a number of additional exposures, but we have no solid data to provide at this point. We are only seven months post-launch at this stage.

DR. STURMER: Thank you.

DR. BROWN: Dr. Hertz, you had a comment? Dr. Beaudoin?

DR. BEAUDOIN: Hi. This is Francesca Beaudoin. I have a question for Dr. Sherman of Insys Therapeutics. This is referring to slide

number 7. When you talked about indications and who the sublingual route can be used in, do you have a sense of what proportion of opioid overdoses that are being treated by laypeople or first responders meet your criteria as opposed to being unresponsive?

MR. SHERMAN: We do not. Actually, I went to a training session of the Chandler Police Department, which is a suburb of Phoenix where Insys is located, and discussed the use of our device with the police there. And we were told that the preponderance of that use would actually, probably -- if it was reviewed and approved by the FDA, most of the use probably would be intranasal. But if the patient was still conscious and could follow directions, they would probably give it sublingually. And if they required a second dose and they were awake, they could administer it sublingually.

DR. BEAUDOIN: So can I just ask a follow-up to that?

DR. BEAUDOIN: Sure.

MR. SHERMAN: So your intent, then, would be that this would be first-line intranasal administration with the option to be a sublingual administration in an awake patient?

DR. BEAUDOIN: When we initially designed the product, we looked at -- we were challenged to look at it sublingually because the FDA wasn't very supportive of sublingual administration.

So they asked us to look at it buccally, and on the tongue, and on the roof of the mouth, and some other places. And we did those PK tests and found out that buccal administration isn't very compelling.

So we just turned the device on its side and used it up the nose, and we got some outstanding data from using the same formulation that worked sublingually intranasally.

MR. SHERMAN: Thank you.

DR. BEAUDOIN: Thanks.

DR. BROWN: Dr. Brent?

DR. BRENT: Thank you. Jeffrey Brent. I noticed in the Amphastar presentation that, if I

understand what you said correctly, using your 2-milligram intranasal dose, there was an average of 1.4 administrations per subject, meaning that, on the average, they had to use the device more than once. Now, we just heard from the Adapt 4-milligram dose people that they had -- with a single dose, I believe they said 99 percent reversals.

Does the fact that, on the average, you have to use the device more than once to get an appropriate response give you any pause at all about the 2-milligram dose?

Then the second question I have for the group in general, does anybody have any data at all about the need for re-administration? Thank you.

MR. MARRS: Can I get slide 9 from Amphastar? Yes. Your point about the average of 1.4, when we look at the number of units used, you can see here that 65 percent of the victims received 1 unit and 33 2 units, so the average is 1.4.

Our feeling is that, 98 percent of the time,

1 or 2 units worked for a reversal. There is the 2 percent that are obviously not in that. But 2 units covers 98 percent, so our belief is that that's an adequate, realistic amount of units.

MR. SHANDELL: And just to add, a lot of our data, because this is off-label, is from the first responders. And the way that these are carried are 2 units. So that's how the current product or the product that's under review would be sold as a two-pack, and that's what would be carried.

DR. BRENT: If I could just follow up on that, do you see any major rationale for not going to a 4-milligram dose, which from what we heard --

MR. SHANDELL: Yes.

DR. BRENT: -- is what we would expect, would give you a much better response for the single unit.

MR. SHANDELL: So we have two thoughts on this matter when we were trying to optimize the dose. And that's why one of my slides, which had the nasal cavities and their volume, we feel that it has come up from many presenters that if there's

a deviated septum or there's other issues with the nose, one, we think a lower concentration in a greater volume will allow the drug to disperse more freely.

So we have talked to first responders who have concern about too low of a volume, if it's not going to penetrate and get into the system.

Then secondly, it goes back to the AWS, although I do acknowledge that it's better to revive somebody than to have that, but one of the statistics that was cited, I thought, was interesting, 15 percent violence. And we believe that could have an impact on future administrations where, if violence occurs, one may be reluctant to administer the higher dose.

DR. BROWN: One more comment, and then we're going to take a break.

MR. MULLIGAN: Just the closing comment on that because I think it's relevant to repeat dosing. In the study that we conducted, the field study, we also had repeated administration of our product, approximately, I think, 25, 30 percent of

the time.

Whether that repeat dosing was as a result of just engrained practice in the first responders because the dose -- and then they're fighting the dose again. I don't know whether, with more experience, there would be less repeat dosing. I can't tell you, but we did have repeat dosing. So the adverse event profile, it takes that into account.

DR. BRENT: Thank you.

DR. BROWN: Thank you. We're now 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 with any member of the audience.

We're going to resume at a little after 10:15. We have more clarifying questions for industry. All of it, we will get to all of those questions as soon as we come back from break. Thank you.

(Whereupon, at 10:05 a.m., a recess was taken.)

DR. BROWN: Clarifying questions for industry? Dr. Warholak?

DR. WARHOLAK: Hi. This is Terry Warholak. It seems to me -- and correct me if I'm wrong -- that several of you recommended that there be one dose product approved for community use or one product approved for each of the different dose forms? Is that what you're saying? No?

MR. SHANDELL: This is Jason Shandell from Amphastar. We're not recommending that because obviously there is the Narcan approved. And we believe that our product should be approved and, again, that goes to some of my issues regarding volume and the concentration.

We feel that more volume is better to help disperse for those individuals that have nasal issues. We don't believe there will be confusion. Clearly, the Narcan is in a very little device that goes in your fingers. Ours is larger, looks more like a syringe. We don't believe there will be any confusion.

DR. BROWN: Dr. Vinks?

DR. VINKS: This is Alexander Vinks, Cincinnati Children's Hospital. I have a clarifying question related to the presentation by Mr. Sherman and Insys, and the statements that are made on slides 13 and 14.

Could you elaborate on what data you used to make this, say, statement about general use of the product in pediatric patients? Because if you do an off-the-cuff type analysis, you would end up with the doses that have been discussed by about a factor 4 to 10 higher Cmaxes and area under the curves. And I was just wondering what data you used to make this statement.

MR. SHERMAN: Thank you for your question. We just looked at the literature, and we looked at the data from American Pediatric Association, where they make dosage recommendations.

But for a single-dose device, to conduct the studies, to determine the dose, we didn't think that was feasible, and because of the high safety margin, we thought that for children and adolescents, the adult dose, if it's comparable to

a 0.4-milligram dose of IM, would be safe and effective in pediatrics.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: This question is I think for somebody from Adapt or Kaleo. In Colorado being more rural, we have areas of really high abuse and low EMS access. So is there any comparative data with regard to the two products, or any products, actually, on whether there's higher survivability where there's low EMS access with either of the products?

I guess, in the secondary question to that, in these areas, do you feel that 2 units in kits are sufficient because of the sometimes long time to EMS, people getting to EMS?

MR. MULLIGAN: I'm not sure I understood the first part of your question. The survivability of the product?

DR. GALINKIN: No, the survivability of patients in rural areas because, obviously, with a long period of time for EMS to get there, it seems like your product would have a longer time of

effect than some of the other products, but I don't know if that's been shown.

MR. MULLIGAN: I think, first, some of your colleagues in Colorado agree with you because they've just purchased the product for that particular reason. And you go back to some of the comments that have been made earlier, especially in rural environments -- and we're hearing this from law enforcement, first responders -- you want to make sure. It's not practical to carry multiple kits, multiple numbers of kits. So our product comes with 2 units per carton, and that's a total of 8 milligrams available.

Now, whether they should have more than that, I can't answer, but that should normally be -- it gives the best possible bang for the buck, so to speak. You're getting significant quick onset and prolonged exposure. As I referenced in the study, we have 5 times the exposure as you would see with the 0.4 mg injection.

DR. GALINKIN: I guess this is still a follow-up to another question, so let me just ask.

When you atomize a product, does it matter what the volume is?

MR. MULLIGAN: I think, again, in drug delivery 101, yes, for nasal drug delivery, the literature would support the fact that the amount of atomization that you use is between 100 and 200 microliters. That's not my invention. That's some of the fuller figures of drug delivery with respect to nasal drug delivery. The volume is important because, most likely, anything more than that is lost down the pharynx.

DR. GALINKIN: I was thinking on the low end, though, since that's what the other company is breaking down to.

MR. MULLIGAN: Yes. Less than 100, I don't have any data.

DR. GALINKIN: They were saying that increasing the volume over a period of time actually might increase absorption, which you don't feel. Once you get over 200 mics, you're done.

MR. MULLIGAN: I don't have any.

DR. BROWN: Dr. Maxwell?

DR. MAXWELL: Thank you. A two-part question for industry. You talked about the various numbers on, call it success rate, the percentage of saves. My question is, has anybody looked at those in light of the potency of the heroin? I mean, there's a lot of difference between white heroin in New York City and powdered brown in Texas. And then there's a second part to the question, which I might as well add in.

Do we have any evidence of the use of any of these kits with these super-potent new opioids that are out there, the U4770, the W18, or the carfentanil?

MR. MARRS: Tony Marrs, Amphastar. The data that I presented was from first responders that collected it themselves, collected the data themselves. As part of that, they didn't do any formal assessment of the concentration or potency of what was taken, other than just their observational experience.

The dates of these were from 2014 to 2015 in New York and New Jersey. And throughout this

process, one can imagine that there's probably quite a spectrum of different potencies during that period.

MR. MULLIGAN: With respect to the study that we presented, even though it was a retrospective study, there were 9 other reversals that were related to fentanyl, as we understand, and 1 related to carfentanil.

Again, just to reinforce the comment, with the safety profile of this drug, the dose of naloxone should be as high as possible.

DR. BROWN: Dr. Hertz? And then we're going to move on to the FDA presentations.

DR. HERTZ: Yes. I want to clarify something, and I'm a little curious why we haven't been cited as the source of the 100-microliter volume by the companies because we have generally requested that for a single spray in one nostril. And the idea being is if you want to ensure that the solution is being delivered to the nasal mucosa, is not being swallowed, or running out of the nose, we explored the volume that would reside

on the mucosa.

We'll hear perhaps later on more about the development and how these all evolved, but I think you've seen some of the data that show that volume and the total dose have an impact on the exposure. So when we approved the 4-milligram intranasal, it was based on that volume creating the profile that was sufficient to meet criteria.

So these other theories are theories, but the source of the recommendation for the 100 microliters comes from us. And so far, the products that have actually studied 100 microliters have shown it to be a reasonable volume in these studies.

DR. BROWN: We will come back to other clarifying questions for industry after the FDA presentation. But for currently, we're going to proceed with presentations from the FDA, and Dr. Nadel will begin.

FDA Presentation - Jennifer Nadel

DR. NADEL: Good morning. My name is Jennifer Nadel, and I'm a medical officer in the

Division of Anesthesia, Analgesia, and Addiction Products. I will be talking today about the clinical and regulatory perspectives of naloxone products intended for use in the community.

As you have heard and will hear more about today, the United States is experiencing a devastating public health crisis associated with the use, misuse, and abuse of illicit and prescription opioids.

Drug overdose has surpassed motor vehicle collisions as the leading cause of accidental death in the United States, and opioids are the most common cause of drug overdose. An overdose can occur in patients prescribed in opioid and also in people who misuse or abuse opioids.

Accidental exposure is another concern and may occur in household contacts. Nationally representative adverse drug event data suggests that, in children under 6 years of age, opioids account for the largest percentage of accidental prescription drug ingestions resulting in emergency department visits and subsequent hospitalizations.

Opioid overdose is characterized by life-threatening respiratory and CNS depression that may lead to irreversible hypoxic injury. Opioid overdose is an emergency and requires immediate treatment.

Naloxone is an opioid receptor antagonist, which means it blocks the effects of opioids, including reversing respiratory and CNS depression. It is the reversal drug for a life-threatening opioid overdose. Naloxone works, but its delivery has to be within the first few minutes of an overdose.

Several challenges are encountered with the use of naloxone in the community. There's a risk of recurrent respiratory and CNS depression after naloxone has been given. The duration of action of most opioids is longer than the effect of naloxone. The effects of the opioid may return as the naloxone is cleared.

This is especially concerning with extended-release opioids. There is additional concern with partial agonists, as some of them do not reverse

easily. After a person has received naloxone, the person requires continued surveillance and possibly repeat doses of naloxone. It is critical that the person is given appropriate medical attention. And I will discuss adverse symptoms associated with withdrawal in the next few slides.

The use of naloxone may precipitate severe opioid withdrawal. Some of the signs and symptoms of withdrawal include diarrhea, tachycardia, fever, nausea, vomiting, and increased blood pressure.

Abrupt post-operative reversal of opioid depression after using naloxone may result in the withdrawal symptoms seen on the previous slide as well as seizures, arrhythmias, pulmonary edema, coma, encephalopathy, and cardiac arrest, which may result in death. Cardiac events have mainly been seen in patients with pre-existing cardiovascular disease.

Acute opioid withdrawal in neonates, manifesting as seizures, may be life threatening if not recognized and properly treated. Other signs and symptoms include excessive crying and

hyperactive reflexes.

Neonates born to opioid-dependent mothers are at the greatest risk. The risk of acute withdrawal symptoms in 1-month-olds to 12-year-olds is low because very few of these patients are taking opioids chronically. They are more likely to acutely overdose from an isolated and accidental exposure.

Naloxone was initially approved in 1971 with the brand name Narcan for use in the healthcare setting. It is labeled for intravenous, intramuscular, or subcutaneous use.

.5 milligrams per milliliter and 1 milligram per milliliter preparations are currently available. The initial recommended dose for opioid reversal is 0.4 milligrams to 2 milligrams. The dose may be repeated at 2- to 3-minute intervals.

The pediatric dose for all children from the approved naloxone labeling is 0.01 milligrams per kilogram IV. Subsequent doses of 0.1 milligrams per kilogram are recommended if the initial dose is ineffective. The neonatal dose is 0.01 milligram

per kilogram. Doses for all age groups may be repeated every 2 to 3 minutes as needed.

The American Academy of Pediatrics issued guidelines in 1990, which are different than the labeled dosing recommendations. Specifically, AAP recommended 0.1 milligrams per kilogram from birth to 5 years of age or 20 kilograms of body weight. The dose is 2 milligrams if older than 5 or weighing more than 20 kilograms. In many cases, the initial dose is higher than what is recommended in adults. These guidelines were not based on controlled data.

The AAP recommendation was based in part on a concern that 0.01 milligrams per kilogram, as is currently recommended in the approved labeling, may not provide optimal reversal in some infants. That AAP statement has been retired. However, the AAP has subsequently issued a new statement on naloxone, and the current AAP policy supports pediatric naloxone at the same dose as recommended in the 1990 guidelines.

The clinical report, entitled Preparing for

Pediatric Emergencies, Drugs to Consider, was first published in 2008 and was reaffirmed in 2011. These recommendations have been incorporated into pediatric resuscitation guidelines, pediatric drug references, and are widely accepted as the standard of care.

Weight-based dosing, as recommended in the initial Narcan label, and fixed dosing, as in products approved for community use, each have advantages in treating opioid overdose in pediatric patients, particularly neonates, depending on the setting.

Weight-based dosing relies on the ability to monitor patients and identify the need for re-dosing. This is feasible in supervised medical settings when dose titration can be supervised by trained healthcare professionals and the patient can be monitored closely.

On the other hand, fixed-dose products have an advantage in the community setting where titration of dosing is neither feasible nor safe, and decisions about dosage cannot be made by a

layperson. In this setting, the risk of administering a life-saving treatment outweighs the risk of precipitating withdrawal.

We are committed to making naloxone products more available as one component of our approach to addressing the opioid overdose epidemic. FDA has held public meetings on naloxone intended for use in the community. We have worked with sponsors to develop a pathway to approval. We have reviewed and approved these products under a variety of expedited programs such as fast-track and priority review.

On February 4, 2016, FDA announced the Opioid Action Plan. Part of that plan is to support better treatment, including providing broader access to naloxone. The FDA recognizes the public health imperative that naloxone may be available in any setting where opioids may be present and, therefore, whether there is potential for overdose.

The FDA has and will continue to expedite the review of naloxone products that address an

unmet medical need and/or would provide a significant improvement in safety or effectiveness. The FDA has multiple programs sponsors can apply to help expedite the development and review of a product, increase guidance on a product, and even shorten the time clock for review of a marketing application from the 10-month standard review to a 6-month priority review.

A public meeting was held in 2012, where expanding access to naloxone in the community was discussed. The only approved formulations of naloxone at that time were injectable products used by medical professionals. We discussed how naloxone is an important tool in addressing the problem of opioid overdose and access to naloxone should be made easily available. FDA was encouraged to expand access by approving non-injectable forms of naloxone.

The FDA discussed the general pathways for approving new formulations of naloxone and making naloxone available over the counter. The approval of new formulations would be based upon a

comparative bioavailability study due to ethical concerns with conducting an efficacy study. There would be a comparison between the new product and already improved injectable formulation of naloxone.

Switching naloxone to over-the-counter status would likely require additional clinical data, and it was concluded that there is a need for better coordination among federal agencies, manufacturers, and stakeholders to resolve regulatory issues and expand access.

A second public meeting was held in 2015, and a variety of scientific, legal, regulatory, logistical, and clinical issues surrounding the use of naloxone were discussed. There was broad general agreement that naloxone should be made widely available to persons at risk for overdose and to those who might witness an overdose.

By this meeting, naloxone access had greatly increased since 2012. Most of the increase was in the form of off-label naloxone kits. Additionally, many states and communities lacked programs to make

it available. Co-prescribing of naloxone with opioids was broadly supported. There was agreement that training on use of naloxone is needed.

FDA has had the opportunity to work with companies that are partnering with the National Institute on Drug Abuse to establish a pharmacokinetic standard for new formulations of naloxone in lieu of conducting efficacy studies. There are ethical challenges associated with conducting efficacy studies in this clinical setting.

Most overdose patients that would receive naloxone are going to get it from EMS. They are unconscious, so of course cannot provide informed consent or a study. Additionally, it would be unethical for them to be in a randomized trial and potentially receive inadequate treatment when there is an approved naloxone product, which already does an excellent job at reversing the overdose and saving lives.

The FDA leveraged what is known about the safety and efficacy of existing approved naloxone

products and pharmacokinetics as a path forward for these products. New products would need to match or exceed the naloxone exposures achieved via an approved route of administration, usually 0.4 milligrams intramuscularly, particularly in the early critical period, the first few minutes following the overdose in healthy adult volunteers.

There are pediatric considerations when new formulations of naloxone are being developed. Ideally, the PK of new products would be studied in children. We do not have that because there is not a clinical setting where that would be possible.

There are age-specific safety questions associated with novel routes and anatomic differences such as intranasal delivery and risk of choking or aspiration in infants. There are questions about local safety, for example IM injectors and needle length.

Human factors validation studies were conducted with a user group of adolescents 12 years of age and over and adults. The human factors validation studies used an adult-sized mannequin to

represent an overdose victim.

In the future, we could consider a user group of younger children who could possibly administer naloxone, for example, 8- to 11-year-olds. Additionally, we could consider use of infant-sized mannequins to evaluate differences in administration of naloxone between adults and infants.

Additionally, the safety of excipients is evaluated for these products, and there may be pediatric-specific safety concerns surrounding some of them.

Two naloxone products have met the standard outline by FDA and have been approved for use in this setting. The indication is for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

It is intended for immediate administration as emergency therapy in settings where opioids may be present. It is not a substitute for emergency medical care. In addition to describing the basic

clinical situation the drug may be used in, the indication statement was developed to encompass the many situations that opioid overdoses may occur in and to emphasize the importance of pursuing medical treatment after the use of naloxone.

The products are approved with instructions for use that are targeted to the layperson so that the patient, their family, or another bystander can understand what to do in an emergency and are tested in human factors studies.

The products need to be easy to use with a limited opportunity for failure and it is expected that the products may be used without additional training. In contrast, the intended administrators of off-label products generally require training on how to assemble and administer those products.

Evzio naloxone auto injector was the first product approved in this setting. It was given fast-track designation and priority NDA review. It was approved April 2014, over two months ahead of the 6-month priority PDUFA goal date. It is labeled for intramuscular or subcutaneous use.

It delivers a 0.4-milligram dose. It is packaged with two single-use auto injectors as well as a trainer, all of which provide verbal instructions. The trainer is reusable.

Narcan Nasal Spray was the second naloxone product approved. It received fast-track designation and priority NDA review. It was approved November 2015, over two months ahead of the 6-month priority PDUFA goal date. It is labeled for intranasal use.

It has a concentration of 40 milligrams per milliliter, and it delivers a 4-milligram dose in a 0.1-milliliter spray. The very low volume of spray is important, as 0.4 milliliters is a volume that is within the range expected to be appropriate for a single nostril. Narcan Nasal Spray is packaged with two single-use devices.

There are off-label drug device combination products used to deliver naloxone via the intranasal route. The naloxone used is only approved for the parenteral route. The concentration of naloxone used is 2 milligrams per

2 milliliters, and it is given as 1 milliliter per nostril.

These pictures represent two different kits with two different approaches. They both require assembly and use of a nasal atomizer device to deliver the naloxone. This is an unapproved route for the approved parenteral product.

Off-label devices are predominantly used by a variety of organizations and state and local programs to make naloxone available in the community. In general, training is provided for these kits. The FDA is aware that the off-label products are saving lives and have shown effectiveness. However, it is unclear if these products meet the standard previously outlined. There is limited pharmacokinetic data for these products, and we do not know how often these products fail.

There are challenges associated with evaluating efficacy of naloxone use in the community. For the off-label products specifically, the failure rate is unknown.

Clearly, there were reports of it working. We do not know the percent of failures. We do not have PK data for the off-label products and do not know how variable the efficacy is across the kits.

When there are reports of failure of naloxone, there are a variety of scenarios, which may be contributing. We do not know if the naloxone was delivered too late, if the person was definitely suffering from an opioid overdose, or if the overdose was secondary to a potent opioid, multi-drug combination, or partial agonist.

There can also be confusion over terminology as Narcan is often used in the general population to refer to any naloxone product, including the unapproved kits.

What is the appropriate naloxone dose? We have two approved products, and they have very different doses. Ideally, the dose should be suited for all subpopulations to avoid potential for not having an appropriate product in any given clinical scenario. However, high-potency opioids may require a higher dose of naloxone.

In the absence of appropriate ventilatory support, it is unacceptable to delay treatment while titrating a reversal dose of naloxone. Additionally, there were reports in the news of heroin being laced with extremely potent opioids such as street fentanyl or carfentanil.

Carfentanil is a large animal sedative that is 10,000 times stronger than morphine. There have been recent overdose outbreaks involving fentanyl in Ohio, Indiana, and Florida. There are also reports of these overdoses requiring as much as a 3-fold the ordinary dose of naloxone.

In conclusion, we have made huge strides with the development of two approved naloxone products. They are suitable for the layperson to understand how to put them to use. They have met our standard for approval.

We still have questions regarding pediatric dosing. Naloxone dosing recommendations vary based on the source of the material. The AAP's guidelines does not agree with the approved labeling for naloxone for pediatric patients. Many

commonly used treatment guidelines cite the AAP recommendations such as those from Pediatric Advanced Life Support, Medscape, and Epocrates.

Initially, there was some concern over the approved products having too high a dose of naloxone. More recently, we became concerned that the dose is too low. There are new concerns over high-potency illicit opioids requiring higher doses of naloxone.

We now have companies approaching us about different dosing regimens for these products. Is our minimum standard high enough? Is there a place for products of different strengths? How would we label a product so a prescriber would know in advance, which would be the appropriate one to choose?

The FDA is seeking advice on how to approach these new questions that have arisen since establishing the minimum pharmacokinetic standard, including whether the current minimum standard for approval is adequate and if higher doses are recommended. Thank you.

FDA Presentation - Yun Xu

DR. XU: Good morning. My name is Yun Xu. I'm a team leader reviewer, Anesthesia, Analgesia, and Addiction Products in the Office of Clinical Pharmacology, Food and Drug Administration.

Today, my presentation will focus on design analysis and interpretation of the relative bioavailability study to support approval of new naloxone product to treat opioid overdose.

Naloxone is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. Following parenteral administration, naloxone is readily distributed in the body.

Plasma protein binding occurs, but it is relatively weak. Plasma albumin is the major binding constitutes. Naloxone is metabolized in the liver primarily by glucuronidation with naloxone's 3-glucuronide as the major metabolite.

A majority of the drug is excreted as metabolites in urine. Naloxone half-life in adults is short, with a mean value of approximately 1 to

2 hours. After administration, usually a sharp peak of plasma allowing some concentration can be observed, but then the naloxone level will drop quickly. Therefore, duration of action for most opioids may exceed that of naloxone, especially for extended-release, long-acting, or ER/LA opioids. Patients should be kept under continuous surveillance. An additional naloxone dose may be necessary.

A naloxone injection product was approved in 1971 under NDA 16636 for emergency treatment of known or suspected opioid overdose. This product has been discontinued from marketing. However, the agency determined that it was not withdrawn for reasons of safety or effectiveness. Several generic products to this NDA are available on the market. Recently, two new naloxone products were approved. One is Evzio, a naloxone auto injector, and the other is Narcan Nasal Spray.

The minimum and maximum dose exposures that can be clinically effective is unclear, which probably depends on multiple factors such as type

and dose of opioid to cause overdose, route of naloxone administration, et cetera. However, it was not feasible to design a clinical study to determine the minimum effect of a naloxone dose since it is not ethical to administer opioids to healthy subjects to create opioid overdose.

Since naloxone injection product is already approved for treatment of this life-threatening condition, there is also great logistical and ethical issues to evaluate efficacy of new naloxone product in patients with opioid overdose, which could result in deaths without timely and adequate treatment.

Therefore, for development of a new naloxone product to fight opioid overdose, the agency has said that the new naloxone product in development can be approved by relying on agency's previous findings of safety and effectiveness for already-approved naloxone injection product.

Throughout agency's previous findings, a scientific bridge via relative bioavailability study between new loss on product and the reference

product is needed.

This relative bioavailability study should be a randomized crossover study in healthy adult subjects with adequate sample size. Both the naloxone products are tested and approved naloxone injection products referenced need to be administered and the label recommending a dose and route of administration.

Adequate wash-out period is needed between treatments. Blood sampling needs to be adequately captured, entire pharmacokinetic profile, especially for the early onset of action phase.

