FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE (NDAC) AND THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC)

Virtual Meeting

Wednesday, February 15, 2023

9:00 a.m. to 4:18 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

Maria C. Coyle, PharmD, FCCP, BCPS, BCACP, CLS

(Chairperson)

Associate Clinical Professor

The Ohio State University College of Pharmacy

Columbus, Ohio

Stephen C. Clement, MD

Associate Professor of Medical Education

University of Virginia School of Medicine

Practicing Physician, INOVA Fairfax Hospital

Falls Church, Virginia

Diane B. Ginsburg, PhD, MS, RPh, FASHP
Clinical Professor, Pharmacy Practice Division
Associate Dean for Healthcare Partnerships
The University of Texas at Austin
College of Pharmacy
Austin, Texas

Ruth M. Parker, MD, MACP
Professor Emerita of Medicine
Sr. Fellow, Center for Ethics
Emory University
Atlanta, Georgia

Paul Pisarik, MD, MPH, FAAFP
Geriatric Physician
Archwell Health
Tulsa, Oklahoma

Katalin E. Roth, JD, MD

Professor of Medicine

Division of Geriatrics and Palliative Medicine

Medical Faculty Associates

The George Washington University School of

Medicine and Health Sciences

Washington, District of Columbia

Leslie Walker-Harding, MD, FAAP, FSAHM

Ford/Morgan Endowed Professor & Chair,

Department of Pediatrics, Associate Dean,

University of Washington;

Chief Academic Officer & Senior Vice President,

Seattle Children's Hospital

Seattle, Washington

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Mark E. Dato, MD, PhD

(Industry Representative)

Retired: Director, Global Technology

Procter and Gamble Healthcare

Evanston, Illinois

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE MEMBERS (Voting)

Brian T. Bateman, MD, MSc

Professor and Chair

Department of Anesthesiology, Perioperative, and Pain Medicine

Stanford University School of Medicine

Stanford, California

Mark C. Bicket, MD, PhD, FASA

Assistant Professor, Department of Anesthesiology

Co-Director, Opioid Prescribing Engagement Network

University of Michigan

Ann Arbor, Michigan

Jennifer Higgins, PhD, MBA

(Consumer Representative)

Director of Grants

Center for Human Development, Inc.

Springfield, Massachusetts

Owner

CommonWealth GrantWorks

Southampton, Massachusetts

Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN

Professor Emeritus, College of Nursing

Founding Director, Nurse Anesthesia Program

East Carolina University

Greenville, North Carolina

Mary Ellen McCann, MD, MPH

Associate Professor, Anesthesiology, Critical Care and Pain Medicine

Harvard Medical School,

Boston Children's Hospital,

Boston, Massachusetts

Timothy J. Ness, MD, PhD

Professor Emeritus

Department of Anesthesiology and

Perioperative Medicine

University of Alabama at Birmingham

Birmingham, Alabama

Rebecca Richmond, PharmD, BCPS

Associate Chief Pharmacy Officer

Central Pharmacy Services

Duke University Hospital

Durham, North Carolina

Abigail B. Shoben, PhD

Associate Professor, Division of Biostatistics

College of Public Health

The Ohio State University

Columbus, Ohio

Michael Sprintz, DO, DFASAM

Clinical Assistant Professor

Division of Geriatric and Palliative Medicine

University of Texas Health Science Center

Houston, Texas

Founder and CEO

Sprintz Center for Pain, PLLC

Shenandoah, Texas

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE MEMBER (Non-Voting)

Jay Horrow, MD, MS, FACC

(Industry Representative)

Clinical Professor, Anesthesiology & Critical Care Medicine

Perelman School of Medicine

University of Pennsylvania

Clinical Lead, Cardiovascular Drug Development

Bristol-Myers Squibb

Lawrenceville, New Jersey

TEMPORARY MEMBERS (Voting)

Jordan Marie Ballou, PharmD, BCACP
Clinical Associate Professor
Clinical Pharmacy and Outcomes Sciences
Kennedy Pharmacy Innovation Center
University of South Carolina College of Pharmacy
Columbia, South Carolina

Jeffrey Brent, MD, PhD
Distinguished Clinical Professor of Medicine and Emergency Medicine
University of Colorado
School of Medicine
Aurora, Colorado

Elizabeth Coykendall, NRP
(Patient Representative)
Emergency Medicine, Paramedic, MHA Candidate
Urgent Care Quality, Safety, and Education Lead
PM Pediatric Care
Raleigh, North Carolina

FDA PARTICIPANTS (Non-Voting)

Theresa Michele, MD

Director

Office of Nonprescription Drugs (ONPD)

Office of New Drugs (OND), CDER, FDA

Jody Green, MD

Deputy Director for Safety

Division for Nonprescription Drugs I (DNPD I)

ONPD, OND, CDER, FDA

Dorothy Chang, MD

Senior Physician

DNDP I, ONPD, OND, CDER, FDA

Barbara Cohen, MPA

Social Science Analyst

Division of Nonprescription Drugs II

ONPD, OND, CDER, FDA

Millie Shah, PharmD, BCPS

Senior Pharmacist

Division of Medication Error Prevention and Analysis II

Office of Surveillance and Epidemiology

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. COYLE: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email is currently displayed.

My name is Maria Coyle, and I will be chairing this meeting. I will now call the February 15, 2023 Joint Meeting of the Nonprescription Drugs Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to order. Dr. Moon Hee Choi is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Coyle?

DR. COYLE: Hello. My name is Dr. Maria Coyle. I'm an associate professor of clinical pharmacy at The Ohio State University College of Pharmacy and Wexner Medical Center.

DR. CHOI: Dr. Clement?

DR. CLEMENT: Hi. Stephen Clement. I am an endocrinologist practicing at INOVA Fairfax Hospital, associate professor at UVA.

DR. CHOI: Thank you.

Dr. Ginsburg?

DR. GINSBURG: Good morning. I'm Diane Ginsburg. I'm a clinical professor in the College of Pharmacy at the University of Texas at Austin and associate dean for Healthcare Partnerships at UT Austin.

DR. CHOI: Thank you.

Dr. Parker?

DR. PARKER: Ruth Parker, professor emerita of medicine at Emory University, senior fellow, Center for Ethics at Emory.

DR. CHOI: Dr. Pisarik?

DR. PISARIK: Paul Pisarik, family physician, Archwell Health in Tulsa, Oklahoma.

DR. CHOI: Dr. Roth?

DR. ROTH: Good morning. I'm Katalin Ross. I'm a professor of medicine at the George Washington University School of Medicine, specializing in geriatrics and palliative medicine.

DR. CHOI: Dr. Walker-Harding?

DR. WALKER-HARDING: Good morning. My name is Dr. Leslie Walker-Harding. I am professor and chair of the Department of Pediatrics at the University of Washington, and adolescent medicine is my specialty.

DR. CHOI: Dr. Dato?

DR. DATO: Good morning. Mark Dato, industry representative, Nonprescription Drugs Advisory Committee.

DR. CHOI: Dr. Bateman?

DR. BATEMAN: Good morning. Brian Bateman. I'm professor and chair of the Department of Anesthesiology, Perioperative, and Pain Medicine at Stanford.

DR. CHOI: Thank you.

Dr. Bicket?

DR. BICKET: Good morning. My name is Mark Bicket. I'm assistant professor and director of the Opioid Prescribing Engagement Network at the University of Michigan, and anesthesiologist and pain medicine physician. Thank you.

DR. CHOI: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins, the consumer representative to AADPAC.

DR. CHOI: Dr. McAuliffe?

DR. McAULIFFE: Good morning. I'm Maura McAuliffe. I'm a nurse anesthetist and professor of nursing emeritus at East Carolina University Nurse Anesthesia Program.

DR. CHOI: Thank you.

Dr. McCann?

(No response.)

DR. CHOI: Dr. McCann?

DR. McCANN: Sorry. Hi. I'm Mary Ellen McCann from Boston Children's Hospital, where I'm a pediatric anesthesiologist and an associate

professor of anesthesiology at Harvard Medical School. Thank you.

DR. CHOI: Dr. Ness?

DR. NESS: Hi. I'm a professor emeritus in the Department of Anesthesiology and Perioperative Medicine at the University of Alabama at Birmingham.

DR. CHOI: Thank you.

Dr. Richmond?

DR. RICHMOND: Good morning. Rebecca Richmond, associate chief pharmacy officer at Duke University Hospital in Durham, North Carolina.

DR. CHOI: Dr. Shoben?

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

DR. CHOI: Dr. Sprintz?

DR. SPRINTZ: Hi. I'm Michael Sprintz. I am board certified in pain medicine, addiction medicine, and anesthesiology. I'm a clinical professor at University of Texas Health Science Center in Houston and CEO of Sprintz Center for

Pain.

DR. CHOI: Thank you.

Due to an emergency, Dr. Zaafran will not be attending today's meeting.

Dr. Horrow?

DR. HORROW: Good morning. I'm Jay Horrow, clinical professor of anesthesiology at the University of Pennsylvania and clinical lead physician for global drug development at Bristol-Myers Squibb. I'm the industry representative for the Anesthesia and Analgesic Drug Products Advisory Committee.

DR. CHOI: Dr. Ballou?

DR. BALLOU: Hi. Yes, Jordan Ballou. I'm a community and ambulatory care pharmacist, and a clinical associate professor in the Department of Clinical Pharmacy and Outcome Sciences at the University of South Carolina in Columbia, South Carolina.

DR. CHOI: Thank you.

Dr. Brent?

DR. BRENT: Good morning. Jeffrey Brent

here. I'm a medical toxicologist and a distinguished professor at the University of Colorado School of Medicine.

DR. CHOI: Ms. Coykendall?

MS. COYKENDALL: Good morning. Liz Coykendall. I am a 911 paramedic, working in pediatric urgent care, in Raleigh, North Carolina.

DR. CHOI: Thank you.

Dr. Michele?

DR. MICHELE: Good morning, everyone. I'm Theresa Michele, and I am the director of the Office of Nonprescription Drugs at FDA.

DR. CHOI: Dr. Green?

DR. GREEN: Good morning. I'm Jody Green. I'm the deputy division director for safety for the Division of Nonprescription Drugs I.

DR. CHOI: Dr. Chang?

DR. CHANG: Good morning. My name is Dorothy Chang. I'm a medical officer in the Division of Nonprescription Drugs I.

DR. CHOI: Dr. Cohen?

MS. COHEN: Good morning. I'm Barbara

Cohen. I'm a social scientist in the Division of Nonprescription Drugs II in the Office of Nonprescription Drugs.

DR. CHOI: And Dr. Shah?

DR. SHAH: Good morning. I'm Millie Shah. I'm a human factors reviewer in the Division of Medication Error Prevention and Analysis II.

DR. CHOI: Thank you.

DR. COYLE: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for the 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 today.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration, FDA, is convening today's joint meeting of the Nonprescription Drug Advisory Committee and the Anesthetic and Analgesic Drug Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the 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 this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

Related to the discussions of today's

meeting, members and temporary voting members of 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 the discussion of supplemental new drug application, NDA 208411/S-006, for Narcan, naloxone hydrochloride nasal spray, 4 milligrams per 0.1 milliliters, submitted by Emergent BioSolutions, Incorporated.

Narcan is proposed for nonprescription treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. The issues for discussion will be on the adequacy of the data supporting the nonprescription application. This product

represents a potential first-in-class product in a new therapeutic category for nonprescription drugs.

This is a particular matters meeting during which specific matters related to Emergent BioSolutions' supplemental NDA 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 product at issue.

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

is retired and Dr. Horrow is employed by Bristol-Myers Squibb.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms 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 the participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. COYLE: We will now proceed with FDA introductory remarks from Dr. Jody Green.

FDA Opening Remarks - Jody Green

DR. GREEN: Thank you.

Good morning, Dr. Coyle and members of the committee, as well as our guests from Emergent BioSolutions and members of the public. My name is Jody Green. I'm the deputy division director for safety for the Division of Nonprescription Drugs I,

and on behalf of the division and all of us here at the FDA, it's my pleasure to welcome you to this meeting.

Before we get started, I just wanted to take a moment to thank the members of the committee for taking time out of their very busy schedules to thoughtfully review the briefing package and to be here today. Please know that your input today is extremely valuable to the FDA, and we take your comments very seriously.

Today, we will discuss the potential prescription to nonprescription switch for Narcan nasal spray 4 milligrams. Narcan, or naloxone hydrochloride, is an opioid antagonist used for the emergency treatment of opioid overdose. Currently, it is approved as a prescription product for community use.

First, I'd like to mention the devastating public health crisis associated with the use of opioids in the United States. Opioid overdose and death can occur at all ages, including patients prescribed an opioid medication, people who misuse

or abuse opioids purposely or victims of accidental exposure. Opioid deaths are the leading cause of accidental death in the United States, and they occur most frequently in those ages 18 to 65, but they occur in children as well. Between 1999 and 2016, nearly 9,000 children and adolescents died from opioid poisonings, with the highest annual rates among adolescents ages 15 to 19.

Opioid overdoses are often witnessed by a family member or friend who has had no contact with a healthcare practitioner or harm reduction group, and that is why it is imperative to develop a naloxone product that can be used without training.

Although prescription opioid use has decreased in the last few years, illicit opioid use, particularly synthetic opioids such as fentanyl, has markedly risen. The black line shows the rise of all opioid deaths and the gold line shows the rise of deaths from synthetic opioids. More than a million people have died from drug overdose, largely opioids, in the last two decades since the CDC began collecting data. Deaths from

opioid overdose rose from approximately 69,000 in 2020 to approximately 81,000 in 2021, a rise of 17.2 percent in just one year.

Narcan was first approved in 1971 as a solution that was labeled for intravenous, intramuscular, and subcutaneous use. It's a non-selective opioid receptor antagonist. The initial indication was for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural or synthetic opioids. It was also indicated for the diagnosis of suspected or known acute opioid overdose; however, this earlier formulation of an injectable form of naloxone was not optimized for use by laypeople.

There are four FDA-approved presentations of naloxone. Ampoules and vials can be administered by injection. Naloxone can also be administered using a prefilled syringe, an auto-injector, and by nasal spray, both 4 milligrams and 8 milligrams. In 2015, Narcan nasal spray 4 milligram was specifically developed and approved for community

use, and it has rapidly become the most widely used emergency treatment of opioid overdose in the United States. This means that treatment can be administered by laypeople in community settings without the need for additional supplies or assembly before use.

Community use with prescription status is likely to be associated with some degree of training or oversight, which is different from nonprescription status. In contrast, nonprescription status means that there is no healthcare provider oversight or any training other than what is provided as part of the product labeling.

The 4-milligram dose of naloxone may be administered to all ages, including children and neonates, but it must be administered as soon as opioid overdose is suspected to reverse the life-threatening effects and to prevent hypoxic associated injury and death. This is why it is critical to develop a simple product interface to guide the user through the essential elements if

used in an emergency without any other training. Currently, individuals may obtain naloxone with a prescription from their healthcare provider. They can obtain it from a pharmacist under statewide naloxone standing orders or through harm reduction groups where they may receive training.

We want to emphasize that naloxone distribution is far greater than the typical pharmacy supply chain. There is a complex distribution chain. It is noted that naloxone products are distributed through the traditional pharmacy supply chain, which includes hospitals; clinics; retail outlets; mail-order pharmacies; health maintenance organizations; home healthcare, universities and government facilities.

In addition, naloxone is distributed in the outpatient setting outside the typical healthcare supply chain to reach those without health insurance, those who are using illicit substances who may be reluctant to seek medical care, and family and friends of opioid users. These distribution channels may include products donated

or sold directly to harm reduction programs, prisons, and other entities.

These units distributed outside the traditional wholesale pharmaceuticals distribution supply chain are not captured in estimates obtained from proprietary databases available to the FDA, which includes data from U.S. outpatient retail, mail-order, and long-term care pharmacies only.

It is important to understand why statewide standing orders are not enough to make naloxone widely accessible. We have heard from stakeholders, including harm reduction groups, that some pharmacies are reluctant to carry naloxone or find the standing orders burdensome. This can make it difficult for harm reduction groups to attain bulk purchases under standing orders.

Additionally, for some who use opioids, the stigma of opioid dependence may inhibit purchase, requiring an interaction with the pharmacist. We believe that nonprescription naloxone may help address these barriers. If naloxone becomes a nonprescription product, it may be sold in many

venues previously unavailable to consumers, including vending machines, convenience stores, supermarkets, and big box stores, just like other nonprescription products.

The FDA has responded to the national opioid epidemic and the call for increasing access to naloxone. FDA commissioner Dr. Robert Califf announced in August 2022 an overdose prevention framework, which aims to prevent drug overdoses and deaths, and includes the goal of increasing access to opioid overdose reversal agents, specifically, naloxone.

In keeping with these goals, the FDA issued a Federal Register notice in the fall of 2022, in which a preliminary assessment was made that certain naloxone products up to 4-milligram nasal spray and up to 2-milligram autoinjector may be approvable as safe and effective for nonprescription use, pending FDA review of additional supportive information and data.

If and when FDA approves the nonprescription naloxone product, naloxone products labeled as

"prescription-only" with no clinically meaningful difference from the approved nonprescription product will be considered misbranded. The notice encourages application holders of prescription naloxone products to contact the FDA as early as possible to initiate discussions about a possible switch to nonprescription status. The notice solicited comments and information from the public, and the public comment period closed on January 17, 2023. Today, we will be reviewing the data that Emergent BioSolutions has presented to determine its suitability for nonprescription status. If switched, this would be the first in class.

The first characteristic of the nonprescription product is that it must be safe in the hands of consumers and have an acceptable safety margin. The product must have a low abuse potential, and there must be little evidence of misuse. The condition being treated needs to be self-diagnosable. Individuals must be able to select the product and use it without the advice of a healthcare practitioner. In our review, we

looked for evidence that the product is likely to be safe and effective, not only by experienced users, but also in the hands of naïve users.

In this application, even though the drug and device are the same as the prescription product, it's important to understand the new supportive data we reviewed. The applicant has provided postmarketing safety data for Narcan nasal spray to evaluate adverse events associated with the use of the product. We looked at common adverse events and serious adverse events, such as precipitated withdrawal symptoms and limited efficacy, including death. We looked for evidence of misuse, medication errors, and device failures.

In addition, the applicant has provided a Drug Facts Label that was previously validated by the FDA, and then was customized with their own directions for use. Finally, they provided evidence from their pivotal trial, a human factors validation study conducted under simulated-use conditions that the user interface for the drug product is safe and effective for the intended

user, the uses, and the use environments.

In this study, they used a mock carton, where the product interface was tested in a broad group of subjects. The study was designed and performed without direct FDA input. Today, we will review the results of the study and highlight issues that might have an impact on the safe and effective use of the product.

Pertaining to the Drug Facts Label, the applicant used the model Drug Facts Label, designed by an FDA multidisciplinary team in consultation with outside experts in addiction treatment and harm reduction, who examined the prescription label and reduced it to the most essential elements required for comprehension and safe use at the time of an emergency. The Drug Facts Label was then validated by another independent team for adequate comprehension.

The FDA undertook this task to expedite drug development of a nonprescription product and to ease industry's regulatory burden. This was an extremely unusual step for the FDA to undertake.

Industry was advised that in preparing their nonprescription labeling, that the only change to the model Drug Facts Label should be adding directions and potentially improving the instruction call 911.

To sum up the issues, Narcan nasal spray efficacy as a prescription drug is well established, but what we will discuss today is the proposed design of the user interface, including labeling, for the nonprescription drug; is it optimized so that consumers will use it effectively without the help of the healthcare intermediary? Secondly, is Narcan nasal spray's safety well established? We know it's well established, but is it likely that the product will remain safe in the nonprescription setting?

This advisory committee is precedent setting, since this will be the first time we considered placing a life-saving opioid overdose emergency treatment over the counter. As such, what we're asking you to focus on, is the applicant's product, Narcan nasal spray, safe and

effective for nonprescription use, based on the product labeling, the results of the human factors testing, and the postmarketing safety findings that has accumulated for the community-use product since its approval back in 2016? Will consumers have enough information from labeling alone to guide the effective use of the product?

Before I close, I just want to mention a little framework that gives the FDA the ability to hold advisory meetings to ask for scientific advice and recommendations from experts such as yourself. As I noted previously, the FDA takes very seriously the advice of the committee; however, the commissioner does have sole discretion on actions taken with regard to drug approval, especially since there may be other issues, such as manufacturing or chemistry, that impact approval decisions that are not discussed at these meetings.

So with that, I'll stop and turn the podium back to Dr. Coyle. Thank you.

DR. COYLE: Both the Food and Drug Administration, FDA, and the public believe in a

transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the beginning of your presentation 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 presentation, it will not preclude you from speaking.

We will now proceed with the Emergent BioSolutions' presentations.

(No response.)

MR. BONNER: This is Derek Bonner with the AV support team. We are unable to hear the Emergent team at this time. If you are using your conference line telephone, you can unmute yourself by pressing star-6.

(Pause.)

MR. BONNER: Once again, this is Derek Bonner with AV support in room. This is for the Emergent conference room line. I see you are muted inside the platform. We would need somebody to touch on their keypad star-6 to unmute yourself.

(Pause.)

MR. VYAS: Okay. Hopefully, you can hear us now.

MR. BONNER: Yes, we can. Thank you very much.

Applicant Presentation - Manish Vyas

MR. VYAS: Alright. Well, apologies for those technical challenges there. I will start with my introduction.

Greetings and good morning to the committee

members, the FDA team, and the members of the public. My name is Manish Vyas. I am senior vice president and head of Regulatory Affairs at Emergent BioSolutions. For the past 30 years, I have worked on development, licensure, and the manufacture of many vaccines and therapeutics around the world, and I'm extremely happy and honored to be here today.

On behalf of Emergent, we are grateful for the opportunity to discuss our OTC switch application for Narcan nasal spray with you. We look forward to our interactions throughout the day today.

For 25 years, Emergent has delivered solutions for complex and urgent public health threats through a portfolio of vaccines and therapeutics that we develop and manufacture for governments and consumers. We are proud of our mission of protecting and enhancing life, and our work on Narcan nasal spray is part of this mission. We are focused on building greater awareness and access to naloxone.

Along with myself, I have an internal Emergent colleague and our external experts, and we plan to cover the following topics. I'll be followed by Dr. Gay Owens. Dr. Hadland, one of our external experts, will review the unmet medical need for OTC nasal naloxone, and Dr. Sarah Farnsworth from PEGUS will review our data from the Human Factors Study. I will then provide the benefit-risk overview and our conclusion.

This is the most recent graphic from the 2021 CDC data that shows we have a crisis. What you see here are the three different waves in the rise of opioid overdose deaths, and it shows the evolving nature of this epidemic. In the most recent third wave, in purple, the deaths are driven by fentanyl.

The results of all of this is that, each day, 187 people will die. This is absolutely tragic. As we think of not only the individuals themselves, but the families, the communities, the workplaces, this has profound human impact, and we are all impacted from this. So with the rise of

synthetic opioids, access is critical, and with having naloxone readily available to potentially reverse an opioid overdose, this is what brings us here today.

Overdose from opioids can lead to injury and/or death quickly if there is no immediate medical intervention. What this shows is there is a very small window between the cessation of breathing and permanent injury or death, and this underscores the need for bystander intervention in community settings.

As various stakeholders have outlined, OTC naloxone is one way to increase access and ensure that naloxone gets in the hands of laypersons for community intervention. Emergent agrees with this approach. We have a shared goal, and that is to increase access to naloxone and decrease opioid overdose deaths. We applaud the work FDA has already done to support the development of OTC naloxone and are here today to discuss Narcan nasal spray as the proposed OTC product.

Here I would like to highlight that

Rx product is the same as the proposed OTC product. Narcan nasal spray is indicated as an emergency treatment of known or suspected opioid overdose. It is intended for immediate administration as emergency therapy, and an important reminder that it is not a substitute for emergency medical care.

Over seven years of having marketed this product, we know that this product is very easy to use. It is being used by a variety of community groups, including lay individuals. It is a single, 4-milligram dose that is safe and effective. It is packaged as 2 doses in a carton to allow for a repeated dose should more than one dose be required. Administration of Narcan does not require specialized training. Inhalation is not required. Assembly is not needed. It is a needle-free and easy-to-carry presentation.

I would like to acknowledge our external experts who can provide perspective regarding the current and potential future use of Narcan to bring wealth of real-world experience as clinicians and pharmacists, and have been at the forefront of

guiding patients and communities in dealing with the opioid epidemic.

With this, I will now turn the presentation over to my colleague, Dr. Gay Owens.

Dr. Owens?

Applicant Presentation - Gay Owens

DR. OWENS: Good morning. Dr. Gay Owens, global medical affairs lead. It is a privilege to have this opportunity to discuss with key stakeholders a topic that I've been personally engaged in over the last 10 years. I've had the opportunity to increase awareness on who's at risk for opioid overdose, as well as the potential life-saving benefits of naloxone.

I look forward to our discussion today with regards to consideration of moving Narcan to an OTC status as a means to continue to increase availability and the impact it will have on the opioid epidemic and saving lives.

Let's review some brief history of naloxone. This slide shows time lines with some important milestones. The World Health Organization has

listed this on its List of Essential Medicines, which means it addresses a public health issue and has data in support of the safety and efficacy. 1966 marked the molecule being first synthesized in the U.S., with 1971, the first approval of Narcan as an injectable for use in treating opioid overdoses in the healthcare setting.

In response to increased opioid overdose deaths, kits containing prefilled naloxone injection and an atomizer enabling nasal administration became increasingly available for public use. These kits are not FDA approved. In 2014, Evzio, a community injection option, was approved by the FDA, followed in 2015 by Narcan, the first community-based intranasal spray. Since the time of its approval, Narcan has had widespread distribution and is now part of the standard of care in the treatment of opioid overdose.