To capture naloxone plasma concentrations in the early phase, adequate numbers of blood samples should be collected in the first 30 minutes after administration. Free or unconjugated naloxone concentration needs to be measured for peak analysis.

Since the original approved naloxone product is no longer on the market, its generic product, designated as a reference listed drug in Orange Book, may be used as the comparator. It needs to

be emphasized that the final to-be-marketed product, including both formulation and the device, needs to be used for test product since both factors can affect PK performance.

Pharmacokinetic parameters, including peak exposure or Cmax, time to peak exposure or Tmax, total area under the plasma concentration time curve, such as AUC zero to t and AUC zero to infinity, and half-life should be calculated.

Onset of action is critical for reversal of opioid overdose. The current FDA guidance on bioavailability and bioequivalent studies recommends the use of partial AUC to assess the onset of therapeutic effect. Therefore, partial AUC of early time points should also be compared to assess onset of naloxone action. Also, demonstrating bioequivalence is not required. A bioequivalent statistical approach is recommended to analyze Cmax and AUC.

The goal of this approach required by the agency is to demonstrate that the new test product matches or exceeds the systemic naloxone exposure

to the reference product by comparing pharmacokinetic parameters of Cmax, AUC zero to t, AUC zero to infinity, and a partial AUC. The entire PK profile will also be examined to ensure this goal.

Since onset of action is critical, it needs to be emphasized that, even if the test product shows comparable or higher Cmax, AUC zero to t, and AUC zero to infinity values, it still needs to demonstrate that the naloxone levels are comparable or higher to the reference product during early phase after dosing by comparing partial AUC values.

This hypothetical plot illustrates the importance of partial AUCs. The solid line represents treatment A; the dashed line represents treatment B. Both treatments have similar AUC zero to t, AUC zero to infinity, and Cmax values. Even Tmax values are the same.

So comparing these PK parameters cannot differentiate the two products. However, it is obvious that treatment B has a lower exposure in the earlier phase of the PK profile. This will

raise concerns for slower onset of action for treatment B.

If partial AUC values in the earlier phase, especially in the first 5 to 15 minutes after dosing, are compared, then these two products can be easily differentiated since treatment B has much lower partial AUC values.

Two naloxone products were approved recently for treatment of opioid overdose. Both products' approval was supported by the relative bioavailability study with approved naloxone injection.

The first product is Evzio, which contains 4.4-milligram naloxone hydrochloride in 0.4-mL solutions in a pre-filled auto injector. The recommended initial dose is 1 injection of 0.4 mg. If the desired response is not obtained after 2 to 3 minutes, another dose may be given.

To support approval, the applicant conducted a randomized crossover study in 30 healthy subjects to compare the pharmacokinetics between the new auto injector and naloxone injection. The

injection was either subcutaneous or intramuscular based on the depths of fat and also the needle ends.

This plot shows the mean naloxone plasma concentration time profile. Closed circle represents Evzio and open circle represents comparative naloxone injection. The two PK profiles are almost superimposed, except for 15 percent higher Cmax values for the auto injector. Mean Tmax values were similar. Bioequivalents were met for AUC zero to t and AUC zero to infinity.

The other approved product is Narcan Nasal Spray, which contains 4 milligrams of naloxone hydrochloride in a 1.1-mL spray. The recommended initial dose is 1 intranasal spray of 4 milligrams. If the desired response is not obtained after 2 to 3 minutes, another dose may be given.

To support approval, the applicant conducted a randomized crossover study in 30 healthy subjects. The comparator, naloxone injection, was administered intramuscularly as a 0.4-mg single

injection. Two dose levels of the new nasal sprays were used, including 1 spray of a 4-milligram dose and 2 sprays of an 8-milligram dose.

This plot shows the mean naloxone plasma concentration time profile. Closed circle represents 0.4-milligram intramuscular injection, which is the bottom line. Closed square represents a 4-milligram dose of Narcan Nasal Spray, which is the middle line. Closed circle represents the 8-milligram dose of Narcan Nasal Spray, which is the top line.

Both Narcan Nasal Spray doses demonstrate much higher naloxone concentrations than the comparator, naloxone injection, at every time point. The label-recommended 4-milligram nasal spray dose shows approximately 5 times AUC and Cmax values to the comparator. This exposure is likely to fall well within the dose recommended in the approved labeling of the reference product, which recommends up to a 2-milligram initial dose and repeating the dose every 2 to 3 minutes, up to a total dose of 10-milligram.

Finally, I want to share two useful guidances published by the agency. The first guidance talks about general considerations when conducting bioavailability and bioequivalent studies, and the second one focuses on bioequivalent statistical approach. More details can be found in these two guidances.

This concludes my presentation. Thank you.

FDA Presentation - Shekhar Mehta

DR. MEHTA: Good morning. My name is Shek Mehta, and I'm a drug use analyst in the Office of Surveillance and Epidemiology here at the FDA. Today, I will be presenting information on drug utilization of naloxone.

The goal of my presentation is to provide information and context on trends in the utilization of naloxone. 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.

Then I will discuss other data sources in

addition to important published literature on naloxone use. These other data sources include the National Emergency Medical Services Information System, the National Poison Data System, and the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project or NEISS-CADES. Strengths and limitations of available data sources will be discussed throughout the presentation.

This table lists the manufacturers and products strengths and approval dates of available naloxone products. In our drug utilization analysis, we included available injectable formulations of naloxone, both in 0.4 milligram per milliliter and 1 milligram per milliliter strengths, as well as the recently approved devices available as single-dose administrations, which are Narcan Nasal, supplied as a nasal spray, and Evzio, supplied as an auto injector.

We will begin with information from proprietary drug utilization databases. The IMS Health National Sales Prospective Database provides

sales distribution data sold from manufacturers to distributors by settings of care. Although sales data do not reflect actual patient use, these data provide national trends in the distribution of naloxone.

Listed here are settings of care where naloxone is distributed. Of note, we have limited granularity of the exact facilities that comprise each distribution channel. For example, distribution to emergency medical services or EMS may be done through sales to the non-federal hospital setting when hospitals stock ambulances, or through the miscellaneous/other setting, which measures distribution to state and local governments that may also supply EMS services.

Sales data were analyzed based on product size and strength. Of note, 1 unit may be considered 1 administration of a vial, or ampoule, or device of naloxone, such as 1 unit of Narcan Nasal Spray.

This table provides the sales distribution data by setting of care for the year ending

June 2012 compared with the year ending June 2016. Overall, the number of naloxone units sold increased by approximately 37 percent from about 2.9 million units to about 3.9 million units by the year ending June 2016.

Although the number of units sold to hospitals remained approximately the same at about 2.1 million units, the proportion of sales to hospitals decreased while the proportion of sales to outpatient settings increased, indicating a shift in sales during the examined time period.

On the next slide, we will investigate naloxone use in the community by focusing on the outpatient clinic and retail settings where most of the sales were distributed subsequent to the non-federal hospital setting.

Focusing on the most recent year examined, this figure shows the nationally estimated number of naloxone units sold by product. In the most recent year ending June 2016, 97 percent of the units sold to the hospital setting were for the single-use injectable products, containing a total

dose of either 0.4 milligram or 2 milligrams per vial. Similarly, in the clinic setting, the majority of units sold were for these single-use injectable products.

However, in the retail setting, 18 percent and 9 percent of the market share was for the most recently approved products, Evzio and Narcan Nasal Spray, respectively, which can also be administered by laypersons. The distribution in the retail channel is important in terms of utilization in the community and will be examined in more detail on the next slide.

This figure shows a nationally estimated number of the naloxone units sold by product across time from July 2011 to June 2016 for the outpatient retail pharmacy setting. Note that the X axis denotes sales across a five-year time period.

The two most recently approved products, Evzio and Narcan Nasal, had increased sales to retail pharmacies. The market share for Evzio more than doubled in the last two years examined, and the uptake of Narcan Nasal Spray increased to

9 percent of the market share in this setting, in the 7 months since approval in November 2015.

Next, we will examine naloxone prescriptions dispensed to patients from retail pharmacies. The IMS Health National Prescription Audit Extended Insights database was used to examine prescription-level data. With this database, we are able to better understand the volume of prescriptions, products dispensed directly from pharmacies to consumers. However, because naloxone is unique, it is unknown when or even if naloxone is administered based on this dispensed 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 shows a nationally estimated number of naloxone prescriptions dispensed in the outpatient retail setting by product and patient age for the most recent year ending in July 2016.

Note that the X axis denotes patient age groups.

The highest proportion of prescriptions were dispensed to patients 40 to 64, followed by patients 20 to 39. However, it is unknown if some of these prescriptions were dispensed to caregivers or family members or for the intended recipient of naloxone administration.

Among adults, Evzio and naloxone vials were the most common products dispensed. Notably, about 2 percent of retail pharmacy prescriptions were dispensed to pediatric patients and were primarily for injectable naloxone products.

These data inform national trends in utilization but are not without limitations. The proprietary databases used do not capture distribution of drugs outside of the typical pharmaceutical supply chain such as donations to community programs or direct sales.

In addition, first responders such as police and EMS may not receive naloxone from these usual supply chains. Prescription-level data are based on prescriptions dispensed only from outpatient

retail pharmacies. Not all dispensed naloxone is used, and the number of administrations per overdose event is unknown. Patients administered naloxone may not hold an actual prescription or be dispensed naloxone from a pharmacy.

Although naloxone may be prescribed and dispensed through a traditional prescription process, many states have standing orders and collaborative practice agreements in place that expand the availability of naloxone to guardians and bystanders that may witness an overdose. To address some of these limitations, I'll provide information on manufacturer donations before moving on to other data sources.

Permission from Kaleo, the manufacturer of the Evzio auto injector, was obtained to disclose donated units of Evzio over the past two years. Between April 3, 2014 and April 3, 2015, Kaleo donated over 42,000 devices of Evzio to community-based organizations not for resale.

This represents over 2 and a half times the amount that was distributed to retail pharmacies

during the same time period. Between April 1, 2015 and April 3, 2016, Kaleo donated over 120,000 devices of Evzio to these community-based organizations, and that represents 25 percent more than was distributed to retail pharmacies during that same time period.

According to a recent published news report in Business Insider, Adapt Pharma, the manufacturer of Narcan Nasal Spray, donated 50,000 doses of naloxone to multiple organizations.

In summary, the drug utilization databases inform on national trends and visibility of naloxone distribution across the U.S. and serve as a surrogate for use, assuming facilities purchase drugs in quantities reflective of actual patient use.

Sales of naloxone are increasing, particularly for those products intended for use by the general public, and our data show that naloxone was prescribed to pediatric patients.

We will now discuss other resources to address availability of naloxone in the community

through non-traditional distribution. The National Emergency Medical Services Information System, or NEMSIS, aggregates data that is voluntarily submitted by local EMS agencies from more than 40 states. Data elements include the type of medical intervention and patient disposition during the EMS event. Public use data are available from 2008 onwards and can be trended from 2010 to the present.

A draft abstract, the result of a collaboration between the FDA and CDC, assessing multiple naloxone administrations was reviewed. In 2015, EMS personnel administered naloxone about 214,000 times to about 173,000 patients. Additional details will be provided later today by Dr. Mark Faul, one of the authors of the abstract.

The National Poison Data System, or NPDS, is a comprehensive poisoning exposure surveillance database, which collects data from poison control centers from all 50 U.S. states. Case records in this database reflect information provided when an individual reports an actual or potential exposure

to a substance or requests information or educational materials. We examined mentions of naloxone use in exposure calls in the U.S. from 2006 to 2014.

The total naloxone administrations captured by poison control centers increased every year from about 14,000 in 2006 to almost 21,000 in 2014, representing a 51 percent increase.

Exposure calls represent administrations of naloxone given by health professionals or laypersons that were ultimately reported to poison control centers. These data are passively collected and likely reflect an underestimate of actual total administrations. The number of administrations, doses administered, and possible offending agent were unavailable in these annual reports examined.

The NEISS-CADES database is a joint project of the CDC, the Consumer Product Safety Commission, and the FDA. Data are collected from a nationally representative sample of 63 hospitals that operate 24-hour emergency departments in the U.S. Adverse

drug event or ADE cases are identified using clinical records where a clinician explicitly links the use of a drug or drug-specific effect to the condition that resulted in the emergency department visit.

Although these data explicitly exclude abuse related events, NEISS-CADES was queried to identify ADEs associated with naloxone administration outside of an abuse setting, however, there are insufficient cases involving naloxone to produce reliable national estimates.

We will now move on to examine published literature on utilization of naloxone. A literature search was conducted to identify published literature focused on trends and characteristics of naloxone use in the community. This search was limited to only U.S.-based observational or randomized studies from the last 10 years, with a specific focus on naloxone use in the community by the general public. Two recent systematic reviews were identified.

The published systematic reviews by McDonald

in 2016 and Clark in 2014 focused on assessing the effectiveness of take-home naloxone programs or THN programs. These are programs where an individual likely to witness or experience an overdose are provided education and training on naloxone administration.

In both reviews, standard electronic article databases were queried for studies related to community naloxone distribution programs and with information on naloxone use and outcomes. Both authors had similar methodologies for identifying studies and evaluating the effectiveness of programs in terms of impact and safety. Many of the studies that were included in the McDonald review were also included in the Clark review, so the more recent McDonald study will be discussed further.

In the systematic review by McDonald, there was considerable variability in the number of naloxone kits distributed among take-home naloxone programs, however, all studies reported nearly 100 percent opioid overdose reversals after take-home

naloxone administration. The most common drug reported to have precipitated the overdose event was heroin. Eight studies in the McDonald review reported some type of adverse event ranging from agitation to vomiting to seizures.

This table lists the studies included in the McDonald review. Data on how many THN kits were distributed and ultimately used during an overdose, as well as information on overdose reversal is listed for each study.

As mentioned, there was substantial variability in the number of take-home naloxone kits distributed. The percentage subsequently used ranged from less than 1 percent to 67 percent, however, the majority of examined studies reported 100 percent or nearly 100 percent opioid reversals with take-home naloxone.

I'll now briefly highlight findings from the studies that were based in the U.S. and captured the highest number of events from the systematic review and our literature search, and I have provided references to the full studies.

In Baltimore, Knowlton and colleagues assessed EMS records matched to emergency dispatch records from 2008 to 2009. Naloxone was administered in almost 1300 incidents. Intranasal naloxone was administered most frequently in 40 percent of incidents, followed by IV naloxone in 27 percent and IM naloxone in 22 percent.

Of the total incidents, over 1100 reported on patient status immediately following administration; 62 percent of patients improved; 23 percent had no change; 0.2 percent worsened; and 91 percent of incidents involved transport for further care.

In San Francisco, Rowe and colleagues evaluated a cohort of 702 overdose reversals reported between 2010 and 2013. Heroin was reported as a precipitating drug in over 90 percent of cases. Heroin was the only drug reported in 54 percent of cases and was reported with another substance in over 36 percent of cases.

In Massachusetts, Walley and colleagues evaluated a cohort of 327 participants trained in

overdose prevention between 2006 and 2009. There were 312 reported rescue attempts. About half reported using 1 dose of nasal naloxone, about half reported using 2 doses of nasal naloxone, and 4 percent reported using 3 or more doses of nasal naloxone in the overdose event.

Wheeler and colleagues conducted a survey of 136 managers of take-home naloxone programs, excluding law enforcement and medical personnel in 2014. Approximately 50 percent of the overdose prevention sites provided naloxone in an injectable formulation, and over one-third provided naloxone packaged in a kit with a nasal and mucosal atomizer that is not FDA approved.

More than 10 percent provided naloxone in both formulations. Eleven of the largest organizations provided over 75 percent of naloxone distributed through these community-based programs during this study period.

This table from Wheeler describes the characteristics of the take-home naloxone programs by program size. In 2013, a total of 38,000 kits

were distributed, and over there were over 8,000 documented reversals.

These data inform on actual patient administration and utilization of naloxone, but are not without limitations. The quantity of naloxone distributed and used through these community-based programs is unknown from a national perspective.

Inferences on the effectiveness of naloxone in the community cannot be made from such programs because of the narrow scope and lack of sufficient detail on overdose events. For example, the reason for multiple administrations is often unknown. Additional data are needed on the amount of naloxone distributed, the circumstances of the overdose event, and the formulations and doses as used in the event.

In summary, the epidemiological analysis of data showed trends in utilization or administration that may be reflective of policies being adopted to expand access to naloxone through these community-based distribution programs to individuals likely to witness an overdose event.

Police, EMS, and other first responders may not obtain naloxone from a pharmacy or traditional distribution channel, and data suggests that multiple naloxone administrations occur in a proportion of events. Existing published data on use of naloxone in the community are generally available from EMS and take-home naloxone programs.

In conclusion, national estimates of naloxone sales and more granular utilization data show increasing trends in community availability of naloxone, however, more data are needed to better understand national patterns of naloxone distribution, utilization, dosing, and effectiveness. Thank you for your attention.

Clarifying Questions

DR. BROWN: We'd like to now move to some clarifying questions. If you would, please remember to state your name for the record before you speak and address your questions to a specific person. Dr. Hertz? Dr. Winterstein?

DR. WINTERSTEIN: I have a question for Dr. Mehta. In the review that you just

provided -- that was a very nice, comprehensive review -- I'm curious whether there was the opportunity to -- you mentioned attrition on one of your slides, but you didn't really elaborate on this, and that's obviously a really important part.

If the finding is that all of those products work 100 percent of the time and are effective, everything is fine, but that of course depends on how well data was captured. So if there were thousands of kits given out, and we have data of 800 of those, whether they were used or not, and the remainder we don't, then we don't know whether this 100 percent effective is really correct or not.

In reviewing those studies that you presented, was there any kind of information on that?

DR. MEHTA: This is Shek Mehta from the drug utilization team. Yes. In the studies that we did review, there was a significant amount of attrition in a lot of the studies in terms of people who had either not come back, because in the studies, what

would happen is the patients who were given a kit of naloxone would have to come back and fill out a survey documenting what types of things happened during the overdose event. And in those cases, a lot of the patients just wouldn't come back and fill out their form after they were given naloxone. So there was significant attrition in that respect, yes.

DR. WINTERSTEIN: So if a patient had died and therefore did not come back because the reversal didn't work, we wouldn't know that?

DR. MEHTA: Right, right, from those studies, yes.

DR. BROWN: Dr. Sturmer?

DR. STURMER: Til Sturmer. I have got a question, two questions, actually, for Dr. Nadel. The first one is, on slide 21, you said there's limited pharmacokinetic data for the off-label product.

We've seen pharmacokinetic data today, for example, by Kaleo. Is my impression correct that the 2-milligram off-label intranasal has pretty

much the same pharmacokinetics as 0.4-milligram intramuscular?

DR. HERTZ: Hi. This is Sharon Hertz. I'll take that one. We have some information. We've seen a variety of programs and some comparators for non-published data. And what I can tell you is, we don't have a consistent understanding of the relationship between the kits that are based on injectable solutions and the PK because they use different atomizers, they use different volumes, different concentrations. Some of them are injectables. Those, we would expect perhaps to have better exposure.

So it's not that the off-label use represents one configuration. So depending on how it's configured and how it's administered, we think there could be a fair amount of variability.

DR. STURMER: Thank you. That makes perfect sense. The other question is about the notion raised on slide 23 essentially about one product, one concentration per route, or one dose per route, to be more specific. I just have a question. Do

you mean this across all settings or within a setting?

Let me be specific. Could there be a different dose in a setting of co-prescribing naloxone to patients with chronic opioids versus in needle-sharing programs?

DR. HERTZ: That is a very good question, and we would like to hear your thoughts on that when we go to the questions. But that's the type of advice we'd like to hear today about how to make sense of what should be out there and how to convey these differences to prescribers.

DR. STURMER: But you say, ideally, dose should be suited for all subpopulations. That would imply to me that it would be the same dose.

DR. HERTZ: Well, we're putting that out as an idea. Part of the questions today will also be, in the setting where there are different products, how do we convey their use to prescribers, because what we don't want to happen, at the time where a product is needed, is for there to be any confusion. We also don't want the prescriber

confused, which might reduce interest in prescribing.

So we have a lot of questions about this. When we have evaluated the currently-approved products, we specifically looked at, for instance, could these be used in children, and if so, how young. That's another part of the questions; should there be the same or different products?

We started with the premise that there should ideally be something good for everything, but I don't know that. We would like to hear your opinions on that as we go into the questions.

DR. STURMER: Thank you.

DR. BROWN: Dr. Zuppa?

DR. ZUPPA: Hi. It's Athena Zuppa from Children's Hospital in Philadelphia. This is for Amphastar, referencing slide 11. That was the slide that had the efficacy across age ranges.

Can you just clarify again, there were 5 subjects that were less than 18 years of age. How old were they?

MR. MARRS: Yes. So the 5 that are listed

here that were less than 18, the youngest was 15, and it just fit between the ages of 15, 16, 17, amongst those 5.

DR. ZUPPA: So would you propose using this 2 milligrams per 2 mLs in children that are 2, or 3, or 4 years of age? I'm just worried about the volume and the aspiration risk.

MR. MARRS: Yes. So the product here is the off-label use of it.

DR. ZUPPA: Right.

MR. MARRS: The product that we have in development is slightly different than this. But we envisioned that that product would be ideal for that population.

So knowing things that we've learned through the process of the volumes, we've optimized our products in order to be more ideal for this setting. So the product that we have, our application that we're proposing, would be less volume than this. So in that, we would expect it to be ideal for this population.

DR. ZUPPA: For a younger pediatric

population?

MR. MARRS: Correct.

DR. ZUPPA: Thank you.

DR. BROWN: Dr. Gupta?

DR. GUPTA: So I have two questions, one for the morning for Kaleo and all the other sponsors. Specifically on Kaleo's presentation on slide number 13, you presented information about human factors and usability studies.

In the table, you demonstrated that after training of the off-label naloxone intranasal kit, in both groups, approximately 43 to 56 percent of the people failed after training. And my question is did you evaluate that population for why they failed, or do we have any information of why that occurred? If there's no signs of the information, maybe anecdotal reports from other industry sponsors--

DR. EDWARDS: Sure. Thank you for the question. I'd like to call up one of the backup slides, please. Slide up.

When we looked at errors associated with

those human factors study, we saw these types of errors that were occurring with the intranasal kits. Some of these errors involved -- and keeping in mind that these are off-label intranasal kits, as Dr. Hertz mentioned, different configurations, we chose one that is commonly configured in the overdose education naloxone distribution programs in the harm reduction community.

In this kit, it had an injectable product with a mucosal atomizer that had to be assembled, and it involves multiple steps. So some individuals did not remove the atomizer from packaging. Some did not remove one cap or there's two different caps you have to remove. Some did not even attach to the injector. Some had errors in assembly, and still others had errors in utilization.

There's another slide I'd like to call attention to, the next slide. Slide up. Referring specifically to what would happen during these opioid-simulated emergencies, you can imagine in looking at the case of this as an off-label

intranasal kit, even after trading, individuals would come back and still, looking at the product, may think that it actually was an injectable product.

They may have familiarity with other auto injector products, for example, such as epinephrine auto injectors. And we actually saw individuals going to administer to the deltoid or the vastus lateralis region, even after training. Thank you.

DR. GUPTA: I have a second question for the FDA. In one of the slides that was discussed by Dr. Yun Zu -- I guess that's how you pronounce it -- there was on slide 10 and slide 12, you presented the concentration time profiles.

I have a question. The Cmax that was demonstrated in both of these are very different. The naloxone concentrations for both of these products were very different, one at approximately 1 or above, I can estimate from the graph. And then the other one, the product's plasma concentrations, were between 4 and 8 approximately.

I guess I'm just wondering, is there an FDA

standard for these products for what the peak plasma levels should be? Are we expected to determine that today?

DR. HERTZ: So our standard is characterized by no less exposure than 0.4-milligram IM. It can be more, and the other part that we evaluate is the initial upsweep of the curve because a product can meet bioequivalence criteria for Cmax and area under the curve, AUC, but here, because time is a critical element and Tmax is not part of those criteria, we look specifically at the first minutes, and we want to see the new product not below the reference for the first minutes.

So zero to 5, zero to 10, zero to 30, we look at all of this. We take a figure like that, and we expand it so we can see what's going on in those first minutes.

So yes. It can't be a lower Cmax. It can be a much later Tmax if that does not impact the initial curve. So for instance, if it's going to exceed the exposure, and it just keeps rising, and the Tmax occurs in an hour, that's fine as long as

those first few minutes are not less.

DR. BROWN: Dr. Meurer?

DR. MEURER: Thanks. Will Meurer. So our group at the University of Michigan, through the NIH-funded Neurological Emergency Treatment Trials Network, conducted a large randomized trial of intravenous benzodiazepine versus an auto injector, delivered intramuscular benzodiazepine for adults and children with status epilepticus in ambulances.

One of the things that we've seen is that it's not feasible to do efficacy studies against a control. But my question for the institute, either for Dr. Nadel or Dr. Hertz, has the agency considered asking for non-inferiority or comparative effectiveness studies to address the questions of dosing in ambulance-delivered naloxone, which currently there's some variability in practice and there's also the range of doses that are approved for intramuscular currently from 0.4 to 2 milligrams.

DR. HERTZ: We've really racked our brains trying to figure out how to look at efficacy in the

setting of an opioid overdose when there is existing effective therapy.

So if we have an ambulance study, whatever products are being administered have to meet the minimum criteria. Right? It's conceivable one could create a study where, in the course of treating the patient as needed, the first dose might be compared or something like that.

The type of study, though, in this setting, it's a complex study to do because you can't get informed consent ahead of study participation, and we have a process for that. It's very challenging. You're shaking your head. Perhaps you've explored that. It's a very cumbersome, and difficult, and challenging process for community notification.

In a setting where there is a known and effective therapy, it's hard to argue why a study without informed consent is okay.

DR. MEURER: Sure. So I guess my argument would be, in this case, the reference standard of 0.4 milligrams to 2 milligrams, which you inherited from 1971, has a little bit been challenged by

current epidemiology and trends in drug administration.

The question that you're asking the committee is, should we have a single dose. What should it be? What should the comparison be? Currently, we can use this large range.

Is it hard to do effect studies, exception from informed consent studies? Yes, although our group has conducted four or five of them so far. Is it necessary to get unbiased information scientifically? In many cases, I believe strongly that it is.

I think we could potentially -- if I was to sort of come up with a design off the top of my head, you could have active groups, including 0.4 and 2, that were administered intramuscularly or intravenously. You could have the approved nasal. You could have the approved auto injector.

One of the things we found in our auto injector study was that the auto injector was actually more effective than starting an IV and giving an infusion, or giving an injection of

lorazepam, because it was administered so much more quickly. The study had the ability to actually show superiority, and it did show that the intramuscular administration was superior. This was the RAMPART study, published in February 2012 in the New England Journal of Medicine.

So I think with the right sort of design, one could potentially answer these questions. And I think the investment in doing -- there's 200,000 administrations of this drug in EMS a year. We were able to complete our study with 1,000 patients over the course of 13 months, which we finished early, which the NIH appreciated.

But I think a design is potentially ethical and is potentially feasible. I think part of it is thinking about what's possible and what could help us quantitatively learn, because I think the thing we're banging our heads against is we have this cloud of a gold standard -- is it 0.4 or is it 2 -- and we have various devices and a lack of certainty as to what the true unbiased efficacy is as opposed to from observational studies.

DR. BROWN: We're wandering off of clarifying questions here, because we're going to have a lot of time this afternoon to discuss issues surrounding the questions that have been asked us by the FDA.

I would like the members of the committee, if we can, to focus their attention on the presentations that have been made this morning and ask clarifying questions. Dr. Walco?

DR. WALCO: Gary Walco, University of Washington. This is a question relating to Dr. Nadel's presentation, specifically, slide 6.

When you talk about some of the severe opioid withdrawal symptoms, is this based on case reports, do we have any data at all on the frequency of these events, and is there any relationship between these events and dose of naloxone?

DR. HERTZ: Dr. Hertz again. It's from the labels. It's not from the experience with outpatient use. It's from the labels.

DR. WALCO: Okay.

DR. HERTZ: The new product's labeling is based on the old product's labeling. We are following the post-marketing safety data for the new products, and if we find anything new, we will update the labels. But no, we don't have quantitative data.

DR. WALCO: My second question quickly is the next slide, number 7. I'm having trouble understanding the third bullet, if somebody can just explain the context of that and how it fits in here.

DR. HERTZ: In imagining the different uses for naloxone in the setting of overdose in someone very young, we have thought about this in the context of the products as they're being developed. And the primary risk, it seems, would be in the very young for accidental overdose.

So in that case, it's more likely a child who is not opioid tolerant and their risk for an acute withdrawal syndrome is fairly low. In neonates, typically use of opioids is exceedingly small. The risk for overdose, certainly

unintentional overdose, is very small, but some children are managed for now with a home taper of opioid, and how do we help that family situation in the case of an error?

So in thinking about that very specific population, we worry about them once again precipitating a more acute withdrawal. We really try to parse out within the more vulnerable pediatric population all the potential scenarios and how these products may or may not serve them.

DR. WALCO: That makes sense. Thanks.

DR. BROWN: Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson from Rutgers New Jersey Medical School. Also back to Dr. Nadel on slide 6, if you can, and I understand with your clarification, Dr. Hertz.

Looking through the literature on this topic of adverse events, we're here in a way to discuss risk-benefit, and I think that we'll tweak the dose in terms of benefit. But I think we have to look back at risk a little bit more carefully because one of the things that's not listed on the slide,

because it's not obviously in the label -- and this is also first a post-operative reversal.

But in the community, when patients are brought in after rapid reversal, the biggest toxicity or the biggest adverse effect that we see is behavioral in nature. And we heard about violence and we heard about other things, but I'll tell you, the few times I've been hit by patients, it's been people who have gotten abruptly reversed with naloxone in the ED or by pre-hospital providers who then bring them in and kind of leave them there. And we're stuck with a patient who's really difficult to control, who often wants to leave, who we know is going to recrudesce again if we let them go, and it's kind of an ethical quandary often about whether we should do that.

So have you seen any data on that, in other words, the behavioral toxic effects? Because most of these studies that we've seen are retrospective in nature, and often that's not well documented in the record, whereas these are all objective findings you can pull out fairly easily. But when

a patient misbehaves, we often don't put that on paper.

A related question when you're looking through the literature, the other sort of concern that a lot of people have, and I do share to some extent, is what some have called the Peltzman effect, really, which is the unintended consequences of implementing a risk reduction strategy and having patients change their behavior. Right?

What a lot of people talk about, for example, is knowing that you have the ability to be reversed, might you push your drug use a little bit further, whether it's for pain or for abuse reasons, and whether there's anything in the literature that would suggest that this might occur; in other words, people taking greater risks because they know they have sort of a parachute.

DR. HERTZ: So regarding the behavioral effects of reversal, when we approved our first product and a second product, we've been getting a variety of comments. People like to give us

comments, a variety of types. And we heard initially a lot of concern that the dose was too high because the dose was likely to exceed the exposure from the kits, and the kits were just fine, thank you. And then we started getting anecdotal reports of needing 1, 2, 3 doses, and EMS arriving, and needing more. And then the comments were, the dose is too low.

So my answer to your question is, we're going to ask you this question because how do we balance the need for reversal in an unmonitored, unmanaged setting, and the risk of all of the full potential? You have the small but potential risk for cardiovascular events, the higher perhaps risk for behavioral effects. And we have a lot of thoughts, but we would like your, the committee's advice on that.

I think that we don't necessarily have -- let me make sure I say this very carefully. I think the experience that provides the best information about risk reduction strategies encouraging bad behavior can be drawn from older,

more established programs like risk reduction for pregnancies.

I think there may be some data on this for some of the naloxone programs as well. But I believe that the lessons learned from these other programs show, in fact, the net benefit, far outweighs any small potential pockets of poorer behavior.

In this case, what we're dealing with is a chronic disease in many persons' addiction, and their judgment may not always be clear with regard to decision making regarding what drug they're going to take, and when, and how often. And what we hope is that through the availability of life-sparing therapies, we can get them to the point of intervention so that their disease can be treated more holistically.

This is an opportunity to get into the medical system, and to be referred, and to ultimately get treatment for the underlying disorder that may have led to this in the setting of intentional abuse.

So we always worry about that, and I know that about 15 years ago, that was a huge concern. But I think that there's adequate data now from other systems that suggest that really tends not to be the overriding result of these types of risk reduction strategies.

DR. STAFFA: Hi. Judy Staffa. I just want to add to that response. We wouldn't normally expect to see reports to our spontaneous reporting system about known issues, what the strength of that system is, to bring to our attention new and unusual kinds of adverse events.

But for the purposes of due diligence, our pharmacovigilance colleagues did look in recent years in the FAERS database to see if there was anything unexpected or different that had been reported to us, given that there's been a rise in the availability, and we basically didn't find anything.

They also extended that to look at case reports specifically in the literature, whereas our epi folks were looking more at program evaluations.

And again, nothing new, or different, or unusual, other than what you see here, has been reported to us. So I just want to add that so that you can know that we looked there.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: This question is for Mr. Mulligan from Adapt and pertains to slide 14. So I wondered whether you can comment on the dose of carfentanil that the volunteers are being exposed to here.

These are 8 healthy volunteers, presumably breathing spontaneously, and presumably the dose that's being administered is far less than what would result in an overdose out in the community. So the data that 88 percent of the carfentanil displaced by 4 milligrams of Narcan may not really reflect, to my mind, the efficacy when administered in the setting of high doses of this very potent opioid.

MR. MULLIGAN: I already said that, and the reason to show a study that's even not yet published was because of the narrative that's

developing outside of this room, but in the general media, that you cannot antagonize naloxone -- you cannot antagonize carfentanil. I think you understood what I was going to say, anyway.

This study was normal healthies. The dose of the radio-labeled carfentanil is very low, obviously, because they're healthy volunteers. So it's a micro from what might be used for someone who is using it for a therapeutic purpose, so to speak.

So it is very low, and really, the only net point I was arriving at from this data is that it does comparatively antagonize it, that it did displace of that very micro-dose 88 percent of the radio-labeled, and that the other, the 4-milligram, was faster. But the data will be available in more detail in the months ahead.

But I just brought it up -- I know it's not the most appropriate to bring up a study like this, but the fact that you're hearing more and more media attention that carfentanil cannot be antagonized, I thought it was appropriate to bring

it to the attention. But you are right, the dose is a micro level of what would be given.

DR. BROWN: We're going to move ahead. We'll come back to some more clarifying questions after lunch, but we're going to move ahead with the presentation from Dr. Mark Faul from the CDC.

Presentation - Mark Faul

DR. FAUL: Thank you. My name is Mark Faul. I'm with the CDC, Centers for Disease Control. I work in the Division of Unintentional Injury. It's the National Center for Injury Prevention.

We've been doing some work in the naloxone space, and our general mission at CDC is basically to count the number of overdoses, categorize them, come up with prevention methods. Naloxone is not the key focus of what we do, but we've been partnering with other federal agencies, and we've come up with some interesting results that might be of interest to this panel.

I'll also say before I start out, as I hear all this discussion -- excuse me -- about dosages, we're more of a big-picture and not the actual

dosage. So I know that will disappoint some people, but there isn't much talk about the big picture of what's going on. And from that perspective, I can inform the panel.

I don't have anything to disclose. These are the federal partners and some of the people in the medical community that we're working with, Peter Lurie with the FDA; Michael Dailey with New York Emergency Medicine; Jeremy Kinsman with NHTSA, National Highway Traffic Administration; Matt Gladden, who's an expert on fentanyl at the CDC; Charmaine Crabaugh with the CDC; and Scott Sasser with the Emergency Medicine and Greenville Health System, South Carolina.

What we wanted to do, and the goal of this session, is to describe changes in multiple naloxone administrations over time in a pre-hospital setting. We wanted to explain the reasons behind the multiple administrations, what the likelihood is that a person gets multiple administrations.

We looked at various independent variables

in this. That's just a small subset of age, geography, ambulance characteristics, dispatch complaint, what's the nature of the 9-1-1 call that comes in, and other variables.

As we step back and take a look at the big picture, the overall burden landscape is changing dramatically in the opioid arena. There's slight increases in commonly prescribed opioid overdose deaths. These are prescribed opioids. The heroin rate is rapidly increasing and we know street heroin is more potent than most opioids.

There's large increases in synthetic opioids such as fentanyl. Fentanyl can be 50 times more potent than morphine. I heard some other presenters refer to this. DEA within the last two weeks issued an emergency notice to law enforcement, indicating that carfentanil has been found in the drug user population. Carfentanil can be 100 times more potent than fentanyl.

These are the overall overdose. These are the mortality counts that CDC publishes on a routine basis. What we do is talk about the method

just a little bit. I think it's important. We get death records from all 50 states. Those death records are put into the multiple mortality file, and we can pluck out the underlying cause of death and some characteristics of the deaths.

The orange line -- there are so many screens here, I'll pick on this one. This one here is the orange line. This is where we've had the traditional focus at CDC, is in the prescription drug overdose. What we are seeing is that heroin, within 2010 forward, is almost up to the overall prescription overdose line, whereas there's been some stability in recent years for prescription overdose.

What is also troubling is the overall increase in synthetic opioids. This would be fentanyl, and carfentanil, and other kinds of substances. When you combine the rates for heroin and synthetic opioids, it easily exceeds the overall prescription overdose problem, which is really front and center of how we started talking about this epidemic.

Methadone is on the decrease. I've done some work in this. They have a publication in the clearance process at CDC. The FDA is partially responsible for the decrease in overdose deaths associated with methadone because there was a huge public warning given out on methadone in 2006.

Further evidence that the landscape is changing is that, for fentanyl, of course we know it's a prescribed product. The dotted line is the medical prescription volume, and it's slightly lower than it was in 2010 versus 2014. It's basically stable, 1.6 fentanyl prescriptions per 100 people.

This is the troubling curves here, is that the number of what they call submissions at DEA is increasing from it looks like about 500 in 2010 to 5500 or so, 5,000 in 2014. It's a huge increase. And when we describe what a submission is, our brain, when we talk about CDC, goes to seizures. What they're really doing is sometimes they purchase drugs, illegal drugs, and they have them tested. That's called a submission. When they

seize a drug and they submit it for testing, that's called a submission. So these are actually combined together to sort of test what's out there in the environment.

So this is such a profound change in what we thought was a problem with fentanyl at CDC. We've decategorized fentanyl as being primarily a legal prescription -- a drug overdose associated with legal prescriptions and put them toward the illegal category.

This is another chart. We have some great federal partners. This is also captured or done by DEA. And we can see where the fentanyl encounters, submissions if you will, are all pretty much in the eastern United States, the northeast corridor, and southern Florida. There's some going on here in the south. Missouri is a little bit red. It's more of an exception. But where we're really concerned is with the synthetic opioids, the growth in that.

I want to talk a little bit back about EMS. EMS is a unique part of the healthcare system.

It's regulated by state and local government. It's really not regulated by the federal system. There is a guide called the National EMS Scope of Practice that says what a paramedic can do, that says what an EMT, basic or intermediate, can do. And that involves the actual handing or administration of prescriptions.

According to one study, naloxone was the most commonly administered drug to adolescents in the pre-hospital setting. What we wanted to do -- this is a study that we're having published. Is there an increase in the percentage of patients that received MNA, multiple naloxone administrations, over time? And what are the circumstances?

So to answer this research question, we used the National EMS System, which is sort of a new national data set. It contains between 19.8 and 30 million records, depending on what year. It includes non-injury. It includes everything. But we're focusing of course on poisonings.

It has a large state participation of 42 to

49 states. It's the most comprehensive collection of EMS data in the United States. It is also deemed to be representative according to this publication on pre-hospital emergency care.

I wanted to also talk a little bit about rural versus urban, that's been brought up a little bit. The challenges in a rural setting -- this is one of the independent variables -- for EMS, the challenges are really striking.

For the white counties in the United States, or classified as urban areas, they have 80 percent of the EMS personnel. For the green counties, that's where 20 percent of the EMS personnel work, and they have to service so much more area.

How this is relevant to naloxone is the response times that are required are just enormous. The one study I looked at was 32 minutes versus 9 minutes, 32 minutes in a rural setting, 9 minutes in an urban setting. So as we talk about 1 minute on graphs, we have to think about how long it takes EMS to get there. That's an important part of all this. Excuse me.

So for this study, we defined the event, a record to be analyzed as any condition where naloxone was administered. It didn't have to be a verifiable drug, opioids overdose, but it's any situation where naloxone had been administered.

We used the statistical procedure of logistic regression, the dependent variable being was there multiple administrations or was there not? There was just one administration. The independent variables, age, gender, U.S. census region; we couldn't go any deeper by state. It's not on the file.

Urbanicity, lay naloxone use. There's an ability to pluck out the layperson use of naloxone, dispatch complaint, primary symptom, what did the patient have, whether or not oxygen was administered, and the patient final disposition in the EMS setting.

What we found is in 2012, the number of patients that required multiple administrations was about 14 and a half. It jumps to about 15. It goes up to about 16.3, and then in this most

current data year that we have, which I got a hold of at the end of August -- so it's actually pretty fresh data in surveillance terms -- it's climbed up to 18.2 percent, and require multiple administrations.

This is a national picture. There's wide variation, we would presume, in local agencies, in different states, where some of these more potent drugs are. But the national picture is pointing to more and more administrations are needed. I will say, too, administration is considered to be a kit, and it's usually intranasal.

These are some specific numbers; 141,000 patients received 1 administration, 25,000 patients received 2, 4,000 received 3, and then it goes on to very small numbers as you go past this.

Looking at just some descriptive data, one of the strongest indicator variables of multiple administration is actually the type of ambulance that's dispatched. Advanced life support is categorized as basic life support, advanced life support and different levels within advanced life

support.

You can see that the kind of truck -- this varies from agency to agency. But in some cases, basic life support is this kind of truck. In some cases, advanced life support is this kind of truck. It's supplied more with different kinds of medications, and it's supplied with different kinds of personnel.

I think it's critical to start looking at rural and geography with these administration questions. Urban settings seem to be very well suited to handle multiple administrations. And I will also say that urban settings are about 85 percent -- 82 percent of the entire data set.

We start thinking about rural and other settings. These other categories are actually smaller. You can see that rural settings do not have as much multiple administrations and neither do suburban settings.

This is the logistic regression. The model used 173,000 patients. Remember, there were 214,000 overall administrations, but there's

173,000 patients that we looked at. Males were more often to receive multiple administrations; for age group 20 to 29, more often to receive MNA.

Northeast, which was consistent with the DEA, collections on fentanyl, they were more often to receive multiple administrations. Urban setting was actually the most likely area to receive multiple administrations.

Look at layperson naloxone. This file allows us to capture that. I want to put this in a little bit of context. Someone showed the Wheeler article of 8,032 reversals, and I hear law enforcement and layperson use a lot, but you have to put it in proportion. That's 8,000 reversals versus 173,000 patients in the EMS setting. By far, the EMS setting has the majority workload in this space.

Previous administration of naloxone, naloxone actually had a higher likelihood of MNA in the EMS setting. So there's only 1600 records that hit this, but even though they got naloxone presumably in a family environment, EMS was called,

and they got more naloxone.

Home residence, somebody else mentioned this. This happens more often in the home than anywhere else. The dispatch complaint, -- when the dispatch complaint was specific to drug ingestion and poisoning, there was a higher percentage of multiple administrations.

As I mentioned before, ALS, advanced life support, level 2, they had the highest MNA. It was a combination of supply issues on the truck, perhaps, and personnel. If oxygen is provided on the scene, that also has a high association with multiple use.

Symptoms, just to see that the symptoms make sense, what we expect to see is that breathing problems and a changing responsiveness are indicators of multiple administrations. And when there isn't a multiple administration, the outcome by EMS is more likely to be treated and transported to a medical care facility, as we would expect.

In summary, there were 214,000 administrations in 2015. Among the 173,000

patients receiving naloxone, only 28,811 of the 9-1-1 calls actually indicated it was drug poisoning. That's an important consideration if you're a dispatch system dispatching ambulances, to actually know more about the situations you're sending the ambulance to.

MNA is growing over time from 14,500 to about 18,200 in 2015. The circumstances where MNA is more likely, I recorded this, but we went over this on the logistic regression slide.

Limitations. One thing that kind of screams for this data is the measure of injury severity, some kind of breaths per minute, some maybe Glasgow Coma Scale integration in this. We do not have that on the NEMSIS 2.2 version. That is coming in future versions of this data set.

The NEMSIS research data set does not allow for state-level analysis. The NEMSIS data is about 95 percent complete, meaning that it resembles approximately 95 percent of what's going on in the United States, which is powerful, but it's still missing some records.

We could only infer that MNA was restricted by supply and personnel issues. We don't know that for sure, mostly because how EMS administers ALS and BLS is so variable across different states and different localities. That's sort of a blanket statement. MNA may be a proxy for drug potency, but it's also confounded by EMS response times and other variables.

We think these limitations are probably consistent over time, so we don't think it has much impact on the overall message of the study.

The public's need to increase the accuracy of the 9-1-1 call may lead to a better dispatch of equipment and staff. In some states, intermediate and basic EMTs cannot administer a pharmaceutical. Naloxone is a pharmaceutical, and they're prohibited from administering it. Ironically, this is more disproportionately true. There's more basic EMTs and intermediate EMTs in rural settings. We've had a publication on this.

Dispatching the best ambulance with the proper equipment and staffing might help increase

MNA and potentially save more lives. Rural settings don't have the sophisticated dispatch systems sufficient for ALS response units. In some rich counties, as the dispatch call is being made, the EMS person has a computer on the truck, and it's getting relayed instantaneously what the 9-1-1 caller is saying. That's not really available in a volunteer fire department and in places like Albany, Georgia.

More guidance is needed on MNA, and the dosage should be examined. I think it should be examined in light of the synthetic drug usage that's growing and becoming strong across the United States. And that's the presentation. Thank you.

Clarifying Questions

DR. BROWN: Thank you, Dr. Faul. We've got a few minutes for clarifying questions for Dr. Faul at this time. Please remember to state your name for the record before you speak. Are there any questions? Dr. Winterstein?

DR. WINTERSTEIN: I might have missed this.

Do you have the failure rate of the reversals?

DR. BROWN: Can you speak up, please?

DR. WINTERSTEIN: I might have missed this. Do you have the failure rate of the naloxone use? So how many patients died, essentially, number one? And then number two, you mentioned this in one of your limitation slides. You don't have a dose of naloxone in your data.

DR. FAUL: That's correct. That's correct. I didn't quite hear the first part.

DR. WINTERSTEIN: The first part, the failure rate of the -- so basically how many patients died? What's the proportion of death?

DR. FAUL: Yes. That is available in the file. We did not look at it, primarily because the lack of injury severity as a variable on this. The number of deaths takes on a different meaning in absence of the severity because in rural situations, it takes 30 minutes to get there. A lot of people -- some people die before they can even be treated.

So we're thinking about doing this, but it's

really tricky without proper injury severity analysis, the variable in this model.

DR. WINTERSTEIN: It would have helped to set the systematic review that was presented earlier, and put that a little bit in perspective because it sounds like it always works.

DR. FAUL: I understand. We can get a hold of those numbers. The problem is, it doesn't necessarily mean that the naloxone is not effective, even if they administer it, because what happens in the EMS setting, it's actually administered when the person is dead to try to revive them.

So we sort of decided not to go there because it could be easily misinterpreted in a way that wouldn't really be beneficial to anyone.

DR. BROWN: Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson from Rutgers, New Jersey. That's a great data set, and I've not actually seen it before, and it's quite impressive. But obviously, along the same lines as that question, is there any way to tell if the

people who got a second dose only partially responded to the first dose as opposed to not responding at all? And is it possible to know if they got a second dose because it was a long period of time and the first dose wore off; in other words, recrudescent toxicity, or based on any metrics that you might have?

DR. FAUL: The first answer is no. There's not that detailed of a data set. The second answer, we can kind of answer a little bit because of how EMS works. By and large, they're not going to sit there at the scene and administer one dose, and then wait. They're going to administer one dose, get the person in the truck, and get him transported, and administer potentially another dose on the way to the hospital.

So there is scene time in there. And EMS is very, very sensitive to amount of times. It's a time-driven system. How long does it take to get there? The scene times, they will get hammered on if they take too long at the scene.

So I think the answer to the second question

is, it's really not a characteristic that you would see EMS do.

DR. BROWN: Dr. Sturmer?

DR. STURMER: Til Sturmer, UNC. Did I hear you correct that there are EMS vehicles who don't have naloxone in the car; and then there are some vehicles that do have it, but the people driving the car or in the car cannot administer it legally?

DR. FAUL: The first part, yes. There are variations in the type of equipment and medications in a BLS unit versus an ALS unit. I cannot say with one sweeping statement what they are because there's so much variation. There are many differences between ALS and BLS on how it's staffed. There's CMS billing records, so many paramedics. They give the details. I don't know them off the top of my head right now.

DR. STURMER: Thank you.

DR. BROWN: Dr. Higgins?

DR. HIGGINS: This goes back to an earlier question one of the panelists had with respect to obesity. Did you measure weight, BMI, and with

respect to the relationship with MNA?

DR. FAUL: I'm sorry. Can you repeat the question, and louder, please?

DR. HIGGINS: Sure. So in regards to an earlier question that the panelist had regarding obesity, did you evaluate any relationship between BMI and MNAs?

DR. FAUL: No. BMI is not on the file. It's not on the data file, weight, anything, nothing. We could make no inferences about the weight of the patient.

DR. BROWN: Dr. Woods?

DR. WOODS: On slide 17, when you talk about percent of MNA by geography, do you find it somewhat surprising that the rural was less than seen in other sites? Especially given the fact that transport times would seem to be longer. If time to get there is longer, it seems like time to get people to emergency care would be longer. So how do you explain that?

DR. FAUL: The group has looked at this, and we need to do a little more subanalysis on this

before the paper is done. But what we anticipate is that the first administration is on a person that's obviously dead. And when there's no response, they don't administer the second administration because the response times are so much longer on the rural setting.

DR. BROWN: We're going to take one more question. Dr. Beaudoin?

DR. BEAUDOIN: Hi. Francesca Beaudoin from Brown. Do you have any data about the routes of administration or doses with this data set?

DR. FAUL: No, I wish we did. I'm sorry. I notice this group, this panel is sort of thirsting for that information. I wish I had it. I just don't. But hopefully, some of the macro trends are beneficial and informative.

DR. BEAUDOIN: Thank you.

DR. BROWN: Thank you, Mark. That was an excellent presentation. We really appreciate you coming up from Atlanta to inform us about this.

We're going to adjourn for lunch now. We'll reconvene again in this room in one hour, at 1:15.

Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch, amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:22 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:16 p.m.)

Open Public Hearing

DR. BROWN: We want to get started with the open public hearing session.

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 open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any industry group, its products, and if known, its direct competitors. For example, this financial information may include industry's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair, and thank you for your cooperation.

Will speaker number 1 step to the podium and introduce yourself? Please state your name and any

organization you're representing, for the record.

MR. BIGG: Thank you. My name is Dan Bigg. I'm the director of the Chicago Recovery Alliance. For a quarter century, CRA has assisted any positive change as a person defines it for him or herself in the Chicago area. Since '96, CRA's OD prevention program, founded in honor of my fallen brother, John Szyler, has empowered over 72,000 non-medical people with a 45-year-old antidote to overdose, and we have received reports of over 8,000 lay reversals to date.

CRA's OD program, while motivated by death, was formed from the beginning by active drug users just like the remainder of CRA's outreach. From the beginning, we were told to utilize 10 cc vials of naloxone along with 10 IM syringes. If we had not done this, there would have been dozens of deaths in multiple overdose situations in the early years.

In more expensive and experience-informed years, we began to utilize 1 cc vials to extend reach and reduce chances of contaminated naloxone

injections. Now, we utilize from 2 to 10 1 cc vials along with an equal number of IM syringes, depending on the person's negotiated needs.

A critical perspective in consideration of the goals of this meeting is to serve life, first and foremost, and reach beyond the repression, which is the U.S. stock and trade on drug-use issues.