Naloxone's mechanism of action, it is an opioid antagonist that competes with and prevents opioids from binding to the mu-opioid receptor sites. Once naloxone binds to the opioid receptor,

it displaces opioids and reverses their biologic effects, intending to reverse respiratory depression and help prevent a potentially fatal overdose. Because the duration of action is shorter than that of many opioids, single doses may achieve transient effects. Repeat doses may be needed to prevent respiratory depression from returning.

Naloxone has no effect on a standard dose in patients who have not taken, or are not dependent on, opioids; however, it can precipitate acute withdrawal in those who are opioid-dependent or acutely intoxicated with opioids. Based on this mechanism of action., naloxone has no abuse liability or potential for misuse.

Naloxone has a long history of safe and effective use. The product was approved as an injectable and has over 50 years of safety and efficacy data. It is now evolved over time to support community use. The initial dosing and labeling was a 0.4 to 2-milligram IM subQ IV. This is the reference range by which all naloxone

products are evaluated. The original Narcan nasal development program needed to establish bioequivalence and demonstrate there were no additional safety concerns with an intranasal route of administration.

This was the definitive PK study for the approval of Narcan. The PK study was performed to evaluate the intranasal formulation compared to the intramuscular. The primary goals were to establish the effective dose that would achieve the systemic exposure comparable to the reference range. The secondary goal was to show there was no increase in AEs due to an intranasal route of administration.

The results showed that a 4-milligram intranasal dose was equivalent to the higher end dosing range of a 2-milligram intramuscular injection. There were no serious adverse events or deaths in the PK study. This data resulted in the approval of the 4-milligram intranasal product, and the entire details of this study are in our approved prescribing information.

Broader access and availability of naloxone

is needed. Under the current distribution model, federal and state policies and regulations enable naloxone access. By adding OTC channels, naloxone can be made available to an even broader population. Despite our success with widespread community access, gaps still exist.

Since the approval of the product in 2015, Emergent wanted to ensure availability to those most at risk who are in need of naloxone in a community setting. We engaged key stakeholders, including pharmacists, community-based organizations, harm reduction, law enforcement, and departments of health.

We worked with policymakers to support legislation on co-prescribing an naloxone access goal, with standing orders to further increase the availability to those on chronic opioids, as well as family and friends, and households at risk. We recognize the epidemic has changed and that we have to evolve, and consideration of Narcan OTC is one more step in this collaboration with key stakeholders to address the needs of the epidemic.

In order for Narcan to be considered OTC, there are key criteria that need to be met. The criteria are listed on this slide: the user must be able to self-diagnose; the product is adequately labeled to drive correct use by the consumer; the benefits of increased access outweigh potential risks; healthcare practitioners are not needed for safe and effective use of the product; and there's low potential for misuse and abuse. We will walk you through these today as part of our discussion.

Since it is already approved as a prescription product with data in support of safety and efficacy, the OTC programs include elements focused on the label and use by consumer. Those included the development of our Drug Facts Label, which was in conjunction with the FDA developed model, DFL; the validation of the DFL through our Human Factors Validation Study; and real-world data to demonstrate utilization and postmarketing safety and surveillance.

I will now turn it over to Dr. Hadland to talk about the medical need for OTC naloxone.

Applicant Presentation - Scott Hadland

DR. HADLAND: Thank you so much. Just given our technical difficulties, let me know if you can't hear me.

It's really an honor and exciting for me to be here today to talk about this. The need for broadened access to naloxone is very high. A little bit about myself, I am the chief of Adolescent and Young Adult Medicine at Massachusetts General Hospital and Harvard Medical School, but I want to clarify that today I'm presenting as an independent expert who practices in pediatric addiction medicine and in public health, and the views I'm presenting today don't represent necessarily those of my employers.

I also want to highlight that as a researcher, I receive research funding from the National Institute on Drug Abuse, the Patient-Centered Outcomes Research Institute, and the U.S. Centers for Disease Control and Prevention, and want to clarify today that none of these funders had any role in my decision to

present or in the preparation of these slides today.

I want to share just a few more details to build on what's already been mentioned about the scope of the U.S. overdose crisis. As somebody who practices in a clinic, taking care of adolescents and young adults, really, between the ages of about 13, all the way up to 30, this has become very central to my work. I've lost patients over the years and have watched as many families that have been devastated by this rising, worsening, and skyrocketing overdose crisis.

Just to put things into context, more than a million overdose deaths have occurred since the turn of the century, and we're now at a point where in the year 2021 alone, there were more than 100,000 overdose deaths. This is the highest annual death toll ever recorded, and this is, as we've heard, a little bit driven by increasingly potent opioids in the drug supply, including fentanyl.

What you can see in this figure, which

represents the most recent full-year data that we have available from national statistics, you can see that, really, overdose deaths have been rising from any opioid, but have really skyrocketed, driven by this darker blue line which is synthetic opioids other than methadone, and this is the category that includes fentanyl. This rising has actually accelerated even more over 2020 and 2021, years that, as we all know, have been greatly impacted by the COVID pandemic, which caused a lot of social isolation and really contributed to an inability of people to access life-saving medications like naloxone and addiction treatment.

I want to highlight what's going on in the age group that I really care for, and this is young people. This was so nicely mentioned in the presentation by Dr. Green, who highlighted that children and adolescents have not been spared from this national crisis. These are data on teenagers aged 14 to 18 from across the United States, and the skyrocketing overdose deaths that we just saw in the last slide is really reflected in young

people.

This figure shows overdose deaths in teenagers ranging from 2010 to 2021, and what you can see is that, again, with the onset of the pandemic, there's just this enormous skyrocketing in fentanyl-involved overdose deaths. Actually, now we're at a point where fentanyl is involved in 5 out of every 6 of all teen fatalities across the United States, which are at an all-time high.

To further drive this point home and highlight the extent to which young people have not been spared by this crisis, and the extent to which they really need to be thought of as we think of solutions to this crisis, including naloxone, opioid misuse begins early in life. Two out of every three adult individuals who are in opioid addiction treatment report that the first time that they used an opioid was before age 25, and 1 in 3 report that the first time that they used was before age 18.

This bottom figure shows national high school survey data that depict the percentage of

teenagers who by the end of high school report that they have used an opioid during their lifetime for non-medical purposes; so they're not using it as part of a prescription. There are a few important things to glean from this figure. The first one is that, yes, opioid misuse is actually at an all-time low right now. It actually has declined quite nicely since 2011 when it was at its peak. But even if you examine this figure that seems to have a reassuring trend, and you pause, and you think about what the numbers looked like in 2020 just before the pandemic started, what you can see is that about 1 in 19 students reports ever having misused a prescription opioid or an opioid more generally, and that's about 1 to 2 students in a typical high school classroom.

So that really demonstrates the extent to which opioid misuse is a widespread problem; that if you multiply it across the many classrooms that are across the United States, it just demonstrates just how much risk there is right now, and I would anticipate that these numbers are going to go back

up again as we see teens interacting again with their peers and having access to substances again.

We've talked a little bit about this, but I want to be crystal clear about what's going on among everybody that may be purchasing drugs off of the drug market, but in particular in a way that is very risky and puts teens at a particular vulnerability; that is that there are an incredibly high number of counterfeit pills in the illicit market right now.

The Drug Enforcement Administration estimates that at least 60 percent of pills being sold in the illicit market are counterfeit pills that contain potentially lethal doses of fentanyl. These figures here demonstrate, side-by-side, real prescription pills with their counterparts that contain fentanyl. This left panel shows oxycodone. The top two pills are real oxycodone and the bottom two are counterfeit oxycodone that contain fentanyl.

This middle panel is Adderall. The top of these two pills are real Adderall and down below

are counterfeit Adderall that actually in this case contained methamphetamine, and then the far right shows Xanax. So the left white tablet here is real Xanax and the yellow tablet immediately next to it is counterfeit Xanax that, again, contains fentanyl, potentially in a lethal dose.

Increasingly, fentanyl isn't just in counterfeit pills, but it's also reported in other drugs that are in the the drug supply, including illicit cocaine that's being sold, MDMA or Molly, and methamphetamine. The result here is that people all across the United States -- and in particular, young people -- are being exposed to highly potent, highly lethal fentanyl without their knowledge, and often this is occurring among individuals with little to no prior exposure to potent opioids, meaning they don't have a tolerance, and when they have a high dose of fentanyl, they're at extremely high risk.

What is the explicit role for naloxone here? Well, let me just trace some important bullet points here that I think will help us to understand

where naloxone fits in. People who overdose usually are found unresponsive in their usual settings, meaning at home, at work, or in public, and emergency care, which really needs to include opioid reversal with naloxone, and respiratory support is absolutely critical to survival.

Naloxone is safe, it's effective, and it's easily administered, including by young people, who I observe use it in my own clinical practice, but on the other hand, many people who use opioids, either intentionally or unintentionally, if they're exposed to them in the drug supply as we just discussed, without their knowledge, are unaware of naloxone and its use or they don't have immediate access to it. So we really need to do a lot to improved access and increasingly normalize the use of naloxone for people who might be exposed to opioids.

I want to talk a little bit more about the context of teen overdoses again because they have been hit particularly hard by the fentanyl crisis. Recent data from the Centers for Disease Control

and Prevention highlight that most overdoses of teenagers occur at home. Two-thirds of the time, there's actually someone else in the home who could have responded, but the teen died, and that person did not respond. Sixty percent of the time, the teen is pulseless by the time EMS arrives, and often it's EMS who shows up and gives the teen their first access to naloxone. In fact, national data highlight that naloxone is given in fewer than 1 in 3 teen overdose deaths.

So there is a huge gap here, where there is an enormous need for opioid overdose reversal, and yet naloxone is not getting to the places that it needs to be. So in my expert opinion, ready availability of naloxone in U.S. households could avert numerous, if not many, overdose deaths that are currently occurring on a daily basis right now as we meet.

Broader access to naloxone is needed for everybody, and in particular, for young people. Programs that increase community access to naloxone and information on how to use it have been shown to

save lives, and this has been a story that has developed here in Massachusetts, which really works to get naloxone into its communities to try to address the rising number of overdose deaths.

But many individuals whose lives could be saved by naloxone don't have access to it or don't have awareness of it. This includes people who use drugs, who experience stigma and may be afraid to go to a healthcare provider and ask for a prescription for naloxone. People without medical insurance or without primary care don't have access to doctors who can prescribe naloxone for them. And then young people and family members that I meet every day, who are afraid of opioid overdose and are worried about it in young people, have no idea that naloxone is out there. So again, we need to destigmatize and normalize the use of naloxone, and make it widely available for all people who can benefit from it.

And why now? Well there's, as I've highlighted, just enormous urgency due to fentanyl. This widespread infiltration of fentanyl into the

drug supply is new, and this needs new approaches. And as I said, many people who are exposed to fentanyl are exposed without expecting it because they've used a counterfeit pill that they thought was actually a prescribed pill, or they're using another drug that is not an opioid, like cocaine, but it's laced with fentanyl, and they get exposed.

Increasingly, there are second-hand exposures that are also rising. We're seeing rising overdose deaths among toddlers who are coming across fentanyl in public settings, or fentanyl that may be elsewhere in the home. Individuals who knowingly use opioids, which is another important population that we need to deliver services to, are our now at higher risk than ever, given the variable potency of fentanyl in the drug supply. They may be seeking to use fentanyl but may not want highly potent opioids, and and can be surprised at how potent the opioids that they use are, and we need to deliver services to them as well.

I'll just tell you what patients, families,

and community members that I talk to every day tell me. Once they know about naloxone, they want it. So parents tell me, and I tell parents back, that naloxone is like a fire extinguisher. It's this thing that you want to have in your home for safety, and you hope never to have to use it, but you want to have access to one so that when you need it, it's right there.

But unfortunately, for most young people, families, and community members all across this country, current avenues of access are challenging. The current access that my patients have to get naloxone are that they get a prescription, but whereas I'm a provider who feels comfortable and knowledgeable about prescribing naloxone, many other pediatricians don't know about naloxone, or they don't know how to prescribe it, or they don't know how to talk to a young person about its careful use. So putting a prescriber between a person and their access to naloxone creates an unnecessary barrier.

Standing orders are present in many states,

including my own state of Massachusetts, but this requires people to go into a pharmacy with discretion left to the pharmacist about whether to dispense it, and the pharmacist may not know about the standing order, or one thing that I've observed in my own practice is that young people will go in, ask for access to naloxone as a standing order, and the pharmacist will say, "Oh, this isn't allowed for young people," which is actually an incorrect understanding of the policy. So again, having discretion left to the pharmacists, another healthcare provider here, creates a new barrier to accessing it that naloxone over the counter would overcome.

Then there are community distribution programs. Many of them are here in Boston, they're present all over the United States, but they really require a consistent supply and consistent access to naloxone, and that can sometimes run out. They're mainly available for people who are known to use drugs, and this isn't helpful for the young people and families who I work with, who want to

keep themselves safe but don't go to community-based programs that are meant for people, largely adults, who use substances heavily. Those services are critical for them, but young people aren't going to use those, so again, this is an unnecessary barrier.

I'll highlight as a final editorial point that the fact that we already distribute naloxone in the community to so many people actually demonstrates just how safely and effectively it's already being used without healthcare providers acting as a gatekeeper. Then I want to highlight as a final piece that many people avoid many of these settings because they are worried about stigma and, again, increasing access to naloxone and normalizing it can help to overcome that stigma.

Again, just let me explicitly state at the very end here what over-the-counter naloxone offers. Well again, layperson use of naloxone is safe and effective, and it's already happening across the United States through community-level

distribution. Over-the-counter availability will help people who are currently unable to access naloxone, and because opioid deaths have been climbing in all age groups and the benefits of naloxone are not age-dependent, I really want to make sure that as we make sure naloxone is increasingly accessible to everybody, it's in particular accessible to adolescents and family members who might, in my view, benefit most from its over-the-counter availability because they can't currently access it through other means.

Yes, instruction on the safe use of naloxone will be needed, and offering this education along over-the-counter naloxone availability is critical, but in my view, it will actually help to battle the stigma that I so often see in my own practice. Thank you so much.

Applicant Presentation - Sarah Farnsworth

DR. FARNSWORTH: Good morning. I'm Sarah Farnsworth, vice president of Scientific Affairs at PEGUS Research. This is a contract research organization that conducted the Human Factors Study

using the Narcan OTC labeling, and I was the principal investigator overseeing this study. My educational background and training is in neuroscience, and specifically the neuropharmacology of various drugs of abuse, so I'm particularly excited about the opportunity to be involved with such an important effort.

As mentioned earlier, the proposed OTC Narcan nasal spray device is identical to the prescription device, which was thoroughly assessed in human factors testing for prescription approval. Those studies, of course, demonstrated that the use-related risks were acceptable, and that laypeople could successfully administer Narcan nasal spray. Thus, the focus of the Human Factors Consumer Study was to assess if the proposed OTC labeling could appropriately guide correct use of Narcan in a simulated overdose emergency.

Ordinarily, an OTC switch program would consist of multiple consumer behavior studies. Label development is an iterative long process, but we're lucky; because of the public health

importance of naloxone, in an unprecedented step, the FDA developed a model DFL, as mentioned, and conducted its own pivotal label comprehension study to confirm the model DFL. You can see the study was published in the New England Journal of Medicine.

This is a snapshot of the proportion of participants who comprehended each key label message, which FDA will present in detail. The study demonstrated that information on the model DFL was well understood by a large, diverse group of consumers. Following that study, as Dr. Green mentioned, FDA specified that sponsor should utilize the model DFL and only update and test product-specific directions as needed, based on their own individual product. Since Emergent adopted the model DFL, additional label comprehension studies were not required, and only a human factors study was needed to verify the effectiveness of the DFL to drive appropriate use of Narcan nasal spray and evaluate any use-related risks.

Again, only the directions for administration in step 2 of the Narcan Drug Facts Label were modified from FDA's model label to be more product specific. Because these directions are product specific and represent the critical procedures to correctly administer Narcan, the three tasks listed as bullet points in step 2 for the primary endpoints tested in the study.

There's no formal hypothesis testing in the study, as is typical for consumer behavior studies; however, each of the primary endpoints was assigned to target performance standard or threshold, and these are based on the assessment of the clinical risk if the task is not performed correctly. In order to achieve these performance standards, the lower bound of the two-sided 95 percent confidence interval for each primary endpoint finding should meet or exceed the associated target performance standard.

A single secondary endpoint was also assessed in the study, which was a composite measure of the proportion of participants who

correctly completed both tasks 2 and 3 under step 2, which together are the most critical steps in administering Narcan. Task 1 was not considered in this composite endpoint calculation for the same reason. It was assigned a lower target threshold because it's possible to hold the device incorrectly but still successfully administer a dose by pressing the plunger firmly in some other way. This endpoint was presented descriptively, as the joint probability of success for composite endpoints is directly and inversely related to the number of discrete performance measures that are included.

All other steps on the proposed Drug Facts Label are from FDA's model DFL and are not specific to Narcan and were assessed as descriptive endpoints. These endpoints included the key subtasks in steps 1, 3, 4 and 5 that could be observed or verbally described in the human factors demonstration and are highlighted in yellow.

One point of clarification about how the study endpoints are calculated is related to the

nuances of some of the label directions. In OTC human factors studies, our experience shows that often some people naturally default to explaining procedures to demonstrate or show their understanding of specific tasks they feel might be harder to act out physically in a research setting or in a simulated-use setting; thus, correct verbal descriptions were considered in some endpoint calculations. Therefore, correct simulated use takes into account the number of participants who adequately performed each task or verbally conveyed a clear understanding of the task.

Those who did not demonstrate a task correctly were asked standardized label comprehension questions to assess their understanding of the label direction, and correct responses were included as acceptable in endpoint calculations. Endpoint findings presented later are calculated as percent correct in their action and percent acceptable in comprehension for the overall endpoint result.

I'll now provide a high-level summary of

study methodology. The study was designed in accordance and with the FDA guidance documents in mind for both the human factors studies and the label comprehension studies. Human factors guidance recommends a sample size of 15 participants per expected or intended end-user group, which in this case would equate to an anticipated sample size of 60 completed interviews. Both the inclusion/exclusion criteria and the user groups recruited for the study were modeled after FDA's label comprehension study, including an overall target of 30 percent low literacy, and the study protocol and all materials were reviewed and approved by an independent IRB.

The study was conducted in four different geographic areas in the U.S. in March 2021, so strict COVID protocols were required to ensure participant and staff safety. Study participants were recruited by the research sites from the surrounding local areas, and social media and digital advertising were also utilized. Community outreach groups and clinics were also enlisted to

help with the recruiting effort.

Once the participants arrived on site, they were re-screened for qualification criteria, and informed consent was obtained. Parents or legal guardians were required to be present with their participants under age 18 to provide consent, and adolescent participants provided their assents. Literacy was then assessed using the Rapid Estimate of Adult Literacy in Medicine, or the REALM test, for adults ages 18 and over, and the REALM-Teen was used for all participants under the age of 18. These brief validated assessments enable us to classify participants as having either normal or low health literacy.

The interview began with minimal introduction or directions to maintain as much realism as possible for the simulated overdose emergency. Separate room at the research site was set up to simulate the experience of walking in to discover a family member, represented by a mannequin, who is in bed and unresponsive, then action-adventure movie playing rather loudly in the

background, and the same scene of that movie was utilized for each participant. This helped create distraction and stress in the environment, and contributed to the naturalism of the simulation.

An OTC carton of Narcan nasal spray containing two water-filled devices was on the nightstand in the room. Participants were told to -- this is a quote -- "use the package directions to physically demonstrate how you would use the product to treat your family members in a real overdose emergency," and they were informed that they verbally describe what they were doing as they completed the demonstration, if they wanted to. No training or prior exposure to the labeling was provided.

Trained interviewer was in the room carefully observing participant behavior and documenting if each step on the Drug Facts Label was performed correctly. Interviewers were trained to observe only and not intervene or answer questions once the simulation had begun, other than a few standardized scripted prompts within the data

collection instrument.

After the demonstration, standardized label comprehension questions were asked to assess comprehension of any directions that the participants failed to perform correctly, and this helps us assess whether the participants did comprehend the instruction but perhaps failed to perform it correctly because of other factors less related to the labeling, like being in a research setting or other personal cognitive factors like embarrassment, or if they truly did not notice or understand the label direction.

After the conclusion of the interview, debriefing questions were then asked to gather participant feedback about any steps they did not perform correctly or comprehend. After the interview, a second independent reviewer viewed the recording to also classify correct or incorrect performance. Any discrepancies between the on-site interviewer and the reviewer were then resolved by a third independent reviewer, and all reviewers were experienced clinical study monitors.

The study enrolled a diverse group of consumers and potential users of intranasal naloxone. Seventy-one participants were interviewed, which is a typical range for human factors studies. Approximately 30 percent of the sample qualified as low literacy after additional recruiting efforts were conducted to enrich the sample in order to meet the literacy target.

All user groups were represented, including adult all-comers or a general population of adults; general population adolescents ages 15 to 17; adults who report recent use of opioids; and then adult associates, which are friends, family, caregivers of a person who uses opioids. Again, these groups were modeled after the groups used to validate the model DFL.

Demographic characteristics of participants were diverse. The average age was 40, and the range was 15 to 76 years of age with really good representation of racial and ethnic minorities and those toward the lower end of the socio-economic spectrum. Lastly, three-quarters of study

participants were completely naïve to naloxone prior to the study and reported that they had not even heard of naloxone before they participated.

The proportion of participants who demonstrated correct or acceptable performance on each primary endpoint task is shown here, along with a two-sided 95 percent confidence interval and the target performance threshold assigned to each endpoint. It's important to note that 95 percent confidence intervals are, by definition, wide in studies with relatively small sample sizes that are customary and expected for human factors assessments.

Both primary endpoints 1 and 2 exceeded the target performance threshold. The lower bound of the confidence interval for primary endpoint 3 fell just short of the target; however, it's noted that 94.4 percent of participants did perform this step adequately, which equates to just 4 participants who were classified as incorrect for this endpoint.

Primary endpoint results for subgroups of interests are presented here. Of note, all low

literacy participants and general population adults performed each subtask in step 2 correctly. It's very rare to see all low literacy participants outperform normal literacy participants, so that's quite remarkable. Two of the four participants who were classified as incorrect for at least one of the primary endpoints were adolescents and two were adults in one of the opioid cohorts.

The results for the composite endpoint were identical to primary endpoint 3, with the same four participants not in the numerator for this endpoint. Again, no target performance thresholds were assigned for secondary and descriptive endpoints.

These are the results of the first two descriptive endpoints, which are the steps taken directly verbatim from FDA's label presented here, and you can see that a majority of participants performed quite well. One point to call out is that all but one participant simulated or described calling 911. Label directs this was done immediately after giving the first dose of Narcan

nasal spray, and most who were scored as incorrect on this subtask actually called 911 prior to giving the first dose.

A couple of participants appeared to have done this by instinct as part of the simulation, and others did that because they happened to start reviewing with the DFL at step 3 on the back panel of the carton before turning to the side panel to see steps 1 and 2. There was one instance of a participant reviewing the wrong panel that did lead to a delay of approximately 50 seconds before he called 911.

Step 4, the majority of participants waited 2 to 3 minutes prior to giving the next dose and verbally stated that they would wait 2 to 3 minutes to give the next dose even if they did not actually pause for that length of time in the simulation. Participants did very well in understanding and then following the directions to give a second dose, if needed. Ninety-three percent of participants said they would wait for emergency services and understood that direction.

While the second part of step 5 did not test as high as one would expect or presume on the surface, this is actually an artifact of the study related to the fact that the box contained 2 doses and participants had already administered the second dose in step 4, so many did not think to mention giving additional doses past that, if needed. And again, participants did understand and follow this general idea of giving additional doses, if needed, in step 4, and this message also tested very well in FDA's Label Comprehension Study.

To summarize, this study utilized a simulated overdose emergency that was in a lot of ways the worst case scenario for the simulation in that participants received very little instruction from the beginning about what was expected of them, they had no exposure to the Drug Facts Label prior to entering the overdose simulation, and a majority of participants had never even heard of naloxone prior to the study. Two of the three primary endpoints exceeded the predefined target

performance thresholds, with the third falling just short; but this, again, represented just 4 of 71 subjects or 5.6 percent.

In conclusion, the results of this human factors study indicate that the proposed OTC labeling for Narcan is sufficient to guide correct administration by a diverse group of potential intended users in an OTC setting, including adolescents and those with lower literacy skills.

Thank you very much for your attention, and I'll now turn the presentation back to Dr. Vyas.

Applicant Presentation - Manish Vyas

MR. VYAS: Thank you, Dr. Farnsworth.

Before I talk about the benefit-risk topic, I would like to clarify briefly about the OTC packaging and the QSG. We had several discussions with the FDA and have proposed adjustments that should address FDA's request, and I will cover this later in my presentation.

With that, let's go to the next slide, please. As Dr. Owens noted earlier, there's over 50 years of history with the use of naloxone, and

our postmarket safety data, with 7 years of community use, further supports the safety of Narcan. Let me preface by saying that the safety overview may be different from or rather differ from what you are used to seeing, and that is based on that naloxone has a well-established safety profile; then the safety data we see for Narcan are consistent with what we see with the use of naloxone and what is already described in the product label.

The overall rate of serious adverse events is low. It is less than 1 per 100,000 doses distributed. The rate of medication error or misuse reported to Emergent is also low. Device failure is also reported very infrequently. Any product complaints that we receive that may be related to the device issue are investigated really thoroughly, and to date there have been no device reportable events identified.

Since the product launch in 2016, there have been a total of 1,078 event reports for 473 individuals or cases. The table provides a

list of events that are greater than 2 percent out of the total 1078 events, and these reports are consistent with what we've been seeing from the FDA, FAERS, and WHO Vigibase databases as well. So when we compare this 1078 safety events with 44 million doses distributed, the overall rate is very low.

So I do want to acknowledge that there are limitations that affect postmarket surveillance, and there's likely more underreporting of these events given the nature of this particular product. However, the greater majority of these adverse events reported are systemic symptoms that would be expected, and that is with the reversal or withdrawal of effects of opioids, and it is with low severity, and this is consistent with the use of naloxone.

As we just saw that the precipitated opioid withdrawal is an expected finding and it is a manageable risk, a few things that I'd like to highlight is that drug withdrawal is a known risk associated with naloxone, and it is reflected in

the current Rx and also the proposed Narcan OTC labeling. The severity and duration of the withdrawal syndrome are dependent on the type of opioid and the dose of naloxone that's being used. So while these opioid withdrawal syndromes are uncomfortable, these symptoms are generally not life-threatening, they are transient, and subside within about 2 hours. The rate of acute withdrawal syndrome with the serious outcome is low. Overall, the benefit of naloxone use and the risk of opioid withdrawal symptoms outweighs the risk of respiratory depression and possible death due to no treatment.

Shown here are some additional safety considerations. Based on the published data from a study among people who use heroin, there was no evidence of increased compensatory drug use following naloxone use and overdose training. Through community distribution programs, there's also been no evidence of increased risk, and as we all know, naloxone is not a controlled substance, and it has no effect on someone who does not have

any opioid in their system. As we have shown from the postmarket data, the medication errors and device failures are very low, and the potential for misuse is also very low.

Now I want to recap the data that we have presented and that demonstrates Narcan is suitable for OTC use. Our Human Factors Validation Study demonstrated that consumers can be directed only by the Drug Facts Label and without the need for specific training. Our package design as tested in the Human Factors Study successfully passed the Human Factors Study requirements.

Additionally, I want to highlight here in these images that you see that these are our proposed updates to the OTC carton and a proposed update to -- or rather an addition of a Quick Start Guide, and this is based on our discussion with the FDA leading up to this advisory committee meeting. The proposed new carton box is larger, but it allows for all five Drug Facts Label steps to be on one back panel as FDA has requested. These two items represent updates to what we have already

demonstrated by a successful human factors study and will further support what FDA has requested.

Narcan has been designed for community use in that laypersons are able to administer Narcan safely and effectively until the emergency services arrive. The label comprehension and the Human Factors Study demonstrated that laypersons are able to diagnose and use the product based on the proposed label.

What we have shown is that Narcan is safe and effective, and it is supported by prior clinical data, literature, and further confirmation of data from the community use. Overall, the benefit-risk profile is favorable and supports Narcan as the OTC product.

So in conclusion, we have just demonstrated from the data that we have presented today that Narcan nasal spray 4 milligram fulfills the criteria for "OTCness" and meets all the OTC requirements. At this point, I would like to thank the FDA and the committees for this opportunity, and we look forward to your questions and the

discussions. Thank you very much.

Clarifying Questions for Applicant

DR. COYLE: We will now take clarifying questions for Emergent. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and to direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of any follow-up question with. "That is all for my question," so that we can move on to the next panel member.

We will begin with Dr. Higgins.

DR. HIGGINS: Thank you very much. My question is for Dr. Farnsworth or Dr. Vyas regarding the Human Factors Study, validation

study. I believe it's page 6 in the sponsor's briefing document, where there's reference to changes made to the product labeling. This was done in conjunction with the FDA, according to the sponsor, but I'm wondering about the reasons for the changes in addition to what was explained today.

Was there something useful learned during the Human Factors Study that impacted the choice of the intent to market labeling? Thank you.

MR. VYAS: Manish Vyas, and thank you, Dr. Higgins, for that question.

Yes, essentially, from the Humans Factors Study, as Dr. Farnsworth presented, we did learn about step 3. With regard to that step was the position, as one of the first steps on the back panel. What we decided to do was actually move that to the side panel instead of the back panel, and move the steps 1, 2, and 3 to the back panel, a proposed approach and what we submitted to the agency. That was based on the Human Factors Study information that we generated.

Let me also ask Dr. Farnsworth to see if there is anything additional she would like to add.

DR. FARNSWORTH: Thank you.

Yes, that's correct. The proposed changes to the label in the briefing book, in the intent-to-market carton that you have in your briefing book, were based on the Human Factors Study, and primarily the issues with some folks going directly to step 3 on the back panel, as was just mentioned. So this was a proposed mitigating change. It seems to be perhaps more instinctual for some participants to flip the box over and look at the back panels first.

Again, while some participants did this, a lot of them reoriented themselves, figured it out, and quickly started with step 1, but because some started the demonstration, that's why some folks called 911 first before proceeding to step 1. Again, not to jump ahead, but that would be mitigated by this intent-to-market configuration, but even further mitigated by the proposed vertical display that Emergent is negotiating with the FDA,

where all steps 1 through 5 are in a vertical, top-down order.

DR. HIGGINS: Thank you. That's all for now.

DR. COYLE: Thank you.

Dr. McAuliffe?

DR. McAULIFFE: Yes. Maura McAuliffe, East Carolina University. I believe this question would be for Dr. Farnsworth. I'm looking at the briefing documents, and on page 22, I noticed -- and this wasn't in the slides -- that the participants in the Human Factors Study were allowed as much time as they needed to review the mock packaging prior to initiating their response.

That really wouldn't be very realistic, and it was a simulated environment, I understand. But did you collect data on how long participants did take to respond after reading the DFLs and the packaging to initiate their response, and can you share that data with us? I think it is important, whether it's 30 seconds or 4 or 5 minutes. Thank you.

DR. FARNSWORTH: Thank you for your question. Sarah Farnsworth, PEGUS Research. That's a very good point. We compiled these data after they were in study report, but we have these data available for you today.

Can I get a slide 10, please? You can put that slide up on the screen.

The study report I think included one sentence in a spot that said they were allowed to review the label as long as they would like to. They weren't necessarily told that, though, so it's sort of unfortunate phrasing. They were told to use the product packaging to administer the product to their family member, and then they were asked to begin.

So in those circumstances, on average, participants administered the first dose quite quickly. You can see here that 1 minute 16 seconds was the average, and the range was 22 seconds up to 164 seconds, the longest time to first dose, and over 70 percent of all participants gave the dose within at least a minute and a half.

That one and a half minutes includes the time it takes to open the package itself if the box was unopened; try to wake the person in step 1; open the carton; retrieve one blister pack; open the blister pack; and then hold the device and prepare to administer. We didn't tell them to rush, but we didn't say take all the time that you need either. We just asked them to review the labeling and begin, in the introductory script prior to the participant entering into the room and the simulation.

DR. McAULIFFE: That's very helpful. Thank you very much. I have no further questions.

DR. COYLE: Thank you.

Dr. Clement?

DR. CLEMENT: Thank you very much. Can you hear me?

(No response.)

DR. CLEMENT: Oh. Here, I'm reading it now, too. So if you can nod yes if you can hear me, that's great. I appreciate it.

I have three questions. The first is

related to Dr. Vyas or any of his team. It's relating to the storage of this product. We're going from an OTC, which is generally -- I mean, we're going from a prescription, where generally it's kept in the pharmacy or there's very clear description to keep at room temperature, et cetera, and so forth. I noticed in the product description that it's stable up to 104 degrees, but I'm thinking, if this is going to be over OTC and it's going to be kept at the work site, there are a lot of work sites that can be quite hot. It may be in a parent's car, in the glove compartment of the car during the summertime.

So my question to you is, do the labels need to be changed? I know there's only so much space on the outside of the label to put things on, but is this a concern to the company? And I'll also address this to the FDA, that as it's rolled out to OTC, this drug can be rendered inactive in an unexpected way when it's kept in these unusual environments.

The question was to the team, Dr. Vyas.

MR. VYAS: Yes, Dr. Clement. Let me tell you, this OTC product is essentially identical to the approved Rx product, and that is actually used and distributed in the community-use settings. So the scenarios you described are pretty common, and we know this from the last seven years, where this product has been distributed, and we know that people keep it in all different kinds of environments.

We do have the data that supports all of the different temperature conditions and some excursions to a higher temperature, and that is on the the boxes as well, in terms of the storage. So there is nothing different between the Rx and then this particular presentation on the OTC. We often get additional inquiries and calls, depending upon the users, and we address those as well. But we're certainly open for any of the thoughts from the FDA, it's part of the review, but this won't be any different from how it's been used so far.

DR. CLEMENT: Okay. That's great.

I have a couple of questions for Scott

Hadland. Being a practitioner, I'm in the trenches all the time, as well as you are, so I had a couple of questions for you in terms of how you would suggest for implementation. Some of the other ideas that came up in my mind if it's rolled out to OTC, first, is keeping 2 doses enough? I mean, we're talking about fentanyl being laced. You talk about fentanyl-laced drugs, fake drugs, that one dose can lead to incredibly high levels.

In your expert opinion, having two drugs in a package, is that enough to to meet that demand?

DR. HADLAND: I think it's a great question. The majority of overdoses are still reversed with a single 4-milligram dose of naloxone in most circumstances. I think the teaching that typically goes with naloxone administration is that step 1 is to administer naloxone and step 2 is immediately to call emergency services. Administration of naloxone doesn't preclude the need for further medical attention, and that folks should still reach out.

I do think that two per kit has been what we

have come to understand, and come to study, and come to become comfortable with in the last many years that we've had access to this product, so I think that having a kit with two is a natural extension of that. Again, certainly this could be a question to be explored further on down the road; whether, through research, if having more access to more sprays in a kit could be helpful.

DR. CLEMENT: Okay. Great.

The other question -- you're not off the hook yet. Being the clinician, there are a couple of things that came up with me.

I've been in a situation of being a first responder, either family members or people in the neighborhood, and stuff like that. Basically, going from prescription to OTC, from the FDA standpoint or from a practitioner's standpoint, we're asking this passerby to be a first responder. Is there enough information on the product label and in the context of the situations that you see, that other forms of coma need to be explored?

I mean, the first one I'm thinking of, being

an endocrinologist, is could it be hypoglycemic in a diabetic kid that's sitting in the bathroom? A lot of these things I'm seeing on the news is that there are no pills around. There's no context that this person ever even took a pill. It was given to them in the bathroom, in the school, or the gym, or whatever. Is this something to think about; is that while the person's waiting for the drug to work, should they look for an ID bracelet, something on them to say, "Okay. Could they be diabetic? Could they have a seizure? Could they have other things?"

So basically, as a physician, we're teaching these people to be first responders, and to go through a differential diagnosis; and your thoughts on that.

DR. HADLAND: Yes, I think it's a good question. I agree. We want to make sure that people are being thoughtful when they respond, and that's why, again, I think the education that goes along with distribution of naloxone is so important, and why with an over-the-counter

availability, we still need to make sure that that education is taking place because, I think you're right, there are other causes of coma, for example, and we want to make sure that, again, just as I mentioned a moment ago, when someone is giving a dose of naloxone, the next step is that they're contacting emergency services just in case there is another cause for a young person or whoever it may be has become unresponsive.

I think the other thing that I would add -- I'll stop there. I'll stop there.

DR. CLEMENT: Okay. Then the last question for you, or anyone, is the legal ramifications. My wife's a lawyer. She's always asking me about things like this. I know this was not the official responsibility of the FDA -- this is more public policy issues -- but for most states, there are Good Samaritan laws to protect the passerbys.

If that's not on the label, or if there's not enough education for people to understand that, would that prevent them from actually responding? I've heard lots of situations, whether it's on the

metro, on the tarmac, or whatever, people are afraid to intervene because they're afraid that they could be held responsible if something happens.

I'm just interested as a practitioner. Have you seen any situations like that, where the person that could have helped did not help because they weren't aware that they're immune from legal efforts?

DR. HADLAND: Yes. I certainly have seen that, and actually not as a clinician but just as a person living in the city of Boston, where we have a number of people who overdose. I've been on the scene of overdoses and seeing how folks respond and, yes, sometimes people don't know what to do. They are afraid to intervene. I think part of making naloxone available over the counter is, again, to make it widespread to normalize its use as something that we want to make available in emergencies, and to really kind of battle the stigma and worries that people have about intervening in these moments.

This is an unprecedented time, where more than 100,000 people are dying every year, and we need to change the public's outlook and the public's response in these moments. And I really think that making naloxone more widely available is the first step to normalizing and educating about how to respond in these moments.

DR. CLEMENT: Okay. Thank you. That's all my question. Thank you very much.

DR. COYLE: Thank you, Dr. Clement. Thank you, Dr. Hadland.

I'd like to move on to Dr. Sprintz.

DR. SPRINTZ: Hi. This is Michael Sprintz, and I had a question for Dr. Vyas.

One of the things I want to acknowledge, too, and I know it's not necessarily part of the FDA's purview, is in pricing. I recognize that the cost of production influences the cost to the consumer, which influences access to care. So obviously, depending on how things are priced, that's going to influence who will actually purchase it or not, which does influence the access

to care.

One of my questions relating to this was, why was the mock carton labeling, or the intent to mock labeling, different from the prescription carton, which had the open panel? I made the assumption that it was a cost issue because it seemed like the prescription open panel had worked pretty well. I do like the idea of having all five together because I know that on the mock panel, the only one that didn't meet the the percent required was the call 911.

I'll stop there. I've got another question after that, though.

MR. VYAS: Yes. Dr. Sprintz, we switched between the Rx to OTC. This is essentially what was part of the FDA's consideration for the switch. So while we know that the Drug Facts Label or the Quick Start Guide for Rx has worked for that setting, as FDA had outlined, based on their Label Comprehension Study and the information that pretty much all of the sponsors were advised to do, was to use that particular label and switch that over for

more of the OTC.

So that's kind of what we used for our Human Factors Study, and that's what we are doing to switch that over. That's primarily the reason. I think, essentially, the cost isn't the factor in this particular thing, but it's more about are the instructions clear enough in an OTC setting and do we have the data to support it.

DR. SPRINTZ: Okay. Great.

DR. COYLE: Excuse me, Dr. Sprintz. Before you begin with your next question, I just want to clarify for everyone that we do have about 10 minutes left and a number of questions still to address. So please consider focusing on this clarifying question as much as possible and keeping your comments as brief as possible for the benefit of your fellow committee members. Thank you.

DR. SPRINTZ: Perfect. Thank you.

My last question, then, is do you have intention or are you planning on putting the instruction inside the blister pack for people that carry it?

MR. VYAS: Yes. The answer is yes. This is something that we've already proposed to the FDA, and we think that it would be appropriate, as we understand that sometimes people separate the blister pack from the box. We do have an image that we can show you.

Slide 122 up. This is very similar to the current Rx version of the blister pack, and then the OTC version would also be essentially very similar, and it would be within that carton. So yes, this is what we're proposing, and we'll work with the FDA.

DR. SPRINTZ: Alrighty. Thank you very much. That's all my questions.

DR. COYLE: Thank you both.

Dr. Parker, please go ahead.

DR. PARKER: Thank you. I'm not sure who's best to answer this, so let me just put it out there. I wanted to ask about the expiration date and how much it matters. I believe I understand from the briefing document that it is proposed that it would be included on the blister pack. I didn't

see it on the principal display, and I wanted to know how much the expiration date matters. I believe in the briefing document, I read somewhere that it would be compared to the use of -- the importance of an expiration date on an EpiPen.

So I'm wondering if somebody could clarify that and also clarify where it is located, only on the blister pack or also maybe on the principal display because it's important, and whether or not that was looked at and tested in any of the studies done by the company.

Then a separate question relates to clarifying the font size on the proposed updated five-step guide on the eventual package that you would put out; just what's the font size on that? Thank you.

DR. COYLE: Dr. Parker, will you state your full name for the record as well for that question?

DR. PARKER: Yes. Ruth Parker.

Yes. Ruth Parker. Thank you.

MR. VYAS: Thank you, Dr. Parker. With regards to the shelf life, it will be on our outer

carton or the package for the OTC, as well as it will be on the blister pack as well. This is consistent with how we had it for Rx as well. We can certainly actually show you how that would actually look like.

Slide 119 up, please. As you can see, this is the blister pack, this is how it would be. So you have a lot number and expiration date as well, and this would be similar to what would be on the outer box as well.

DR. PARKER: If I could just clarify, that's on the blister pack, which is inside of the carton. Where is this information on the outside so the consumer who's making the purchase knows how long this product is good for?

MR. VYAS: Yes. It will be likely on the top panel of the box. Currently that's where it's being located, so it would not be in the front of the PDP, but the top. That's kind of where it is, and that's also part of the FDA review. But it will be visible. I think the key is that it will be visible to the consumer as they look at the

expiration date for the product.

DR. COYLE: Dr. Parker, does that --

MR. VYAS: And if I can -- sorry. Go ahead.

DR. COYLE: I was just checking to see if that addressed all of her questions.

DR. PARKER: It addresses that one, and I think when we come back, having a mock of what you anticipate, where that'll be located. And then if you can also address the font size of your intended final packaging, both that of the principal display, the instructions on the back, and the Quick Guide, just the font size of those. Thank you so much for your help. I appreciate it.

MR. VYAS: Yes.

DR. COYLE: Thank you, Dr. Parker.

MR. VYAS: Yes. To answer that question, we can certainly pull up a slide that would show you exactly the side-by-side between what we had proposed that's currently on two panels versus the proposed on one panel.

Slide up, please. As you can see, on the left, that is what we basically submitted as part

of our OTC switch application, and through the discussion with the agency, what we are now proposing is a larger box which would accommodate all five steps on the single back panel.

Our main purpose -- and this is not really to the scale, but the main purpose is to ensure that the size of the pictograms and the fonts could be maintained the same, so this is part of the consideration. Just to give you an idea, the smaller box is consistent with the Rx box size, and that was primarily done to make sure that the consumers who are used to seeing Narcan, they are familiar with it, and it's easier to carry. But as we recognize, having all five steps is very important, so we will move towards one back panel, and that should address it.

Then the next slide, let's put that up as well, and I think that will show you a really good view of what that looks like. If you see it on the left, you see the instructions are split on that box in two sides, and the proposed box is larger, about, I think, 45 percent larger or so, but that

would accommodate everything that the FDA has requested.

DR. COYLE: Thank you. Thank you both.

I'm going to move on to Dr. Ginsburg. Before you ask your question, Dr. Ginsburg, I just want to note for the panel, for the committees, that this will be our last question before we head into a break and the remainder of our agenda. If at all possible, we will circle back to allow those of you with your hands raised to come back. So stay tuned for that opportunity, if it becomes available.

Dr. Ginsburg?

DR. GINSBURG: Thank you. Diane Ginsburg. I appreciate the presentation. My question is a little bit related to something that Dr. Clement asked earlier, and it's related to the proposed packaging in step 4, about continuing to give doses every 2 to 3 minutes until the person wakes up. In the current labeling instructions, which I believe that's step number 7, talks about if available.

My question is related to knowing that

there's only 2 doses that are available and thinking about confusion of the individual trying to administer if the patient does not wake up after 2 doses. I know earlier, Dr. Green talked about response time for EMS, but I'm just a little bit concerned about that. I appreciate what Dr. Hadland said in regards to typically what is needed, but I just am a little uncertain about that piece of it, and I was wondering if anybody could speak to that. Thank you.

MR. VYAS: Yes. Thank you, Dr. Ginsburg. We have an expert, Dr. Jacobson. She does a lot of this education and training, and she does a lot of work within the community. I would like to invite Dr. Jacobson to provide her perspective on this.

DR. JACOBSON: Hi. Thank you. Yes, I'm Anita Jacobson, and I'm a clinical professor at the University of Rhode Island, College of Pharmacy, and a practicing pharmacist.

As far as the overdose response amount needed, as was previously stated, typically people are responding to 1 or 2 doses of naloxone, even

with fentanyl and potent fentanyl analogs that are in the unregulated drug supply. We do community distribution and often provide individuals who have high risk with more than one kit, And that's something that as over-the-counter naloxone becomes available could be expanded. It's going to only enhance our ability to provide multiple kits to individuals, so I think this would be a step that would allow us to make sure that they have those additional doses that they need.

DR. GINSBURG: Thank you.

DR. COYLE: Thank you all for your questions and for your thoughtfulness in responding.

We are going to take a quick 15-minute break at this time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during this break. We will reconvene at 11:10 a.m. Eastern time.

(Whereupon, at 10:57 a.m., a recess was taken.)

DR. COYLE: Welcome back to all of you.

We're going to now proceed with the FDA presentations, starting with Dr. Dorothy Chang.

FDA Presentation - Dorothy Chang

DR. CHANG: Good morning. My name is Dorothy Chang. I'm a medical officer in the Division of Nonprescription Drugs I. In this presentation, I will provide a brief summary of the regulatory history of Narcan nasal spray, as well as a summary of postmarketing safety data related to intranasal naloxone use, including data from the applicant's general analyses from its company safety database, ARGUS, and FDA's analyses of safety topics of interest from FDA's adverse event reporting system or FAERS.

Narcan nasal spray was approved in 2015. It was the first approved intranasal naloxone product in the United States. The basis of its approval relied upon the safety and efficacy of an approved naloxone product under NDA 016636. Specifically, Narcan nasal spray demonstrated naloxone exposures exceeding that achieved by a 0.4 milligram intramuscular dose of naloxone. The product was

launched in 2016.

Before we discuss the postmarketing safety data, it is important to caveat that analyses of this kind of data have inherent limitations. These include underreporting, duplications, poor quality or incomplete reporting, and reporting biases, all of which lead to difficulty establishing a causal association between a suspect drug and a reported adverse event. In addition, it is often difficult to interpret the significance of an adverse event finding due to not knowing the total patient population using the drug.

While it's not possible to truly know the amount of patient exposure to a drug, we often use information about a drug's availability as a rough estimate for patient exposure to help provide context. FDA used a proprietary drug utilization database to provide the estimated annual number of naloxone units, including syringes, vials, and nasal sprays, sold by manufacturers to U.S. channels of distribution from 2017 to 2021. During this period, the total number of naloxone units

sold almost doubled, from approximately 5.1 million units in 2017 to 9.7 million units in 2021. Specifically, for intranasal naloxone during this period, the total market share for nasal spray formulations increased from 21 percent in 2017 to 54 percent in 2021, translating to 5.3 million nasal spray units distributed in 2021.

We know that there are some limitations in these data, as they do not include direct sales or donations for manufacturers, for example, to harm reduction organizations; and we're aware that these direct sales and donations account for a substantial supply of naloxone, and therefore, these figures are underestimates of total naloxone availability.

FDA also analyzed dispensed prescription data. In 2017, the estimated annual number of dispensed naloxone prescriptions increased from roughly 359,000 prescriptions to just over 1.5 million prescriptions in 2021, and this was mostly due to an increase in the nasal formulation prescriptions, which increased from 240,000

prescriptions in 2017 to nearly the 1.5 million in 2021. Nasal formulation prescriptions accounted for 97 percent of the total dispensed naloxone prescriptions in 2021.

Again, although these data provide insight into the extent of naloxone available as prescription, it is an underestimation of potential patient exposure because it does not include naloxone that individuals receive outside of the pharmacy setting such as from harm reduction organizations. In addition, we note that naloxone is obtained as a preventive measure and stored until it may be needed in an emergency situation. If naloxone is not used before the product expires, the product may not end up being used at all, and thus another limitation is that the number of dispensed prescriptions does not necessarily reflect individual use of naloxone.

Moving on to our discussion of the ARGUS data, as noted previously, ARGUS is the applicant's pharmacovigilance safety database, and may be the most concentrated source of intranasal naloxone

postmarketing safety data, as all cases reported to ARGUS are presumed to be associated with an intranasal presentation of naloxone, and a majority of cases reported involvement of Narcan nasal spray specifically. As you can see in the table, of the 397 cases reported for naloxone within the database, over 75 percent reported Narcan nasal spray specifically.

This slide provides descriptive characteristics of the cases identified in ARGUS. When age and gender were known, the majority of cases were reported in individuals 18 to 65 years of age, and more cases were reported in males than in females. Additionally, serious outcomes occurred in 93 cases or 23.4 percent of all cases. Serious cases most often occurred in adults 18 to 65, with very few cases noted in adults greater than 65 or children less than 18; and notably, no serious cases occurring in children less than 2.

The adverse events reported in a case are recorded as preferred or PTs, and this table displays the most frequently reported preferred

terms occurring greater than 1 percent among serious cases. The top five PTs included death reported in 14 cases, followed by drug withdrawal syndrome, seizures, drug ineffective, and loss of consciousness. You can see the remainder of the list in the table. Most of these are not unexpected, considering the condition being treated and naloxone's known side effect profile.

As noted in the previous slide, the preferred term "death" was reported in 14 cases; however, we note that there were actually 26 cases, or 6 and a half percent of all cases, marked as having a fatal outcome. The applicant provided case summaries for our review.

Out of the 26 cases, it is noted that 9 cases reported use of naloxone for an overdose; however, the overdose event involved other agents besides opioids as a potential cause of death. Two cases reported the victim had been given naloxone too late. One case reported naloxone use for the wrong indication that was unrelated to an overdose, and in the majority of fatal cases, there was too

little information to conclude a causal association between naloxone use and the fatal outcome.

With respect to special populations, in the pediatric age group, a total of 8 cases were reported; 5 cases reported a serious outcome, including 2 fatalities. When we look at the case details from these serious cases, 4 cases reported adverse events that appeared to be related to an underlying non-opioid drug overdose, including the 2 fatalities. The remaining serious case reported seizure and mini-strokes in a setting of naloxone use for an opioid overdose.

In the geriatric population, a total of 21 cases were reported with five having a serious outcome and no fatalities. Looking at the case details and preferred terms, we note that there were no predominant preferred terms reported. The top five preferred terms among serious cases in this age group generally did not appear to be related to naloxone use but could be the result of intoxication or the clinical sequelae of an intoxication event.