Some lessons from our experience over 20 years of opioid overdose prevention, we have never received a report of failure to utilize available injectable naloxone in an OD situation where it was present. This utilization of IM naloxone holds true with active drug users, family, friends, law enforcement, et cetera. While most reports collected utilize 1 cc of 0.4 milligram IM, a large number report an additional dose, which worked immediately. We often refer to this as the panic dose. This is an important variable to take in consideration in considering doses.

We have received single digit reports of naloxone's failure to revive, including with

suspected or known synthetic opioids. Always when there's been failure to revive, it's been related to late administration; titrating to respiratory sufficiency, not sobriety, or Republican Party debate status as someone has said. The idea of using per the product insert 25 doses of naloxone seems insane. We're also fooling with pulse ox symmetry in terms of this.

I very much urge the FDA to fund research on these issues so we don't have to guess about them and play about them in the press, full of hysteria. The absolute definition of inadequate dosing must be insufficient affordability and access to naloxone. Thank you.

DR. BROWN: Thank you. Will speaker number 2 step up to the podium and introduce yourself?

MS. DOE-SIMKINS: Good afternoon. My name is Maya Doe-Simkins. I have been working on expanding naloxone access in overdose prevention for about 12 years. I do program implementation support, some research, and some technical

assistance. And I came here today to ask that your decisions increase access to all naloxone products because we have practical on-the-ground experience that all of them work. There are pros and cons of each and every one of them, and a local context should play prominently in decisions about which products work best for folks.

I came here to advocate for some choice. I would like to show you how prescribers and pharmacists providing naloxone access right now also want choice. I co-direct Prescribe to Prevent, which is a web-based resource for prescribers and pharmacists. It's referenced in the SAMHSA opioid prevention toolkit. It is included in the CDC opioids prescribing guidelines. It is included in toolkits developed by professional organizations like the American College of Emergency Physicians.

We don't have any industry funding or support. It consists of 18 volunteer experts, a considerable majority of whom have written every single study on take-home naloxone that's been

referenced here today and performed in this country. We have been in operation since 2012, and visitors are invited to use and adapt all contents.

I wanted to illustrate how providers' interest in multiple products -- sorry. Let me back up. I'd like to show you some of our utilization statistics that reflect providers' interest in a variety of program, a variety of products. Here's a little map of our users. It's developed for folks in the U.S., but we did have some folks in other parts of the world, which is interesting to us. But over 90 percent of our users are here in the U.S.

In 2012, on the left-hand side, you can see are the number of unique users annually, and then most recently just this, up until now, part of 2016, we've gotten over 25,000 unique users.

That one is screwed up; the titles aren't working, but I wanted to just point out here that these are our most popular downloads in 2016. On the right-hand side, we have an naloxone product comparison chart. We have an overview of how to

bill for naloxone. The two popped out ones are both for intramuscular naloxone and intranasal information sheets. Then the whole left-hand side is all a variety of a bunch of different products. People want research. People want legal opinions. So that's an enormous number, but only five make up an entire half of our unique downloads.

That's all the time I have. Bye. Oh. I had -- no, I guess I don't. It's telling me to go away. So thank you for your time and attention on this today.

DR. BROWN: Thank you. Will speaker number 3 step up to the podium and introduce yourself?

MS. NAMKOONG: Hi. My name is Hyun Namkoong, and I work for the North Carolina Harm Reduction Coalition, and I'm the program coordinator for our agency's overdose prevention program. Since 2013, our agency has distributed over 34,000 overdose rescue kits containing naloxone, which has resulted in 4,659 reports of community members who have successfully used naloxone to reverse an overdose.

Our agency distributes two types of intramuscular naloxone, the 0.4 milligram vial and the auto injectors from Kaleo, as well as intranasal naloxone manufactured by Adapt. Ninety-five percent of the reported overdose reversals to our agency have been performed with IM naloxone. The option of having different doses of naloxone is a vital importance to the financial sustainability of our program and the work that we do in the community.

The rise in the price of naloxone coupled with increases in fentanyl related overdose is frankly quite literally a deadly combination for community-based agencies operating on shoestring budgets. We have also observed a geographic variation of heroin-laced fentanyl, and as such, it isn't necessary to distributer nasal naloxone to all of the communities that our agency works with and not to all people who use opiates.

A strong batch of heroin cut with fentanyl is not the only risk factor that can lead to an overdose. Other factors such as people changing

the route of administration, or having low tolerance, or mixing drugs all play a role, and as such don't necessarily require a high dose of naloxone to reverse the overdose or multiple administrations of naloxone. In most of those cases, only one dose of 0.4 milligram of naloxone is used.

For areas where heroin-laced fentanyl is more prevalent, we do distribute nasal Narcan overdose rescue kits due the higher dose of naloxone, or we provide extra intramuscular naloxone kits. The availability of intramuscular naloxone, though, is critical, as we have had some people specifically request IM naloxone over the nasal Narcan due to the severe symptoms of withdrawal it can cause.

It is important to not administer more naloxone than necessary, as it is extremely unpleasant and uncomfortable for people to experience withdrawal. And while we are seeing a rise in fentanyl related overdoses, another variable to consider for reports of people

administering multiple doses of naloxone is time. We have received anecdotal reports of people who have told us that they panicked and freaked out, and administered multiple doses of naloxone after 30 seconds.

I hope that the information provided to you today will help you understand what we are seeing at the community level. Thank you for your time.

DR. BROWN: Thank you very much. Speaker number 4, would you go to the podium and introduce yourself?

MS. HAAS: Good afternoon. My name is Erin Haas. I'm with the Department of Health and Mental Hygiene, behavioral health administration in Maryland. I came by to provide some local context to today's conversations.

In Maryland, we've seen a dramatic spike in overdose deaths. From 2014 to 2015, they jumped 20 percent, and we've seen that trend continue into 2016, where so far we've seen one third more deaths than we did at the same time last year. Most of those are attributed to fentanyl and fentanyl

analogue, about 80 percent of our deaths right now. So this reflects a very unpredictable heroin supply and drug market in Maryland.

Naloxone is a critical component to the department's comprehensive strategy to address overdose and opioid misuse. In 2014, the department established the Overdose Response Program, which is centralized at the state level and authorized as local overdose education in naloxone distribution programs. It allows for a public health outreach motto that takes naloxone directly to people who are at risk for overdose, their friends and family, as well as law enforcement and other service providers.

There are 55 authorized training programs and counting right now in Maryland. Half of those are local health departments. The rest are community-based organizations, law enforcement agencies, substance use disorder treatment providers, medical providers, and others, and we're constantly recruiting more. We've received over 1,000 reports of naloxone use in the community

since the start of the program. In the majority of successful reversals, 1 to 2 doses of naloxone was used or medical help was on its way, which I think is an important point.

The department distributes some funding to local health departments to support their programs, otherwise, the rest of the authorized programs are on their own to find funding to support the training as well as the purchasing of naloxone. Most programs are purchasing the Amphastar product and are starting to switch over to the Adapt Narcan. We have a couple programs that are still using Hospira, and it just kind of depends on the needs of the community that they're serving.

We appreciate that the FDA is taking time to look at naloxone and its use in the community. And I just want to make points that it's critical that we have naloxone products that are easy to use and require little training and that will reliably work in an overdose situation. It's also important that we have a lot of product options that allow for competitive pricing because funding can be limited

for so many different programs.

The outcomes of this meeting may influence the production and distribution of naloxone, and that's not just at the federal or manufacturer level, but that will affect these 55 and counting programs that operate in our state. In the chaos of this current crisis, I think the only certainty is that naloxone works in an opioids overdose, and we simply need more of it in order to see the full benefits of these local community programs. Thank you.

DR. BROWN: Thank you very much. Speaker number 5, if you could come to the podium and identify yourself?

MS. LYNCH: Hello, everybody. My name is Pam Lynch, and I'm a behavioral health and addiction specialist from Michigan. I teach for Grand Valley State University there. I've been doing naloxone work since 1999 when I worked with Chicago Recovery Alliance. And since that time, I've worked with Sharon Stancliff in New York, in New Jersey, and also in Michigan, programs that

were all researched by some of our most respected academic institutions in this country: Yale, Brown, Loyola, good data coming out of those programs.

In Michigan, as we saw in the slide from Dr. Faul from the CDC, the area where I work is non-urban metropolitan. But like in much of this country -- and it really reflected the green on slide number 16 in his set -- naloxone programming in Michigan is nominal because public health is in conflict with law enforcement. I must also respectfully remind all present here today that the importance of the take-home naloxone programs represented in Wheeler's survey is critical.

These community-based organizations played, and continue to play, a critical role in the use of naloxone with active drug users. Addiction is very stigmatized in our culture. Community-based organizations were able to gain the trust and respect of people who are used to being treated very poorly, and even by those who are charged with helping them. It is these CBOs in Wheeler's survey

who demonstrated to opioid addicts that their lives mattered.

The only way to reverse this trend of the opioids epidemic in this country is to be inclusive, not exclusive. I implore that you look at products that can be inclusive to the community-based programs that have existed to date and that continue to exist. Therefore, not only is there a place for different products, it is imperative that we continue to make different products like the 0.4 milligram/milliliter vial affordable and available. Thank you.

DR. BROWN: Thank you, Dr. Lynch. Could speaker number 6 --

MS. SCHOLAR: Hello. My name is Shoshanna Scholar, and I'm the executive director of Los Angeles Community Health Project. We're a harm reduction organization, and much like a couple of the other folks who spoke today, we've been doing naloxone distribution since 2003, directly to drug users and other people who are in a position to respond in a community setting. I am here to urge

this committee to consider the impact of setting guidelines for community-based naloxone programs. We need options to get naloxone where it's needed.

The community-based organizations serve many people of color, people experiencing homelessness and poverty. The programs are generally poorly funded. They're at around $300,000 or less a year, and they are extremely price sensitive. My board chair and I got very concerned when the price sharply increased of the injectable naloxone. That's what we've been giving out this whole time. We're at about 1200 doses a year -- or 1200 kits a year with 3 ccs in each kit. We have received news of no adverse events, no product failures, and no deaths due to not having enough naloxone in those kits.

Due to that price increase in 2015, my board president and I conducted a survey to figure out what the price point is that would allow us to continue the work we're doing. Of all the programs that we're distributing at that point, a dollar per cc, they could maintain what they were doing at

that point in time, so that's last year. At $3 a cc, they were rationing, and at 5, they were closing. They were closing programs.

So we decided to start our own 501(c)(3) to figure out some way of getting a dedicated access for CBOs to naloxone that they could afford. So we're in the process of developing our own. But we wanted to make sure that you guys -- that's sort of separate from this. If this market figures out how to do it without us, that would be fantastic. I would like to just run my program.

What I wanted to tell you about your guidelines is that we're concerned that by putting out guidelines that favor a more expensive novel product, it will guide and influence government entities that are setting up their policies and procedures, health departments, and that it could influence developing legislation that is meant to sustain and expand existing programs.

We want to make sure -- we just need -- we can't afford to lose any more lives and, in particular, this one really great access point for

people that we care a lot about, for homeless people, for people experiencing poverty, for people of color, who are people who use drugs. We want to encourage you to keep that in mind as you move forward. Thank you.

DR. BROWN: Thank you very much. Speaker number 7?

MR. CLEAR: Good afternoon. My name is Allan Clear. I'm the director of the Office of Drug User Health at the New York State Department of Health AIDS Institute. My office oversees the distribution of both intramuscular and intranasal naloxone to community-based organizations throughout the state. Thank you for allowing me to testify.

The experience of New York State has been that 2 milligrams per 2 cc intranasal has been effective in addressing opioid overdose situations. Options on formulation and delivery mechanism need to remain viable and available to government, community, and individuals so that variables such as cost and ease of access and use can be

evaluated.

Since we inaugurated our program in 2006, we've trained over 130,000 responders. That includes law enforcement officers, firefighters, correctional staff, family members, and individuals who use drugs. Each individual that's being trained receives intranasal or intramuscular naloxone. The intranasal device used by New York State delivers 2 milligrams per 2 cc, and the intramuscular delivers 0.4 milligrams of naloxone. Responders have used naloxone over 5,000 times with a demonstrable effect.

Last year, we shipped 68,000 kits comprised of 2 doses to the state's programs. Of these, 86 percent were intranasal devices. Among law enforcement, who only use the intranasal product, there have been nearly 2,000 reported uses of naloxone between June 2014 and August this year. For the first half of 2016 alone, there were 947 reported uses of naloxone. Eighty-eight percent were reported to be responsive post administration; 98 deaths were reported.

In 2016, the use of no more than 2 doses of naloxone has been the norm; however, the use of more than 3 doses has risen from zero in early 2014 to 12 percent in the quarter ending June 2016. We looked more closely at the county reporting the most frequent use of naloxone by law enforcement, a county where fentanyl is endemic.

All 144 naloxone administration reports from January through June 2016 were reviewed, 87 percent of uses and held no more than 2 vials. The frequency of 3 or more doses rose from zero percent in the first half of 2014 to 13.5 percent in the second quarter of 2016. Of the 6 deaths reported, none were suggestive of insufficient dosing. Two of the victims were apparently dead at assessment. Seven of the 144 naloxone administrations had unknown incomes. Case review of these 7 showed no instance of insufficient naloxone.

What we have seen in the use of naloxone, consistent with an ongoing small scale equipose study being conducted with EMS personnel, is both the legacy intranasal formulation and the

FDA-approved intranasal product are performing comparably well, and the incidence of multi-dosing is roughly the same. Thank you.

DR. BROWN: Thank you very much. Speaker number 8?

DR. STANCLIFF: My name is Sharon Stancliff. I'm the medical director of the Harm Reduction Coalition based in New York City and Oakland, California. I'm boarded in family medicine and in addiction medicine.

First I'd like to, based on the data received, express some concern about the standard that has been set for these deliberations at 0.4 milligram levels consistent with that. We have a long story of success with the legacy intranasal product for which we don't know of the levels, and perhaps that should have been included as part of the standard.

I'd also like to point out that in the medical community, there's a recent review that finds that even clinicians in emergency and anesthesiology settings have not really settled on

what their initial starting dose should be. 0.4 is the standard, but the literature is as low as 0.1 milligram.

So I really want to emphasize that much of the data that's gotten us here today is based on the community distribution of our generic products that are currently out there, and I'm referring to the city Department of Health from New York; state Department of Health from New York; Oakland, California; and Pittsburgh. Those are the places that are reporting the successes that have pushed this program.

I also want to say a little bit more about the study that we're doing in New York State that Allan just mentioned. So yes, we can compare these products. Until recently, EMS in New York State was using the intranasal product -- well, the product made by Amphastar used intranasally -- so it really didn't present an ethical problem to have them use, part of the time, the new Adapt product, and part of the time the Amphastar product.

We have about 83 total now, so that's very

small numbers. A very preliminary peek at the data finds that the number of doses -- people receiving 1, 2, or 3 doses -- is extremely similar across the two products. Who would have thunk? We're also seeing similar results in terms of returning to level of consciousness. There's a lot of data out there to be gotten, and there are ways to get it. So I think we have insufficient data at this time to say what the lowest dose should be -- I mean, what the lowest level should be. We need to get some more data and figure that one out.

This is vital. We are in an emergency time right now. We've got these two great generics. They should not carry any kind of implication that they are substandard unless we've got really good data to say so. Price matters. I know that's not the FDA's problem. In many ways, they have a different standard and a different mission. But in New York State, 6 million is projected to be spent this year on the intranasal product that we're currently using, the Amphastar product. If it were switched to the Adapt, the way the prices are set,

it would go to 9 million. That is non-sustainable. The best Narcan is the Narcan that people can be carrying on the streets. Thank you.

DR. BROWN: Thank you very much. Speaker number 9?

DR. KUNINS: Good afternoon. My name is Dr. Hillary Kunins. I'm an assistant commission at the New York City Department of Health and Mental Hygiene, and clinical director of the New York City Opioid Overdose Prevention program. We purchase and dispense intranasal naloxone, and dispense it to community-based programs throughout the city.

Since 2009, the New York City health department has distributed more than 35,000 overdose rescue kits free of charge to community-based programs. As you have heard, each kit contains 2 0.2 mL doses of the 1 milligram per mL naloxone, so-called off-label naloxone. We also include two mucosal atomizers for intranasal administration.

We are currently supplying more than 50 community-based programs, including syringe

exchange programs, substance use disorder treatment programs, homeless shelters, visitors to Rikers Island, the largest New York City jail, and New York City Police Department. Due to a rebate negotiated by the New York state attorney general, the increasing cost of this medication has been somewhat mitigated compared to price increases seen in other jurisdictions, but nonetheless remains challenging.

I want to share with you our extensive field experience data with New Yorkers that I think supports the use of this particular formulation. Since 2009, 900 overdose reversals have been reported to the city, New York City's health department, which we know is greatly underreported.

To assess more completely, we conducted a one-year prospective cohort study of our naloxone distribution program, which is under peer review. Among a sample of 400 individuals at high risk for overdose and who were trained in opioid overdose prevention and administration of naloxone, the group reported 326 witnessed overdose events. All

but 5 of these events, the victims survived. And overall, the cohort of about 400, one quarter, had the opportunity to witness and then respond to the event with intranasal naloxone. Virtually, all participants were able to assemble the device easily and then use it to respond to the event. There were no serious adverse events reported.

In summary, an affordable community-based intranasal naloxone distribution has been really key to the New York City strategy and we believe has afforded many, many life-saving events. We realize that these data may not be the usual pharmacokinetic data typically heard by the FDA, but feel that in this emergency, our field evaluation data, along with that of many others, demonstrates the success of this intranasal naloxone program. Thanks for the opportunity to speak.

DR. BROWN: Dr. Kunins, could I ask you a question? I missed the dose administered during these field trials.

DR. KUNINS: So the dose was 2 2 mL doses

that contain a 1 mg per mL vial concentration. So the whole dose is administered. Each kit contains 2 vials so a second dose may be administered. And participants are educated to administer a second dose after 3 minutes of non-response.

DR. BROWN: And these kits are being given to folks in the community; professionals, EMTs?

DR. KUNINS: Our kits that are coming out of the New York City health department are dispensed to community-based programs who have trainers who educate, at the street level or in small groups, people to recognize and respond to overdose in as little as 3 to 5 minutes. Kits are then dispensed to those community members, who then carry them with them in the community and have occasion to respond where they will.

DR. BROWN: Are these kits written with a prescription?

DR. KUNINS: The kits come with a pre-filled prescription. In New York State, standing order is allowable, so it's the clinical director of the program. Or for programs that have access to

medical director or medical staff, they may issue the standing order. So the kit comes with a pre-filled prescription.

DR. BROWN: Thank you, Dr. Kunins. Speaker number 10?

DR. PLUMB: My name's Jennifer Plumb. I thank you for the opportunity to speak. I'm here as a pediatric emergency medicine physician and also as the medical director for Utah Naloxone, which is the only organization dispensing naloxone within the state of Utah.

I wanted to speak with you about our situation in the hopes that you can understand some of the challenges we're facing. Utah, unexpectedly to many, is fourth highest in the U.S. for its rate of overdose deaths, unexpected to many of us who live in Utah, and likely here as well. And what this looks like is as this epidemic has spread out across our state, now nearly every county in the state of Utah has an overdose poisoning death rate of greater than 20 per 100,000 population. And what this looks like in real numbers is that we're

averaging about 1 opioid related death every day in 2014. It's breaking out for us that about two thirds of those are prescription opioids, and one third are heroin.

As it does with many things, Utah is actually a little behind where the trend is being seen in other states, and our anticipated projectory is that our heroin deaths will continue to increase as they have elsewhere.

What this looks like for me as a pediatric emergency medicine physician -- and I have heard pediatrics mentioned several times today -- is that looking at our data from rate of opioid related ED visits by age through our state, you can see that patients less than 1 year and 1 to 4 years are being seen almost with the same frequency in our emergency departments as our 55-plus population.

Now, we have a lot of kids, and we have a very young population in my state. But this was a little alarming to me when I first saw this. These are not kids experimenting. These are not kids looking to get high. These are kids getting

exposed to substances within their homes.

For me as a practitioner alone what that looks like, I used to rave about how I had a 4-week period where I had 8 children overdosed on medications, opioid medications, from within the home. Until just a couple weeks ago, on one shift, my personal shift, I had 4 children under the age of 14, all in my ER at the same time, all overdosed on opioid medications from within the home. All of them did receive naloxone, and all of them did survive. And all families were ultimately equipped with naloxone rescue kits for their home, not only to protect those children, but also to protect the adults in the home who had been prescribed those in the first place.

For me, my concerns today are that as we talk about dose civility, we really have to talk about availability, period. My program is limited funding. I have no state funding. It has been almost all achieved of our own doing. And to give you an idea, we've put out about 3200 kits, 6400 doses of 0.4 milligram injectable naloxone in the

last 15 months. If I were to have to only be able to afford the 0.4 milligram intranasal device, that would be about 1200 kits, and the auto injector, 21 kits.

I know this isn't about money, but dose availability does influence what happens in these communities. I've relied on the decades of experiences of programs with 0.4 milligram dosing to save lives, and I hope that I have that ability to continue. Thank you.

DR. BROWN: Dr. Plumb, could I ask you a question about --

DR. PLUMB: Of course.

DR. BROWN: -- you seem to have a pediatric experience that we can call upon.

DR. PLUMB: Sure.

DR. BROWN: What kind of dosing scheme are you folks using?

DR. PLUMB: We typically start with the 0.4 milligram dose if a patient presents initially to us in the emergency department overdosed. We see EMS providers giving both 0.4 milligram as well

as 2 milligram dosing prior to arrival.

DR. BROWN: IM, IV?

DR. PLUMB: You know what? I would say generally in our ER, it's IV, but in the field EMS, it's typically intramuscular. I think the size of the kit always is a little more nerve-racking for folks to get an IV. So my personal experience would be 0.4 IM if they come in from the field. Now, if they're older, 15-plus, 14-plus, they're more likely to have an IV in place. Again, I think it depends on what the reg has. If they have the 1 mL vials of 0.4, that's what they go to. If they have the 2 milligrams per 2 mLs, that's been my experience that's more what they go to.

DR. BROWN: Thank you, Dr. Plumb.

DR. PLUMB: You're very welcome.

DR. BROWN: Speaker number 11?

DR. WINSTANLEY: Hi. I'm Erin Winstanley. I'm the associate professor at West Virginia University, School of Pharmacy. I do not have any financial disclosures. For the past, eight years, I've been conducting research on substance abuse

and overdose in southern Ohio.

The impact of the opioid epidemic in suburban and rural areas extends beyond high rates of overdose deaths and the images of children watching their relatives overdose. It reflects systems that are stretched beyond their means. It's the EMS that say, and I quote, "They used everything on the truck in an attempt to reverse overdose."

It's the hospitals that were worried that they were going to run out of ventilators when 10 to 20 people come into their emergency departments within a few hours. It's the family members that lose two children within one week. It's the loved ones that make the difficult decision to end life support after the person who overdosed spent three weeks in the ICU.

Ohio has the highest rate of DEA seizures of fentanyl in the entire country, and we've seen significant increases of fentanyl related deaths, including 502 such deaths in 2015. The CDC came and investigated those deaths. They found that EMS

responded to 82 percent of the fentanyl related deaths, but only administered naloxone to 41 percent of the decedents.

Naloxone is a life-saving medication, but something is going terribly wrong. While research needs to be funded to investigate why so few people receive naloxone, we could guess that perhaps, one, people are waiting too long to call 9-1-1; and two, EMS is taking too long to arrive on the scene, which is not surprising in rural and suburban areas, hence, underlies the importance of community-based distribution of naloxone.

Basic level EMS may not be allowed to administer intranasal naloxone -- only allowed to do intranasal naloxone, and this is particularly problematic in rural areas, which are disproportionately impacted by overdose deaths. In geographic areas with confirmed heroin adulterated with fentanyl, one might think that it is essential for all ambulances and first responders to have multiple doses of intranasal naloxone and to prioritize having people able to administer IV

naloxone.

Even with this CDC report, I'm not sure if we know the impact of adulterated heroin and increased risk of death. Healthcare providers are not routinely screening for fentanyl, fentanyl analogues, and other novel synthetics, and this is really important to some of the guidelines about the appropriate naloxone dose and administration.

For over a year, we've been hearing reports in the greater Cincinnati area that they are taking more than one dose of intranasal naloxone to reverse an opioid overdose, and certainly it's the use of multiple doses of intranasal naloxone that is escalating the cost and depleting the supply. When 1 to 2 doses of intranasal naloxone doesn't reverse an overdose, people think naloxone is ineffective, and they may be unaware of the safety profile. Our mayor has been pleading to our governor to have increased naloxone, and it's really problematic from that standpoint.

We could save more lives if naloxone were cheaper, we could save more lives if naloxone was

available to every first responder, and we could save more lives if we can improve access to IV/IM naloxone in areas known to be having fentanyl or other novel opioids adulterating the heroin supply. Thank you.

DR. BROWN: Thank you very much. Speaker number 12?

(No response.)

DR. BROWN: Speaker number 13?

DR. LAWSON: Good afternoon. My name is Mark Lawson, and I'm an employee of Mundipharma International Limited, based in Cambridge, UK. Opioid drug overdoses, predominantly associated with heroin, are consistent and associated with high mortality and morbidity in the EU.

For these reasons, Mundipharma is developing a concentrated intranasal spray that is optimized for European and World Health Organization guidelines. The product would be intended for use by anyone who is likely to witness an overdose. European and World Health Organization guidelines recommend that when IV naloxone is not available to

give 0.5 milligrams of intramuscular naloxone injection, then to repeat every 2 to 3 minutes if there's an adequate response.

Mundipharma has recently completed a phase 1 bioavailability study comparing plasma concentrations of our intranasal naloxone spray compared to IV and IM naloxone. An intranasal spray dose of 2 milligram in a 0.1 milliliter solution closely matched the early efficacious exposure to naloxone from 0.4 milligrams of IM naloxone injection up to a medium Tmax of the IM injection, providing evidence that a 2 milligram intranasal naloxone will be least efficacious as a 0.5 milligram IM naloxone.

The study results provide evidence that the relative bioavailability is 50 percent of IM compared with IM naloxone. This means that the total exposure provided by 2 doses of 2 milligram intranasal naloxone spray, 4 milligrams in total, would be equivalent to that provided by 2 milligrams of IM naloxone given in 5 separate 0.4 milligram doses.