In pregnant women, there were a total of 4 cases reported overall, with one resulting in a serious outcome with no fatalities. The single serious case reported premature delivery, but the case was confounded by maternal use of multiple psychoactive medications and nicotine.

Turning our attention to FDA's independent review of FAERS cases, the main focus of this analysis was to evaluate the postmarketing safety data for adverse events associated with intranasal naloxone products used in the community setting. FDA covered three safety topics of interest in greater detail, including an evaluation for naloxone-induced precipitated withdrawal, issues associated with limited efficacy, and device use errors, as well as other medication errors.

FDA's analysis of FAERS covered cases reported between January 2016 to November 2022. The analysis included any U.S. case reporting intranasal naloxone use in the community setting as determined by a detailed review of each case narrative. Exclusions are shown on the slide and

are in the briefing document.

A total of 318 cases were identified that involved the use of an intranasal naloxone product in the community setting. The top line characteristics for these cases show that there were 81 cases with serious outcomes, indicating that most cases reported outcomes that were not serious. About half the cases were administered by the general public or untrained laypeople, with relatively fewer cases describing administration by trained laypeople or a healthcare professional.

When information on the number of doses and cumulative dose of naloxone administered were available, most cases described use of 1 to 2 doses of naloxone, up to a cumulative dose of 8 milligrams. Very few cases described administration of three or more doses or administration of greater than 8 milligrams of naloxone. Lastly, most cases reported the reason for use was emergency treatment of known or suspected opioid overdose, reflecting appropriate use of intranasal naloxone by a majority of the

general public. We will discuss other reported reasons for use in a later slide.

The set of cases involving intranasal naloxone in the community setting were then further evaluated for adverse events associated with naloxone-induced precipitated withdrawal. Cases were included where opioid withdrawal after naloxone administration was reported by a healthcare provider or reported by a layperson with supportive case details. For each of these cases, the Clinical Opioid Withdrawal Scale, or COWS, was applied to assess the signs and symptoms of opioid withdrawal.

COWS is an 11-item scale that provides a reproducible assessment of signs and symptoms of opioid withdrawal. COWS is used by clinicians to diagnose and manage opioid withdrawal, and further information about COWS scoring is included in the briefing document. For all cases meeting selection criteria, a COWS score was calculated to support the determination of opioid withdrawal, and if possible, quantify severity.

For cases not reporting on specific elements of the COWS score, for the purpose of the calculation, it was assumed that individual did not demonstrate that sign or symptom. For cases reporting specific elements, it was assumed that individual met the lowest point total for that sign or symptom unless enough detail was provided to meet a higher point value. As such, the COWS scores derived for each case represented the minimum score. Actual COWS scores for the cases may have been higher.

A total of 180 cases, or 56.6 percent, of intranasal naloxone cases were identified that either reported naloxone-induced precipitated withdrawal or described symptoms consistent with it. Thirty-five cases, or 19.4 percent, reported a serious outcome, but notably none resulted in death. Nearly 87 percent of cases reported a correct reason for using naloxone. About half of the cases reported use of less than or equal to 8 milligrams of naloxone, while only 2.8 percent of cases reported cumulative doses greater than

8 milligrams. Among the 180 cases, a majority of cases scored a COWS score of less than 5, which is technically below the score for mild withdrawal.

For the topic of limited efficacy, the set of intranasal naloxone cases were further evaluated for any cases reporting naloxone use as ineffective in the case narrative and were supported by case details.

A total of 24 cases, or 7.5 percent, of intranasal cases were identified for having limited efficacy; 14 cases reported a serious outcome, including 2 cases that resulted in death. When information on the cumulative dose of naloxone use was available, a majority of cases reported less than 8 milligrams when naloxone was used, and most cases involved administration of 1 to 2 doses.

The reasons reported for limited efficacy included 6 cases reporting either too much time had elapsed since the overdose or the elapsed time was unknown; 5 cases reporting no response to a first dose but response occurring with a second dose; 5 cases reporting various product issues such as

nothing came out; and 2 cases reporting not having enough naloxone. We note that multiple factors can contribute to the effectiveness of intranasal naloxone, including the severity of the overdose, if other substances were involved, the time elapsed between the overdose event and when naloxone is administered, as well as the administration technique.

The evaluation of limited efficacy cases was challenging. Seventy-five percent of cases did not report the specific opioid to be reversed, for example, partial agonists, or if other substances were involved in the overdose, both of which could affect the efficacy of naloxone. In most cases, it was not possible to fully ascertain causality of limited efficacy.

Device use error and other medication errors was our third topic of interest. A separate search was conducted with a strategy that included any U.S. FAERS report involving devices errors or medication errors involving naloxone nasal spray devices. Exclusion criteria are listed on the

slide and in the briefing document.

Nine cases were identified where device use error occurred. From these 9 cases, four types of errors were identified. In three cases, users sprayed the product into the air instead of the patient's nose. In three cases, users did not wait 2 to 3 minutes between doses. In two cases, there was general confusion about the use of the device, and in the remaining case, the user administered 2 doses into the same nostril.

Of the four main types of devices use errors, the error with the highest risk of harm is related to users spraying naloxone outside of the patients nostril because doing so will waste the dose of naloxone. Of the 9 cases, 6 cases described errors occurring in the setting of an emergency. Notably, there were no serious outcomes, and all 6 patients responded to treatment despite the device use error. The remaining 3 cases described complaints from users trying to train themselves on the use of the product in a non-emergency setting.

Besides devices use errors, FDA identified two other types of medication errors. The first was related to the use of naloxone nasal spray for the wrong indication, which was noted in 58 cases. In these cases, some patients reported accidentally using intranasal naloxone instead of another nasal spray, such as a sinus or allergy treatment. Some patients reported not knowing naloxone's indication but using the product anyway, and some cases did not report the reason for wrong use. Notably, only 3 cases resulted in serious outcome.

A second type of medication error was related to accidental wrong storage conditions in which consumers stored their intranasal naloxone product in freezing or very high temperatures such as in the glove compartment of their car. It was noted that there were no serious outcomes related to these storage issues.

In conclusion, the postmarketing safety data for intranasal naloxone use in the community setting did not indicate any new or previously unrecognized safety issues. Cases demonstrated

that in the community, consumers generally administered intranasal naloxone for the correct indication, and the majority of cases had non-serious outcomes. There are relatively few cases identified reporting serious naloxone-induced precipitated withdrawal or limited efficacy.

The assessment for device use errors demonstrated that the user error with highest risk of harm is related to a potential missed dose from users spraying naloxone outside of a patient's nostril. The applicant's plan to continue co-packaging 2 nasal spray devices per carton may help to mitigate this risk. Lastly, errors related to use of the product for the wrong indication, as well as wrong storage conditions, may be mitigated by clear and prominent labeling that displays the product's name, indications, and storage information. Thank you.

FDA Presentation - Barbara Cohen

MS. COHEN: Good morning. I'm Barbara Cohen, the social scientist in the Division of Nonprescription Drugs II in the Office of

Nonprescription Drugs. I'm here today to discuss FDA's nonprescription naloxone model Drug Facts Label or DFL study. I want to acknowledge the overall work of my FDA statistical colleagues for their collaborative role in the design and analysis of this study, really, since its inception, as well as Dr. Chang's input into today's presentation.

Before I discuss this study, as background, I want to note that our clinicians consulted with a number of outside experts on the contents of the Drug Facts Label. I'm going to be discussing this pivotal Label Comprehension Study that validated the DFL so that you're knowledgeable about the previous relevant work that has gone into development; however, the DFL content and the pivotal study are not the focus of this meeting.

I'd now like to provide a brief overview of what label comprehension studies are for those of you who are unfamiliar. Label comprehension studies are conducted for many nonprescription to nonprescription switch NDAs. The objective in a nutshell is to assess consumer understanding of the

proposed DFL that the applicant is putting forward. The basis of recommended study design and conduct for these studies are discussed in FDA's Label Comprehension Guidance for Industry, which was published in 2010.

To touch on a few key points here about study methodology, for one thing, these are quantitative studies. FDA asks that demographically diverse populations be enrolled. The limited literacy subpopulation should be at least 30 percent, reflecting the estimated representation of the actual population. Participants are given a DFL to read at their own pace, and then asked questions about it. It's not a test of memory. They can refer back to it whenever they want. Ultimately, however, these studies can only address comprehension; they cannot predict actual behavior.

As a brief explanation about endpoint, typically, the applicant identifies the primary endpoints and establishes the target thresholds for those endpoints a priori. Each endpoint should

reflect the clinical significance of the DFL statement that is being assessed. Findings are typically reported as not only point estimates but also as to how they align with the lower bound of the 95 percent confidence interval. Typically, label comprehension studies have multiple primary endpoints and are designed to assess comprehension of all of them. Additionally, there can be secondary and exploratory endpoints, which typically are reported as point estimate with no associated threshold.

It's important to note that, also, in the case nonprescription consumer behavior studies, the thresholds are targets. They're not hard pass/fail stops. If an endpoint comes relatively close to meeting a threshold, and we can discern why it didn't, there may be other potential ways to enhance consumer understanding. Regardless, ultimately that becomes part of the risk-benefit analysis in deciding whether to approve the drug.

I want to step back for a minute and differentiate between label comprehension studies

and human factors studies. In label comprehension, the goal is to evaluate consumer comprehension of the DFL as a whole. In human factors, the goal is to evaluate whether the product user interface is safe and effective for the intended users, uses, and use environments.

Label comprehension studies are quantitative with target thresholds established a priori. Typically, a label comprehension study has hundreds of participants. Human factors studies are qualitative with at least 15 participants per user group. In addition, label comprehension studies require at least 30 percent of study populations to be of limited literacy, whereas human factors ask for the sample to be based on the intended user population.

Finally, with regard to the assessments of steps in the administration of a product, label comprehension studies, as this one did, can employ cognitive walkthroughs, where participants are asked to verbalize the steps they would take. In human factors studies, the participants are asked

to physically simulate the steps that they would take using, for instance, a mannequin, and perhaps employing techniques to simulate a high-pressure emergency situation.

Now back to label comprehension. Typically, the applicants conduct these studies, and FDA analyzes the data and reviews the findings once the NDA is submitted. Often, the companies, as a preliminary step, conduct formative research to craft and optimize this label before finalizing it, and then conducting pilot and the pivotal studies.

In the case of nonprescription naloxone, some potential applicants in 2015 told FDA that they did not have the resources and bandwidth to conduct all of this research on their own; therefore, FDA decided to take on the responsibility and cost of developing a model DFL on its own, contracting out for all of the requisite research. Under this paradigm, the only task for applicants would be to assess those parts of the DFL that pertained to their particular product.

There are many challenges for our clinicians in developing this particular model DFL. Atypical for a nonprescription product, this product is to be administered in an emergency, life-threatening situation. We needed to assume the worst case scenario, namely that consumers might never look at the DFL prior to the need to use it; therefore, the key steps in product administration needed to be presented clearly and succinctly and with accompanying pictograms for optimal clarity.

Furthermore, FDA did not know which dosage forms would be proposed for eventual nonprescription use, and we also did not know how the applicants would eventually choose to package the product; therefore, general language needed to be utilized in this model. Applicants were advised that they would need to develop and test specifically the new information that needed to be added about the use of their particular products.

FDA initiated development of the DFL in 2016. Our clinicians consulted with outside experts in addiction treatment and with internal

experts in communication, with the result that an innovative draft DFL was developed, innovated with adjacent pictograms to enhance communications of key concepts. We awarded a contract to conduct all of the prior label comprehension research, not just the pivotal study, but also the formative work. This project is sometimes referred to by the acronym of its name, CONFER. The pivotal report and accompanying data were reviewed by a firewall FDA team, and a special report on the study was published in the New England Journal of Medicine. There's a link to that in your backgrounder.

Now I'll discuss the pivotal study itself. The study populations were as follows. Adults who use opioids, either heroin or nonprescription; friends and family members of adults who use opioids; and general population adults and adolescents; that is, they were all-comers recruited from typical marketing research databases.

This slide depicts the diverse demographics of the study population. In the interest of time,

I'm not going to go through everything. Continuing on this slide, you can see almost 20 percent of the sample is under the age of 18. Here are the thresholds that we established a priori. As you can see, comprehension of step 3, "Call 911 immediately," was determined by our clinicians to be the highest level of clinical importance. The rationale was that if nothing else was done according to the label, the calling of 911 hopefully meant that emergency help would be on its way with trained EMTs.

As contact, 90 percent is typically the highest threshold level that is incorporated into the consumer behavior study. Comprehension of the other four steps were assigned a prior threshold of 85 percent, which typically is assigned to endpoints that are not as critical as the 90 percent one, but still important. Finally, comprehension of what the product is used for and signs of overdose were assigned an 80 percent a priori threshold, determined by our clinicians to be important enough to be a primary objective but

not as important as the others.

Here are the results. As you can see, comprehension of most of the endpoints met or exceeded the lower bound of the 95 percent confidence interval. The exceptions were call 911, which had an 87.9 percent lower bound, and closely approximated the 90 percent threshold but did not achieve it, and the comprehension of steps 1, 2 and 3 combined, which at 78 percent did not achieve the desired 85 percent threshold.

Here are the key results for the other primary endpoint. Even though the thresholds for these were only 80 percent, comprehension of both of these scored above 90 percent. There are also secondary endpoints in this study, and here you can see that these scored relatively well, with the exception of the comprehension of steps 1 to 5 combined.

Finally, with regard to exploratory endpoints, the vast majority of people understood the concept of waiting 2 to 3 minutes between doses, and the majority could proactively offer a

correct definition of what was an opioid. In summary, call 911 closely approximated but did not reach the target, and we therefore recommended that applicants further assess whether comprehension of the instruction to call 911 immediately may be improved. However, the DFL was acceptable with appropriate changes to the model DFL to address individual products' delivery system and those specific instructions for use. Comprehension of those would need to be assessed through human factors or additional label comprehension, if appropriate. Thank you.

FDA Presentation - Millie Shah

DR. SHAH: Good morning. My name is Millie Shah, and I'm a human factors reviewer in the Division of Medication Error Prevention and Analysis II. Today, I will be presenting on the Human Factors Validation Study. I will start with a description of the nonprescription Narcan product's user interface, along with a comparison to the prescription Narcan product, which will provide the context for why a human factors

validation study was necessary for the nonprescription Narcan product.

Next, I will provide an overview of general HF study methodology principles, along with a summary of the nonprescription Narcan product's HF validation study design. Then I will provide a summary of the key HF validation study results, and end with potential recommendations for the AC panel's consideration.

I'd like to start by first defining the term "user interface." Here you see images of the nonprescription product's user interface, which refers to all points of interaction between the product and the user, including elements such as packaging, like the carton and the blister; the product's labels, including the Drug Facts Label, which is required for nonprescription products; and the device. It's important to remember that the user interface includes any element of the product that the user sees or touches, not just the device.

I'd like to note that I'm going to present the information, including the Human Factors

Validation Study results, and labels and labeling submitted by the applicant on September 29, 2022; however, we acknowledge that aspects of the user interface that the applicant just presented in their slides differ from what was originally submitted with the supplemental NDA.

Here you see a comparison of the prescription Narcan product directions on the left and the originally submitted nonprescription product carton directions on the right. FDA previously reviewed the HF validation study results for the prescription Narcan product, and concluded that the study results supported safe and effective use.

So why was an HF validation study necessary for the proposed nonprescription Narcan product? Well first, the change in marketing status from prescription to nonprescription warrants HF data to evaluate whether intended users can use the product safely and effectively without the intervention of a healthcare provider; second, as you can see here, the way the directions are presented and the

directions themselves differ between the prescription product and the nonprescription product.

For the prescription product, the carton contains a flap on the front that opens to directions on the same viewable surface, whereas for the nonprescription product, the DFL directions span over two different panels, the back and the side, making the complete directions viewable only after rotating the carton. I will discuss the implication of this when I summarize the HF validation study results in subsequent slides.

So although the model DFL tested well for comprehension in the CONFER label comprehension study, the nonprescription product represents an unvalidated user interface that had never been evaluated in a simulated use scenario that mimics actual use with representative users performing the tasks.

Here you see a comparison of the prescription blister packaging on the left and the originally submitted nonprescription blister

packaging on the right. Another important difference to note is that while the prescription product includes a Quick Start Guide with the directions folded in each blister package, the nonprescription product does not. Because some users may remove the blister package from the carton and only have the blister package available during an opioid overdose emergency, thereby not having access to the DFL directions, this change to remove the Quick Start Guide from the blister package also represents an important difference to the user interface that warranted evaluation in the HF validation study.

Here is a comparison of the nonprescription product's DFL on the left and the model DFL evaluated in the CONFER Label Comprehension Study for comprehension on the right. Although steps 1, 3, 4 and 5 figures and texts for the the nonprescription DFL directions are identical to the model DFL, some key differences I'd like to point out with the originally submitted nonprescription DFL include the directions being split across two

panels, with steps 1 and 2 on the back panel and steps 3, 4 and 5 on the side panel; whereas the model DFL includes all five directions on a single panel. Also, in step 2, although the figure is identical to the model DFL, there are differences in text. Here is a figure of the proposed nonprescription device, which is identical to the prescription product.

Now, I'd like to provide an overview of human factors studies, which are conducted under simulated use conditions with representative users, where no drug is administered to participants; rather, participants administer a placebo-filled device to a mannequin in a test environment that mimics real-world use conditions.

The objective is to evaluate whether the product's user interface is safe and effective for the intended users, uses, and use environments. The results are analyzed qualitatively by observing user's interactions with the product user interface and collecting subjective user assessments of their experience to assess the adequacy of the user

interface design.

So although the number of use errors is recorded, the goal is not to quantify the frequency of any particular use error; instead, the purpose is to evaluate every use error to identify whether any aspect of the user interface contributed to confusion or caused people to use the product incorrectly. In summary, the number of use errors is not as important as why they occurred.

When sponsors are designing the Human Factors Validation Study, FDA encourages them to submit the HF validation study protocol for review prior to conducting the study to ensure that the methodology is acceptable and to provide recommendations for the user interface from a medication error perspective. It's important to note that the applicant did not submit the HF validation study protocol for the agency's review prior to conducting the study. Upon our review of the HF validation study results, we identified several methodology limitations that need to be considered when interpreting the study results.

In the next few slides, I will discuss specific study design elements; general human factors validation study methodology principles in the second column; summarize the details of the Narcan HF validation study methodology in the third column; and finally discuss the limitations of the Narcan HF validation study.

First, in terms of user groups, generally a minimum of 15 representative users are included per distinct user group. The Narcan HF validation study included 71 participants across 4 user groups, including adolescents aged 15 to 17 years old; therefore, the HF data collected cannot be generalized to users less than 15 years old.

Second, in terms of limited literacy users, for nonprescription products, FDA generally recommends that each distinct user group include 30 percent limited literacy participants to ensure adequate representation of the intended users in the study. However, the Narcan HF validation study did not include at least 30 percent limited literacy participants in 2 of the 4 user groups,

the adult general population and the adult opioid user associates; therefore, the distribution of limited literacy participants may have introduced a bias with tendency towards positive performance in the affected user groups.

In terms of study sequence, participants are observed performing tasks in a simulated use scenario and should be given an opportunity to use the product user interface as independently and naturally as possible. However, in the Narcan HF validation study, all participants were allowed as much time as needed to familiarize themselves by reviewing the nonprescription product and its DFL, and then were asked to demonstrate administration of the product.

While some users may have the opportunity to familiarize themselves with the product labeling before administration of the product, in an actual emergency, some users may have limited time to interact with the product labeling; therefore, the data collected does not capture this highest risk use scenario.

Next, in the Narcan HF validation study, moderators used leading language and a "think aloud" method, where all participants were instructed to review the product labeling and told to think aloud as they completed the demonstration. Use of leading language and the "think aloud" method are unrealistic and may have introduced a bias towards positive performance because during actual use, users will not have someone reminding them to use the instructions or to talk through what they are doing. In summary, the familiarization period, leading language, and "think aloud" method are not representative of actual use scenarios and may have influenced participant behavior and performance.

Next, in terms of data collection, participants should be observed performing steps needed to use the product without interruption, and then are interviewed on their experience after the simulation. The HF validation study should collect qualitative data using information gathered from every use error, close call, or use difficulty to

identify whether any part of the user interface contributed to the use-related event and investigate the causes so that the design of the user interface can be optimized for safe and effective use.

Participants' successful completion of a task is based on observed performance rather than verbal descriptions of what they would intend to do. Use errors are recorded but, again, the purpose is not to quantify the frequency of any particular use error or establish acceptability with respect to a numerical acceptance criteria.

In the Narcan HF validation study, the applicant used quantitative thresholds for success to score each participant's performance of tasks as correct, incorrect, or could not be observed. Additionally, if participants did not perform the step or performed it incompletely, but clearly articulated the procedure they would intend to follow, the performance may have been scored as acceptable.

There are several limitations to the

applicant's data collection methods and analysis, including that some use errors, close calls, use difficulties, or instances of moderator intervention are scored as correct or acceptable, even if the participant failed to complete a step. Additionally, the applicant did not conduct a root cause analysis or collect participants' subjective feedback to understand why use errors, close calls, or use difficulties occurred in all instances. Therefore, FDA requested the root cause analysis and participants' subjective feedback for all use errors, close calls, and use difficulties, and read the participants' verbatim transcripts to determine the root cause and subjective feedback in some instances. FDA's review is focused on the qualitative data set.

Next, in terms of test materials, generally, the final intend-to-market user interface, including the labels and labeling, should be evaluated in the HF validation study. If changes are made to the user interface post-HF validation, generally, additional HF data may be needed to

support that the changes are effective and don't introduce new risks. However, the carton labeling evaluated in the Narcan HF validation study is different than the proposed intend-to-market carton labeling submitted with the supplemental NDA, which I will show in the next couple of slides.

The applicant has made several changes post-HF validation, and there is no HF data to support that the changes are effective and don't introduce new risks. Here you can see the extensive changes the applicant made between the carton tested in the HF validation study on the top and the intend-to-market carton labeling originally submitted with the supplemental NDA on the bottom. Some changes are in response to use errors observed in the HF validation study, which I will discuss in subsequent slides. Most importantly, the carton labeling has been modified post-validation by switching steps 3, 4 and 5 from the back panel to the side panel so that the back panel now starts with step 1, "Check if you suspect an overdose."

Here is a comparison of the principal

display panel of the carton evaluated in the HF validation study on the left and the intend-to-market carton on the right. Some changes appear to be cosmetic in nature, such as the colors and branding, while other changes to the principal display panel include different statements, relocation, and/or changes to the font size of important statements, such as the package type term and the quantity that impact use of the product.

Now I'd like to transition to reviewing and interpreting the HF validation study results. When interpreting the study results, it's important to focus on the qualitative results, which is done by assessing each use error, close call, or use difficulty first by identifying the root cause and determining whether any aspect of the user interface contributed; next, by determining the potential for harm, and then determining whether additional measures to eliminate or mitigate risks are necessary; and finally, determining whether additional HF data may be needed to support that the changes are effective and do not introduce new

risks.

Before providing a summary of the key HF validation study results, I remind you of the following study methodology limitations that need to be considered when interpreting the study results, including the age range of the adolescent user group that did not include participants less than 15 years; the inadequate representation of limited literacy participants in two user groups; the familiarization period, leading language, and "think aloud" method that are not representative of actual use scenarios; the data collection method that did not report root cause or participants' objective feedback for all instances of use error, close call, or use difficulty; and the changes made to the user interface post-HF validation.

Despite the study limitations, such as the familiarization period, leading language, and "think aloud" method that may have introduced a bias towards positive performance, several use-related events occurred that can be directly attributed to the user interface design.

In the next few slides, I'll be providing a summary of the HF validation study results, focusing on the key results with root cause or participants' subjective feedback that indicate some aspect of the user interface contributed to the use error, close call, or use difficulty. The complete qualitative data set is available in the AC briefing document.

Here are the key results related to the user interface for step 1, "Check if you suspect an overdose." I want to highlight a few examples from the full qualitative data set for the panel's consideration.

Several participants experienced use errors or close calls that were directly attributed to the layout of the DFL directions on the carton. Participants provided feedback, such as, "I started on step 3." "For some reason in the panic mode, I just read the back of the box and jumped into action and usually instructions are on one panel. It did kind of confuse me because when it says call 911 and wait 2 to 3 minutes after the first dose, I

was like, 'Wait' I haven't given the first dose yet. I need to go back to the beginning," and "Where is step 1?" These participants provided feedback that directly points to the user interface design contributing to use errors that can result in no dose or delayed administration of naloxone.

Here are the key results related to the user interface for step 2, "Give the first dose." Participants provided feedback that indicates confusion surrounding how to hold, orient, and operate the device correctly. For example, one participant did not keep the nozzle fully inserted in the nostril. Another participant tried to squeeze the device rather than pressing the plunger.

For some participants, the confusion stemmed from reviewing the DFL on the back panel first, which started with step 3, "Call 911." For example, one participant who started with step 3 on the back panel was confused about whether or not the device contained a cap that needed to be removed because they did not see the directions in

step 2. This caused a delay in naloxone administration while they tried to figure out how to operate the device.

Here are the key results related to the user interface for step 3, "Call 911." As we saw with the results for step 1, some of the use-related events for step 3 can also be attributed to step 3 being presented on the back panel of the carton, which led some participants to call 911 first rather than administering the first dose of naloxone. One participant spent about 50 seconds reading the wrong panel of the DFL first while determining how to proceed, which could result in delayed medical attention.

Here are the key results related to the user interface for step 5, "Stay." There were several use-related events attributed to confusion regarding the number of doses in each device. Participants provided feedback such as, "I couldn't figure out if there was more than one dose in one of these," and "There is nothing that conclusively tells me that there is one dose." Confusion

regarding the number of doses in the device may result in delayed administration of additional doses of naloxone or reuse of a used device.

As presented in the previous slides, several use-related events occurred that can be directly attributed to the user interface design, with participants turning to the back panel of the carton and starting with step 3, "Call 911," bypassing step 1, "Check," and step 2, "Give the first dose," which appeared on the side panel of the carton. Users' difficulty locating where to start on the DFL directions or understanding the sequence of steps may result in delayed administration of naloxone. Furthermore, if users start with step 3, "Call 911," they may miss important information in step 1 regarding how to hold, orient, and operate the device, and that the device is to be administered in the nose. This may result in no dose or in wrong route of administration error.

Based on the use errors that were observed in the HF validation study, in the labeling

submitted on September 29, 2022, the applicant originally implemented a post-HF validation revision to the DFL by presenting step 1, "Check" and step 2, "Give the first dose" on the back panel, and step 3, 4 and 5 on the side panel; however, it's important to note that with this revision, the directions remain split over two panels.

We acknowledge that users who refer to the back panel of the carton first will now see step 1 and step 2; however, it's unclear if this mitigation will effectively address the use errors observed without introducing new risks for error. For example, some users may overlook steps 3, 4 and 5 on the side panel.

The applicant did not validate this proposed mitigation strategy, so we do not have supporting HF data to demonstrate that the proposed mitigation will address use errors; therefore, we propose the AC panel consider whether the applicant should redesign the carton such that the back panel includes all five steps of the DFL directions

uninterrupted and in the appropriate sequence, and whether the applicant should package a quick start guide within each blister package that displays steps 1 through 5 using text and figures consistent with the DFL directions. The Quick Start Guide should include steps 1 through 5 on a single-side page without breaks to minimize the risk of users missing steps.

It appears that in their presentation today, the applicant has prepared a mockup implementing our recommendation for the AC panel's consideration. We note that the applicant has not formally submitted the labeling presented today, and it has not been evaluated by FDA yet.

For step 2, "Give the first dose," some use-related events were related to device orientation, operation, and hand position on the device. Additionally, the second bullet of step 2 states, "INSERT the tip of the nozzle into either nostril."

The word "tip" may result in users not fully inserting the nozzle into the nostril, which may

result in partial dose administration. Therefore, we propose the AC panel consider whether the applicant should revise the bullet to state, "INSERT the nozzle into either nostril," removing the word "tip," and whether the applicant should improve the carton labeling, including step 2's pictogram, for example, by incorporating elements of the hand and finger positioning on the device from the prescription Narcan pictogram.

For step 5, "Stay," use-related events occurred that can be directly attributed to the user interface due to confusion about whether each nasal spray contains a single dose or multiple doses. Therefore, we propose the AC panel consider whether the applicant should add a statement that each nasal spray contains only one dose of naloxone to the labels and labeling, and whether the applicant should revise the carton labeling to depict two nasal spray devices to minimize confusion on the number of nasal spray devices in each carton.

In conclusion, it's important to consider

the HF validation study methodology limitations I discussed previously when interpreting the study results, most important of which include the familiarization period, leading language, and "think aloud" method that are not representative of actual use; the data collection methods that did not report root cause analysis or participants' objective feedback for all use-related events; and changes to the user interface post-HF validation that do not supportive HF data.

Despite the study limitations, such as the familiarization period, leading language, and "think aloud" method, that may have introduced a bias towards positive performance, several use errors occurred that can be directly attributed to the user interface design. These use errors may result in no dose or delayed dose administration of naloxone.

FDA has identified some potential recommendations for the user interface based on the root cause analysis and participants' subjective feedback. We ask that the AC panel take the study

limitations, the use-related errors observed in the HF validation study, and our potential mitigations into consideration during your discussion. Thank you.

Clarifying Questions for FDA

DR. COYLE: We will now take clarifying questions for FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member. And I might suggest also that we limit the number of questions that we might be asking at a given time just out of courtesy for our

fellow panel members so that we can be sure to include as much participation as possible in the time allowed.

I'm going to start with Dr. Pisarik.

DR. PISARIK: Paul Pisarik. I just have a question. It may not be as important now as it may have been earlier, but in terms of the pictures that are on the back panel, in the prescription, they're labeled as 1, 2 and 3 with large numbers of 1, 2 and 3.

Would it be wise to have 1, 2, 3, 4, 5 in big numbers next to the picture so that people know they should go from 1 to 2 to 3 to 4 to 5? Thank you.

(No response.)

DR. PISARIK: Sorry. Did you did you hear that?

DR. COYLE: We've heard the question.

FDA, can you respond?

DR. GREEN: This is Dr. Jody Green. I'm going to ask Dr. Millie Shah to respond, and then perhaps Ms. Cohen might have additional comments.

DR. SHAH: Hi. Thanks for the question. This is Millie Shah from DMEPA. Thanks for that comment. We'll take that into consideration.

DR. PISARIK: Thank you.

DR. COYLE: Hearing no additional comment from FDA, I'm going to call Dr. Horrow.

DR. HORROW: Yes. Thank you, Dr. Coyle. I have a clarifying question for the FDA relating to the minimum age requirement --

DR. COYLE: I apologize for interrupting. Can you please state your name for the record?

DR. HORROW: Yes. This is Dr. Jay Horrow. Thank you. I'm the industry representative.

I have a clarifying question for the FDA relating to the minimum age requirements. I tried the FDA links applied at the end of their slide to the guidance document, but it results in a page not found. So perhaps you can help me understand, does the FDA have in their guidelines a minimum age requirement for the label comprehension studies that are used, and does it have one for human factors?

I ask this because I note that the Label Comprehension Study conducted by the FDA involved no subjects younger than 15, yet the FDA wishes to have subjects younger than 15 in the Human Factors Study.

MS. COHEN: This is Barbara Cohen. Thank you for that question, and it's an important one. To answer the first part of your question, no, the label comprehension guidance does not specify a minimum age because that really depends on who the intended population is for a particular product.

Now, to your question about why we didn't include participants under the age of 15 in the Label Comprehension Study, I wanted to note that in our statement of work, when we envisioned this project and we sent it out for solicitation, we said that we would like middle schoolers to be included in that study population, so that was definitely our intent in the beginning.

What happened was that shortly after the project actually was awarded and started, we received a bit of informal feedback from our IRB,

and our IRB does not typically deal with consumer behavior studies. They were concerned about adolescents of any age, anybody under 18 being involved in these studies. They had a big concern about anybody under age 18, so we decided at that point that we needed to focus our further discussions with them on including ages 15 to 17 in the study.

Does that answer your question?

DR. HORROW: Yes. Thank you very much.

MS. COHEN: Okay.

DR. HORROW: Nothing to follow.

DR. COYLE: Thank you very much.

Ms. Coykendall?

MS. COYKENDALL: Hi. Liz Coykendall. My question deals with the packaging, and I guess either Millie Shah or Barbara Cohen could answer.

As the packaging will undoubtedly be presented by both Emergent BioSolutions, and after while, more generic opportunities to buy it from other companies or different types of packaging, is the packaging instructions going to be identical on

each box so that one can flow from the other no matter what package you buy? Thank you.

DR. MICHELE: Hello. This is Terri Michele. I can respond to that question. With regard to projecting, essentially, out into what the marketplace might look like ten years from now, I think one of the advantages of FDA actually conducting the Drug Facts Label Comprehension Study is that it does provide sort of a baseline of what consumers might expect to see on each package.

But remember that each device, each product, is going to be a little bit different in terms of what their specific product looks like, so by definition, some of the instructions for use will have to differ; and hence, why we are expecting sponsors to actually conduct these human factors validation studies to make sure that the instructions for use are well understood by consumers, and a naïve person could pick it up and figure it out.

MS. COYKENDALL: Perfect. Thank you.

DR. COYLE: Thank you.

Dr. Brent?

DR. BRENT: Thank you, Dr. Coyle.

I have a question for Dr. Green or any of her colleagues at FDA. It really relates to the content of the information on the label, on the DFL. I appreciate the fact that FDA took a lot of initiative here in getting it moving. I think this is an extremely important and innovative thing to do, but in putting together the label, I noticed that one of the recommendations that concerned me from the minute I started reading the briefing document was for somebody who doesn't respond to the first 2 doses, to continue to administer doses every 2 to 3 minutes, it's very unlikely that anybody who is opioid toxic -- and that includes the newer fentanyl derivatives, and that includes the nitazenes, which are very potent opioids, which are now proliferating through the drug supply.

Any of these people, despite having been exposed to one of those drugs, is very likely to respond to the first, and certainly to the second dose. And if they don't, it's because they're not

opioid toxic. They're down for some other reason. If it takes, say, 10 to 12 minutes for EMS to arrive in that intervening time period, a person could administer 5 or 6 additional doses of the drug, basically depleting any that's applied if they may have.

While you might say, "So they used a couple of extra devices," people carrying these devices are going to be most likely bias towards the population of people who are likely to come in contact with people who use drugs, and if they deplete their supply by using a lot of unnecessary doses, they may not have it for subsequent needs. So I'm really concerned about that particular recommendation, and I will stop now. Thank you for listening to this comment.

DR. MICHELE: Thank you, Dr. Brent. This is Terri Michele, FDA. So when the model Drug Facts Label was initially designed, we actually went through a series of iterative steps; and Ms. Cohen may comment further. But it wasn't just the study that was presented today; there was a lot of basic

work that was done, including discussions with a variety of different harm reduction groups, with academics, with a whole group of outside experts who had experience in this area, and then there were multiple steps in the initial iteration of the label.

One of the things that we discovered was that consumers may fear that -- let's say they give a dose, and they were very fearful that they couldn't give any more because they might be overdosing patients on naloxone. And while I fully acknowledge that if you are in a city, chances are pretty good that you call 911, and EMS is going to be there very rapidly. But let's suppose you are living in a rural area somewhere. It may take a very long time for the ambulance to arrive, and as such, you may need to give an additional dose sometime later when the patient starts to become sleepy again.

So the reason that that instruction is there is really to address this kind of inherent fear that we found in our initial testing, that patients

would be overdosed on naloxone.

DR. BRENT: May I follow up, please, very quickly? I appreciate that, and I think that's a very good point about there are situations where there might be delay for EMS to arrive. But there is a separate instruction on the label about if somebody wakes up and becomes re-sedated, then they should be re-dosed. And I wasn't really talking about that instruction; I was talking about the one to just continue to give it every 2 to 3 minutes if you don't get a response initially.

DR. MICHELE: Thank you for that comment.

DR. COYLE: Thank you for that.

DR. BRENT: Thank you for listening to me.

DR. COYLE: Thank you for that clarification, Dr. Brent.

I'm going to move on to Dr. Walker-Harding.

DR. WALKER-HARDING: Yes. This is Dr. Leslie Walker-Harding. I had a question, again, about the less than 15 years, looking at this study. Given that a lot of people have kids who could be much younger, even 7 and 8 years old,

in the home, and the device is there in the home, and they're the only person to administer the medication. There are kids who live with this every day and their parents.

How did we manage that kind of thing in the past when kids have to be the one to administer the medication with their siblings, their grandparents, their parents as the only person possible to do it? Are we assuring that labeling -- I think somebody mentioned having large 1, 2, 3, 4, and then the pictures universally understood. Regardless of the age that we put on there -- it's only tested 15 years and older -- clearly a number of people much younger would be able to help deliver this life-saving medication in their home if it's there for them to do so.

So how is that being envisioned to be addressed given the IRB limitations that you have?

DR. COYLE: FDA, do you have a response?

DR. MICHELE: Yes. Terri Michele, FDA. So again, it's certainly ideal if you can test all the way down. Sometimes that's not entirely practical,

so we do ask the committee to opine upon that. We also ask -- perhaps the sponsor may wish to comment on their Rx experience, which I certainly think would inform in this case. I'd note that the labeling does not say that you can't use this if you are under a certain age, so the labeling is very permissive, and certainly, as you note, there are very young children who are experiencing opioid overdose in their home.

DR. WALKER-HARDING: Thank you.

DR. COYLE: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. This is Michael Sprintz. Thank you. I did have a question for the FDA. I was thinking about the emergent situation, really, the panic time. A consumer's first attempt at reading instructions during an event where someone they care about or someone they know is unconscious, and they've got no medical background and the probability of panicking, one of the things that I was wondering is, has the FDA considered possibly a bright label on the blister pack,

stating, "If you do not know how to use this product, please use package instructions," because as I understand, at least they're talking about placing the package instructions in the blister pack, and especially if there's a literacy question, it may give them a moment to pause rather than fumbling with things and waste a dose, especially if it's their only dose.

So I was just wondering if the FDA has considered a label, or an additional label on the blister pack?

DR. GREEN: This is Dr. Jody Green speaking. We just want to say that the purpose of this meeting today is to gather your opinion. We've considered things, and we're very interested in what you have to say about what you think would be appropriate.

(Laughter.)

DR. SPRINTZ: I wasn't sure if it should be a clarifying question or a comment, so I would suggest that that be something that is considered.

DR. GREEN: Thank you. We'll certainly

considerate it.

DR. SPRINTZ: Thank you. That's all.

DR. COYLE: Thanks to all of you, and I guess a reminder to the panel that there will be time later for us to discuss recommendations, so as much as possible to focus this part of our meeting on clarifying questions for FDA.

I'm going to call on Dr. McAuliffe.

DR. McAULIFFE: Hi. Maura McAuliffe. I have a question. I don't know who in the FDA this would be addressed to, but there are two recommendations in your documents for the sponsor, and one is to consider if the step 2 pictogram could be further improved using the pictogram that's utilized in the prescriptive Narcan. And I agree; that is a much clearer pictogram than what I see currently being used.

The other recommendation was about language, inserting the tip of the notch of the nozzle into either nostril, where the word "tip" could result in user error, and I agree with that as well. I also noticed that in step 3, "Call 911," there's

lots of space there that could be improved upon. That's a very important step.

But my question is, would the sponsor, then after making these changes, go back and do another label study and a human factors study as well?

DR. COYLE: Is there someone from FDA that can respond to that question?

DR. MICHELE: Yes, indeed. Hi. Terri Michele, FDA. Just in general, the way that we think about human factors studies is that as a general principle, if there are major changes that you're making from a human factors study -- your human factors study kind of failed miserably -- you would then go back and repeat that study. It is a small study, not a huge kind of thing to do.

But if there are fairly minor changes that were pretty clearly identified, then there is the potential to just make those changes and go forward with marketing. So that's another thing that we'd ask the panel to opine upon, is if any of the recommendations that you're making you would want to see retested.

DR. McAULIFFE: Thank you. That's helpful. I don't have further questions.

DR. COYLE: Thank you. Thank you, Dr. Michele.

This is Maria Coyle. I'm going to ask a follow-up question to that. It sounds like there is some latitude in terms of determining whether or not a human factors study needs to be repeated, and that would also be something that we could be thinking about in terms of the changes that the sponsor has made thus far to their label.

Is that correct?

DR. MICHELE: Yes.

DR. COYLE: Thank you.

I'm going to go ahead and call on Dr. Parker, and we have time for just one to two more questions.

DR. PARKER: Thank you. It's Ruth Parker. I think this should go to Ms. Cohen. My congrats to the FDA on the model DFL, which is incredible, and I think really helps with moving this along.

I noticed that step 2, it seems like there

were instructions about product-specific directions for administration and the need to perhaps modify that. But I wanted to go back to the work that was done by the agency in creating the model DFL. What I like is there's more potentially words that were -- if I read it correctly -- "INSERT in nose and press," because the pictogram there seems to be aligned with the one that's being proposed by the sponsor here.

I wanted to know what we know about the comprehension around that wording because it seems like enhancing those specific words to "tip of the nozzle" could potentially be a source of confusion. What do we actually know about the DFL as you presented, the model one, "INSERT in nose and press"? Was that well understood, and do we have a sense of whether or not that language needs to be enhanced in some way for the current product? Thank you.

MS. COHEN: This is Barbara Cohen. Thank you very much, Dr. Parker, for your question. In response, I'll say that step 2, we needed to make

that really a placeholder step in the label because people needed to see something to know that they had to give a dose, but the intent was not to assess the specific wording of that step as it was assessed at that time with the participants. We more wanted to know did they know the concept of give a dose.

That's what we were assessing in the Label Comprehension Study, did they know that, first, they should check; second, they should actually give a dose; third, call 911, et cetera, so that the specific wording in that step was just to give people context for what the type of product might be, and it wasn't to actually test the wording specifically of that step because we had no idea what product and what type of product might be proposed for the OTC introduction.

Does that answer your question?

DR. McAULIFFE: It does. That's great. Thank you so much.

MS. COHEN: Thank you.

DR. COYLE: We'll wrap up this session with

one more question.

Dr. Clement?

DR. CLEMENT: This is for anybody. Can you hear me? Yes? Okay.

As you were giving those presentations, I'll give you a context. One of the things that came to my mind is the times I've been in this particular situation, most of the time you're not alone. I mean, it could be a situation at home, but you could be on an airplane with a bunch of people. You could be the coach with a whole bunch of people around you.

So my question to the team, to the FDA is, has anyone thought about what if you have two people there? Two people are always better than one. One could be reading the instructions while the other person is actually doing the work. Is that something that would be useful on doing -- I don't want to create more work for the company, but two people are always better than one. One could be reading the instructions while the other person's actually conducting the stuff. If you

think of two-people CPR, team CPR works really well.

I know this was the first application to the OTC committee for a rescue drug, so that may be the first time something like that has been brought up. So I'm just curious from the FDA standpoint, is that something to be considered? If there is another human study done, is that something you could ask, is what happens when there's two people in the room?

DR. GREEN: Let's see. This is Jody Green speaking. Oh, go ahead, Terri.

DR. MICHELE: Yes. It's a very valid question. I think it's probably impossible to test every single scenario that might be out there, so the instructions, in the model DFL at least, were derived based on a single respondent. But certainly if more than one respondent were there, they could tag team it however they wished.

DR. CLEMENT: Thank you. I'm done. Thank you.

DR. COYLE: Thank you all. As we wrap up

this session, part of the session today, I just want to send another reminder that as you're speaking into the record, it's always ideal if you can restate your full name, and if desired, your affiliation, really for the benefit of those who may be listening to our proceedings here for the public. I know it's an easy to miss step, but please be as attentive to that as you can.

At this point, we are going to break for lunch. We will reconvene at 1:30 p.m. Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, if you could, please plan to reconvene at around 1:20 p.m. to ensure that we can all be connected before the meeting resumes at 1:30 p.m. Thank you very much.

(Whereupon, at 12:32 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. COYLE: Hello, and welcome back to the afternoon session of our meeting. We will now begin the open public hearing session.

Both the FDA 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, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in 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 for 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 chairperson. Thank you for your cooperation.

Speaker number 1, please unmute and turn on

your webcam. Speaker number 1, begin and introduce yourself. Please say your name and any organization you are representing for the record.

DR. MUKKAMALA: Thank you.

Good afternoon. My name is Bobby Mukkamala, and I'm a practicing otolaryngologist head and neck surgeon in Flint, Michigan, and I also serve as the immediate past chair of the Board of Trustees at the American Medical Association, as well as the chair of its Substance Use Disorder and Pain Care Task Force.

The AMA supports naloxone being available over the counter because increasing access to naloxone will make the nation safer. Since it was created more than 50 years ago, naloxone has done one thing, and one thing exceptionally well, save lives from an opioid-related overdose. Were it not for the availability of naloxone, there would be tens of thousands more Americans dying from overdose related to illicitly manufactured fentanyl.

The AMA is proud to have supported dozens of

laws and policies to increase access to this life-saving medication. Physicians have increased naloxone prescribing and harm reduction organizations have continued to distribute naloxone. Barriers to naloxone, however, limit these efforts, including the fact that naloxone is currently tucked behind the pharmacy counter.

Data continue to show that community-based harm reduction organizations get naloxone directly to the people most at risk of opioid-related overdose. The AMA commends the FDA for removing some of the regulatory barriers last year to allow harm reduction organizations to purchase naloxone directly from manufacturers. This has undoubtedly saved thousands of lives already. Removing the prescription status of naloxone will make it even easier for community-based organizations to purchase and distribute naloxone to those who need it most.

This slide shows just a few examples of impactful ways to increase access to naloxone, and OTC status will make these efforts even easier.

Removing the prescription status of naloxone and making it available over the counter will send a powerful message that naloxone is a critical public health tool for everyone, and that message is important to destigmatize obtaining and using naloxone. Individuals should be able to pick up a package of naloxone without having to face the potential stigma or shame of having to ask for this life-saving medication.

Pharmacists have increased access to naloxone locally and regionally, but the AMA believes greater access will occur when naloxone for overdose risk is just as easily accessible in a pharmacy, grocery store, or other common locations as acetaminophen is for a headache or a decongestant is for a stuffy nose. The AMA has long supported the state and community-based efforts, just as we have long urged naloxone manufacturers to submit OTC applications.

When naloxone is OTC, we urge all payers to continue to cover naloxone at no or low cost. There are multiple OTC preventative health

medications that are already covered by insurance, and this should be added to that list: aspirin, fluoride, and folic acid. Affordability, however, will also require manufacturers to responsibly price their products and work constructively with payers and PBMs to ensure OTC naloxone is affordable to those with and without insurance. These important stakeholders must ensure that OTC status equates to OTC access.

Finally, we believe that removing the prescription status of naloxone will allow for many emergency departments, health clinics, colleges, universities, high school, and physicians' offices to better distribute naloxone. Having it behind the pharmacy counter is not nearly as effective in getting it into the nose of a blue patient as if it were readily available in the places I just mentioned.

Many businesses in public places already have AEDs to save lives from a heart attack. These devices literally shock a heart into the right rhythm and are more available in the halls of our

schools, malls, and airports. Let's make sure that we have this nasal spray and overdose prevention education to save lives from overdose. We urge states to use opioid litigation settlement funds to purchase naloxone and distribute it to emergency departments and other locations where naloxone can be put directly into the hands of those at risk of an opioid-use disorder, as well as into the hands of individuals and loved ones who can help prevent an opioid-related overdose from leading to death.

Making naloxone OTC is a vital step to ending the nation's overdose epidemic. We once again thank the FDA for holding this important hearing, and look forward to naloxone becoming an over-the-counter product. Thank you.

DR. COYLE: Thank you.

Speaker number 2, please unmute and turn on your webcam. Speaker number 2, would you please begin and introduce yourself. Please state your name and any organization you're representing for the record.

DR. MILAS: Hello. My name is Dr. Bonnie

Milas. I have no disclosures other than I am an ASA member. As a professor, I normally have slides for my talks, but today I'd like you to concentrate only on my words.

If I ask the attendees of this hearing to raise their hand if they have ever administered naloxone nasal spray in their home to a relative, performed CPR on them, and also use the same measures on patients, I'm guessing that I may be one of the only ones with my hand in the air. I'm uniquely qualified to speak here today.

Although I had rescued my sons with naloxone on a number of occasions, I tragically lost both of my sons to accidental fentanyl overdoses. I have no remaining children. Ironically, as an anesthesiologist at the University of Pennsylvania, I administer fentanyl to patients safely every day for heart surgery. I'm an expert at recognizing opioid overdose, how to administer naloxone, and how to perform life-support maneuvers.

I want you to walk in my shoes for just a bit and imagine yourself watching someone in the

process of dying from an overdose in your home. Late at night, I walked into the kitchen, only to stumble on my son's collapsed body. Even in the dark, I can see his lips are blue. He was not breathing. I called out for help, "Get the naloxone! Dial 911!" I cannot remember if I checked his pulse, but I could not pry his mouth open. I immediately started breathing for him through his nose and doing chest compressions. I administered the critical naloxone.

As he regained consciousness, the police and the EMTs were in my house and neither were compassionate or polite. One EMT was overheard saying, "I don't know why we waste naloxone on these people." That is my lived experience.

After having lost my sons, you might say, why would I argue to have naloxone over the counter? It's because naloxone gave them a chance at recovery. Early in our family's experience, the only naloxone option was intravenous, which I gratefully administered in my home on one occasion; yet, no other members in my family could save our

sons by placing an intravenous catheter. Having nasal naloxone spray was a blessing because that meant my non-medical husband and father-in-law could rescue our sons.

Drug addiction is a horrible relapsing disease and overdose is common. Each rescue of our sons with naloxone was yet another chance to live with additional recovery care. It was a chance to live a full life. Every family in the United States should have this same chance at survival for their loved one. Easy over-the-counter access empowers laypersons to respond immediately to emergency medical needs. This is a public healthcare activity.

Precious few community members may have my medical knowledge or lived experience; yet, it only takes a basic level of knowledge and having naloxone nasal spray immediately on hand to save an overdose victim's life. Most of these deaths are due to fentanyl. Fentanyl analogs are a game changer. They are killers. If taken orally, there may be minutes before the victim becomes

unconscious and stops breathing. If smoked or injected intravenous, those lethal events can happen in 90 seconds. It's rapid suffocation. There's not enough time to wait for police or EMS to arrive with naloxone. Family and friends must be the immediate responders on the scene.

Over-the-counter naloxone improves [inaudible - audio gap] -- treatment by medical professionals and helps prevent permanent brain injury or death. Naloxone must be in every home and next to every AED in public spaces.

There's been an unwillingness to stop the flood of fentanyl across our borders, so we must make a dramatic move to have immediately accessible naloxone and basic rescue skills in the hands of citizens. This dire need is why I'm spearheading the REVIVEme.com campaign with my American Society of Anesthesiologist colleagues. Counterfeit pills contaminated by fentanyl are causing accidental poisonings and deaths of our youth. This has led to the One Pill Can Kill Initiative.

The morbidity and mortality report of

December 16, 2022 points out that overdose deaths in 10 to 19 year olds have increased by 109 percent. In 80 percent of these cases, there was one or more bystander on the scene who did nothing, nothing to revive the dying youngster. We must do better for our children. Education, skills, and naloxone on the scene are vital steps.