In Europe, the posology for IM administration recommends up to 2 milligrams in 0.4 increments. The IM regimen of 5 times 0.4 IM doses given every 3 minutes has been simulated compared with two administrations of 2 milligram intranasal naloxone spray given 3 minutes apart. This simulation has been supportive of the 50 percent relative bioavailability, which means that 2 administrations of 2 milligram of intranasal naloxone given 3 minutes apart would be expected to perform the same as 5 times 0.4 mg IM doses given 3 minutes apart, both in terms of rate of rise of plasma concentrations and peak concentrations achieved.

In conclusion, clinicians may see different merits of various time course profiles of naloxone preparations with a different speed of onset and duration of effect, and Mundipharma hopes that this new emerging data is useful to the committee. Thank you.

DR. BROWN: Thank your, sir. Speaker number 14?

DR. LAFFONT: Celine Laffont. I'm the director of quantitative clinical pharmacology at Indivior. Indivior is a company with a long history of dedicated experience of treating patients with opioid use disorders. We are here today to share our experience in the development of naloxone nasal spray for the treatment of opioid overdose to be used by the persons within the community.

The challenge with intranasal administration is that absorption is slower than by the intramuscular route. Therefore, in order to achieve similar plasma concentrations at the early time point, you need a higher dose to compensate for this slower absorption. In our case, targeting such a dose will result in 4-fold higher plasma levels of naloxone compared to the intramuscular reference.

Such increase in exposure is associated with an increased risk of occurrence of withdrawal symptoms in opioid-dependent subjects. These withdrawal symptoms are appropriately managed in a

skilled medical environment such as an emergency room, however, they can be problematic in an uncontrolled environment, such as a home and public space, thereby limiting the adoption of naloxone rescue medication by the community.

Intranasal administration of naloxone injection product by means of a mucosal atomizer device has been used by several emergency departments in the U.S. and by community programs for harm reduction. Published data were used to compare the pharmacokinetics and the effectiveness of intramuscular naloxone with intranasal naloxone administered using this mucosal atomizer device.

These data indicate a relatively flat exposure response curve with large differences in early plasma concentrations resulting in only small changes in the average response time. In other words, plasma concentrations lower than those obtained by improved intramuscular injection appear sufficient to effectively restore breathing.

In summary, after consultation with multiple clinicians within the U.S. and overseas regarding

the appropriate use of naloxone in the community setting and regarding the risk of withdrawal symptoms, Indivior chose to target a titration dosing regimen for its nasal naloxone product. The strategies align with American therapeutic guidelines and published medical practice. Presently, Indivior naloxone nasal spray is available under temporary-use authorization in France. I thank you for your attention.

DR. BROWN: Thank you. Speaker number 15?

(No response.)

DR. BROWN: Speaker number 16?

MS. AWAD: Hi. Good afternoon. My name is Susan Awad, and I'm here on behalf of the American Society of Addiction Medicine or ASAM. ASAM does not conduct original research on naloxone use, and we don't have data to share with you on dosing or the relative merits of the different products on the market. But we thought it was important to speak up today to share our society's position and support of broad access to naloxone.

Since 2010, ASAM has supported the increased

use of naloxone in the case of respiratory arrest due to opioid overdose. Naloxone can be administered quickly and effectively by trained professionals and by laypersons trained in the administration of naloxone.

ASAM supports broad accessibility for anyone who would be witness to an opioid overdose. This includes persons who use or are prescribed opioids, family members and companions of those who use or who are prescribed opioids, EMTs and paramedics, corrections officials and law enforcement officers, among others.

ASAM encourages the co-prescribing of naloxone for people at risk of overdose, including those receiving high doses of opioids, those who are on chronic opioid therapy, and those who are being treated for an opioid use disorder.

It is expected that ASAM's board of directors will approve a new policy statement this weekend regarding naloxone, and that draft statement includes a recommendation that naloxone be available at pharmacies either by standing order

or by over-the-counter availability. It also includes recommendations that pharmacists be encouraged to recommend naloxone when indicated to patients who are filling prescriptions for opioids. Thank you.

DR. BROWN: Thank you very much.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as public comments.

Dr. Sharon Hertz will now provide us with the charge to the committee.

Charge to the Committee – Sharon Hertz

DR. HERTZ: Good afternoon. So we've had a lot of really interesting presentations. We've heard a variety of approaches from industry to the development of their products. We've heard, you've heard, about our regulatory approach that's developed since we first stated it in 2012, and we've heard about a lot of experience in the

community with use and some of the available data. What we haven't heard is a lot of specific data that I know you all want, and that's frustrating for us as well.

So we have a series of questions for you. We try to organize them in a logical way. We always try that. You often school us on our ineffectiveness with that, but we try. The first question for discussion will be talking about the standard, is the equivalent exposure to 0.4 milligrams of intramuscular, or subQ, or IV naloxone a good target? Is it too high, too low? How does this intersect with the dosing recommendations for children?

We're going to ask you to vote on some of these questions so we can really get very clear indication of your thoughts, but the discussion will be just as important as we hear why you have voted the way you have. We have additional questions in pediatrics that we really haven't covered much in the background, but we'll be asking you if you have any additional thoughts on

information we should be collecting in children.

Another question that's come up, and we've heard a variety of comments on this today, is what do we do with more than one strength within a product line? Somebody asked me, well, are you going to ask about across product lines? No, we didn't think of that one, but yes, go ahead and comment on it.

How should we consider that as an agency? How should we consider labeling such products to help prescribers choose? What are the implications of products that are suitable for one setting but not another being available? We worry about confusion. We worry about inaction because of confusion. Are the worries reasonable? We ask for human factor studies. We've presented some information on some of the characteristics of those studies, and we'll ask you some additional questions about any thoughts you have on improving them.

So your advice and recommendations really will be incredibly important to us as we move

forward trying to help facilitate the development of more products of naloxone for use in the community, and we're very grateful that you have all come to help us with this meeting and this important discussion. I want to particularly acknowledge that we've had a very large number of meetings this year, and I really do appreciate your time, taking away from your busy careers. Thank you.

Questions to the Committee and Discussion

DR. BROWN: Thanks, Dr. Hertz.

We'll now proceed with the questions to the committee and the panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

If we could have question number 1? Question number 1 is a discussion question. The current pharmacokinetic standard for approval of naloxone products for use in the community requires demonstration of naloxone levels comparable to or

greater than he levels achieved with the approved starting dose of 0.4 milligrams of naloxone injection administered by one of the approved labeled routes of administration in adults -- intravenous, intramuscular, or subcutaneous -- with a minimum of two doses packaged together.

A. Discuss whether matching or exceeding the naloxone exposure from a 0.4 milligram injection of naloxone represents a high enough naloxone exposure to remain the basis for approval of novel products. Please take into consideration the variety of opioids that may be involved in an overdose in the community, including prescribed versus illicit opioids. And those would be heroin, heroin laced with fentanyl or carfentanil, and in addition partial agonists versus full agonists.

Now, is that question clear to everyone? Is that a question that we can comment on and discuss? If it is, who would like to start out the conversation? Yes, ma'am?

DR. WARHOLAK: This is Dr. Warholak, and

this is a question I think for the FDA. Just to clarify this question, if we decide that the 0.4 milligram dose is no longer optimal, what happens to the legacy product? Will it be like the DESI drugs and grandfathered in, or will it decrease the options available in the community?

DR. HERTZ: For right now, I would say let's not worry about how we will take into consideration currently approved products. Depending on the recommendations of the committee, we'll go back and sort out what to do, so whatever that ends up meaning. I mean, the injectables would not be directly impacted. And for the two products currently approved for use in the community, we'll work with individual companies if we do hear strong advice and adopt the advice to change the standard.

DR. BROWN: Dr. Emala?

DR. EMALA: I wanted to comment on the standard of 0.4 milligrams, and I guess I have some concerns how that efficacy was originally defined. And I have to assume it was defined in a clinical setting where patients may be getting this dose but

also are getting supplemental oxygen, perhaps ventilatory support in an emergency room and so forth, with the luxury of being able to give subsequent doses. I'm concerned that that standard and those ancillary options aren't available in the field and whether this is a bar that may be set too low.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: Has there been any -- I don't know who this -- it's probably to Dr. Mehta. Has there been any effect on the cost of these medications and the availability of the products that affects the distribution, and has there been any analysis of cost and efficacy of these products? I know this 0.4 injection product is particularly high, and we got cost data I saw on the intranasal product, but we never got cost data on the other products. That I think might be helpful.

LCDR CHAI: We'll get back to you on that answer. This is Grace Chai, deputy director for drug utilization. We're going to look into your

question.

DR. HERTZ: Regarding information on cost, we would have to defer to the company for the other product. And in terms of cost benefit analysis, we don't have that function.

DR. BROWN: Dr. Zuppa?

DR. ZUPPA: Dr. Mehta has a slide 12 that has a reference from businessinsider.com that talks about the injectable form initially starting at about $375 per dose, and as of February 2016, it's up to $2,250 per dose. So that's in that reference right there.

DR. GALINKIN: It says $4,000 [inaudible - off mic].

DR. ZUPPA: Based on what we read in there, it would seem that way.

DR. BROWN: Dr. Brent?

DR. BRENT: Thank you. Jeffrey Brent from Colorado. We talk about this 0.4 milligram injection standard, which really is not a standard; it's a dose. And that dose can vary depending upon the route of administration. And I don't think we

actually -- and we don't normalize really to that standard. What we do is we normalize to an indirect measure from that, which is the achieved serum concentration and the AUC.

If we look at the AUC for that 0.4 milligram standard, it's about 0.9 nanogram per mL, which is pretty low. And it certainly is a lot lower than is achieved by any of these other preparations. It certainly would be a lot lower than is achieved by IV naloxone at that same dose, or even a 2 milligram dose.

So the question is which is more appropriate? I think there's a general consensus, as I listen to everybody here, that there are two very different scenarios whereby naloxone is used. One is in a in-hospital setting, where we can really finesse the dose and titrate the patient up very safely using supplemental oxygen and other supportive care, whereby we can avoid, to some degree at least, significant withdrawal, and yet very safely do it with a little bit of luxury of time knowing that we have a well oxygenated

patient.

The situation is very, very different in the field, and this is really what we're discussing today. We can't really analogize the two. In the field, there is going to be one out of two outcomes. We're going to resuscitate the patient or the patient's going to die.

So what we need to strive for is an outcome where we know we're going to get patient resuscitation. And that does not involve using these low doses that allow us to comfortably titrate up over time. We basically have to win the battle, and we have to win the battle over a very short period of time.

On top of that, we're hearing about more fentanyl derivatives on the street -- carfentanil; I read this morning of albuterol fentanyl -- that will require higher doses. And we've even heard from the Amphastar people a 2 milligram nasal dose -- which achieves a serum concentration, I think probably as best as I can tell, a range of almost 4 nanograms per mL, which is 4 times the

standard here -- requires more than one administration on the average.

So I think we really have to be looking at significantly higher doses, and we have to be looking at doses that are going to give us serum concentrations that probably approximate what we would expect for 2 milligram IV doses, which might even have to be repeated, which probably mean about 5 nanograms per mL, per dose, which is substantially greater than the standard we're using here.

DR. BROWN: So would that be a recommendation that you would make, then, 2 milligrams per mL rather than 0.4, as a dose being recommended to the agency?

DR. BRENT: What I would recommend to the agency is that we move away from dose and we move to achieve serum concentration, peak serum concentration or AUC. Serum concentration would be easier. And I'd say we probably would want to hit about 5 nanograms per mL, and that should be our standard.

DR. BROWN: Dr. Maxwell?

DR. MAXWELL: Let me muddy the water even more. I think this has been a fascinating experience because, to me, it's shown how little we really do know. And all the factors, the new drugs, the protocols, when I look on the Web, people are writing things on webinars about -- writing things about how to dose. I think we need a whole lot more solid research before we really can make a sound decision.

So my recommendation would be FDA go back and do some serious research and get more input through the people who testified here as to what this is going to mean. I know that's not what you wanted to hear from me, but --

DR. BROWN: I won't touch that.

Dr. Davis?

DR. DAVIS: Just for the few neonatologists that are here in the audience and on the panel, and at FDA, this seems to be the only drug that I know of where the dose for a newborn infant is the exact same as the dose for an adult. So someone who

weighs 400 pounds is getting the same dose as a infant who weighs 8 pounds. It's either I'm giving too much or you're giving too little.

But I think, in seriousness, there's a lot of data that we've heard today suggesting that this dose is efficacious and maybe needs to be repeated in a certain population, which is no surprise because now the heroin and other drugs that we're seeing are so much potent and so much more dangerous, and that may mandate higher doses.

I think the data suggests that, but at least from my read of the data, overall, most of the data suggests that patients respond to this dose, and I don't see necessarily a compelling reason to change it. But yet we may need to if the composition of the drugs being seen in the community are different. But again, I don't know of another drug where the neonatal and the adult doses are the same.

DR. BROWN: Dr. Winterstein?

DR. WINTERSTEIN: Just summarizing the data that we have seen, we have seen that the

utilization of 2 milligram doses have increased. And in Dr. Mehta's presentation, he showed that over the years, the 2 milligram utilization rate has become higher. So there seems to be a larger demand, yet the 0.4 milligram dose, of course, was still in there.

We have also seen that the death due to heroin and fentanyl have increased. But I thought what was striking to see was that for the children, as well as for elderly patients, it's more the prescription opioids that seem to be the culprits.

So there really seems to be two populations. We have clearly already focused on the children, and I don't think that anybody recommends that we need a high dose for children. But I'm also wondering for geriatric patients whether a high dose would always be indicated.

The other thing that I wanted to raise was that many of the testimonies we heard during the public hearing seemed to suggest that providers use this more or less interchangeably depending on what is available, which suggests to me that the

0.4 milligram cannot be completely not efficacious because else people wouldn't use it, which makes me wonder what it really is that should be used.

The only suggestion that I have is it seems like the providers who are using it, whether this is an emergency provider or a physician who ultimately prescribes a kit to a caregiver or a patient, perhaps they can really assess the situation themselves as opposed to us making guesses. I don't know.

One thing that I would recommend if there were 2 doses on the market, that it might make sense to standardize this in something like here's low dose. And here's high dose, and it doesn't really matter whether this is -- we have seen that the nasal applications have really the same bioavailability and bioequivalence to the subcutaneous or IM doses. So if this is the case, it might be easy to simply say, okay, here's a low dose, here's a high dose, and whoever feels one should be used, it might be up to their discretion.

DR. BROWN: Dr. Meurer?

DR. MEURER: Yes. Will Meurer here. I guess now I get to talk about this sort of stuff. With respect to this question, I agree that it's hard to know if this is the right dose from regulatory approval, given the age of the studies where this lower dose was derived and the change in the epidemiology. My gut feeling is that I would want to give as much of this stuff as possible. In fact, I have previously run a hospital out of its naloxone.

However, what we are hearing, though, is that there is substantial uncertainty as to the proper dose. There is a problem with community use in that the clinical judgment to titrate dose or use different doses is not there. So we need to balance a dose that people will use versus a dose that's effective.

I think in contrast to our general belief that we ought to just make this higher, we have empiric evidence from the professor who spoke of EMS units in southern Ohio, where only 41 percent of patients in whom they're suspecting an opiate

overdose are actually getting naloxone. And to me that would suggest that these paramedics don't want these folks defecating, vomiting, or jumping up and punching them, or trying to jump out of the back of their moving ambulances. And that suggests that there is truly potential toxicity from higher doses, which I think illustrates more the need for emergency comparative effectiveness trials to establish the answers to these questions in an unbiased and quantitative way.

I drew something out on this piece of paper that I'll give to Dr. Hertz after the meeting. But I think we should learn scientifically in a way so that we can help many more people by improving access but also making sure that we don't do anything to discourage use by getting bystanders hurt when they try to help people.

DR. BROWN: Dr. Sturmer?

DR. STURMER: Til Sturmer. Thank you. I totally agree with the points that were made about the empirical evidence because I'm an epidemiologist. PK's definitely not my forte, so

I'm leaning a little bit out of the window here with answering or trying to contribute to that question.

Two things strike me here, as you don't specify the labeled routes of administration for your comparator, which seems striking to me because the plasma concentrations with IV application will obviously be different, especially if the time course then was intramuscular injection. And the other one is that you only have a greater word in there, which strikes me, too, because I would think that if you want to achieve something, then you would probably also need an upper level for this.

So coming back to the point made about the plasma concentration, which is probably the most important measure that you could have, I would just add that the relevant time frame here, not the maximum but the one that you achieve, was in the first 5 to 15 minutes as has been already pointed out, and then the duration, how long it stays in the system. And that relates back to the kicking, and that has already been mentioned several times

today.

DR. BROWN: Dr. Chai?

LCDR CHAI: Grace Chai, deputy director for drug utilization. Back in July 2015, FDA presented analyses conducted at a public meeting that we held here based on sales distribution data, and those sales distribution data found that the prices for many formulations of naloxone rose by about 50 percent or more in a span of just a few months in 2014. Since then, we have updated our analyses, which we do plan to publish. Actually, Matt Rosenberg is also here to talk more about the granular data.

DR. ROSENBERG: Hi. Thank you, Grace.

I'm Matt Rosenberg. I presented the data at our public meeting last July, and I'm on the economics staff here in the Center for Drug Evaluation and Research.

We did update our data since the last public meeting, and these results, we're trying to publish those, so we haven't quite put them out, but we're planning to in the future. We found that the price

increases for most of the formulations have basically slowed down or leveled off in most cases, so most of the formulations have only gone up by a couple of percentage points in the last few years in terms of the price that we see in the IMS sales data, which is of course a little bit challenging to measure because everyone's getting rebates and discounts because some people are no buying it through the wholesalers.

So we see a certain subset of this, not necessarily all what's going on in the market. So it's possible that people could be paying different prices for the drug. But for most of the formulations, the increases were kind of a one-time thing, and we haven't seen that really continuing at quite the same pace since then.

DR. BROWN: I'm going to try to bring us back to question A, which relates to whether or not the naloxone exposure of a 0.4 milligram injection of naloxone represents a high enough naloxone exposure. And I really want to get some more conversation from the committee about is there

anyone that believes that 0.4 milligrams represents a perfectly appropriate dose for the agency to continue to consider.

DR. HERTZ: Hi. This is Sharon Hertz. We're going to vote on that, so we'll get a head count specifically there.

DR. BROWN: I'm just trying to get some conversation around what the actual question is. Dr. Zuppa?

DR. ZUPPA: So it seems, after the discussion today -- and I really want to represent the pediatric population here, so not the neonates, not the adults -- that there's a population of chronic opiate abusers that if you reverse them too much, they can punch and do bad things, and that might be pretty bad and for lots of different reasons that we've talked about.

Then we saw a slide that showed younger children who are at risk of overdose from taking mom's drugs, or dad's drugs, or grandma's drugs, and they're probably not chronic users. If there's a kid that's at home and has overdosed and is not

breathing, I kind of would prefer them to kick and scream and maybe pull my hair as opposed to having hypoxic ischemic encephalopathy after their incident.

So I'm wondering if there's a need to push the plasma concentrations, the exposures higher in that subpopulation, which is kind of counterintuitive to how you would think, right? You would think that a pediatric population should probably get a lower dose, and an adult population should get a higher dose.

But I'm wondering if in that population of kids that are really at risk from a one-time overexposure, if that's where it's safe to push the dose because you don't have a window to titrate them. You don't say we gave 10 mics [ph] per kilo, and they're not doing well, so we'll intubate them and put them on a ventilator and support their oxygenation and their ventilation. You don't have that luxury at home.

So I, again advocating for the pediatric population, I advocate for pushing the dose and the

exposures to making that one-time intervention as fast and efficacious as possible because you probably won't get a second time.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: I agree, obviously there's not a lot of great data here. But to me, the consequences of underdose here are far greater than the adverse effects we may have if we give too much. We saw data from the national EMS system, most of which were intranasal injections that I presume at either the 2 or 4 milligram level, and there, there was about a 20 percent failure rate, which is quite high.

So I guess I would advocate for pushing the dose higher. But I'm not sure we're going to find that perfect dose where we thread the needle between effectively reversing the respiratory depression in all patients without creating the adverse consequences.

I guess one other observation is, on the label, the serious adverse effects that we saw associated with naloxone administration -- cardiac

arrest, coma, encephalopathy -- all of those are consequences of hypoxia, and so very well could have been observed with co-administration of naloxone and have nothing to do with the actual reversal that occurred.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: Abby Shoben. I guess I think I'm in a little bit different position as a biostatistician here in terms of trying to think about the dose and not having administered it myself and seen people with overdoses. But I came sort of fully expecting to think that I was going to recommend a higher dose because its safety profile seems really good. There's some concern about the violence and consequences of the withdrawal symptoms, but otherwise the safety profile looked really good. And of course we'd rather have people be alive and kicking you than other things.

But I've really seen no evidence that this 0.4 dose is not working. There's just no -- it just doesn't seem to be that that evidence is

there. And the data about the repeat administration, you see sort of the same, about 30-35 percent repeat doses regardless of what the initial starting dose was, which suggests maybe there's this panic like, oh, my God, I gave the dose and the person didn't wake up, so I'm going to give them another dose right way kind of thing.

There's just no data to me that says that this 0.4 is insufficient. So if you believe that there was data initially that supported 0.4 as the initial dose, then that seems like an appropriate standard to maintain before we can get more data.

DR. BROWN: Dr. Woods?

DR. WOODS: Well, it's a real pharmacokinetic/ pharmacodynamic conundrum, but I see too many things telling me that current dosing based on reviving patients in a hospitalized setting really don't apply in the community. We're seeing a big increase in the potency of the agents that are being abused, and we've seen data about the rise in carfentanil and other synthetic use.

I think an equally important question is how

frequently should we re-dose patients. And we saw data from Dr. Faul earlier today that the number of patients who are being re-dosed is on the steady increase. And I wonder if that's actually a reflection of more synthetic opiate use, the need to pay closer attention to that, especially in view of the fact that we're seeing extended times for people to receive appropriate medical attention.

Another issue with respect to this re-dosing is over the last few years, we've seen the approval of lots of new extended-release opiates, and what impact those have on the need for a higher initial dose and re-dosing I think is yet unknown. And we really haven't talked very much about that today.

Finally, we know what's happened with respect to body mass over the last few years, and I think that's kind of a wild card in this that would also suggest that we probably need to consider higher doses, and we also need to think about how frequently do we need to re-dose these patients.

So I wish I had an answer as to what the right number is. I think maybe it's pick a number,

pay your money, take your chances.

DR. BROWN: Dr. Fuchs?

DR. FUCHS: Susan Fuchs. I think what's hard is that we actually have two very different populations that we're talking about almost. One is the ones in terms of prescribed opioids, and the other are the illicits, because the illicit is we're talking about heroin and fentanyl and carfentanil. And those are the ones who keep needing more and more and more and more.

There are going to be new drugs coming out probably -- like you said, something was mentioned today -- that's going to need yet higher doses of Narcan, whereas if you look at the people who have prescribed opioids, yes, if they take some extra, when you go there -- hopefully, we've heard that what's out there is working, whether it be the off-label intranasal, the regular intranasal, and the IM.

So for them, it's working, and you don't want to send them into acute withdrawal by giving them almost too much. And then from the EMS

community, too, is they just want to wake them up until they're breathing. They don't want them punching and fighting them either or kind of trying to refuse actual care. So I think it really is a very different group that we're trying to work on, and trying to figure out one dose for almost two different populations is very difficult.

DR. BROWN: Dr. McCann?

DR. McCANN: Mary Ellen McCann. I agree. I came here exactly like Abby did, thinking that I was going to advocate for 2 milligrams. But listening to all the testimony and listening to the community people speak, I haven't seen any evidence that 0.4 milligrams doesn't work, just like I haven't seen any evidence that 2 milligrams is too much. So that's one thing I'd like to say.

The other thing I'd like to say is I've heard several times people say, well, we probably should go higher because it takes more -- on average, it's more than 1 dose per patient. But by definition, since you can't give a half a dose, it's always going to be more than 1 dose per

patient. It's just the way the math works. So I think that's kind of a false thing to think about. Thank you

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: One of the things, I think there's actually a third population. I think we're talking about you have your in-hospital population, which really a lot of this stuff doesn't apply to. Our second population is the one we're talking about, which we're sending home with opiates.

One of the problems I think we have is this population now that we're advocating for patients to take this take-home approach of Narcan. If we're advocating for rural communities to be getting these and people who are far away from EMS, you want as high a dose as possible, and you want it with a very long half-life so that the EMS provider can arrive. And that's going to be only with a higher dose of this.

This 0.4 dose will not provide a high enough plasma level to get your 5 nanograms per milliliter for more than like 5 minutes. And they won't have

enough Narcan available, even with the 2 doses, to maintain that for 45 minutes to an hour, which is sometimes what it takes the EMS providers in our area to get to people. So I'd advocate for a much higher dose.

DR. BROWN: How high is much higher?

DR. GALINKIN: I think the 4 milligram product would be -- looking at the data from their, the plasma level stayed up for about an hour, I think, if I recall.

DR. BROWN: Dr. Parker?

DR. PARKER: So I share the same sentiment expressed about concern certainly in an emergency of not giving enough, that being the risk given the general safety that's been expressed. I share the sentiments that were expressed there. And I also think the CDC data on the increasing use of the illicit opioids is just very compelling, and the 0.4 milligrams was in place prior -- that's been a longer standing. So I'm concerned about that being enough, the same sentiments that have been expressed.

I also just wanted to call attention -- I was looking at the background materials and the labeling that was provided in those. The way this point is discussed is that you're required to give a 2-dose pack, but if you look at the instructions about whether or not you can repeat it, and how many times you can repeat it, and what you do, if you look at the dosing instructions that were provided, if the dose response is not obtained after 2 to 3 minutes, then another dose may be administered. If there's no response, available additional doses can be administered every 2 to 3 minutes until emergency medical assistance arrives.

Thinking about how that plays out in the field and whether or not in looking at this, looking at how much, up to what, and whether or not that is actually a part of the official labeling and how that plays out with the increased used of these other forms of opioids and the extended release, I think is really important.