Naloxone nasal spray is easy to use. Safe and effective labeling has already been established at the FDA. There are no harmful effects if the medication is mistakenly given when a victim is not overdosing. Naloxone spray takes 2 to 3 minutes to be effective, and giving repeated doses should be avoided. The medication lasts 30 to 60 minutes, so the victim can fall unconscious again if the opioid is longer acting. That is why calling 911 and getting medically trained help is key. Following an overdose, a plan needs to be put in place for drug abuse treatment. All of these measures can be made clear to the public and easily conveyed in packaging and public education to avoid misuse.

Naloxone can cause symptoms of withdrawal

like sweating, nervousness, nausea, and vomiting. These symptoms are the primary reason why recreational use of naloxone does not occur. Contrary to what you might read on the internet, naloxone does not increase someone's high. There is no risk of abuse of naloxone. The critical issue is get the victim awake, breathing again, and to save their life. My sons never liked the discomfort of withdrawal that came with naloxone, but they were so grateful to have been revived.

Access to over-the-counter naloxone must be in a manner that is equitable while avoiding barriers and disparity. The cost of changing the status of naloxone from prescription to over the counter must not prohibit widespread availability. Current free access to naloxone must be enhanced to avoid disparities and accessing this life-saving medication. Naloxone free mailed to home, just as was done with COVID-19 testing supplies, is simplest and avoids stigma. A voucher system to retrieve it from a pharmacy is also feasible. An equitable solution is within our grasp with federal

and corporate cooperation.

As the only antidote to opioids, naloxone saves lives. According to studies by the CDC on addictive behaviors, naloxone in the hands of laypersons is safe and decreases overdose deaths by 15 percent and in African-Americans by 25 percent. So if you look at the last year's numbers of overdose deaths at 108,000, over-the-counter naloxone could potentially save 20,000 lives. That number alone should be a cornerstone of this hearing decision.

Brand name Narcan with its convenient packaging, with the appropriate 4-milligram dose and a ready-to-use nasal spray, is a lifesaver. This product is preferable over the 2-milligram generic nasal Bristojet that needs to be assembled in the trembling hands of a nervous layperson.

My sons are never coming home again. Life is precious and can slip away suddenly due to an overdose. Over-the-counter naloxone is the next game changer, and the time is now. I will not stop until this medication is universally available. I

thank the committee for my time to present.

DR. COYLE: Thank you.

Speaker number 3, please unmute and turn on your webcam. Speaker number 3, begin and introduce yourself by stating your name and any organization that you are representing for the record.

MS. HULSEY: Thank you so much. My name is Jessica Hulsey, and I'm the executive director of the Addiction Policy Forum. APS is a patient and caregiver advocacy organization that covers all 50 states, representing patients, caregivers, and practitioners. I'm also an impacted family member. I work in this field because I lost both of my parents to opioid-use disorder.

The reality right now is that this is an unprecedented crisis. We're losing 295 people or more a day to overdose, and we at APF represent many of those families and communities that are really at the center of this crisis. Last year, we released a framework for necessary steps that every state and community needs to take to address the opioid epidemic, this crisis, and at the top of

that list is the need to increase distribution of naloxone, and to make sure that linkage to care exists after each overdose reversal.

In that same vein, the Addiction Policy Forum supports making naloxone available over the counter. We believe that this should be as easy to access as Tylenol, or Nasonex, or other medicines that you can find at your local pharmacy, without any barriers to obtaining this life-saving medication and without any stigma for the families, patients, first responders and communities, and practitioners who are accessing and searching that out.

However, while we support the availability of naloxone over the counter and see it as a major opportunity, we also recognize it could present some challenges and potential unintended consequences for our patient community. In response, we conducted a stakeholder focus group to collect feedback and really make sure that we can share some perspectives from the patient, family, and practitioner community about this potential

change.

Our focus group participants were very diverse: addiction psychiatrist; individuals in the recovery field; individuals with lived experience and receiving treatment or in recovery from addiction themselves; caregivers; individuals from the criminal justice system, jails and re-entry programs; as well as advocates and leaders from our harm reduction partners.

We would like to share with you three main categories of consideration from our community for you to consider. Number one is to ensure that the change to over-the-counter naloxone does not affect the funding and resources currently available for free naloxone and active distribution of naloxone to high-risk populations. We as a community recommend that over-the-counter products supplement, not supplant, our current distribution mechanism.

We like to describe this from a sort of practitioner network and a patient network, as there are both active and passive ways to

distribute naloxone to communities. Active or proactive distribution of overdose education and naloxone to at-risk populations commonly is happening at harm reduction programs; at hospitals or emergency departments; distribution to individuals released from prison or jail; or co-prescribing of naloxone with an opioid prescription. Passive methods would make available naloxone to those who seek it out on their own, which would include, let's say, a vending machine or something next to that, an AED box, or at pharmacies.

To be clear, making naloxone available over the counter is an additional passive mechanism, not an active distribution to at-risk communities. We are fully in support and see this as a mechanism and a real opportunity to expand access across the board to our communities, and we ask and are hopeful that this will be a supplement. This will be in addition to the current mechanisms that are in place and the funding and resources that are available to harm reduction, first responders,

emergency departments, and criminal justice systems. That is our biggest concern and our worry about a potential unintended consequence.

Another consideration that we would like to share is around pricing. For example, given the prevalence of fentanyl and our illicit drug supply, multiple doses of naloxone are frequently required to reverse an overdose, sometimes 3 or 4 doses. We urge the FDA to consider the price point that does not create a financial barrier for most American households. Our patient and caregiver focus group was recommending or hoping for a ceiling of $20 per dose, and even the potential of naloxone being as affordable as a large bottle of Tylenol.

Another consideration that's sort of in that pricing category is, are their extra barriers? Is this going to still be behind the counter at a pharmacy? Will it be in lock boxes with razors and other products? What is the training going to be for pharmacy staff to make sure that this is a location for accessing naloxone that is not rife with stigma, judgment, or mistreatment of our

patient and caregiver community that is seeking resources to save a life?

Our third recommendation or area of consideration is around education and intervention. There are some concerns, particularly among our treatment partners, our addiction psychiatrists, and addiction physicians that are part of our network at APS, that we don't want to eliminate or reduce our point of contact with patients who have just had their lives saved. They've just used a life-saving medication, and naloxone is critical. It can reverse that overdose, but we want to make sure we get people into care.

Right now, our current distribution system includes that education point. It often includes that linkage to care. It creates a touch point with a healthcare professional, with an addiction specialist, or a well-informed volunteer that can make a connection, and can create that linkage to care if, and when, and at the point of time that that patient is ready for that.

These interactions allow for education

around addiction and you know where to go for possible treatment options. It allows for education of a family, and it also can allow for a positive interaction with a healthcare system that has received that training and that has received those resources to build that relationship. It also builds harm reduction strategies, so if that patient is not ready for treatment at that moment, if they're not ready to begin using a medication for an opioid-use disorder, that we can ensure that we are sharing harm reduction strategies to stay safe and well and also be a point of contact for that patient in the future.

We urge the FDA to consider packaging, or inserts, or follow-up, or training, or pieces that are available in that pharmacy to ensure that that follow-up piece is not lost in the over-the-counter availability of naloxone. Naloxone is life-saving but it is not a treatment. It is critical, but we hope to not lose sight of the need to connect each individual who's had an overdose reversed to care that they need to prevent another overdose, or

potentially to prevent another fatal overdose.

Another example is to think of this, that if we had over-the-counter availability of a medicine to stop a heart attack, we would still want that patient to engage in healthcare and even emergency medicine to make sure that they're ok. If we had other things that were available over the counter after a life-threatening incident, we would want to get that patient into care, and we hope that some of the wraparound supports and the mechanisms that are available, along with the OTC provision, take into account that need for connection to care.

From our larger network, this is a major opportunity to make sure that we address the barriers that do exist currently. This could potentially mean we could order the naloxone that we need from Amazon or pick it up at our local CVS or Walgreens; that we have a net increase in the naloxone that's available nationwide; and that we also start to normalize the availability of naloxone to address the stigma and make sure that people know that every life is worth saving, and

that our individuals who are struggling with substance-use disorders need to have access to medications that can keep them alive without any stigma, or judgment, or mistreatment that is connected with that.

Thank you for including a patient advocacy organization to share our perspectives and our concerns or considerations in this change. We look forward to working with you, and at the end of the day think that any effort that we can make to have more naloxone available and in more hands with education is a net positive for our patient community. Thank you.

DR. COYLE: Thank you.

We'll move on to speaker number 4. Please unmute and turn on your webcam. Speaker number 4, you may begin and introduce yourself by stating your name and any organization you are representing for the record.

MS. WILCOX: Hello. My name is Terry Wilcox, and I am the CEO and founder of Patients Rising. It's an organization that advocates on

behalf of patients with rare and chronic diseases. We support reforms in legislation aimed at advancing patient access to afford quality health care. Formed in 2015, we have developed a significant following of over 110,000 patients and caregivers, and have guided them on their journey to advocate for themselves and their loved ones to get the care and treatments they need. I will disclose that Patients Rising has received funding support from both Emergent BioSolutions and Teva for our program, none of which has driven my desire to speak here today. Expanded naloxone availability is a personal issue to me, having lost my cousin to an opioid overdose in 2013.

The opioid epidemic in America is far-reaching and larger than it's ever been. Since 1999, opioid overdose deaths have been on a meteoric rise. Opioid overdose deaths in the year 2020 totaled 68,630, dwarfing the death total in 1999 by a factor of nearly 4. When examining NIH data, overdose deaths, in general, which opioid-related overdoses comprise the lion's share

of, are now so prevalent that they rank among the annual leading causes of death in the country. The root cause of this building crisis, it's tough to pin down and address, so the necessary course of action becomes preventing overdoses as they occur.

Fortunately, treatments such as naloxone are effective and largely available. The subject of the joint committee hearing at hand is whether or not the existing data support naloxone being able to be offered over the counter for purchase with no insurance required. There are data and reports which absolutely indicate this.

A CDC report from September 2020 investigated relevant characteristics in 16,236 overdose deaths from January 2019 to June 2019. The findings reveal key insights for preventing death. Of those 16,236 deaths, over 3 in 5 overdose deaths -- a total of 62.7 percent -- had evidence of at least one potential opportunity for intervention, and 37 percent occurred with a bystander present.

Further, a different CDC report from 2015

shows a survey tracking naloxone kit distribution and is used in reversing opioid overdoses. In calendar year 2013, nearly 38,000 kits were given out and used to save over 8,000 lives. In this same report from calendar year 1996 to June 2014, 26,463 opioid overdoses were prevented thanks to naloxone. The exact number of lives that would have been saved had naloxone been more readily available cannot be determined, but it's certainly an aspect of this discussion that deserves consideration in federal rulemaking.

These statistics point to a strong need for increased access to naloxone given the high potential to save someone's life in the event of an overdose. Designating naloxone as an over-the-counter treatment presents an opportunity to save thousands of lives while keeping the treatment accessible and affordable. Designating naloxone as an over-the-counter treatment would not only increase its availability, it would also give a strong headway to combatting a major barrier to access, this stigma associated with addiction. It

can be uncomfortable for someone with substance-abuse disorder to pursue treatment, which prevents overdose, because of these societal stigmas.

The current order of operations for procuring naloxone requires discussions with doctors, insurance companies, and pharmacists. Any or all of these steps put substance-use disorder patients in an uncomfortable position while seeking a life-saving treatment. As a result, the people who need this treatment the most are, for lack of a better term, sometimes discouraged from seeking it. Being able to acquire naloxone independent of a doctor's or insurance company's approval would decrease the stigma, increase access and availability, and save lives.

In the wake of an ever-increasing epidemic of overdose deaths, there is a strong responsibility for federal administrators and stakeholders to take corrective measures. The potential of designating naloxone as an over-the-counter treatment, preventing and saving

thousands of lives, can neither be understated nor ignored, and it is my strong hope that both committee recommend proceeding with this course of action. In closing, thank you for the opportunity to offer my testimony today.

DR. COYLE: Thank you.

We will move on to speaker number 5. Please unmute and turn on your webcam. Speaker number 5, please begin by introducing yourself. You may state your name and any organization that you are representing for the record.

MR. BRASON: Good afternoon. My name is Fred Brason, and I represent Project Lazarus as the founder and CEO, and Project Lazarus is a community-based nonprofit with a public health approach for addressing substance-use disorders that we began in 2007. I have no disclosures. I'm here on my own accord.

I first learned, through the process of working as a director and chaplain at hospice, about the nature of the opioid-use crisis that we have incurred in the United States. 2007 was the

first time I learned about naloxone, and when I heard about it -- and realized that with our hub-and-spoke model of working with providers, and ED policies, and people with pain, and harm reduction, addiction treatment, and community education -- my first logical question was, "Well, who has the naloxone if it reverses overdose?" Our county in northwest North Carolina, Wilkes County, in 2007 was the third worst county in the United States for prescription drug overdoses and obviously had a great need for naloxone.

When I learned about it, I asked the question, "Who has it?" and I was told EMS and emergency departments are the primary areas where it's accessible. And then I said, "Well what about people at risk?" because the folks in my county weren't dying in the ambulance or in the hospital. They were on their own bed, on a friend's couch, living room, or wherever in the community. So I posed that question to then Dr. Janelle Rhyne, who was head of our medical board for North Carolina, about that question, "Why isn't naloxone readily

available for people who are at risk?" She thankfully said, "Good question. Let's find out."

They gave us a hearing towards the end of 2007 to present our case about who's at risk: the person who is on high-dose opioids; the person who has a methadone prescription; the person who's in an opioid treatment program; the person who's coming out of jail who's been incarcerated. I can go on and on about where the risks are, and they've, unfortunately, increased over the years because of the use of heroin, and fentanyl, and others.

We had that hearing, and they gave us half an hour to speak, and we did, and it went on for 45 minutes. Then the policy director, the medical director that was on the the judges panel -- there were five of them -- stopped us and raised his hand and said, "You know, before you came in here as Project Lazarus, we pretty much had a discussion, and we were against a program like this." And he said, "But you have convinced us and shown us that we are prescribing to individuals in our own

practices who are at risk for an overdose."

So the North Carolina Medical Board became the first one in the United States that said the goals of Project Lazarus are consistent with the board's statutory mission to protect the people of North Carolina. The board therefore encourages all licensees to abide by the protocols employed by Project Lazarus and to cooperate with the program's efforts to make naloxone available to persons who are at risk of suffering drug overdoses.

That was published in 2008 for all the licensees in North Carolina. Here we are in February of 2023, nearly 15-16 years later, and just now looking at over the counter for individuals who are at risk. Yes, we have more dispensing through harm reduction. Yes, we have standing orders in the pharmacies. Yes, we now have available nasal devices and still intramuscular, whereas when we first started to dispense and distribute naloxone, we had to get a prefilled syringe, an off-label atomizer, put it into a kit and make it accessible, which was

extremely difficult and cumbersome, and obviously not easy to put together in a panic situation. So I'm thrilled we do have more devices, and I'm thrilled we're talking about over the counter.

Now, as we talked and looked at people at risk and how to reach them from a community public health perspective, I remember working early on with the Clinton Foundation, who looked at naloxone and had discussions with them over and over again, and everybody kept looking at what's the best way. What's the new way that we can get naloxone out to the general public and others who are at risk? And I said, "Well, there perhaps are new ways, but we don't look at our current infrastructure and determine are all of the avenues of our infrastructure being utilized to dispense and distribute naloxone."

And thankfully, they agreed with that aspect that, yes, it should be co-prescribed to that individual who's at risk? Yes, it should be provided in the prison or the jail for the inmate who's being released, who has substance-use

disorders, or previous history. Yes, it should be given and accessible to somebody who's presented in the emergency department because of a withdrawal episode or an overdose episode. They should be walking out with it; the same with somebody who's been hospitalized for endocarditis and other issues because of injection of prescription, or heroin, or fentanyl products.

So there are different avenues for every single aspect of our population. Should over the counter be one of those avenues? Yes, it should. Is it the be-all/end-all? Not necessarily. We cannot remove all the other avenues just to provide one more. I think it's in addition to. And as we do that, yes, it's going to enhance harm reduction. Yes, hopefully it'll bring in the price range that individuals can afford.

DR. COYLE: Number 5, I need you to wrap up your comments.

MR. BRASON: I was at one of our local high schools today in one of our neighboring counties with the school nurses, the school social workers,

the school counselors, and providing them training on critical incident stress management for children they knew, and they were all interested in obtaining naloxone. "How can we have it? I want to send it to my kid who's in college to make sure that he and others in that dorm are safe," and so they're asking me how to get it.

DR. COYLE: Number 5?

MR. BRASON: Thankfully, we're harm reduction, and we can provide it to them.

(Crosstalk.)

DR. COYLE: Number 5, final comment.

MR. BRASON: But the aspect of being able to say, well, you just go into your pharmacy, and look now where certain opportunities are for receiving that, and you can pick that up. So I encourage you to agree for over the counter, increase that avenue for that, and I thank you for your time today in allowing me to speak. Thank you.

DR. COYLE: Thank you.

We need to move on to our public speaker number 6. Please unmute and turn on your webcam.

Speaker number 6, you may begin by introducing yourself. Please state your name and any organization that you're representing for the record here today.

MR. SPANGLER: Good afternoon. I'm David Spangler with the Consumer Healthcare Products Association. We represent over 65 manufacturers of nonprescription medicines, dietary supplements, and consumer medical devices. While we do have members with an interest in naloxone, Emergent BioSolutions is not a current CHPA member.

Access matters. Access is about time, it's about place, it's about removing barriers. Since this meeting began this morning, if you take the yearly average, over 50 people would have died from an opioid overdose. I've followed prescription to nonprescription switch, the process, for many years. All prescription and nonprescription switch candidates have to be shown safe and effective on the basis of their labeling, but few, very few, OTC medicines can truly save a life.

OTC asthma medicines when immediate use may

be essential and the asthmatic can't access their Rx medicine; nicotine replacement therapy to extend the life of a smoker seeking to quit; chewing an aspirin at the time of a heart attack -- and that's a professional indication, that's not on the OTC label -- that's three. I might have missed one or two, but I can't think of others. Naloxone would be another.

FDA, the healthcare community, and emergency responders have already come so far in improving access to naloxone. From FDA's recommendations to prescribe naloxone liberally, FDA's approval of naloxone kits for community use, state laws or regulations allowing more people to carry and administer naloxone through nonpatient-specific prescriptions or standing orders, these have all been life-saving means to expand naloxone access.

FDA's own label studies and opening a docket on naloxone, things you heard about this morning, are two more illustrations of trying to remove barriers to access. Now is the time to finish the job. If you're satisfied the sponsor can move

ahead with FDA on label enhancements on the use of their spray without further delays, the expanded access that nonprescription status can provide will remove still more barriers; barriers such as the stigma some feel in interacting with a healthcare professional; or using their insurance to get naloxone; or removing hurdles for community-based harm reduction groups to access product in bulk; or perceived, or real, perceptions that naloxone is unavailable without a patient-specific prescription. Access does matter. Now it's time to finish the job.

Clarifying Questions (continued)

DR. COYLE: Thank you, speaker number 6.

The open public hearing portion of this meeting has now concluded, and we will no longer take any comments from the audience; however, we do have some time in our agenda to take remaining clarifying questions to Emergent from the advisory panel members.

I believe that Dr. Brent, Ms. Coykendall, and Dr. Pisarik had their hands up when we had

previously indicated we had some time for questions for Emergent, so I'll reach back to those three in that order to see if they have additional questions that they would like to have clarified.

Again, just a reminder to please state your name into the record when you're beginning your question, and also indicate when your question has been answered. And again, we'd like to focus this time to addressing questions for the applicant rather than focusing on recommendations. We'll have time for that later.

At this point, Dr. Brent, did you have a further question for Emergent?

DR. BRENT: Thank you. No. That was covered in my prior remark.

DR. COYLE: Thank you.

Ms. Coykendall, did you have a question that you'd like followed up for Emergent?

MS. COYKENDALL: Thank you. No, my question was based on labeling, and it has been answered. Thank you.

DR. COYLE: Dr. Pisarik?

DR. PISARIK: Paul Pisarik. I just had a comment, and it kind of backs off what Dr. Clement had said earlier, in terms of the fact that we're assuming that people will be treating an opioid overdose, but it may not be an opioid overdose. It might be something else, which is a cardiac arrest, or hypoglycemic coma, or something like that.

So in the prescribing labeling, it does mention something to the effect that after you've administered the first dose, rescue breathing or even CPR might be an option. So I was wondering if that was a consideration, putting some wording to that effect that there might be other things you can do while you're waiting for naloxone to kick in, if this is truly an opioid overdose. Thank you.

Dr. Pisarik, can you clarify for me? Were you hoping that Emergent could respond to some of those concerns or you would just like to have that thought out there for future discussion?

DR. PISARIK: Maybe just for future discussion. I think it's complicated, and just

like Dr. Clement had said, we're not trying to train the lay public in being first responders, but by the same token, not everybody who collapses has an opioid overdose; so some sort of wording in the labeling that might state that after you give the first dose with Narcan, should you also be doing rescue breathing, or if they don't respond, besides calling 911, maybe start doing CPR or something to that effect.

DR. COYLE: Thank you. We can circle back to that during our discussion among panel members.

Let me open this time to other panel members. Are there any further clarifying questions, starting with the sponsor, anything that we can use this time to further understand or share across the group?

(No response.)

DR. COYLE: I'm going to scan for any raised hands.

(No response.)

DR. COYLE: Dr. Clement, if you have a clarifying question for Emergent, please share.

DR. CLEMENT: Hello? Can you see me or hear me? This is Dr. Clement. I remembered to say my name now. Actually, I had one more question for the FDA people, but should that just wait for the discussion part later on?

DR. COYLE: It looks like we may have some time to address questions to FDA, but let me do one last call to make sure that there aren't any questions for the sponsor.

(No response.)

DR. COYLE: Seeing none, we can move on. If there are questions for FDA, you may raise your hand and indicate that. Again, please remember to state your name for the record.

I will begin with the first question, if you will allow me, and I think this question would be directed to Dr. Michele. We've heard through both presentations of the morning that there are several aspects of this Rx to OTC switch that are quite unique. I think one that we have not discussed is if this is actually an OTC product that would be administered to a patient not making the choice for

themselves; in fact, a patient for which a bystander or somebody who might have Narcan doesn't even know anything about.

I'm just curious if there are additional considerations that haven't been brought up in the discussion that are relevant to that particular aspect of this Rx to OTC switch.

DR. MICHELE: This is Theresa Michele, director of Office of Nonprescription Drugs, and thank you, Dr. Coyle, for that question. You are absolutely correct, that that is a very unique aspect to the switch, and one that we batted around quite a bit on our side, as well. At the end of the day, what we came to was the need to make the instructions as simple as possible for consumers who may potentially be picking up this product, knowing very little, if anything, about it, and giving it to a person who, as others have brought up, may or may not be having a drug overdose.

So it really comes back to the overall safety and effectiveness and the risk-benefit of naloxone, recognizing, as others have stated, that

not everyone who is unresponsive may be having a drug overdose. So I'd turn that back over to the panel, and I'll be very interested to hear your thoughts on that.

DR. COYLE: Thank you. Thank you for that information.

Dr. Clement, thank you for your patience, while I asked my question, and I'll turn the floor over to you.

DR. CLEMENT: Thank you. Again, Dr. Clement, C. Clement, active practitioner, and have been a first responder in some of these situations; not always.

My question is to the FDA, to basically come back to the previous advisory member that said -- it basically alludes to the idea of how much education is really needed because we're going way past just an antidote for a drug. If that first dose doesn't work, how much should be put in the label? And you want to keep the label so simple, and that's totally understood. Are there other ways that the manufacturer can help educate

the lay public about this?

So my question to the FDA is, how much leeway do you have? I know there are restrictions on the label, but can you ask them to put it on their website, do videos, make a video about what to do and how to actually approach a patient that's unresponsive, that may or may not be used? Are those available?

Some of the ideas I'm thinking of is that you give the first dose; give the second dose; and follow all the label things. But while you're waiting for the ambulance, do you want to check a pulse? You may want to check for breathing. If things aren't going on, get your team member to help do CPR, those type of things.

So I'm just curious from the FDA's standpoint, since this is the first application for OTC for something that's actually done by not the consumer but a responsible bystander, this really is a unique opportunity to get it right in terms of the type of things that should be done by the provider. Obviously, this would be on the website,

but clearly there's going to be a huge amount of education needed that can be branched out to people. So I'll stop there with my comments and ask for your response on that. Thank you very much.

DR. MICHELE: Thank you, Dr. Clement, for that question. Again, Theresa Michele, Office of Nonprescription Drugs.

So when we boiled all of this down, we came to they call 911, which was why we listed that as the number one thing that we tested in our model Drug Facts Label. In terms of education of consumers, you are absolutely right; consumers will need a whole lot of education on this. Much of that is kind of beyond what you can put in a Drug Facts Label, but there are a whole variety of venues by which consumers get education, and certainly we always encourage sponsors to provide as much educational materials to people as possible on their websites and on other places.

We also rely on the community-at-large. Certainly, we've heard from a lot of stakeholders

today who are very into consumer education, and those are incredibly valuable resources, academics, physicians. It really takes a whole community to work on this problem, which is, of course, so multifactorial. Thank you.

DR. COYLE: Thank you, Dr. Michele and Dr. Clement.

I would like to recognize Dr. Ness.

DR. NESS: Yes. I just wanted to make a comment as sort of a follow-up to that. Can you hear me?

DR. COYLE: I can hear you. Please say your full name into the record.