So that was one thing. Then the other

thing, I always look at these dosing label things, at the labeling instructions. The other one really had to do with the patient counseling information section of labeling that's made available, and these were the drafts of those; making sure that Evzio's present whenever persons may be intentionally or accidentally exposed to an opioid to treat serious opioids overdoses.

So that pretty much says anybody who gets one prescribed or anybody who could ever have one. So we're talking about a really, really large use and thinking about the implications of that, that any person given an opioid, prescribed an opioid, would also be looking at getting this and how the labeling impacts the different patient populations that would be on the other side of that. So those are my thoughts.

DR. BROWN: Dr. Craig?

DR. CRAIG: That was fast. Thank you. Just this thought about dose, I would agree with Dr. Galinkin that 4 milligrams probably in that patient population, who probably would need to be

reversed, makes the most sense to me. I think the 0.4 in a hospitalized patient, clearly in my institution, we have more of an overuse problem than an underuse problem. Particularly patients who get 400 micrograms have significant adverse events, so we actually recommend 40 micrograms, not 400 micrograms, which is, generally, after a dose or two, that's enough.

So a total dose of 80 micrograms in a hospitalized patient is generally sufficient, even to reverse huge doses. Again, we have a cancer pain population, so we see patients have an exaggerated response from naloxone. That aside, I think in the field, I think the higher the dose, the better, and that's my feeling.

One other thought about the duration of effect of naloxone, there's a product that hasn't been mentioned here, and I think naloxone truthfully is the wrong product. I think we need to bring back nalmefene. Nalmefene, as you know, is Revex. Revex has a half-life of about 8 hours. Narcan has a half-life of about 60 minutes. So

just looking on PubMed, the half-life of carfentanil is somewhere around 8 hours, and the half-life of nalmefene is 8 hours. Half-life of naloxone is 60 minutes. To me, that's a big mismatch. I would speak to pharma and say, why don't we have a nalmefene auto injector. That's really what we need.

DR. BROWN: Dr. Sturmer?

DR. STURMER: Thank you. Yes, this is actually a good segue. There are people here who have seen kicking and screaming more recently than I have. But the last patient I've seen kicking and screaming in the ER -- and that is over 20 years ago -- he died because he left the ER, and he got only one dose of Narcan, and he died. And this is exactly the point.

So I think the kicking and screaming is not an annoyance; it's also a problem because these people are much less likely afterwards to get the second dose that they need. So I just wanted to mention that point.

Coming back to the 0.4, I think we need way

more evidence to change something than to leave it, and I haven't seen any evidence that 0.4 doesn't work.

DR. BROWN: Dr. Vinks?

DR. VINKS: So to add to that, one aspect, what we haven't discussed today, is variability. And when you look for a dose, it's very hard to find good doses. What we have seen here were average concentration profiles.

I don't know if anybody looked at the tables that were presented. The variability around those concentration measurements are about 120 percent early on, and then taper off to 60 percent, which means that the standard 0.4 dose in 40 to 50 percent of patients is way lower than the 1 nanograms per mL that we might want to target. And that is contrasted by the evidence from the field, but also from the data that is presented by the companies, that apparently this dose seems to be working well.

I think we don't have enough data to say, well, here is the target concentration exposure

that we need to match, and then go from there. This concentration comes from an older time when there was no carfentanil. But that is a little bit of a different discussion.

But I also would second what was said before, that if you have people and you wipe off the opioid from their receptors and they go into massive withdrawal, that is not what you want to achieve, and rather you have multiple doses that you can give, and then basically titrate, or 2 steps titration, than to give as high as possible a dose, that then leaves some of the people in the field with a real problem.

Then to address the pediatric dosage, I can appreciate your comments. But I would want to ask the FDA, you have a beautiful division of pharmacometrics, and they have very well educated people who could simulate or even predict -- based on everything of what we've learned from adults and adolescents, into the youngest age, even into neonates -- what the likely exposure distribution would be.

That would give us some real evidence or some good data that we can then start looking at. And then say, look, how would this relate to the likelihood of adverse events? Because as has been shown by several speakers, it's not so much the heroin used by kids, but it's accidental overdose. And there we would want to make sure that we have enough naloxone on board, but definitely don't want to overshoot.

I did a simple, off-the-cuff little simulation. The concentrations that you would get with the standards doses as we have them here, if we were to give them to a 2-year-old, are up to a factor of 20 higher. That should be enough. I think we need to -- we have those tools, so we can take those things in consideration and then add some of our real-time experience to that.

DR. BROWN: Dr. Meurer?

DR. MEURER: So when you phrase the question at the beginning of our discussion, the question we were going to vote on, I think you said something to the ilk of if you are perfectly happy with 0.4

milligrams. And as defined, I don't know that anybody is perfectly happy with it, but I think would I be as happy with it as 1 milligram or 2 milligram, or do I have basic indifference within that sort of range? I think that's the collective answer.

Now, the individual answer is if I had -- what would I want to have lying around my house for my 10-year-old or my 15-month-old? I'd squirt the whole Narcan Nasal Spray into that kid. So I think there's a difference in what we would do on the individual level, but also what is the best thing to do for the population that can lead to the best use for the broadest population out there.

I think if we're going to make decisions that affect the whole population, we need to be as quantitative as possible. And I think right now the amount of quantitative information that we would have to reject 0.4 is limited. I think intuition says we want to use more, have more available, but we could collect evidence just by a back-of-the-envelope conversation, or if Evzio's

manufacturer gave out 120,000 of those things last year, and they sell them for 2 grand, that's 240 million. So I could design a pretty good clinical trial if you guys want to talk to the University of Michigan.

(Laughter.)

DR. MEURER: With that amount of money, we could answer all of these questions in a year. So I hope that the question is phrased for us to vote in a way that -- I'm not perfectly happy with 0.4, but I'm not perfectly happy to discard it yet either.

DR. BROWN: Now, I'm not sure that we're helping Dr. Hertz and her group that much here, and I'm going to push back a little bit and say that -- ask was nobody -- the CDC evidence that showed an amazing increase in the number of re-doses of the drug implies that 0.4 might not be the best for the patients that we are dealing with and that they are asking us about. They're not asking us about patients in hospitals. They're asking us about patients that are found down on the

street.

So if we're getting a ton of re-dosing, does that suggest to you that 0.4 is the right dose when you only have a limited amount of time?

DR. MEURER: I don't know about how many -- if this is directed at me. And you kept looking at me, so it's okay. I answer. I know Dr. Nelson wants to talk, too. But from at least the NEMSIS database, which I've used for other things, we don't really know about the doses that the paramedic agencies are stocking. We don't know if they've moved to the 2 milligram vials. We don't know if they're exclusively using the 0.4 milligram vials, at least from that database.

DR. BROWN: We're talking about the re-dosing.

DR. MEURER: So with respect to re-dosing, I think the other part of that that we don't know is how much no dosing was occurring. Those people wouldn't be in the database because they were only identified in that database if there was administration of Narcan.

So I think there's lots of -- observational data can always cause us to see things that may not be -- they may be different from what the reality is. So I think re-dosing is going up. I think that that is true. But I don't know what dosages all those agencies are using right now, so it makes it hard to understand. I think the trend is that we probably need more of that, but I don't know that I can say that with a lot of quantitative intelligence.

DR. BROWN: Except that for your children, it will be more.

DR. MEURER: Of course. I going to go prescribe that Narcan Nasal Spray to them right now.

DR. BROWN: Dr. Wu?

DR. WU: I appreciate Dr. Meurer actually. I look at it from a different perspective, as I think about lesser on the populations of patients. The question specifically says what is the proper comparison for novel delivery. In my mind, it seems to be two different paths for the type of

drugs.

Yes, we've talked about hospital. We've talked about intravenous injections. And there's a potential you could titrate that within a controlled setting. But looking at the data that we saw from the CDC around hospital use of naloxone, it's staying fairly flat. Outpatient use or out in the field use is increasing. Similarly, we see the trend of synthetic opioids going up, as well as opioids and heroin overdose.

I think both those trends, clearly we're not dealing here in hard facts across the board that can answer every specific question, but I think I would much prefer -- given the fact that we know that the outpatient world and the field use is going up -- this is for novel injections of naloxone -- functionally all of the industry colleagues have already tested that, at least a minimum of 2 milligrams. So they've already started a higher dose than even the 0.4.

If I look at the risk tolerance and the risk profile, I in this case will tend toward more of a

type 2 risk of how many patients may end up being harmed by not having the right amount of adequate dose from the very beginning as opposed to the type 1 risk of potentially precipitating an adverse event from violence or from opioid withdrawal.

So for me, I would advocate -- given the fact that the trends are moving toward more outpatient use of novel injectables, more heroin overdose, more synthetic overdose, this is likely the population that's going to be using this specific type of naloxone, that at least a 2 milligram if not a 4 milligram dose would be what I would consider. I'm willing to put a number out there, I guess, to consider. But again, thinking from a population perspective, the risk from the type 2 error as opposed to from the type 1 here in this drug, I would just look at it differently.

DR. BROWN: Thank you. That was very erudite.

We have a part B and a part C to this discussion. Would it be okay if we went on to the second portion of this, attempting to get some

clarity from some other things we discussed? Is that reasonable?

I'm supposed to try to summarize what was said, and I think it's safe to say that it's not clear where the initial dose came from, but there's much to speak for higher doses, except by the people that would only agree that they should have the same dose.

(Laughter.)

MALE VOICE: No one wants to go lower.

DR. BROWN: Yes, that is true. What we see is that there is some indication from some of the data that the 2 milligram per mL doses are more common. People are using more re-dosing. This might suggest that the higher dose would be appropriate, but perhaps not.

It's not clear what the basis is to choose what the absolute correct dose would be. It's not clear that the studies that could be done, or should be done, to derive that information can be done ethically and in a timely fashion. We haven't established that yet. The risk of not having a

high enough dose, though, in the big picture, is much greater than not having enough because a dead patient is a dead patient. Based on the epidemiology of poison in children, it's unlikely that most children would be harmed by even the highest dose of naloxone.

Having said that, for the inference that are on methadone for NAS and are coming home on methadone, I can see that it would be a really good thing if parents who are bringing their children home on methadone are taught to use naloxone in an appropriate fashion.

Does that seem reasonable?

(No audible response.)

DR. BROWN: Let's move on to part B of this question. If you think a higher minimum naloxone level is more appropriate as the basis for approval of new products intended for use in the community, describe the target naloxone level and the rationale for this approach. And I'm going to say that we've really talked about that, so let's move on to C, unless somebody wants --

Dr. Zuppa?

DR. ZUPPA: I think we keep talking about dose, and the true metric is exposure. What is your C effective? What is your effective concentration? And I think that's a moving target amongst all the different populations that we've talked about. I think there's more than three. I think there's more than four. And as synthetic opiates continue to hit the streets or these people, I think that target again changes, which makes additional research even more difficult compounded with the difficulties that already exist in an ethical approach to doing that.

So I think as a pharmacologist, it's important to focus on exposure and not dose, but I think focusing on exposure here is very difficult and will continue to move, moving forward.

DR. BROWN: I'm going to move to question C if that seems reasonable. Question C is, for discussion, in controlled settings with trained healthcare providers and adequate ventilatory support, naloxone can be titrated to reverse an

opioid overdose and minimize the risk for precipitating an acute withdrawal syndrome in an opioid-tolerant individual. In the community, trained healthcare providers and adequate ventilatory support may not be available, and naloxone may be administered by a layperson relying solely on the instructions for use that accompanies the naloxone product.

In this latter setting, there's a 5 to 10-minute window before hypoxic injury becomes irreversible. Discuss how to balance the need for rapid reversal of an opioid overdose with the risk of precipitating an acute opioid withdrawal syndrome when selecting the minimum naloxone exposure that forms the basis for approval of novel products.

DR. NELSON: Thank you. Lewis Nelson from New Jersey. If you could just let me go back for one second to answer your original question from the first question because it does feed into this.

We don't really know what re-dosing means, and I've worked with paramedics and others for a

long time, and I think that there's this expectation that you see kind of in the movies, that when you give somebody naloxone, they're going to sit up and get better. And when they give a dose, and the patient's not better five seconds later, there might be a sense that they need to give a second dose or something along those lines.

Remember, our goal in the emergency department, and I'm sure in the operating room and other places, is to make the patient breathe, not to make the patient wake up, and certainly not to put them into withdrawal. In the operating room, withdrawal is probably not as big a problem as it is in the unselected patients we see in the emergency department, but I don't think we should minimize the risk of opioid withdrawal.

I know we've talked a lot about this and maybe made some light of it, but it's both physiologically and behaviorally very problematic, and it truly disrupts the flow of an emergency department, and it truly disrupts the ability of paramedics to do their job. So optimally, we would

want to dose this to that point, as suggested by somebody else, that would make them breathing, awake enough that you know that they're breathing, but not quite in withdrawal.

Now, that being said, I'm unclear that we really have an understanding that the point for dose and the concentration to go along with it don't reverse all of these other opioids enough to make the person breathe. I would agree that -- we saw some carfentanil data that shows that it displaces the drug from the receptor, which would suggest to me that it does do that. We know that the Ki's and the binding affinities of a lot of these drugs are all within the same range, for the most part, and there's no reason to believe that naloxone shouldn't displace some of that drug.

We know that when you buy heroin on the street that contains fentanyl or a derivative, we have no idea what the concentration is? Right. So we know what the concentrations are post-operatively because you've given the drug to somebody, but when they buy a bag on the street, it

can contain 1 X of that drug or it contain a 1,000 X of that drug.

So you're right, we can't possibly know how to dose naloxone based on that, but I haven't ever seen data that suggests that even if you got a 1,000 X amount of carfentanil, a dose of naloxone wouldn't displace enough of that drug to allow you to breathe, and it wouldn't save their life.

Remember, we keep hearing about reversals. We don't know how many of those people are actually going to die without the reversal. We just know that they got the drug, and it's a good thing, and I'm fully in support of that. But to move off of this dose and risk precipitating withdrawal in so many more people, when we know that 0.4 works -- and I know it works because we give it all the time, and we've actually cut back our IM dose because 0.4 cause too many problems.

So I'm very hesitant to suggest that we raise the dose and risk more withdrawal because I do believe, and we've heard from many others, that empirically that dose does work in most people.

And you know, some are going to die because people are going to die with or without naloxone. But I think we need more data to say that risking withdrawal in more people is worth it because it is not an insignificant problem. And I do believe that that dose, especially that can get into the blood and the brain quickly enough so that the Tmax is short enough, it should be safe and effective.

So I think that answers A and C from my perspective.

DR. BROWN: Dr. Winterstein?

DR. WINTERSTEIN: My pharmacology training is 30 years old, but I've entertained myself by reading some pharmacodynamic studies on PubMeds in the last few minutes. And they actually prove what Dr. Nelson just wonderfully described. It appears that an increased dose doesn't affect the speed of reversal because what is needed is simply that enough is displaced from the receptor, and as long as that enough is enough, that seems to be fine.

So the studies that I saw -- and I am not a pharmacologist, anymore at least -- do seem to

prove that increasing dose doesn't do anything.

Now, the duration of reversal is the other topic because clearly if there's more fentanyl available, then eventually the naloxone will be gone. And I think that is the other question that was raised earlier in terms of half-life of naloxone, but that's not in question C. What is in question C is speed of reversal, and that doesn't really seem to be as dose dependent as we think.

Now, in terms of the duration of reversal, that's really where we need to look at the need for multiple use. And as Dr. Nelson also pointed out, we really don't know whether this trigger to administer multiple doses is really steered by need or steered by trying to be overly cautious. So there is a little bit of a problem there as well.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: My question's been addressed.

DR. BROWN: Dr. Walco?

DR. WALCO: I'm going to just pause for a second and raise a question that hopefully we can dismiss fairly quickly. And that is, I'm listening

to the cost benefit analysis. The cost of using too little naloxone is death. The cost of using more naloxone than one may need is putting somebody into withdrawal.

If you think about a lot of the drugs that are used for various and sundry issues, our tolerance for side effects, with chemotherapy for cancer for example, is ridiculously high. We almost kill people giving them drugs that will potentially save their lives. So why is it in this situation, we're sitting here going, oh, well, some people are going to die; we just need to accept that, or we say, we can go with a lower dose?

So all I'm saying here is can we pause for a moment and maybe examine our biases. Is there some bias that's entering into all of this because we're talking about people who are using illicit drugs on the street? Would we be having a different conversation if it was a different population? It's a rhetorical question, but going through my head listening to this, as Dr. Brown has said, when you're dead, you're dead. That's it. So that's

all I have to say.

DR. BROWN: Dr. Hudak? Dr. Meurer?

DR. MEURER: Just one other thing. I was looking through to see if I could find -- and maybe one of the public commenters had a slide on the relative prices of all the different vials. But I'll just give you one other potential explanation for the repeated re-dosings that was observed in the NEMESIS database.

Since we don't know the exact dose, what we do know is that a vial, a 0.4 milligram vial, went for about 15 bucks in 2015, whereas a 2 milligram vial went for about 40 bucks. And those prices changed, and they probably changed the distribution of purchasing across the country.

So if people were buying -- if I was running an EMS agency and I had to buy drugs to treat very many diseases, I'd buy the $15 one and hope that it -- maybe I'd have two. If the first one didn't work, I'd use the second one. And that could be an explanation for why there's so much re-dosing. It could have been cost pressures changing the

distribution of dosages that were stocked throughout the country. There's probably some data that might be able to inform us more on that. But there are other reasons, other than -- because I think a lot of the clinical experience in the emergency departments is that 0.4 is something that works in the individual setting, although it's a controlled setting.

So I think, just one thing to consider, that before we put too much stock in the re-dosing, we have to recognize that observational data has some flaws, and with these cost pressures, EMS agencies may be purchasing less of the more expensive vials.

DR. BROWN: Dr. Beaudoin?

DR. BEAUDOIN: I just wanted to touch base on the point that Dr. Walco made because I think that it's an important one to discuss. My gut reaction is probably the same as many of you, to say that when you're dead, you're dead, and so what if we make somebody puke their guts out and combative, that that shouldn't matter.

But I think what we need to pay attention to

is that that reaction and that adverse reaction is potentially going to cause behavior modification, and not just among rescue personnel, but among the people using them, among the people perhaps with substance abuse problems. I think this is more of a problem in that population than in somebody who is opioid naive or a high-risk COPD patient that gets a prescription for Vicodin that we decide to prescribe naloxone to.

I think we do have to worry about precipitating withdrawal in a population of substance abusers where if we make them dope sick, they might not want to use this product again. It's not rational behavior to us, but I think that has to be a concern. And I don't know the answer to that. I don't know that there are focus groups out there which have addressed that. But I think that that is a legitimate concern.

Getting back to Dr. Nelson's point, we have not seen anything really that drives us to change away from this 0.4 milligrams of standard dosing. I also have that gut reaction that we're seeing the

intranasal doses need to be repeated. We saw the CDC data that there needs to be repeat dosing, but we really don't know what is the minimum effective dose to reverse opioid withdrawal in a variety of conditions.

So I think that we probably need better evidence to move away from that standard that's there, although I share the reaction that a lot of you do, that we should go higher. We should not care about withdrawal. But I do think we need to think carefully before we do that because it may have ramifications.

DR. BROWN: Dr. Sturmer?

DR. STURMER: If you pose the question as you did, then the answer is very obvious, but I think the reality of running such a program is way more complex. And from what we've read in the materials and what we've heard during the public discussion, all of these programs seem to work. And we've heard anecdotal evidence that the higher dose leads to more side effects.

So I think we need to accept that for a

program, a community program, to actually be implemented so that it works to prevent lives -- saves lives, not prevent lives; sorry about that, it is way more complex than the question you just posed.

DR. BROWN: Ms. Berney?

MS. BERNEY: Well, I'm not a doctor. I'm not educated in these things, and half of what I've heard today has flown right over my head. But what I do get from this, and as a patient, and having had an experience with opioids myself, and having a nephew who perished two years ago next week from an overdose, I can tell you that I would rather err on the side of too much than too little to save someone's life.

On the other hand, I hear that you can re-dose; you can give multiple doses. So it seems to me -- and I don't know whether this is feasible or not, but that perhaps we need a larger range of doses to deal with these different kinds of situations. Somebody who has taken fentanyl, and you know they've taken fentanyl, probably needs a

larger dose than somebody like me who took one Darvoset and was gone.

So this is very difficult for me because I know what withdrawal looks like. I've seen it, and it can be very difficult. And I'm thinking, supposing your 10-year-old child sees you -- just something in the paper yesterday. A child went to school and said, "Oh, my parents won't wake up." They were dead from overdose. Supposing this child has been taught how to use this and revives a parent, or whoever, and it causes withdrawal and violent behavior? That child is then at risk.

So there are a lot of different facets to this that we have to think about. And if you're using it in the community setting where too much could be too much, you have to think very carefully about how you're going to dose that.

DR. BROWN: Dr. Brent?

DR. BRENT: Brent, Colorado. Just to bring the conversation back down to part C, which is where I think you were trying to go, and we seem to be meandering back to the other question, I think,

from my experience, and I suspect from every clinician's experience here, dosing in the emergency department with naloxone, or in the post-anesthesia unit, is not a problem at all. We have great supportive care. We can keep patients very well oxygenated. We could titrate them up with very low doses and bring them up to what they need.

So I don't see that at all as a relevant problem here for us to have to consider, other than to say that it has no relationship, really, to what we're dealing with in the field.

DR. BROWN: And last but not least, Dr. Galinkin?

DR. GALINKIN: I don't know if I saw any data that shows that there's more acute withdrawal syndromes with 0.4 versus 4 milligrams. Was there any data presented to that effect? Because everybody keeps making that assumption, that we're going to see a lot more withdrawal based on everything, but I have not seen that data.

DR. BROWN: Dr. Parker?

DR. PARKER: So just again, I share the don't underdose line of thinking, but I do notice in the labeling -- I see these instructions about repeated doses with no limit on how many. So just say I've given it. I waited 2 or 3 minutes. I gave it. Nothing's happened. I wait 2 or 3 minutes. I give it again. I'm waiting. I'm waiting. I've called. Nobody's there yet.

If I had access, do I just keep on giving it every 2 to 3 minutes? Because there's nothing here that would tell me not to do that if I did have $4,000 to buy the double pack, or whatever it is, or whatever I ended up paying.

So I think the idea of it, I don't know. I don't know the answer to that, but I know it's not clear to me when I read it. So if there is a maximum that you don't want me to go beyond, I think it would be helpful to tell me.

DR. ZUPPA: But in the outpatient setting and in the community setting, you're going to have maybe 2 doses, right? So you're not going to have the ability to repeat the dose and repeat the dose.

I mean, that's in-hospital kind of recommendations.

DR. PARKER: Depending on the outpatient, where you are, what that access if at whatever community-based treatment center, or whatever. I don't know what the stock is.

DR. ZUPPA: The kids that are being distributed, what we heard from the community, with a 2 milligram per 2 mL or 1 milligram per 1 mL, there's two doses in there. If that works, that works; if it doesn't, it doesn't.

What I would do is I would give 10 mics per kilo, and if that didn't work, I'd go to 100 mics per kilo, and I would dose-escalate my subsequent doses to get my response, which is not an option. So that first dose matters.

DR. PARKER: I get that. I was just thinking like in a community, in a real-world setting, it may not happen that often, but it could happen. If I have access to more, do I just keep doing it? Do I just keep doing it and keep doing it up to whatever dose? And the fact that it isn't

there just leaves me wondering. That's all I was commenting around.

DR. BROWN: Can I respond to that a little bit? Because a lot of these patients show up to the EMTs that come and see them, having had not just opioids but multiple drugs, sometimes many. When we have patients that come in to the University of Kentucky, they have opioids, and Dilantin, and gasoline, and everything that you can think of. And I think that some of that labeling relates to getting people to begin to think about what else could be going on there.

I honestly -- I have two sentences here to sum up what we have. And that is, there is broad disagreement about where the balance is. We do need to have some more data to assert where the point is set. And I apologize, Dr. Hertz, but that's all I can derive from our discussion.

DR. BATEMAN: Rae, can I just ask one quick question? The PK data we saw for the 4 milligrams intranasal injection showed that the plasma concentrations were 4 or 5 times higher than

0.4 milligrams IM. And I'm just wondering for the folks on the committee who work in emergency departments, do you see differences in the frequency of these withdrawal symptoms or patients acting out in those that receive the IM versus the 4 milligrams intranasal? Both products are commonly used.

DR. MEURER: Unfortunately, Dr. Nelson stepped out. But in my clinical experience, which is not a ton -- and I was telling Abby this before. The only time I've seen floored withdrawal actually precipitated, a patient was inadvertently administered 4 milligrams intravenously when 0.4 milligrams was intended. It was in our brand new resuscitation bays. He stood up, he threw up, pulled down his pants, defecated, and the drain in that resuscitation bay never smelled the same ever since.

But apart from that, for other usual doses 0.4 to 2, I never saw -- the people are mad at you. They've got somewhere else to be. They're usually -- but they look like they haven't had

opioids in 3 days, although it's happened directly. But I have not witnessed more profound acute withdrawal symptoms being precipitated. But that's, again, somebody who's in the emergency department.

DR. BATEMAN: I mean, those comments make me think that FDA could go up on the 0.4 standard without -- we're talking about maybe a false dichotomy between creating a little more margin of safety for some of these high potency opioids and creating lots more acute withdrawal.

DR. MEURER: That was my case series N equals 3, so I don't know.

DR. BROWN: So let's move ahead to question number 2.

I tell you what. Why don't we take a break so that we can go clear our heads a little bit, and then come and do question number 2. And then tomorrow we'll do question number 3.

(Laughter.)

(Whereupon, at 3:36 p.m., a recess was taken.)

DR. BROWN: Okay. If everybody can take their seats. We're going to change things around a little bit, and we're going to have some discussion about question 2, and then we're going to vote on question 4, which relates to some of the things that will be discussed in question 2.

Under A, question 2, the approved dosing for known or suspected opioid overdose in adults is as follows. An initial dose of 0.4 to 2 milligrams of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at two to three minute intervals.

If no response is observed after 10 milligrams of naloxone, the diagnosis of opioid-induced, or partial opioid-induced toxicity should be questioned. Intramuscular subcutaneous administration may be necessary if the intravenous route is not available.