DR. NESS: Oh, I'm sorry. I'm Timothy Ness from University of Alabama at Birmingham. In terms of this education thing, I was just hearing over and over also about this sense of a connection-to-care aspect of the education in the sense that naloxone is a uniquely different drug that we have used. You give someone ibuprofen, you don't insist on a connection to care about headaches or things like this. But this is a

life-threatening event, and somehow I feel there is a moral obligation on the part of companies that may be making a profit on selling things to stop these things, to have to provide that connection.

So my question would be actually towards FDA. Is there any ability to insist on the the insert that there be this, again, website connection? I mean, certainly with opioids, we have the REMS strategies that we had that were an FDA-led process. Could they not have a similar thing, that they'd at least be required to set up with a consortium, or a company sponsored, or something of an information site that would be a connection to care?

DR. MICHELE: Once again, Theresa Michele, nonprescription drugs. There are no postmarketing requirements or REMS for nonprescription drugs.

DR. NESS: So there is no -- you can't ask for that?

DR. MICHELE: So that's probably a bit beyond OTC labeling, but certainly, again, I'd turn back to that call 911, which is the immediate

connection to care.

DR. NESS: No more questions.

DR. COYLE: Thank you. Thank you all.

I don't see any further requests for an opportunity to speak. I don't see any hands raised in our roster here among our committee members, so at this point I would like to move on and proceed with the charge to our committee from Dr. Jody Green.

Charge to the Committee - Jody Green

DR. GREEN: Good afternoon. Thank you, Dr. Coyle.

My name is Jody Green. Today, I will provide the charge to the committee, and introduce the questions for discussion, and try to provide some context. The key points discussed today include the following.

Naloxone hydrochloride, 4-milligram nasal spray is an opioid antagonist used for the emergency treatment of opioid overdose. Currently, it is a prescription product for community use, meaning that it can be administered by individuals

in the community without formal medical training. As a prescription product, it may be administered through traditional pharmacy channels such as from a healthcare provider or using a variety of community-based naloxone distribution programs such as harm reduction groups.

Although the drug device product discussed today is the same one that has been used in the community for the last few years, what is new is that the applicant is seeking nonprescription status for their product. If approved as a nonprescription product, naloxone nasal spray may be sold more broadly through the United States, in a greater variety of retail outlets, and may reduce the stigma for some obtaining an opioid reversal agent.

I want to remind you that in the United States, under the Food, Drug, and Cosmetic Act, there are two classes of drugs. FDA-approved drugs is either prescription or nonprescription. FDA approves a drug as a prescription product if it is not safe for use, except under the supervision of a

practitioner licensed to administer the drug because of its toxicity or other potentially harmful effects, its method of use, or other collateral measures necessary for use such as requiring monitoring.

If the drug does not meet these requirements, FDA can approve the drug as a nonprescription drug. A nonprescription drug can be used safely and effectively by a consumer without the supervision of a healthcare practitioner and does not meet the criteria for prescription-only dispensing.

Under the Code of Federal Regulation, the FDA can approve the supplement to an approved prescription drug application, requesting to market the drug as nonprescription if the following two conditions are met: FDA finds that the prescription requirement is not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect; or the method of its use; or the collateral measure necessary for its use; and FDA finds that

the drug is safe and effective for use in self-medication as directed in the proposed labeling. This requires the review of adequate data to make this determination. Both conditions must be met.

Nonprescription drugs generally have the following characteristics. They can be adequately labeled such that the consumer can self-diagnose, self-treat, and self-manage the condition being treated; no healthcare practitioner is required for the safe and effective use of the product; the drug has a low potential for misuse and abuse; and the safety margin is such that the benefit of the nonprescription availability outweighs the risk.

We're going to ask you to vote later today on the questions that we will ask you to discuss. The discussion will be just as important for us as how you vote. Our discussion today will include what we know about naloxone safety since it was first approved in 1971, and particularly what we can glean from the last six years of community use, particularly with regard to serious adverse events

such as precipitated withdrawal.

In addition, we will ask you to discuss aspects of the applicant's Human Factors Validation Study and associated user interface as adequate support for approval. We will ask you to discuss if there's a need for additional labeling materials to further mitigate risk. Finally, we will charge the committee today with discussing whether the applicant's product, Narcan nasal spray, is safe and effective for nonprescription use based on the information presented today to help guide us in our decision.

So now for the questions, but I must preface the questions by saying that they are based on the submitted application and our review. The sponsor's most recent proposal for an enlarged carton and a quick start guide has not yet been officially submitted or reviewed.

The first question, discuss the safety profile for use of Narcan nasal spray in the nonprescription setting. We've shared with you today both the common adverse events, as well as

the serious adverse events associated with naloxone that have been observed in the postmarketing setting.

Question number 2, discuss if the results of the Human Factors Validation Study support that consumers are able to correctly administer naloxone nasal spray in an emergency setting. This discussion is in four parts.

Discuss the Human Factors Validation Study design and the interpretability of the study. We shared with you the methods of how the study was conducted and how the subjects performed on the testing.

Part B, discuss the use errors observed in the Human Factors Validation Study where participants started with step 3, "Call 911," during the simulation and they bypassed step 1 and 2. Could the intent to market nonprescription cartons be further improved to mitigate risk of delayed administration?

Part C. Discuss the incorrect finger placement on the nasal spray observed during the

Human Factors Validation Study. Could the pictogram be further improved to optimize correct administration?

Part D, discuss whether the Human Factors Validation Data, submitted under the "mock" nonprescription user interface, support the safe and effective use of the proposed nonprescription naloxone nasal spray and the modified intend-to-market user interface. If not, what additional data are needed?

Then question 3 is, discuss whether there is additional labeling information that might mitigate risk of use errors. As consumers cannot be assumed to have received any advice from healthcare professionals before using this product, please share with us what other information you think is essential for consumers who are using the product on an emergency basis.

Next, the voting question. Is the benefit-risk profile of naloxone nasal spray supportive of its use as a nonprescription, opioid overdose reversal agent? If you vote no, what

further data should be obtained. When you vote, we're interested in knowing not just yes or no, but also your reasoning. We are also interested in knowing, now that we have new information regarding labeling plans as discussed by the applicant, how this new information would affect your vote.

In summary, I want to thank you again for participating in our advisory meeting today, and now I'll turn the meeting back to Dr. Coyle.

Questions to the Committee and Discussion

DR. COYLE: Thank you, Dr. Green.

The committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussion. 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.

After I read each question, we will pause

for any questions or comments concerning the wording itself. After that, we will open the question to discussion. I would just like to advise the panel to please make sure that we're focusing on the specific question that is being asked. Because we do have such a large number of questions, I think it will greatly facilitate our discussion if we're able to do that.

So we will begin with question number 1. Discuss the safety profile for use of Narcan nasal spray in the nonprescription setting.

Are there any questions or comments concerning the wording of the question?

(No response.)

DR. COYLE: Seeing none, I will now open the question for discussion. And again, please use your raise-hand feature as we have been doing throughout the meeting, and please make sure to state your name into the record as you begin speaking.

Ms. Coykendall, please go ahead.

MS. COYKENDALL: Hi. Elizabeth Coykendall.

I've been a 911 paramedic and just wanted to speak to the safety profile. I know a few times there have been comments about mistakenly given Narcan in other situations where it could be cardiac arrest or hypoglycemia.

I have been on multiple scenes where that has happened, where either a firefighter, or police officer, or a bystander has given Narcan unknowingly before EMS arrival, and they've given multiple doses of Narcan, sometimes 8, 16, it depends on how many milligrams, multiple times, and in each of those cases, there have not been any adverse effects when that person was successfully resuscitated in whatever was going on. So we were able to bring them out. If they were hypoglycemic, we were able to give them the blood glucose to bring them back out.

So never have I seen Narcan being used in a operation where it was not indicated, and I have not seen an adverse reaction from it. Thank you.

DR. COYLE: Thank you.

I'm going to call on Dr. Brent next and

encourage us all to keep our comments brief and to the point so that we can really allow time for all members of the panel to participate in the conversation, which is a little bit more standard setting here for our discussion. Thank you.

Dr. Brent?

DR. BRENT: Thank you, Dr. Coyle. I just wanted to say, as a medical toxicologist -- this is Jeffrey Brent -- I can attest to the fact that naloxone is a very safe medication. I totally agree that giving it to somebody who is not opioid toxic will have no adverse effect on them. The few reports that are out there in the literature concerning significant adverse effects by rapid reversal of opioid toxicity really do not apply to the community setting. It's totally other circumstances that are non-applicable.

We received information today that serious adverse effects are less than 1 in 100,000, and if you look at those adverse effects, most of them are actually not true adverse effects. They are more things like putting somebody into withdrawal, or

non-responsiveness, or somebody who is already deceased not waking up. So based on that, I think we could all conclude that naloxone, as would be used in the community setting, would be extremely safe.

DR. COYLE: Thank you, Dr. Brent.

I'm going to call on Dr. Bicket.

DR. BICKET: I'm Mark Bicket at the University of Michigan with the Opioid Prescribing Engagement Network. When it comes to the safety discussion, one point that I think merits bringing up is the fact that while we haven't been able to really incorporate data from harm reduction programs and other non-traditional distribution methods, that these all do increase the amounts of product that's available, and we've seen increases in use. So while we do have data on some of these adverse events, the significance of them may actually be less, given the higher numbers of its availability and use out there.

It does seem like a unique situation where the availability has actually been close to mimic

what a nonprescription situation may be. I do want to recognize the barriers that have been acknowledged before about that, though that does seem unique and one way to promote the safety profile to only consider the risks and the benefits. Thank you.

DR. COYLE: Thank you.

I do not see anyone else in line here. I'm going to, I guess, call on myself to add a further comment about the safety profile. This is Maria Coyle, Ohio State University College of Pharmacy.

One comment that I want to highlight is that I think one aspect of safety that we've heard about a few times today is the potential concern about not administering it fully or not administering it entirely correctly. I would just say that I think that is not a risk per se, or is not an unsafe consideration, given that we don't have an alternative treatment that somebody might be employing for a patient who is actually experiencing a naloxone overdose, except in the situation, which Ms. Coykendall mentioned, where we

are delaying something like CPR for patient who might have coronary arrest or something along those lines. That would only be a consideration, I think, occasionally, but it might be something to think about in terms of are we impacting the safety. Thank you.

I'll call on Dr. Bateman

DR. BATEMAN: Thank you. As we consider the safety, I think it's worth considering the data that's available regarding programs that expand abuse and what the impact was on overdose death rates. Probably the most compelling data I've seen is from Massachusetts. I think one of the speaker's alluded to this.

But there was an interrupted time series analysis where they looked at the expanded introduction of naloxone into communities in Massachusetts, and then compared them with similar communities where naloxone wasn't expanded and its availability, and there were really quite significant reductions in opioid overdose death rates that were observed.

So I think the safety of this medication is very clear. If you give it to someone who's not opioid-dependent, it's not going to do anything, and if you give it to someone who's opioid-dependent, there may be adverse reactions associated with withdrawal, but that's a life-saving effect. Yes, I think the data are quite clear regarding the safety, and anything we can do to expand the availability of this medication in the community is going to be an important component of the public health response to the opioid crisis.

DR. COYLE: Thank you. Thank you very much.

I'll call next on Elizabeth Coykendall. Please state your name for the record.

MS. COYKENDALL: Hi. This is Elizabeth Coykendall again. I just want to, real quick, speak to the delay of care in case it is not an opioid overdose. As number 3 on the list of things to do in the instructions is to call 911, most 911 centers will then instruct the person that is on the phone to do compressions. The hands-only CPR

has been shown to help, even with respiratory depression, so I don't really see the delay in care as being as important or as detrimental if 911 is called. Thank you.

DR. COYLE: Thank you for that response.

Dr. Parker, please go ahead.

DR. PARKER: Thank you. Ruth Parker. I certainly agree that naloxone has a strong safety profile, and there is very good data to support that, that has been covered very clearly.

I also am encouraged to know that there was no data presented, no evidence of the unintended consequence of greater misuse of opioids, based on a higher availability of naloxone being present in certain settings, but I think that's something that will deserve careful data monitoring going forward as a potential unintended consequence that is a safety issue. But it's encouraging to note that there's no data of that at this time, and there's certainly a strong safety profile for naloxone itself. Thank you.

DR. COYLE: Thank you.

Dr. Walker-Harding, please go ahead.

DR. WALKER-HARDING: Hi. It's Leslie Walker-Harding. I also just wanted to agree along with everybody else that is saying that there's evidence of a strong safety profile. There's also nothing to indicate this is unsafe for children, young people who need it, as well as young people who administer it. So I think this drug has had a lot of use, and I see no concerns at all with the safety profile or anything that's been brought up.

DR. COYLE: Thank you, and thank you for that addition, addressing pediatric exposure and data in that regard.

I'm going to acknowledge Ms. Coykendall for our final comment here, and then we'll summarize and move on.

MS. COYKENDALL: Thank you. I just want to respond to Dr. Parker and the concern where users will end up using more often. In my experience going on responding calls, the users absolutely have Narcan, and they all know how to use it. And since Narcan has been available to more people

through places like Walgreens with easy-to-use prescriptions, I have had to administer less Narcan as an emergency responder, and the users are surviving more because they do know how to use it. So just having Narcan over the counter will give them more opportunity to stay alive. Thank you.

DR. COYLE: Thank you.

I do want to wrap up this part of the discussion, so Dr. Walker-Harding, if you have a brief comment to add, that would be great, But otherwise --

(Crosstalk.)

DR. WALKER-HARDING: Yes. I forgot to say something about that as well. I think that fear that people are going to overuse something, it's a common concern without understanding the mechanisms for why people use. I heard the same thing with over-the-counter Plan B. People were worried kids would have more sex if they had Plan B. That's just not how people think, and it's not how people who have an opioid-use disorder would think. So I think that's something we really don't have to

worry about.

DR. COYLE: Thank you very much.

So we will move on from question 1. Just to summarize, I think we heard some clear comments that the safety of Narcan nasal spray has been very well established. There appear to be very minimal risks, if any, in terms of unintended effects or unintended serious effects that are worse than the alternative of not treating a patient, as well as down-the-line effects on behavior and use of opioids, or we're increasing exposure down the line. So I think, overall, we as a committee appear to be in support of the safety profile without substantial concerns related to that.

I'm going to move on to our discussion question number 2, and once again, I'm going to read the question and first ask if there's any issues or questions about the wording itself before we move on. For question number 2, since there are a number of subparts, I might suggest that we focus on the subparts included on the slide in front of you for our conversation right now, but again, let

me start with the question itself.

Discuss whether the results of the Human Factors Validation Study support that consumers are able to correctly administer nonprescription nasal naloxone sodium in an emergency situation. Particularly discuss the Human Factors Validation Study design and the interpretability of this study.

Discuss the use errors observed in the Human Factors Validation Study where participants started with step 3, "Call 911," during the simulation and bypassed steps 1 and 2. Could the intend-to-market nonprescription carton be further improved to mitigate risk of delayed administration?

First, let me check. Are there any issues or confusion around the wording of these discussion questions?

(No response.)

DR. COYLE: Seeing none, I will open the floor to discussion. Please wait to be called on and, again, restate your name. I'd especially like to encourage anyone who has not yet participated to

please share if they have information or a perspective that could be valuable for consideration before our vote.

Dr. Clement, you may begin.

DR. CLEMENT: Yes. Steve Clement again. Clearly, these are very important and vital questions to be answered. I'd like to put it in the context from the industry/sponsor standpoint.

This is a new area for them, too. Right? These guys, they're developing compounds or developing packaging they've got to work out through the whole supply line. But to come up with this whole human factors issue, this may be the first time they're doing this. So I'd just like to consider that they're rookies on this, and they're going to make mistakes, but I think these are all mistakes that can be remedied.

I clearly think they need a new study. The whole issue is this is a condition that's killing people. Is there something that could be done postmarketing, so to speak, and fix it, and basically take the first stab? And get together

with FDA folks -- because you guys have a lot more experience on this area than they do, clearly -- and come up with the best label that you can potentially have, and just go with it, and then do a study on it after the drug's out. I'll stop there. Thank you very much.

DR. COYLE: Thank you, and I will turn the floor over to Dr. Sprintz.

DR. SPRINTZ: Hi. This is Michael Sprintz, and I definitely agree with Dr. Clement about the idea of when we talk about risk-benefit ratio, absolutely, I think the benefits outweigh the risks. And while the study could do better, I think that the solutions that were brought up earlier in the day that were being discussed with the FDA in terms of having all the steps all on the back package, or at the very least, the three first steps on the back of the package is key, as well as inserting the package into the blister pack.

Both of those I think could improve it and mitigate the risk of delayed administration, but I think those have already been put in. At the end

of the day, I like the suggestion also of is there a way to do postmarketing improvement on it because it really does need to get out as soon as possible. Thank you.

DR. COYLE: Thank you.

Dr. Horrow?

DR. HORROW: Yes. Thank you. Jay Horrow. I'm the industry representative on the Anesthesia and Analgesic Drug Products Committee. I do believe that any study design will be less than perfect. Certainly the agency has gone through great lengths to point out the imperfections in the Human Factors Study that was presented, and it could have been better.

Nevertheless, I think we need to consider the extent to which it has resulted in tremendously good suggestions for improvement; suggestions that, in fact, the applicant has taken into consideration. As best as I can recall, applicant's slide number 60 clearly displays their updated proposed carton that has all five of the steps, including the pictographs on one panel. And

if I'm not mistaken, that is what they are proposing, along with including the Quick Start Guide.

So I would suggest to members of the panel that they seriously consider whether or not it will be appropriate to insist or recommend another human factors validation study after considering approvability. Such a move I believe will delay the availability of the product to much needed patients, and it will not be a trivial thing to undertake. Thank you very much. That's my comment.

DR. COYLE: Thank you. I think just to restate, really, the spirit of the comments from both of our two previous speakers, acknowledging that not only is there a risk potentially to using a product incorrectly but perhaps a far greater risk of delaying the availability of a product, given the climate of this crisis and the devastating consequences.

I'm going to call on Dr. McAuliffe next.

DR. McAULIFFE: Hi. Maura McAuliffe, East

Carolina University. In looking at the limitations of the studies, the human factors verification study, the part that kind of strikes me the most is that pediatric users between the ages of 10 and 14 were not included, and we don't have that data. I think we do need to have it. I don't think that it's, for me, a reason to stop this from going forward; however, I think these studies by the FDA, with their Drug Facts Label study as well, could be accomplished concomitantly, and we could get data that might help with the design of the labeling in the future. So I think those do not need to be overlooked. They need to be done concurrently.

Then to add to other people's comments about the pharmacovigilance, there's got to be some way to collect that data on an over-the-counter drug, especially one that is saving lives. We've got to be able to have a handle on that data. Thank you.

DR. COYLE: Thank you, Dr. McAuliffe.

I'm going to call on Dr. McCann.

DR. McCANN: Sorry. I would just like to echo the comments that were just made. My

question -- Mary Ellen McCann from Boston -- is why didn't anybody from the FDA or the company think about testing children less than 15 years of age? It just seems like in future studies, that should be part of it. I don't know the history of the FDA and childproof caps, but at some point you must have had babies and older children trying to open up caps to see if they were actually childproof. And it just seems, since we know that children and young teens will be using this medication, that that should be part of the testing process. And that's it. Thank you.

DR. COYLE: This is Maria Coyle. I'm going to just respond to that to say that I think in the FDA presentation and the clarifying questions, they did actually provide some rationale as to why that happened in the original comprehension study; however, they did not say that they thought it was an ideal situation. I think they didn't know. Just to summarize that, and I'll invite FDA to follow up on my comment with anything further, if needed.

DR. McCANN: Thank you.

DR. MICHELE: Hi. This is Theresa Michele, nonprescription drugs, FDA. Just a couple of comments. First off, with regard to postmarketing studies, unlike in the prescription setting, FDA does not have the ability to require postmarketing studies for nonprescription drugs. So while certainly sponsors are welcome to conduct those, we cannot require those.

With regard to child-resistant packaging, that is not under the jurisdiction of FDA. That is under a different federal agency, under the Poison Control and Prevention Act under the CPSC.

DR. COYLE: Thank you, Dr. Michele.

Dr. Horrow, do you have another comment?

DR. HORROW: Thank you. This is Jay Horrow. Just very quickly, with respect to the point made by Dr. McAuliffe, I do recall hearing FDA mention that it was the IRB in the Label Comprehension Study that expressed concern for subjecting people less than 18 years of age to the trauma of having to read a label about someone who is in distress.

I find it hard to believe that we would want to recommend that the sponsor conduct a study that would subject this same population to the trauma of having a mannequin before them and having to perform a resuscitative type procedure such as administering nasal naloxone. I'm just a little bit confused by the disconnect of these two situations, and would hope that maybe the panel could discuss it if they really believe that it's important to investigate -- [inaudible - audio gap].

DR. COYLE: Dr. Horrow, we've lost your audio, so I'm going to move on.

DR. HORROW: Oh. I'm sorry. I beg your pardon. Did you hear none of that?

DR. COYLE: I think maybe all but the last few sentences, but I think what we heard from you is --

DR. HORROW: You get the idea. Thank you.

DR. COYLE: -- you do have some concerns that a young participant in such a trial might find some trauma, and you would be interested in having

the panel discuss that further --

DR. HORROW: Thank you.

DR. COYLE: -- if there is time.

DR. HORROW: Very good. Thank you. Sorry.

DR. COYLE: Perfect. Thank you.

I'm going to move on to Dr. Higgins first, and then Dr. Parker.

DR. HIGGINS: I do agree with Dr. McCann that there must be ways in which to make it safer for use, but I'm a little concerned about the packaging changes with respect to youth. I'm not terribly old. I have trouble getting open child-resistant objects and packaging, as do other people who are even older than me. So I wonder about that and the delay that it would cause trying to fuss with packaging.

DR. COYLE: Thank you.

Dr. Parker? Please state your name for the record.

DR. PARKER: Yes. Ruth Parker. I just want, for the record, to also underscore the difficulty of commenting on what the sponsor now

proposes to use in a label and what has been reviewed by the agency, and we're being asked to comment on what the agency has reviewed so far. So that makes it difficult because, in my mind, and I think in many, the proposed label now incorporates some changes that are very significant, and they've not yet been reviewed by the agency, and we're commenting on what has been reviewed up to this point. So I just want to make sure that's clear in the record.

That said as background, the Drug Facts Label and label comprehension that was done by the FDA and made available to the sponsor is incredibly important in underscoring how well the label is actually comprehended. That's not human factors, that's not the actual use, which is picked up in the Human Factors Study.

Two things about the human factors that I wish had been done, but we know they were not done, but I can only imagine that they would enhance the results that we have from human factors that are made available based on the label -- that is not

what they now say that they would go forward and use is -- one, there is no quick user guide, so we don't know from the human factors trial whether or not the Quick User Guide, which the sponsor now says would be included in the product, might enhance the use of the product. I don't think it would make it worse. I think it only would stand to make it better.

The other issue is that the ordering of the steps and having them all presented on one drug back panel seems to be a really big issue, and the use errors that are reported seem to relate, many of them, to the fact that there was confusion about where to start and where to turn. And putting those sequentially all on one panel, again, aligns with the strong comprehension that came out of the Label Comprehension Study.

This leads me to the question of whether or not there needs to be another human factors study. I don't think, based on what I've seen, that the proposed improvements -- they do need to be reviewed. That label does need to be reviewed

carefully by the FDA, but whether or not another human factors study is actually required, I'm not certain at all that that needs to be required because the base validity is just so high that those things are going to make results better and not worse, and there's such an urgent need from a public health standpoint to move forward with that.

So I just wanted to put those points onto the record, and just state that it's hard to respond to those studies that were reviewed by the FDA when incorporated improvements are now being noted by the sponsor, and those seem to be very good improvements. Thank you.

DR. COYLE: Thank you for those contributions, Dr. Parker.

This is Maria Coyle again, and I just want to state that I think what you have just shared actually represents the spirit of many of the comments that we have heard thus far heard and discussed, in that many of the aspects of this case are unusual or unprecedented. We would like more information, more reassurance, more study in many

situations, or we could recommend ways to maybe enhance the package without having any authority through the OTC process and the FDA necessarily to enact those recommendations, and yet a sense of urgency that this is a critical question that cannot be delayed in being addressed. So I think that summarizes much of what I've heard thus far.

I'm going to call on Dr. Ginsburg, and then Dr. Ballou, and then maybe we'll move on to the next question.

Dr. Ginsburg?

DR. GINSBURG: Thank you. Diane Ginsburg. I want to echo something that Dr. Horrow said. I guess when I look and see what expertise the various members of this advisory council brings to this group, and being the person who brings the biomedical ethics and pharmacy law piece to this, quite honestly, when I saw that limitation of not studying adolescents and children 10 to 14, I wasn't upset about that at all because my concern of doing research with that population, with this type of product, would have been very concerning to

me.

I think about this in regards to programs that we have here on our campus at the University of Texas at Austin, where we do significant outreach in the communities, and in communities where we're talking to children who are of that age. So in thinking about, again, weighing risk versus benefit, we can always make research and studies better, but that really was not a concern to me. And if anything, I think getting the product out there, knowing that education will be a piece of this, and the role as a pharmacist that I see perhaps we can even have in educating, that limitation would in no way negate the work that was done in this research. And I applaud them for doing a human factors validation study on a product like this. Thank you.

DR. COYLE: Very good. Thank you.

Dr. Ballou?

DR. BALLOU: Jordan Ballou. I'm a community pharmacist and a clinical associate professor at the University of South Carolina. I don't know

that I have anything else to add after Dr. Ginsburg's comment, which was pretty comprehensive of what I was going to share as well.