The approved dosing for known or suspected overdose in the pediatric population is as

follows. The usual initial dose in pediatric patients is 0.01 milligram per kilo of body weight given IV. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 milligrams per kilo of body weight may be administered.

The past AAP recommendations for naloxone dosing in infants and children are as follows: 0.1 milligram per kilo for infants and children from birth to age 5, or 20 kilos of body weight; children older than 5 years of age or weighing more than 20 kilos may be given 2 milligrams. These doses may be repeated as needed to maintain opioid reversal.

For discussion question A, discuss whether the minimum exposure criterion, naloxone levels comparable to or greater than the levels achieved with 0.4 milligrams of naloxone, is appropriate for managing opioid overdose in children.

If you do not think the standard is appropriate for children, discuss the criteria that should be used for naloxone products intended for

use in children. Discuss whether the recommended criteria are suitable for use in adults.

Let's discuss that A first.

Dr. Zuppa, do you have --

DR. ZUPPA: My hand was up from before, but I have something to say anyway. I mean, it's just math. The 0.4 milligrams is lower than -- so if you are 20 kilos -- if you're 10 kilos, you would come and you would get a milligram IV, where the bioavailability is higher than that of 0.4 of the IM.

So this is effectively a much lower dose than what's recommended in a population that probably, for the most part, unless they are on long-term opiates for a disease process or something, were just a one-time overdose. So this is worrisome to me. So I think that the 0.4 milligrams is not an appropriate standard by which future products should be developed.

DR. BROWN: If the standard is found to be 0.4, if the agency considers that the standard of 0.4 continues to be what we should be using, does

it make sense to have two standards?

DR. ZUPPA: I'll repeat what I said before. I think that there are very different populations. And if they're a population of children who are at risk for overdose because there's opiates in the house that are not theirs, the downside of giving more is minimal to none.

So I think that they are a unique population that is different from any population. And yes, I think that they probably warrant a dose that's more in line with what the AAP had recommended, and what I would give if I saw a kid at CHOP.

DR. BROWN: Dr. Hertz?

DR. HERTZ: Thanks. I just wanted to clarify where this question is coming from, and it relates back to that remarkably long amount of information that we just had to read into the record that preceded the question.

Part of the problem is, we try to determine where the recommendations for the pediatric dosing that differs from the approved label came from. We contacted a variety of people, and we weren't

really ever able to find out why children need that much more than adults.

So as you think about the answer, it's not just, gee, the American Academy of Pediatrics says use this. I guess it's -- you know, in part the question is, for those who may have more experience or thoughts about that particular aspect, the difference in -- so we have the adult dosing that we provided to you, we have the labeled pediatric dosing, and we have the American Academy of Pediatrics dosing.

As we look at that, conceptually, if we went by the labeled dosing, the pediatric doses would be well covered by the exposure comparable to 0.4 milligrams in an adult. So we're trying to get to that a little bit more. So it may not answer the question.

DR. ZUPPA: I think then that would -- you know, there's been some talk in here about not letting go of the 0.4 in the adults because that's been efficacious, and we've seen good outcomes with that. But I think it would require maybe a polling

of the children's hospitals in the country to see what dosing recommendations they're following. At CHOP, we're following the 10 mics per kilo followed by the 100 mics per kilo.

We could really only speak to our experience with that. And that experience has been, I mean, we haven't changed the formulary dosing in as long as I can remember for that. So I don't know if --

DR. BROWN: We're discussing administration in the community.

DR. ZUPPA: Correct, but I'm going on the doses that -- for pediatric doses that I've been familiar with. So if you want to dose that in the community, it's not going to be IV, and it will be IM, so the exposures will be less.

DR. BROWN: Dr. Hudak?

DR. HUDAK: I guess I can speculate about the ontogeny of this recommendation that dates back to 1990. I think that it was based at a time when there's a focus on making sure that there was weight-based dosing in children rather than a certain dose for everybody. And there had been

some limited experience with neonates, at which a dose of 0.1 per kilo administered IM was effective.

So having been on the committee of drugs in the past for seven years, I think that that is how that recommendation got started, and I was not able to find any real evidence to justify that dose. Certainly having a step function where you go from 2 milligrams at 20 kilos to 0.4 milligrams after 20 kilos doesn't make any physiologic pharmacokinetic sense.

In the hospital setting, I think if we would do that survey of hospitals, you would find that kids were getting about a 0.1 per kilo dose IM in delivery room if they needed it. But I think that the use of that in the delivery room has become increasingly uncommon.

I have not seen a baby in five years that we've had to give Narcan to in the delivery room. There are warnings all over the place, don't do it because you could precipitate withdrawal. I think that's been reported a handful of times in the literature, so I'm not sure how frequent that is.

In the other pediatric population, I think the information that was presented showed for the kids, kids less than 14, that they have a very different exposure, and there's absolutely no evidence that 0.4 milligrams in that population does not work.

So I think to say that we need to give these kids 2 milligrams just because, just because, I think is not based on any data. So I think 0.4 milligrams in that population is appropriate given the nature of their exposure.

DR. BROWN: Dr. Fuchs?

DR. FUCHS: Susan Fuchs. I have the 2008 Committee on Drugs document, and they're revising it now. And I will tell you they have two different doses of naloxone in here. One is for reversal of opioids, fentanyl, morphine. The other says opioid agent, induce respiratory depression. So we're going to have to reconcile this even within the AAP.

DR. BROWN: But is that for in-hospital use or --

DR. FUCHS: It's basically for pediatric emergencies, more for in hospital, but they don't really -- they go through both IV, IM, subQ, and nasal in here. But like I said, the doses are different, so we're going to --

DR. BROWN: Yes, that's the problem. The way the AAP works is that they compartmentalize to some extent, and we've been asked questions about things that the AAP heretofore hasn't really considered very much, which would be somebody giving a child a naloxone in the home.

DR. FUCHS: Correct. Like you said, one doesn't mention it because it's IV; the other does, but that's a whole new category in this document. So it will have to be kind of worked on with them, too.

DR. BROWN: Dr. Nelson?

DR. NELSON: Lewis Nelson from Rutgers in Newark. So two things. One is that if you look -- and somebody can confirm this later perhaps. I had a table that I happen to have that looks at the pediatric recommended doses in Harriet

Lane and Nelson's textbook. And in Harriet Lane, they recommend 0.1 milligram in children, and in Nelson's textbook, which is not any relation to me, they recommend 0.4 milligrams.

So I know that the official recommendations of those other organizations is different, but the textbooks at least recommend something that we would probably consider to be more typical.

The reason that they might actually recommend high doses in children is because children take adult doses of opioids, which are relatively large overdoses for the child, if that makes any sense. So they feel like they need to get a relatively large dose of a naloxone. I don't think there's any empiric research-based evidence for this, but I know we've seen this happen in little children who get into methadone in New York City, and often do require fairly high doses of a naloxone. But it's a little bit more this reversing them that's the issue. It's obviously much more of a duration problem.

So I think there might be a lot of

extrapolation from total dosing to initial dosing and things like that. Again, because if a child got a milligram per kilogram dose that was the same as an adult, there would certainly be no reason to think they would need a different naloxone reversal dose, but perhaps because they're getting a relatively large overdose that, there might be some concerns. But again, the textbooks, if that's of any interest to anybody, do recommend more of our typical doses.

DR. ZUPPA: But that's for inpatient though, right?

DR. NELSON: It's just a table. I think it's just the -- the way we crafted this table was the initial dose of naloxone. It is not for out of hospital use. It is for hospital, whether it's ED or inpatient or something, but it's medical use. And it doesn't specify the route either, but still the doses are pretty low. It's not this high dose.

DR. BROWN: Dr. Vinks?

DR. VINKS: I just wanted to reiterate I think what Dr. Zuppa said before, that we're

talking about doses in children, but what we actually mean is exposure, which is true to us for adults as well.

So a lot of these dosing regimens were based on empirical data, and I think we have an opportunity here to really look to, potentially, the help of this division of pharmacometrics, to look at exposure and then come up with practical dose bands, if you will; not body weight dosing, but something that would work outside of the hospital, because again, in the hospital, it's a very different situation.

But I think that is definitely something for the pediatric population, because we talk about an age range from birth, zero, to 18 years of age. So that's a wide age range, where especially in the first couple of years, there's a lot of maturation ontogeny going on that would play into differences in pharmacokinetics and with that exposure.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: So this is kind of going to the second question as well. But again, I want to

deal with the practicality of this. Currently, in the United States, there's somewhere around I think 2 million prescriptions of methadone out there, 600,000 prescriptions of Suboxone, and a lot of these people have kids. And so are you going to send 2 doses of naloxone home with patients so that when there's an overdose, there's confusion over which dose of naloxone to use? I would say the answer is probably no.

So the question gets to be, make sure that the dosage is appropriate for both the adult and the child, and the dosing formulation is appropriate for the adult and the child. And one of my questions about that is -- you know I hadn't thought about this -- but is the nasal applicator on the nasal administration thing small enough to go in infant or neonate's nose? And I guess that's for the company.

DR. BROWN: Any other comments before we go on to B? Dr. Nelson? Dr. Zuppa? Dr. Parker?

DR. PARKER: I think this is probably pretty obvious, but just to put it on the record. So Ruth

Parker. We have to do the math for people. We can't ask them to do the math. And the weight-based dosing I think would definitely, given the circumstances under which you would be administering it in a non-hospital setting, would heighten that.

So I think it is really important to come to clarity on what is the pediatric dose that is available for use in a community setting, that is not calling among people to have to do math on the spot based on weight when they don't know it. So I think it's actually -- I would just underscore that sort of variable based on whatever in the way -- I mean that's not going to do it.

DR. BROWN: Anyone else? Dr. Hertz?

(No response.)

DR. BROWN: All right. If there's nothing else, it appears to me that the baseline dose would probably be appropriate for most children if administered. So the use of 0.4 milligrams as a dose to start with in children in the home, since we don't have any historical evidence.

I can tell you from being a pediatrician for many years and looking at Dr. Nelson's family's textbook of pediatrics, that the data that is supported there informs us of inpatient pediatrics rather than what we're dealing with. So I'm pretty clear that this is going to be -- that the usual dose would be, standard dose would be clearly safe.

Let's move on to B. If different standards and resultant naloxone products are recommended for adults and children, one concern is that the presence of more than one naloxone product in a home may result in confusion about which product to administer. Discuss how the risk of medication errors can be reduced in this setting.

DR. ZUPPA: I find it interesting, so children with status epilepticus get sent home with Diastat. So that's rectal administration of valium. And status epilepticus can really bad. I mean you could seize and seize and seize.

Not to throw another wrench in the mix, but it was curious to me when I was reading all these documents that there was no thought of a PR form, a

per rectum form, of naloxone for pediatrics.

You think about giving an intranasal dose to a child, their nerves are small. Injecting them is another -- I mean EpiPens do that, but it was just interesting to me and whether or not that could be something that could be developed.

DR. BROWN: Any other comments? Yes, ma'am?

DR. MAXWELL: I was thinking about -- I worked on the SAMHSA methadone overdose. And in reading the death certificates of adults and people, "He was snoring loudly. He was making gurgling sounds, and he died." Well, I've never understood he was dying.

I just wonder about of these parents who may well be on drugs or heavy users of drugs themselves, do you really want them administering naloxone? I don't know, I just keeping about some of the people who would be -- have plenty of oxycodone or heroin or whatever themselves, and would they be capable of following these instructions? And that's for you all. You all are the pediatricians.

DR. BROWN: Ms. Berney?

MS. BERNEY: Well, regarding question B, one of the ways to negate the risk of medication errors with two different products is to make sure that they are completely different in the way they look. And as a graphic designer, I can tell you that something that's red and yellow and blue will be much more associated with a child than something that is black and red, or whatever the package was.

So you can differentiate by color or by the typeface. There are all kinds of things you can do by the graphics on a piece, so that when you're going to grab one, you grab the right one.

DR. BROWN: Dr. Hudak?

DR. HUDAK: I guess going through the scenario here, you would posit you would have different doses for the child and the parent, so 0.4 for the child and 2 for the parent. And so the errors would be in the child, giving the child the dose of 2 milligrams, which is probably a non-issue, right? And in the adult, giving the adult 0.4, which may be too little, in which case

there's still the 2 that's available that someone intelligent could give the adult. So I'm not sure.

I agree with the labeling suggestion. I think putting the child product as pink and blue or something and the adult as another color would be helpful, but I don't know that there is a big issue with risk medication errors in this scenario.

DR. BROWN: Dr. Parker?

DR. PARKER: I'm just thinking about the broad implications of if this medication is given and put in the household of everyone who has a prescription for an opioid in America.

If you simultaneously instruct everybody to have this in your home, which as I understand it from reading the patient counseling and looking at this, you know that's what it says, that make sure Evzio is present whenever persons may be intentionally or accidentally exposed to an opioid to treat serious opioid overdoses.

If this played out that it ended up in the household of every person who had been prescribed -- I mean, somebody knows the number of

how many households that would be. And I'm thinking about that standard dose being 0.4, and I'm looking at how you know to give it to your child, and how often that might happen: extreme sleepiness, okay, hmm; breathing problems; and then other signs and symptoms that could accompany the sleepiness.

I'm really thinking about how you would instruct somebody on when to give it, and just really thinking carefully about how often this could end up happening, and whether or not there could be potential unintended consequences from it being something that could happen very frequently.

It strikes me that when you're talking about putting this in that many households and telling that many people to repeatedly potentially give to the child who is sleepy, or extremely sleepy and has breathing problems, how much you could be giving them. I'm just thinking about the implications of that on a large public health scale. And it raises concern in my mind, I have to tell you.

DR. BROWN: Dr. Meurer?

DR. MEURER: Will Meurer. I think the quick answer to this is, at least in my opinion, I think avoiding confusion would be good and having single products that you just use. One other confusion that this sort of brought to mind was a flashback.

I used to have an Auvi-Q inhaler, or auto injector in my house, and it has like the exact same forum and the exact same voice as the injector we were shown at the beginning.

That could introduce additional -- it's not currently marketed, but certainly it could be marketed in the future. That could also be a risk of a medication error. And I think making sure that for -- and there may be other auto injectors that are marketed in the future for other emergency conditions.

I think medication errors should be reduced by making this as simple as possible. I think we have broad support that generally pediatricians are fine with us giving as much Narcan as we want, in which case having a single agreed upon adult

formulation that can be given and repeated for adults and kids would reduce the risk of medications errors, and I would favor that.

DR. BROWN: Dr. Emala?

DR. EMALA: Just again trying to address point B, I do think minimizing the number of medication concentrations would be very important. And we've heard time and time again that the typical scenario in the pediatric population is going to be an inadvertent overdose of a non-opioid dependent child who gets naloxone. It doesn't seem to be dangerous that they get a high concentration, except perhaps in the neonatal population on methadone. So I think the idea of having multiple doses creates more problems than not.

The comment about having the drugs in the household and the drug being inadvertently given in a non-opioid overdose situation, I think is also not a huge concern because of a lack of effect of naloxone in the absence of the presence of opioids.

DR. BROWN: I think this is a good conversation. Opioid poisoning is common in

children. We saw from our open public forum some indication from Utah that there are children down to age 2 and 3 that have had episodes of opioid poisoning. With as much opioid as there are in homes, children will find it.

I think we've agreed that children down to -- not neonates certainly, but children down to at least age 2 should be able to have a dose similar to that of adults under almost all circumstances.

Now, I think that if a parent has a child, that is that child is taking chronic opioids, that's a whole different story. But that's usually, in a pediatric population, less than about age 12. That's usually not the issue. It's usually a poisoning rather than a child inadvertently getting too large a dose of drug.

So single products and simpler administration is important, so one dose would seem to be reasonable.

Question C, discuss the need, if any, for PK and safety information in pediatric patients,

depending on the route of administration and inactive ingredients, and any recommendations for how these data can be obtained. Dr. Galinkin?

DR. GALINKIN: In theory, I would love to see safety and PK data. I think there's only really one population I can think of in pediatrics that actually gets these dosages. And we do give pediatric patients who have side effects from opiates, we do give them naloxone infusions, and we do sometimes give them small boluses of naloxone. So that would be probably the only population we could do PK data, and then you have to extrapolate it to higher doses, which I don't know how useful that would be. I don't know of there being another population in pediatrics where you would use naloxone.

DR. BROWN: Dr. Winterstein?

DR. WINTERSTEIN: Using that population, I would just like to amend it would be good to have PK/PD data. I think what we all are struggling with is how much naloxone is needed to combat how much plasma concentration of morphine. So it's not

so much the pharmacokinetics as it is what is actually the plasma level needed to address a varying amount of plasma levels of whatever morphine has been used.

I did find one study on the adult population, sorry for that deviation, that looked at exposure to 0.15 milligram morphine per kilogram in adult patients and showed that the 0.4 milligram dose reversed that completely.

That is my guess where the 0.4 milligram originally came from. That's the study from the 1980s. I haven't seen anything like that in the adults -- in the pediatric population, but we probably would want to see something like that. So it's not so much the pharmacokinetic data as it is the pharmacodynamic data that is really needed.

DR. HERTZ: Hi. This is Dr. Hertz. I just want to add on a little piece of the question or emphasize it. We struggle with all of our pediatric studies for all of our products because a lot of these are just hard to do for a variety of reasons. Again, we deal with how do we enroll

children in a study for a drug they need on an urgent basis, even if it's in the hospital. So if you have any thoughts about that part of it.

The challenge with this setting versus with the adults, where at least we have PK data and safety from the exposure data, is it's much harder to try and do any type of study in a normal child, and it's not really clear that we would get through the ethics process for something like this. So if you have any thoughts on that, it would be helpful.

DR. BROWN: Dr. Hertz, I agree with Dr. Galinkin in that the only model that I can think of is a model that we use for patients that have acute usually post-operative pain in the hospital setting. Now, those patients are not having dramatic respiratory depression. Most of them are getting naloxone because of some of the other complications or adverse side effects of opioids, such as itching and nausea and vomiting.

Naloxone administered under those circumstances, along with a given amount of an opioid compound, it would be probably possible to

get some of the data that would be required. But the ethical construct here of getting children who are, in extreme, enrolled in a naloxone trial is beyond me.

Dr. Zuppa?

DR. ZUPPA: I can suggest a couple of ways to do this. One of those ways is what Sandra was talking about before. You can use adult PK data and allometrically scale it, or however you want to use it to scale from the adult population to get PK parameter estimates in a pediatric population.

You can inform that model with some PK information, like 1 mic per kilo per hour or something like that, right, for the --

DR. GALINKIN: You could also potentially give small boluses. I think sometimes we just start kids on this. I mean, I don't think it would be unethical to put children on these infusions --

DR. ZUPPA: No, it would be basically an observational trial.

DR. GALINKIN: -- but you can do it prospectively.

DR. ZUPPA: Yes, so the dosing would be a standard of care, so it wouldn't be dictated by a study protocol. And you could collect PK samples, and you can get an estimate of what clearance is and volume of distribution, and then inform an adult model with that and do some clinical trial simulations to pick a pediatric dose.

The other thing that you could do is you could do a study with a waiver of consent. And for any child that gets a dose of Narcan in the hospital, you can work with your IRB to see if you could get some blood draws at that time, or a delayed waiver of consent. But it would have to be drug delivery as standard of care dictated by the clinical team, and then you would draw some PK samples, but it's not impossible.

DR. GALINKIN: You could do with dry blood spots, too, which would actually make it even easier to do the study. Then you could decrease, have it as a minimal risk trial.

DR. HERTZ: So basically, consider everyone coming in for surgery to potentially participate?

DR. ZUPPA: We've done studies like this before, where you get -- when an order goes in to the pharmacy, you get a page on your phone, you set it up, and Narcan is being administered in the emergency room. And there's someone in the hospital -- either it's a PICU fellow, or an ED fellow, or an attending, or a research coordinator -- who goes down and is present for that, and tries to obtain samples at that time if you're operating under a waiver of consent; or you can get consent if there's a guardian there.

But there are alert systems, so you know when the drug is being administered, and you can do real-time kind of interventions at that time that are study related.

DR. VINKS: Can I respond to it? I just wanted to reiterate, this is what the pediatric trials network has worked out as their pediatric opportunistic pharmacokinetic studies, and you can add pharmacodynamics -- where basically you do it under a waiver of consent, or consent later, where samples are being collected, basically blood

samples that are being drawn anyway that are ending up in a biobank. You can do population pharmacokinetic, dynamic analysis on sparse sample across a large group of patients. You would be able to also look at some of the dynamic side of things because you know how much opioid is on board, and you could even measure that. So the answer would be, yes, that's fairly doable.

Just to give you an example, one of our fellows, neonatology fellows, finished a study. He recruited 130 neonates in one year where we collected 300 samples on morphine. So this was standard of care pain treatment with morphine. We analyzed all the samples. We have a beautiful idea of how these babies handle the drug, and then you can turn this around and come up with reasonable dosing strategies. And a similar approach could be taken for naloxone while it's given as part of standard of care.

It works. And yes, you could do dry blood spots. We have all these measurement technologies -- I mean, these nano technologies

where you have high sensitive LCMS technology, where you don't need a lot of blood. You could do this on probably 10 microliters of serum, and that's easy to get.

DR. ZUPPA: There's dry blood spot, and there's also micro tips that you just need 10 microliters. If you think about it from an IRB perspective, these children are obtunded, so the pain component will probably be minimal, and they won't really feel a heel stick or two heel sticks.

DR. BROWN: Any other comments? Dr. Galinkin?

DR. GALINKIN: Yes. So the other place, you can actually use the Ativan valium study that they did in the emergency room, which they used an emergency waiver of consent as a model potentially for this. They enrolled several hundred kids across the country to do that trial, and I think you could do the same thing with this and probably would be less controversial than that trial.

DR. BROWN: Okay. So to summarize, it appears that there are some models that might help

us to determine more PK and PD data that would be required for a safe continued use of naloxone in children. We would have to do most of these on an inpatient basis, and some models such as waiver of consent could be possible, or emergency waiver of consent models may also be possible.

Now, any other comments about question 2?

(No response.)

DR. BROWN: If there are not, I would like to move, since we've spoken a lot about the issues with adults and children, to voting question number 4.

We're going to take a vote on this, and the question, should there be different minimum standards used to support the approval of products intended for use in adults and in children? First I'll ask, is that a question -- is that question understandable, and is that a question that we can answer? Yes?

DR. GUPTA: Can you just clarify? Is that adults versus children, or are you talking about both populations as separate, different minimum

standards? I mean should it be two separate questions or one?

DR. BROWN: I believe it's different minimum standards for adults and children.

MALE SPEAKER: Is the minimum standard only with respect to the dose?

DR. HERTZ: So what the question is intended to mean is right now we're using the exposure equivalent to 0.4 milligrams IM subQ in adults. Do you think that's adequate for kids? And I know I heard the ones who said no, but when you vote, do you think that's okay, or do you support approval of a different standard, based on exposure, for a different dose?

For instance, the equivalent of a 2 milligram exposure IM or sub-Q would be one way to think about it. So if you think that 0.4 is in fact enough for everyone, you would say, no, there shouldn't be a different minimum. And if you think it's not okay, you would vote, yes, there should be a different.

DR. ZUPPA: Question. So what happens if

you think that the 0.4 is not enough for adults but would cover kids?

DR. HERTZ: If you think the standard of exposure for children and adults should be different and that we shouldn't find -- so the question is, some people have said there should be one dose that's sufficient for everyone based on exposure, one product that should cover everyone based on a certain exposure standard. And others who have said there should be different exposure standards for different age ranges, for adults versus children.

So, regardless of what that standard should be, do you think there should be one standard so that one product is suitable for everyone, or should there be an opportunity for there to be to two standards so that one set of products would be appropriate for, presumably the youngest children, and one for adults and the large kids?

DR. VINKS: So you talk about exposure. You talked about dose, but you mean exposure?

DR. HERTZ: We're using them synonymously.

I understand they're not synonymous, but I think we've just gotten a little loose with our language. So when we talk about the 0.4 milligram dose, we're really I think -- when I say it for instance, I just mean the exposure associated with that in adult. So it's a shorthand, I think, and if someone doesn't mean that when they're saying it, they need to specify.

So the standard is the exposure associated with the 0.4 milligram dose in adults. And that's what is meant here with use of the word "minimum standards."

DR. BROWN: Any other questions or comments? Dr. Hudak?

DR. HUDAK: I just wanted to clarify, this is really for the type of use we've been really focused on. I wouldn't want to eliminate the ability to titrate the dose in the hospital.

DR. HERTZ: We are talking about products intended for use in the community by a variety of persons.

DR. HUDAK: Thank you.

DR. ZUPPA: And this is saying that the exposures attained with the 0.4 milligram dose IM are much lower than that obtained with the 4 milligram intranasal and the 8 milligram intranasal. So the 4 milligram intranasal approximates about 5 nanograms per mL and the 0.4 IM approximates about 1, right.

DR. HERTZ: I don't have the dose exposure.

DR. ZUPPA: I'm just looking at right now --

DR. HERTZ: Okay, I don't have that in my head.

DR. ZUPPA: Yes.

DR. HERTZ: So, yes.

DR. ZUPPA: Okay. Fabulous.

DR. BROWN: Okay. We're going to be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing on your little baby here. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until

the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record. Next, we'll go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you care to. And we'll continue in the same manner until all the questions have been answered or discussed.

(Vote taken.)

DR. ZUPPA: It keeps flashing even after you vote?

DR. BROWN: Yes.

DR. ZUPPA: I'm just going to keep pushing it until it stops flashing.

LCDR SHEPHERD: For the record, 7 voted yes, 21 voted no.

DR. BROWN: So we're going to start down here on my right. And if you could announce your name and your vote, and if you care to tell why you

voted that way, please do.

DR. WOODS: Mark Woods. No. I think given the fact that there's very, very minimal toxicity and the potential it could cause for confusion, adults versus pediatrics, I voted no.

DR. WARHOLAK: Terry Warholak. And I voted no for the reasons already mentioned.

DR. VINKS: I voted yes because I think at this point there is not enough data to substantiate why it should be the same. So that's why.

DR. PARKER: Ruth Parker. I voted no, same reasons as mentioned previously.

DR. MEURER: Will Meurer. I voted no. No additional reason other than what I've talked about before.

DR. HUDAK: Mark Hudak. No, and the additional comment that I think that the issue of dosing is really something for which we don't have sufficient data and which should be resolved through careful additional research.

DR. HIGGINS: Jennifer Higgins. I voted no, largely because I feel comfortable with what we've

spoken about today and the safety profile for children with the 0.4 milligram.

MS. BERNEY: I voted no. This is Barbara Berney. I voted no for the same reasons that have been given.

DR. DAVIS: I'm John Davis. I actually voted yes for the same reasons. Children are different than adults, and even thought the dosing may be similar, I think they should be examined as different populations, and ultimately agree that the safety profile may be the same for each.

DR. STURMER: Til Sturmer. I voted no for the reasons we discussed. But I think also to not impede distribution of the drug to the population.

DR. McCANN: Mary Ellen McCann. I voted no basically for the same reasons that have been mentioned. I think it's much simpler if there's a single drug in house for emergency use.

DR. EMALA: Charles Emala. I voted no because I think there's a dose that could be chosen for both populations that would be safer than having mixed populations, although I think that

threshold needs to be higher than what it is.

DR. GALINKIN: I voted yes for the same reasons because I think I misunderstood the question. But I also think there should potentially be one dose, but I think it should all be potentially driven by the pediatric data because the pediatric data seems to indicate that initially we wanted a higher dose for children.

DR. CRAIG: David Craig. I voted no for some of the same reasons that other members have mentioned.

DR. GUPTA: Anita Gupta. I voted yes. I believe that the information that was presented on pediatrics was really insufficient for me to draw any conclusion. I understand the need for one single dose, absolutely, but I just could not draw a clear conclusion on whether or not the 0.4 was adequate. So yes, to really more research to enhance the understanding of how naloxone works in neonates and children and a variety of young adults.

DR. BROWN: Rae Brown. I voted no for

reasons that have been clarified before.

DR. WALCO: Gary Walco. I voted yes, largely for the reasons before. And I think that it's the lack of data, one could conclude that there's basically equivalence, but given that we don't have the data to show that, I think it's more conservative to keep them separate.

DR. WINTERSTEIN: Almut Winterstein. I voted no. I don't think we have enough data to support that the dose would be something different than what the minimum standard currently is, which would be 0.4 milligram. And that seems to apply to both populations. We definitely need more research that's specific to children.

DR. BATEMAN: Brian Bateman. I voted no given the absence of evidence of toxicity for children at this dose and the need to avoid confusion with different doses being introduced in the community.

DR. SHOBEN: Abby Shoben. I voted no for the same reasons Dr. Bateman just said.

DR. HARRALSON: Art Harralson. I voted no,

again, the context is community and trying to get the drug into people's hands. And at this point, it doesn't seem we have enough information to set up a different standard, so at this point you really couldn't do it.

DR. ZUPPA: It's Athena Zuppa, and I voted no, hoping that the standard for adults would be more than the 0.4 dose, because I don't think that we were talking about a standard in the specific voting; and specifically because I would hope that we could have children get as much as possible because I think that the adverse event profile would be low in them.

DR. BEAUDOIN: Francesca Beaudoin. I voted no for many of the other similar sentiments. And while I think there's not enough evidence to support a minimum standard, I hope that we can strive toward a standard that's similar in adults and children.

DR. BRENT: Jeffrey Brent. I voted no, pretty much for the reasons that I and everybody else here, or a number of people here have already

articulated. The serum concentrations in AUC should be higher than with the 0.4 dose, but there's no reason for making a differential between adults and children. It's a low toxicity drug.

DR. FUCHS: Susan Fuchs, and I said yes for the reasons stated by many other people.

DR. MAXWELL: I'm Jane Maxwell, and I voted yes because the data aren't there. If further research shows that the protocol, based on the data the protocol shows they should be same, I support one protocol.

DR. NELSON: Lewis Nelson. I voted no for the reasons stated. But the one area that does give me a little bit of concern, as many of you can imagine, are the small children who are opioid dependent in whom this will be a very large dose and might produce fairly severe opioid withdrawal, which obviously is unpleasant and dangerous.

DR. WU: Victor Wu. I voted no. Nothing new to add.

DR. BROWN: We're going to move to question 3. It's our second voting question, and

I'll just read it for the group.

Is the pharmacokinetic standard based on 0.4 milligrams of naloxone, given by an approved route, appropriate for approval of naloxone products for use in the community, or are higher doses and/or exposures required? A, continue with the current minimum standard of comparable or greater exposure compared to 0.4 milligrams of naloxone; B, increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone.

This is the question that we've been aiming towards all afternoon. For strictly adult patients, are we looking at maintaining a standard of 0.4 milligrams of naloxone or a higher dose of naloxone, without any determination of what that higher dose might be? Dr. Hertz?

DR. HERTZ: Actually, it's kind of good that you switched the order on these because I would like to modify what you said a little bit. We didn't specify adult or children in this question, so this is an opportunity for you to decide what

you think the standard should be. And when you tell us why you voted that way, if it's because of the pediatric piece, you can let us know if that's the reason why you think the standard should be increased for -- it would basically be for everyone.

So I'm asking you to accept the latitude, to respond in a way that you feel comfortable, and then just explain it when we go around. If you're not comfortable putting the peds in, that's okay. But if you are, just let us know when you move around.

DR. BROWN: Is that understandable to the members of the panel? Is that a question that we can answer?

(No response.)

DR. BROWN: Is there any discussion before we vote? Anybody? Dr. Beaudoin?

DR. BEAUDOIN: If we vote B, what will be done I guess to see what that other minimum standard is, or is that beyond the scope of this dialogue?

DR. HERTZ: No. If that's informing your vote, you can tell us that's why.

DR. BROWN: So you assert that when you're discussing why you voted the way you voted.

DR. BEAUDOIN: Okay.

DR. BROWN: We're going to use our electronic voting mechanism here. And what you will see on the microphone is that it doesn't say A or B, but it says 1 or 2 is flashing, and then A or B below it. So if you vote A, you will be voting to continue with the current minimum standard of comparable or greater exposure compared to 0.4. If you vote B, you will be voting to increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection.

(Vote taken.)

LCDR SHEPHERD: For the record, 13 voted A, 15 voted B.

DR. BROWN: Dr. Woods, we're going to start with you again. If you would give your name, what your vote was, and a short piece about why you

might have voted that way.

DR. WOODS: Mark Woods. I voted B, and a couple of things in particular. One is the increase in the use of the potent synthetic opioids I think is really concerning. And one thing that was said a few minutes ago that we haven't discussed is that in the CDC data, we didn't have any information about what dose of naloxone patients received, but we do know that more and more patients are requiring additional doses.

That makes me even more certain that we may need to increase the dose because we have no idea how many patients got low dose versus maybe the doses are accelerating, and we just don't know that yet. So I have concerns about that.

DR. WARHOLAK: Terry Warholak, and I voted B. While I do think there's much more research to be done to determine the specific dose that's appropriate, I feel like the benefits of increasing the dose outweigh the risks.

DR. VINKS: Alexander Vinks. This is a hard one. I voted A because the data presented today,

and also the data that we heard from the different organization, it seems that the current dose seems to be working. Now, I definitely share all the concerns that were raised about the higher potency opioids.

I think my compromise would be to move forward with the current standard, and then do the research, ongoing research, to then learn more about the true exposure-effect relationship, as that is not really well categorized for naloxone.

DR. PARKER: Ruth Parker. I voted B, really related specifically to the data from the CDC presentation about the changing landscape with an increasing number of heroin overdoses and synthetic opioid overdoses, and the impressive increase of multiple naloxone administrations over the last couple years.

DR. MEURER: Will Meurer. I voted A. At this point in time, I'm not entirely clear that there is enough unbiased data that says that 0.4 isn't working okay, and would like to see more. And I'm concerned about cost pressures driving the

epidemiology of repeat dosing in EMS agencies.

DR. HUDAK: Mark Hudak. I voted A. I feel, same as many people, that we don't have good evidence to suggest that the 0.4 dose fails more frequently than the higher dose. And keeping it at the 0.4 gives us more flexibility and products, and allows us to basically let the research set the recommendations for lower or higher dosing depending upon the circumstances identified in the field.

DR. HIGGINS: Jennifer Higgins. I voted A. I think, to my mind, the present dose seems to be effective and wouldn't cause harm to the pediatric population.

MS. BERNEY: Barbara Berney. I voted A for the reason that the last two mentioned.

DR. DAVIS: John Davis. I voted A. Ditto.

DR. STURMER: Til Sturmer, A. I think I stated my reasons. I think industry has shown that under this standard, they can bring a variety of drugs on the market. And I think we should urgently compare these by whatever means needed.

DR. McCANN: Mary Ellen McCann. I voted A. I think the evidence presented today showed that almost all the doses were fairly safe, so I don't see any compelling reason to change the dose. I think one thing that gave me pause was for rural patients that need to travel a great distance, not having an initial super high dose means that their duration of action is possibly going to wear off. I think we could give additional drug to those rural patients.

DR. EMALA: Charles Emala. I voted B, mostly because I'm concerned about a very significant need for second dosing. I think 3 minutes or more of additional hypoxia is not an innocuous consideration in the need for a second dose.

I think it's also remarkable that the packaging currently requires a second dose. That sends a message to me that there's not a lot of confidence that perhaps the first dose is going to be adequate, coupled with the fact of the growing potency of the opioids. And finally, raising the

standard of the adult dose I think could bring it in line with an acceptable dose in pediatrics and solve the problem of single dose as well.

DR. GALINKIN: Jeff Galinkin. I voted B. And I think this is due to the availability of both carfentanil, fentanyl, and the high availability of long-acting opiates in the community. I think that you need a much -- and in rural communities, the long response time requires a long half-life of the drug to stay around. And I really think there should be one standard for both adults and pediatrics. And I think this is more about saving more lives than avoiding acute withdrawal syndromes.

So I would actually support the 4 milligram dose because that's the only one that was getting that 5 nanogram per milliliter dose that Dr. Brent had mentioned earlier.

DR. CRAIG: Dave Craig. I voted A to keep it as is. I just didn't see enough evidence that actually the dose that we were given was ineffective. I saw a majority of it where it

actually was effective, so I hate to move away from what's most familiar, especially giving dosing errors.

Like you had mentioned before, somebody received 4 milligrams versus 0.4. That darn decimal point always burns you whenever you have it in the wrong place. It's lucky we've moved away from handwritten orders, but things like that I think don't make a lot of sense. I think keeping the standard as is, although it's not perfect.

I like the idea of having multiple dosage forms, like for example, a nasal spray that has 4 or 5 doses. Something like that I think makes a lot of sense, whether it's a duration of effect, like with naloxone, for example, or whether you need higher doses to overcome more of the synthetic opioids is really not that clear.

I'll also finally put in another plug for the availability of nalmefene as an option. Maybe you don't need a second dose of naloxone if you've given nalmefene.

DR. GUPTA: It's Dr. Anita Gupta. I voted

yes. I have more questions today than I did before I came here. I think that really what was presented today, there was a lot more confusion on what conditions re-dosing was occurring when naloxone was failing in a reversal situation. And because those questions were unanswered in my mind, I could not drift from the current standard.

I do believe that having one standard avoids confusion. It offers a familiarity in a time when patients and physicians are not clear on how to use naloxone appropriately. The impact of human error and medication error could be enormous, which we haven't really examined very closely, and there's multiple factors, in my opinion, that could really affect how the naloxone is being -- how it's reversing the opioid overdose.

DR. BROWN: Well, my vote, and I voted B. It's Rae Brown. I voted B. My vote was informed by the fact that, in part, because I live in Kentucky. And in Kentucky, there are many, many potent semi-synthetic opioids. And the data didn't show it today, but carfentanil has moved into

Kentucky, and there have been dramatic increases in the number of folks that have been coming in to our emergency departments for which 0.4 milligrams of naloxone do nothing.

So I believe, based on my experience, that an increase in dose would salvage more patients. I also know that when we get patients from the Appalachian region, they travel a long way, and 0.4 milligrams of naloxone is not going to carry them.

For pediatric patients, if we raise the dose standard, I don't really have any problem with that causing a problem for the vast majority of children, given what I know about the epidemiology of poisoning in children.

I go back to the one or two different scenarios where children are on chronic opioids, and I think those should be treated somewhat differently. But for children that are poisoned with opioids, I don't think that giving them an adult dose is going to harm them.

DR. WALCO: Gary Walco. I voted B for

reasons already stated.

DR. WINTERSTEIN: Almut Winterstein. I voted A. I think there may be a place for both strengths, and we need to find out what exactly that looks like because the emphasis here was on a minimum standard, not on removing a 2 milligram dose. And that's why I thought it makes sense at this point, given where practice is and how practice seems to utilize both strengths, to keep it that way until we have found out more.

I would like to emphasize that I think we do need PK/PD studies using various opioids, including synthetics, to get a better idea what is actually needed. And I think that they should be done not only in pediatric patients, but also in geriatric patients to get a really complete idea about the best way to dose this.

DR. BATEMAN: Brian Bateman. I voted B. I think with this question we're being asked to weigh the risks of undertreatment, which can have clearly catastrophic consequences against the potential for causing more cases of acute withdrawal by requiring

a higher dose formulation.

I think with the data we saw from the CDC showing that in 20 percent of instances, the EMS providers have to re-dose the naloxone, and a rate that's rising, suggests that there may be undertreatment with the current doses.

I'd also note that the inhaled 4 milligrams naloxone creates plasma concentrations that are 4 to 6 times higher than the plasma concentrations created with 0.4 milligrams of intramuscular injection. We're not hearing reports that there are large numbers of patients experiencing acute withdrawal at those doses, suggesting there is some safety margin to go up without causing a lot more withdrawal.

Then finally, by raising the dose threshold, it will bring it in line with the recommendations for dosing in pediatrics.

DR. SHOBEN: Abby Shoben. I voted A. As I think I said previously, I don't see the data that said that this minimum standard of 0.4 was ineffective, and that in fact there is a fair

amount of data that suggests it is effective.

I would also just add that I'm not very swayed by the argument that the repeat doses or the synthetic opioids would necessitate a higher dose. And we don't really have the data to show that's necessary, so I'd echo Dr. Winterstein's comment that we need more actual data before we raise the minimum standard.

DR. HARRALSON: Art Harralson, and I voted B, although I heard compelling arguments on both sides, and I changed my vote at least three times. Again, if the context is moving a product into the community, I'm assuming that other products are still available.

We really don't have a lot on the downside for moving it up, and there are some reasons, although not entirely data driven, that perhaps we need to be a little bit higher. I just think that the higher dose is just as safe as the lower dose.

So I would advocate for products moving into the community without expert monitoring and that sort of thing, that we have a higher standard. And

I don't think it would create any problems in the children.

DR. ZUPPA: It's Athena Zuppa, and I voted B for a couple of reasons. Unless I misheard, from what we heard from the community, it sounds like the 1 milligram per mL formulation has been used quite a bit, and there really hasn't been much side effects with that. So I think there's evidence there that the higher dose is efficacious and safe.

The other reason is that we talked about obesity, so if we're really trying to do one size fits all, given the drug is very lipophilic, a higher dose could, in theory, cover the obese patient, the normal body weight person, and I don't care that it's a higher exposure in pediatrics because I think it's warranted, except for the kids that are on chronic opiates. So I think it kind of fits the whole population.

Number 3, which is the most important for me, you can resuscitate withdrawal. You cannot resuscitate death, so death is final.

DR. BEAUDOIN: Francesca Beaudoin. I

voted B. Although I crave the data that will let us know what the minimum standard should be, I felt like given the available data, I was compelled by the argument about rural use, synthetic opioids, and repeat dosing, as was presented by the CDC.

DR. BRENT: Jeffrey Brent here. I voted B. The reason that I did that is for several reasons. I think actually today, we've heard some rather good data that the current standard is too low. We have heard data that many patients will respond to the current standard, but we also have heard data that some will not, and not an insubstantial number will not. And yes, we can repeat dosing, and possibly they will respond to the repeat dose, but once again that's probably going to give them 2 to 3 to 4 minutes of hypoxia between those doses, which can be very detrimental.

The reference dose that we're using, remember it gets us to a blood concentration of about 0.9 nanograms per mL. We know from the data that Amphastar has presented that concentrations up to about 4 nanograms per mL will require repeat

dosing more often than not, or 1.4 times on the average.

We know from the data that Adapt showed us, where they reached concentrations up about 5 nanograms per mL, that they get 99 percent responders. There is clearly a dose dependency, and clearly it levels off at about the level where Adapt is, for most cases, which is going to be in the 5 to 6 nanograms per mL range, which is 5 to 6 times higher than our current reference range.

We have not heard any data today that says that higher doses have a significant downside, other than withdrawal. And really, when we're talking about withdrawal, we expect to get withdrawal in the field. We modulate a little bit in hospital where we can control it better. In the field, we're going to get withdrawal. If we reverse somebody, we're going to get withdrawal. We're just not going to finesse it well enough, and it doesn't make a difference what the dose is.

It makes perfect sense that our current reference dose is too low. It's old. We now have

much higher potency heroin. We now have fentanyl. We now have fentanyl derivatives, including carfentanil. And the CDC has shown us that as these drugs come on the street, there is an increasing need for higher doses, i.e., higher reference plasma concentrations.

So for that reason, I voted B. I will also say that there probably is some wisdom in looking into nalmefene, although that itself will require another whole reference dosing concentration discussion.

DR. FUCHS: Susan Fuchs. I voted B, mainly thinking about the adult population and what's been said, that I think you're going to see that dark red spread all across the country and not just stay in the sort of the Appalachia area with carfentanil, and that they're going to be able to make some new meds, and we're going to need more and more Narcan in a higher dose.

DR. MAXWELL: Jane Maxwell. I voted B for the reasons already voiced.

DR. NELSON: Lewis Nelson. I voted A,

primarily because I'm not convinced that the other agents that we're concerned about, like the fentanyl derivatives, et cetera, are not going to be appropriately responsive the way we think they will be. And there are a lot of other issues associated with them in terms of the rapidity of death and the ability to get naloxone to the patients anyway.

It's a much more difficult set of circumstances than I think we're simplifying it to be. So I do think there needs to be a little bit more data to look at to compare heroin and other opioids with the fentanyls and its conjoiners.

So I don't really see that as a particular issue here. And I'm certainly not concerned about having to give multiple doses to get effect. I think even out in the community, titrating the drug does make some sense. And as I've said before, I don't think withdrawal is as benign as we consider it sometimes.

DR. WU: Victor Wu. I voted B. Again to reiterate, I agree with the comments around the

safety profile, the risk profile, given the fact with the increasing epidemic. And then the only other comment I'll add in there is just the fact that functionally now as we speak, the industry has already moved their dosages out there to at least 2 milligrams. And even in that level, there are signs from the case study that Amphastar presented that they were needing re-dosing. So again from a practical perspective, the dose itself is already higher than the 0.4 milligrams IM injection. Thanks.

DR. BROWN: We're going to move forward here. For those folks that have flights that are 6:30 or 7:00, we would like to ask, after I get through here, that you, if you could, comment on questions 5 and 6 prior to leaving us. But for folks that have flights after 7:00 or so, we're going to try to move through these. We will move through them pretty rapidly.

Is there anybody that needs to go right now and would like to give some comments on -- so Dr. Parker, could you give us some comments about

questions 5 and 6?

DR. PARKER: I think for there to be multiple dose strengths, there has to be good data to drive it. Otherwise, it's a source of confusion that could probably be avoided, so I think the 0.4 for the pediatric and adult, although I also voted that the 0.4 should be higher than that. We definitely wouldn't go below it.

But I would think a relook at it, a careful relook at it, with the consideration of raising that up to 0.6 or 0.8 as a starting point might work well for everyone. But I do not think there needs to be an army of 8 doses to choose from, especially given the data that we have now.

DR. BROWN: Okay. We're just going to talk about question 5. Anybody else that's going to -- Terry, do you have some comments about question 5?

DR. WARHOLAK: Yes. I agree with all of the comments made by the previous speaker. One of the things I was concerned about initially was that there would be some unintended consequences of

increasing the minimum standard such that the community would have lesser options. It doesn't look like that would be the case. And so given that, I believe that there should be one standard, but it should be based on evidence; although, I do think that it should be higher that what it is now.

DR. BROWN: Dr. Meurer?

DR. MEURER: Thank you. Will Meurer. I would advocate for simplicity. If different products have different doses, I think that that is okay if they're over the minimum threshold, but different doses like the junior version within a product I don't like. I want to make this as simple as possible for users.

DR. BROWN: Anybody else want to make a comment before they eject the premises?

(No response.)

DR. BROWN: If not, I'm going to read through question 5. Some sponsors have proposed marketing more than one dose strength for their naloxone products intended for use in the community. When these strengths all meet or exceed

the minimum naloxone exposure level set forth by the agency, it is unclear what factors to describe in labeling to assist health care providers in making a decision to prescribe one dose strength over another.

Discuss what, if any, data sponsors should provide to support the approval of more than one dose strength for any one naloxone product and that can provide guidance to assist clinicians in dose selection.

Any comments? Dr. Maxwell?

DR. MAXWELL: Quickly, I think this is premature. We haven't even talked about the other synthetic opioids that are out there besides carfentanil. I think we need to get some experience with the treatment of these different drugs and what are the reactions when this happens. Do we need super-super Narcan or what?

I think we've got a lot to learn about it because these drugs are now being reported on the DEA NFLIS site, but they're very little, and they tend to lag in being identified, because of what

you have to go through to identify them. The forensic guys have to wear bunny suits with helmets and everything else.

We're dealing with some drugs we know nothing about, and I think it's premature right now, because once these hit, and how many more will come in, then we can move forward on what we tell the physicians about how to dose.

DR. BROWN: Dr. Gupta?

DR. GUPTA: Since everyone left, I guess I can comment. I agree with what you're saying, that to have any increase in strengths for naloxone would be really premature. I mean I do appreciate that there's escalating synthetic opioids and that there is definitely a population of patients we need to serve, or individuals who are overdosing, that this dose may not help, but the ability to re-dose is there, but there are so many unanswered questions.

We don't know what those substances are. We don't know what populations this is occurring in. We don't know what naloxone failed

reversals -- what conditions did that happen in? Were there multiple drugs involved? There are so many variables, and to identify that, it's like a moving target.

So I think that having more strengths, which is causing more confusion for someone like me who gives opioids for chronic pain -- a clinician or a primary care physician saying, well now, what am I going to use in conjunction with my chronic pain patient who takes pain opioids just regularly every day?

Physicians are having a hard time just grappling with just prescribing opioids, co-prescribing that. And now if you add multiple strengths, I just don't know if it will be done properly.

DR. BROWN: Dr. Brent?

DR. BRENT: Jeffrey Brent. I think if we go to a higher dose of opioids as a standard, there would be absolutely no reason to use multiple doses. It's just going to be confusing, and we're not going to gain anything.

DR. BROWN: Dr. Emala?

DR. EMALA: So the question asks about multiple doses and information they give to prescribers, and I think that we're hearing that a lot of these drugs are ending up in the community through community organizations where there are no direct contacts between prescribers, with open prescription policies being distributed at community centers and so forth.

So I'm not sure that this is some sort of safety mechanism, that if multiple doses were available, that there would be informed clinicians making those recommended doses. So I have a problem with the question, assuming that there's going to be an interface of a prescriber with the recipient, when in fact many of these are going into the community directly.

DR. HERTZ: So it's Sharon here. Instead of it being directed at the prescriber, how about if it's directed at creating information in the label that anyone would be able to refer to? How do we distinguish different strengths of the same product

once it meets the minimum standard?

DR. EMALA: Yes. So I'll go back and agree with Dr. Brent. I think if you find the right dose, it's an unnecessary exercise to try to find and prescribe multiple doses. I think the lack of toxicity of the ceiling effect is a luxury in this situation, that you can go to a dose that's going to work in the vast majority of both adults and children without the need and confusion of multiple strengths and extensive education.

DR. BROWN: Dr. Nelson?

DR. NELSON: I think this is just a concept of titration. If we don't know what dose we're supposed to be giving, it's always easier to start low and go slow, right, and go up, because you can't take it back once you give it. So again, I'd rather see us create a system where we have a single dose that might be on the safer, but maybe not as effective side, and then we can re-dose it.

Again, I'm not clear that there's no efficacy to lower doses. I'm not sure it's an all or none phenomenon. But if start low and safe, we

can always give more. So I'd rather see that happen than try to go to higher doses, and then ask people to choose among a selection of unknowns.

DR. EMALA: Can I just follow up?

DR. BROWN: Absolutely.

DR. EMALA: I just have a fundamental problem with the concept of titration in the community setting, and I think a lot of the discussion has been biased by those of us in clinical medicine who live by titrating medications in the ER, or in the operating rooms, et cetera. And I think the scenario we're looking at is an addict who's passed out in an alley where another addict may or may not deliver this medication.

So I think the denominator here is very different in thinking about the complexity of dosing than what we usually bring to clinical medicine.

DR. NELSON: If I could just comment on that. You're right, although I think that the concept of titration isn't as far into them as we think is. I mean, this is how they live their

life, titrating doses to keep themselves alive, but high, if we're talking about those sorts of users, and if it's a pain patient, perhaps titrating their dose to get rid of the pain.

So the idea's not totally foreign. I would agree that titrating naloxone is going to be a foreign concept, but I think they could probably figure out that when somebody doesn't respond adequately by their determination, they can give another dose. I mean, this is unknown territory. I think it's something worth exploring further before we go out and start to do any of this, perhaps.

DR. BROWN: Any other comments before we let Dr. Hertz have the last word?

(No response.)

DR. HERTZ: I'm sorry. I was commenting. Did you ask me for the last comment?

DR. BROWN: I asked you to say whatever you want to say.

DR. HERTZ: To the hearty souls who stuck around, thank you very much. Appreciate all the

input. Very helpful today. Thank you.

Adjournment

DR. BROWN: Panel members, please take all your personal belongings with you as the room is cleaned at the end of the day. All materials left on the table will be disposed of. We will now adjourn the meeting. Thank you very much.

(Whereupon, at 5:09 p.m., the meeting was adjourned.)