My work as a community pharmacist, I am behind the counter a lot, and I am doing the dispensing and doing the educating. I've worked with a lot of harm reduction coalitions, particularly youth coalitions, in the work that I have done, and working with high school-aged children. I feel like that comment is coming up a lot about pediatrics, and actually they are the leaders of these groups that I've worked with, and seeing them doing the work alongside their peers, doing peer-to-peer education and training as well.

I don't know that this is the right place for my comment, but just because pediatrics has been coming up so much, I wanted to just make that note, as well as I think that we have to also underscore the work that so many harm reduction groups are doing out there already in this space.

I'm particularly looking at question 2b about the error where people call 911 first. I

don't think that's a huge problem. They're going to say, "Do you have naloxone right there with you? Let's go ahead and administer it." So particularly, to just bring the point back to this particular question on the slide, I don't know that what we've seen so far should prevent this from moving forward at the discussion at this time. Thank you.

DR. COYLE: Thank you, Dr. Ballou.

I would like to ask the committee, the panel members, to look specifically at those subquestions, particularly the use errors, the issue of starting with step 3 rather than with step 1, which is to administer the naloxone spray and further improvements, and ask if there's any additional comments that are germane to the specific question as we wrap up this part of the conversation. A final thought?

Yes, Dr. Sprintz?

DR. SPRINTZ: Hi. This is Michael Sprintz. Yes, I actually had struggled with the idea of having step 3, calling 911, being the third step as

opposed to the first step. I think there's a good argument on both sides in terms of hurry up, minutes count. Minutes are brain, and that matters. But at the same time, I had thought about the idea of a lot of people are freaking out and they don't understand how to utilize the product, so picking up the phone and calling 911 gets EMS there and starts that process moving, and oftentimes, I believe they were talking about how an EMS dispatcher can also help guide the person to deliver the naloxone. I don't have a clear decision on which one should be first, but I see benefits to both.

DR. COYLE: Thank you, Dr. Sprintz.

Dr. Walker-Harding, go ahead.

DR. WALKER-HARDING: Hi. Yes. I think in that sense, in a perfect world you would actually have a phone answered and somebody addressing it. People wait on hold for 911 in many parts of the country, and if you're waiting on hold for a few minutes, you might have lost your window to use the -- just like with CPR, I'm very much for not

having that be the first thing you do necessarily. Get the treatment there, and then get the backup second because not everywhere -- in many places, you don't get immediate phone answering or help when you call 911. So that's what I'd say about that.

I'm not concerned about people calling out of sync or any of those things. I think the most important thing is they have a life-saving medicine in their hands, and that they try to use it the best they know how to use it by reading the instructions that saves a life. Outside of that, that life is not saved, but it goes for kids.

DR. COYLE: Thank you.

Dr. Dato?

DR. DATO: Hi. Thank you. Mark Dato, industry representative, nonprescription drugs. I'd just like to say in a high level here that I'd like us all to remember the study as designed. I would say successful, so the HFVS was successful. Could it be improved in some ways? Of course, and I think a lot of people made suggestions on further

things that could improve that.

I think taking in totality the absolute safety of this compound, the absolute overwhelming need, I think some of the suggestions of move it forward and improve as we go is a good suggestion. As they say, the evil of good is perfect. That's my comment. Thank you.

DR. COYLE: Thank you very much.

Okay. One final question to FDA. Have you gotten sufficient input on this question and this set of subquestions for us to move forward?

DR. MICHELE: This is Theresa Michele, nonprescription drugs. Yes. Thank you so much, Dr. Coyle.

DR. COYLE: Okay. So we will move on to the next slide. This is still question 2, overall addressing the results of the Human Factors Validation Study and supporting whether consumers are able to correctly administer the nonprescription naloxone in an emergency situation. Once again, I'm going to read the specific subquestion, ask for any input as to wording or

clarification, and then I will open the floor for general discussion.

Question 2c before the committee, discuss the incorrect finger placement on the nasal spray in the Human Factors Validation Study. Could the pictogram be further improved to optimize correct administration?

Discuss whether the Human Factors Validation Study data submitted using the "mock" nonprescription user interface supported the safe and effective use of the proposed nonprescription naloxone nasal spray and the modified intend-to-market user interface. Then, if not, what additional data are needed?

First, I'm going to ask only hands be raised if there needs to be clarifications on the wording or the question. It's a lot of words to process.

(No response.)

DR. COYLE: Okay. It seems that the questions are clear, so we'll go ahead and open the floor for discussion. I do believe it was Dr. Ballou and then Dr. Ginsburg.

Dr. Ballou go ahead, please. Again, restate your name for the record.

DR. BALLOU: Yes. Jordan Ballou. With regard to 2c, I am strongly in favor of the FDA's proposal for our consideration of including, I think, a picture that clearly labels what is nozzle or tip, or whatever word is chosen to be used, and clearly labeling what is plunger. I like the picture that is shown where the plunger is a different color than the nozzle. I think that makes it much clearer.

So I would absolutely be in favor of that proposal that FDA gave for our consideration, to include a picture with labels, and then also showing an actual nostril and what that insertion should look like.

DR. COYLE: Thank you.

Dr. Ginsburg, you have the floor.

DR. GINSBURG: Thank you very much. Diane Ginsburg, and I concur with Dr. Ballou. I'm thinking of this from the perspective of trying to teach students how to inject, and when their thumb

is on the plunger, how a lot of times the drug or vaccine never even goes in the arm, and it was my first reservation when I saw the pictogram related to how to administer the drug. So I think anything that they can do, as was suggested, to enhance that, I think would be very helpful. If healthcare provider students have difficulty, and we're asking laypeople to try and utilize this device, anything that would enhance that I think would be very beneficial.

DR. COYLE: Thank you.

Ms. Coykendall?

MS. COYKENDALL: Thank you. Elizabeth Coykendall. One suggestion for the pictogram is just to make sure that the picture and the color differences on the picture -- like if the plunger is green, make sure it correlates with the actual material that's in the package because that could make somebody think that they have the wrong thing. So as long as the colors correlate, I think that would be a great idea.

DR. COYLE: Thank you.

Dr. Higgins, go ahead.

DR. HIGGINS: Jennifer Higgins. We're all making assumptions about what would be the best way of approaching the labeling, and I'm wondering about consumer participation in this process. Might it be useful to have a use survey to see what would be appealing to them, what would come across clearly to them, rather than making assumptions? I don't know if the IRB would be in favor of that or not.

DR. COYLE: I just want to invite anyone who has not yet spoken, specifically about the issue related to incorrect finger placement on the nasal spray.

Dr. McAuliffe?

DR. McAULIFFE: Hi. Maura McAuliffe from East Carolina University. I think the data around the prescription pictogram is there, and I think the data are that it's very effective. From my viewing of it, in figure 6 of the FDA documents, it's very clear where the plunger is and where the finger goes, and I think that they might want to

use what they've already got. Thank you.

DR. COYLE: Thank you, Dr. McAuliffe.

This is Maria Coyle again. I think I will just add that I think what Dr. McAuliffe was referring to is the proposed pictogram, the adjustment; not what was currently in there.

Is that correct, Dr. McAuliffe?

DR. McAULIFFE: Yes, that's correct. Thank you.

DR. COYLE: Any final comments on item C before we move to discuss the subquestion and subparts of item D here on the slide?

(No response.)

DR. COYLE: Let's move on and see if there's any further discussion, then, about the mock nonprescription user interface, particularly both the proposed nonprescription naloxone interface and then the modified one.

Can I clarify from FDA, does that mean that the one that the sponsor has suggested to modify, or the one that the FDA has suggested for modification, or both?

DR. MICHELE: Hi. This is very difficult because I appreciate the position of the panel here because you're being asked to comment on sort of a moving target. That was actually the position that we were in as well when we were reviewing this because the sponsor tested one thing, and then proposed something else, and now they're proposing a third thing.

So I would just ask the panel to do the best you can, and please be clear about what specific label you're speaking about.

DR. COYLE: Thank you, Dr. Michele. That's very helpful.

Dr. Clement, you're up. State your name, please, first.

DR. CLEMENT: Yes. I think we were trying to see how many angels go on the tip of a pin at this point on trying to decide all these little things because --

DR. COYLE: [Inaudible].

DR. CLEMENT: Can you hear me?

DR. COYLE: I just need your name for the

record.

DR. CLEMENT: Oh. Dr. Clement, Steve Clement. Yes, we're sort of circling around this same issue. There are huge amounts of data that FDA now knows on how to make a really good pictogram. I think there are lots of things that, particularly, if you put it in a quick start guide, then you have a lot more room because it's bigger. It's not just on the side of a package.

I would recommend use the comments that you have to get the best from the FDA, and work it out with the sponsor, and get something that intuitively looks great, and just go with it, because this drug needs to get out to patients, essentially. That's the end of my comments. Thank you very much.

DR. COYLE: Thank you for that.

Dr. Brent, please go ahead.

DR. BRENT: Thank you, Dr. Coyle. Jeffrey Brent here. I would just like to, once again, stress that the information on both of the interfaces is such that it calls for the continued

re-administration of doses every 2 to 3 minutes, which would just very, very quickly add up to a lot of doses for no particular reason, and this is an ill-conceived suggestion. I suggest maybe going back a little bit more to the drawing board and thinking critically about that suggestion because it really does not make any sense, and it gives the user no guidance about do they stop at 3 doses, 5 doses, 8 doses?

This is different than the instruction that if a person wakes up and then later becomes re-sedated, that they should get administered another dose. That obviously makes a lot of sense, but this idea that if somebody does not respond, to continue to re-dose them every 2 to 3 minutes after they've gotten 2 doses makes no sense at all, and I think can be very confusing to people and cause them to use an awful lot of these devices that they don't need to be using. Thank you.

DR. COYLE: Thank you very much. I think that comment will do well to lead us into question 3.

I think before we close out question 2, I would just like to add a comment. This is Maria Coyle from The Ohio State University College of Pharmacy. One thing that we have not discussed in regards to the Human Factors Validation Study was the less than ideal representation of adults with low literacy in this study and what impact that might have. So I'd just invite any comments or thoughts from the panel on that issue in particular if we feel like there may need to be accommodations or if there should be further work in regard to that low literacy complication.

I'm looking at you, Dr. Parker. Go right ahead.

DR. PARKER: Hey there. Ruth Parker. I'm going to give a little nod to the Drug Facts Label of the FDA. I think the pictograms that are being utilized in this label are enhancing the ability to understand the content of multi-step instructions. I was not feeling like there was a need to include a higher percentage of patients and, again, my inclinations on this whole thing relates to the

urgency of doing something and the importance of it from a public -- perfect, no, but looks really good, and incredibly encouraging.

So I did not feel like there was a need to target more low-literate patients and, really, that Label Comprehension Study is incredibly encouraging, and I think those pictograms are really quite good.

I agree with the comments before that inclusion of the two pictograms around placement of the fingers and nozzle will enhance. I point out the importance of the pictograms because, obviously, we're discussing having the label available in English only, and the pictograms enhance the ability for people who are non-native English speakers to hopefully be able to also understand and use the product. Thank you.

DR. COYLE: Thank you. I see that prompted a few more hand raises. I'm going to go through this list and ask that you just keep your comments brief and focused on additional considerations, if possible, just so that we can be sure to have

sufficient time for question 3 and our voting question as we go.

Ms. Coykendall?

MS. COYKENDALL: I actually don't have anything further to say. Dr. Parker covered the fact that the pictograms not only deal with low literate, but also anybody that is non-English speaking. So I think the pictograms make it very clear, and that's how it's going to be handled best.

DR. COYLE: Thank you.

Dr. Ballou?

DR. BALLOU: Yes. Jordan Ballou. I was just going to bring a comment, and again, I'm not sure if this is the most correct version, but it is in our briefing materials, page 45, table 11, the intend-to-market carton submitted September 29, 2022.

On the very front of the package, it says the phrase, "no training required," and I just take a bit of issue with that just in the fact that I feel like people do need to at least look at the

product, and that phrasing seems a little misleading to me to say, "no training required." So I wonder if there's just a different phrasing that could be used in so that individuals who are purchasing this product familiarize themselves with it at the time of purchase as opposed to waiting until they actually need to use it. Thank you.

DR. COYLE: Thank you for that perspective.

Dr. Walker-Harding, go ahead.

DR. WALKER-HARDING: Hi. Leslie Walker-Harding. I am also very supportive of the pictograms for the sheer number of different languages that are spoken in the country, and also for kids who may be needing to use this who do not even read yet. I think the pictograms are very helpful and solve that concern.

DR. COYLE: Thank you.

This is Maria Coyle. I'm going to summarize our conversation around the set of questions on this particular slide. I think the committees are strongly in favor of including the pictograms and perhaps even enhancing them under the FDA's

guidance so that it's really understandable and accessible to all users, not just English-reading users or adults who have a good grasp of written word.

I think in terms of the overall nonprescription user interface, the panel really appreciated many of the suggestions that were shared today by both the sponsor, in terms of moving all of the stuff under one panel, as well as some of the additional considerations in the FDA presentation. Our bottom line is that we would really like those two entities to work together to develop the best possible label while still moving this product forward as best as possible, so that it is more accessible, acknowledging that urgency to act and not letting maybe too much of the fine tuning stand in the way of getting the product available as appropriate.

Could we move on to the next slide and to our discussion question number 3? As a further reminder, another reminder, I'm going to just read the question first. If you have a question or

issue with the wording, please raise your hand, and we can address that, and then I will open the question up for discussion.

Discussion question 3, please discuss whether there is any additional labeling information that might mitigate risk of use errors.

Any issues or concerns with the wording?

(No response.)

DR. COYLE: Seeing none, I will open the floor for discussion.

Dr. Walker-Harding, you may begin.

DR. WALKER-HARDING: I don't know if you mean wording, the numbering. I do think the numbering of 1, 2, 3, 4, 5 should be big, bigger than what we saw in these, but I'm sure people at FDA can work on it who have done this before. But that's what I noticed.

DR. COYLE: Thank you.

Dr. Ness?

DR. NESS: This is Tim Ness from Birmingham, Alabama. For me, I guess one of the important things that should be added, because I keep

hearing -- we're all working on this thing of people are grabbing this package and they have to use it right now, but I think most people who buy these because they're worried about their child overdosing, it's going to sit down and spend some time going through the thing. So the labeling is very important and worthwhile, or immediate, got to do it right now, but we don't have anything there if people want more information.

I could easily see that if the labeling included something like a QR code to go to a YouTube, or something that shows how you actually go through this whole process -- I mean, I know if I was a parent and I was worried about this, I'm going to figure out how I'm supposed to do this before I have to do it in an emergency. So that would, I think, help mitigate risk of use errors by adding that. It also gives a portal, then, for extra information that could potentially be out there related to connection to care things, too. It would be changeable. You could have it in multiple languages, these sorts of things. It

would just have to be providing a link or something for more information.

DR. COYLE: Thank you, Dr. Ness.

Dr. Shoben, go ahead. Please state your name for the record.

DR. SHOBEN: Sure. I'm Abby Shoben, and this is a quick comment that was brought up earlier, which may be opening a can of worms, given the studies that were already done on comprehension of the label. But there was a point that if there was a second person available, that having that second person call 911 right away could be happening in concert, and that might be clearer on the label. Thank you.

DR. COYLE: Thank you for that comment.

Dr. Parker?

DR. PARKER: Ruth Parker. I had a couple of specific suggestions, and I recognize that I'm talking about -- I'm going to speak to the proposed updated labeling that the sponsor presented us that has not yet been reviewed by the FDA, assuming that that gets presented to the FDA and is reviewed by

the FDA. So I'm going with that. So it was kind of like the improvements, the formative improvements that incorporated some of their human factors study.

My suggestion would be that the Quick Start Guide, yes, be included, and the Quick Start Guide should, in my mind, be the exact same content that is on the labeling on the back so that when somebody opens this thing, I'm assuming the Quick Start Guide is on some of that really thin paper that's folded 25 times, and when you undo it, you then have the exact same content all the way down to the carriage return so that if you haven't read it, you look at it and say, "Oh yeah. These are the same."

Your font can be much better in terms of accessibility on that quick start because it's going to be bigger. I never got the exact number of the font size on the back of the panel, but I'm assuming it's pretty dadgum small because you got a lot of content that you're squeezing into a smaller amount of real estate there. But I think for

understandability, if you can make those look just alike -- I don't know if you incorporate the same color on the back of the panel that you'll end up using on the Quick Start Guide, but the more you can do to make those things look the same, I think it will improve the end user's ability to see it and take advantage of the content that you're trying to communicate clearly.

So that's one thing. I think the front display panel should include instead of one, two devices so that it's clear that those are in there. And at least if I'm understanding correctly, the proposed eventual display panel of the front, I can't even read that white on pink down in the left corner, so I would really take a careful look at the use of color. White on top of pink is not a quickly readable label, and if this is something that people are buying and you really want to make sure they understand it, be sure that the use of color is enhancing the readability and not in any way making it less accessible to the end user. Thanks.

DR. COYLE: Thank you. Thank you for those comments.

Over the last few discussion points, I've heard a suggestion for a QR code leading to a website or perhaps a demonstration video, more clearly defining or acknowledging the role of the second rescuer, if available, and then a little bit more detail on the Quick Start Guide, and in fact the coloring of the package, as well.

FDA, are there any particular aspects around the labeling information that we have not addressed that would be helpful for you?

DR. MICHELE: No, nothing further. We appreciate all of the great comments from the panel.

DR. COYLE: I'm going to just do a quick scan down my participant list. If there are any advisory committee members who have not yet had an opportunity to speak or to share perspective -- there might be one or two here -- I'd just invite you to do so now, and I'll start with Dr. Roth.

DR. ROTH: Thank you. Katalin Roth from GW

University. I'd like to say that in the hospital setting when we use naloxone or Narcan in the event of people losing consciousness, we give it repeatedly without any problems. My experience in palliative care also is that with parts of symptoms of withdrawal, Narcan is effective. There have been no adverse effects.

I teach medical ethics as well, and I agree with what was stated earlier, that it would be potentially traumatizing and probably not allowed by an IRB to have adolescents weigh in on the directions. I think the labeling is good enough. As somebody over 60, I think that we should try and avoid very tiny type, and I agree with the comments about color and making the graphics as clear as possible. But I think the studies are adequate to support this product being over the counter. Thank you very much.

DR. COYLE: Thank you, Dr. Roth.

I'll call on Dr. Walker-Harding.

DR. WALKER-HARDING: I just have an overall comment. Probably the most concerning thing I

heard was that people were concerned about the IRB and concerned about testing this and children. That was very concerning because what is traumatizing to a kid is watching their loved one be unconscious, dying, and not being able to do anything about it.

I spent a whole career working with kids, teaching them CPR, and teaching them all kinds of rescue things that they do much younger than the ages you're even talking about. I think we have to stop thinking that we are paternalistic and protecting children. The children that are going to be in a situation like this are living with a lot more trauma, and when you want to do these studies, you study the population that is experiencing this that could help with that.

But I do just want to register that we should be looking at kids as young, at least, as 10, even younger, that have to be in this situation, and to not have specific studies to really hone in on how to make instructions readable to them is a failing of us in trying to develop

things.

I do not think we need to wait with this because every day we wait, there are more people that are going to die. I don't think we need to re-look at that, but in the future, I do think we have to get beyond this thing that we're thinking we're protecting children. Children can protect us and can protect themselves, and are humans all on their own.

DR. COYLE: Thank you, and thank you again for adding that perspective of the younger patient or the younger participant.

Dr. Brent, go ahead.

DR. BRENT: Thank you, Dr. Coyle. This is Jeffrey Brent. I just want to point out something that I think might be an error, but it's potentially very significant.

If one looks at page 70 of 97 of the Emergent briefing material, they have a Quick Start Guide there, and there is an instruction in there which doesn't appear on all the other instructions, and that is that the first thing you do after you

shake the patient and ask if the person will respond, is you do things like you check their pupils to look for pinpoint pupils before thinking about administering naloxone.

That is a very bad instruction. We don't want people trying to figure out how to assess somebody's pupil size before giving the naloxone. That instruction does not appear in other labels that are in the briefing documents. It is in the Quick Start Guide that is given in the Emergent document, and I suspect it might be an older version or an error, but definitely should not be there.

DR. COYLE: Thank you, Dr. Brent. We'll make sure that is included in the feedback that the FDA is taking down from the panel.

Alright. I'm looking to see if there's any final questions before we take a short break.

(No response.)

DR. COYLE: Seeing none, again, to summarize, we've discussed a variety of issues related to the labeling and to the studies that

informed that labeling. I think we've provided some strong recommendations to FDA to keep in mind, as well as some strong recommendations to the industry sponsor to perhaps keep in mind regarding the product, and we'll come back in about 15 minutes, after a 15-minute break, to consider our last question, which is the voting question.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during this break. We're going to reconvene at -- I have to do my mental math, sorry -- 3:53 p.m., 3:53 p.m., Eastern time. Thank you.

(Whereupon, at 3:38 p.m., a recess was taken.)

DR. COYLE: Thank you to all, and welcome back. We are now going to move on to the next question, which is the voting question. Dr. Moon Hee Choi will provide the instructions for the voting.

DR. CHOI: Question 4 is a voting question. If you are a non-voting participant, you will be

moved to a breakout room. Voting members will use the Zoom platform to submit their vote for this meeting. After the chairperson has read the voting question into the record, and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

A voting display will appear where you can submit your vote. There will be no discussion during the voting session. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the "submit" button, you will not be able to change your vote. Again, please note that once you click the "submit" button, you will not be able to change your vote.

Once all voting members have selected their vote, I will announce that the vote is closed. Please note there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to; however, you should also address any subparts of the voting question.

Are there any questions about the voting process before we begin?

(No response.)

DR. CHOI: Okay. Thank you.

DR. COYLE: Thank you.

I will begin with reading the voting question, and once again, we will pause for any clarification or issues with the wording of the question.

Question 4, our voting question, is the benefit-risk profile of naloxone nasal spray supportive of its use as a nonprescription opioid overdose reversal agent? If you vote, no, what

further data should be obtained?

Any questions or confusion around the question itself?

(No response.)

DR. COYLE: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 4.

DR. CHOI: We will now move non-voting participants to the breakout room.

(Voting.)

DR. CHOI: The voting has closed and is now complete. After I read the voting results into the record, the chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to; however, you should also address any subparts of the voting question, if any.

For the record we have 19 yeses, zero noes, and zero abstentions.

DR. COYLE: Thank you.

We will now go down the list and have

everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to.

Dr. Choi, can you just confirm that line 9 on the screen is the top of our list?

MR. BONNER: This is Derek Bonner with AV support. Line 9 is the top of the list.

DR. COYLE: Thank you very much.

We'll start with Dr. Shoben. Please state your name and your vote into the record, along with your reasoning.

DR. SHOBEN: Alright. I'm Abby Shoben. I voted yes. Everything that was covered today influenced by vote on this in terms of there's a really substantial benefit to making this nonprescription, making naloxone available nonprescription with minimal risks. There just didn't seem like a very substantial risk at all, so I interpreted the question that way without respect to any of the labeling discussions that we've had.

DR. COYLE: Thank you.

Dr. Bateman?

DR. BATEMAN: Brian Bateman, and I voted yes. I think this is a very important step from a public health perspective. The key component of our addressing the ongoing opioid crisis will be broadening access to this medication and decreasing the stigma associated with the purchase of naloxone. We know from long experience that this is a safe and effective medication, so there's very little reason not to move it to an over-the-counter status.

Certainly there's room for iterative work on improving the label, and additional human factors studies might be conducted in the future, but as one of the panel members said, "Perfect shouldn't be the enemy of the good," and I think the evidence we saw today provides clear indications that the drug can be used without the direction of the healthcare provider.

DR. COYLE: Thank you.

Dr. Ginsburg?

DR. GINSBURG: Diane Ginsburg. I voted yes, similar to comments that have been stated. All of

the evidence in the data that has been presented today is supportive of approving for this drug to go over the counter. I think about collectively the work, not only our working today, but at the FDA and all others who have been involved in addressing this crisis. And this vote today, hopefully we can leave today and know that we are saving lives, so thank you.

DR. COYLE: Ms. Coykendall?

MS. COYKENDALL: Elizabeth Coykendall. I voted yes. There's no reason to keep this as a prescription. Let's get it out there and save some lives. Thank you.

DR. COYLE: Dr. Brent?

DR. BRENT: Brent here. I voted yes. I made earlier remarks about the safety of naloxone, so I'll just reference those without repeating them. And let me just say that I think the unanimity of the committee is a very profound statement about how important this is.

DR. COYLE: Thank you.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I voted yes. The risk of opioid overdose to me is far too great to prevent the product from coming to the OTC market, and I'm unconvinced that the labeling problem presented today will have deleterious effects to product users.

I would suggest, though, that additional labeling research be conducted, and I know that that's not a requirement necessarily, but that could even happen after the nonprescription label application is approved.

DR. COYLE: Dr. Ballou?

DR. BALLOU: Yes. Jordan Ballou. I voted yes. My vote is a yes for persons with opioid-use disorder; and it is a yes for persons with chronic pain who need this product; and it is a yes for people who love those people, and their ability to care for them should the need ever arise. So I voted yes.

DR. COYLE: Thank you.

Dr. Roth?

DR. ROTH: My name is Katalin Roth, and I

voted yes because of the compelling public health need, the overwhelming evidence that the drug is safe and has no important side effects, and the high benefit ratio. So for the sake of the public and saving lives, I believe this medication should be available over the counter to the public as soon as possible. Thank you.

DR. COYLE: Dr. Walker-Harding?

DR. WALKER-HARDING: Hi. Leslie Walker-Harding, and I voted yes. The overwhelming benefit way outweighs the minimal risk for children, adolescents, and adults.

DR. COYLE: Dr. Coyle. This is Maria Coyle. I voted yes. I want to just comment, as another has stated, on the overwhelming positive support for this, which is not something I've encountered before in my work on these advisory committees. It just really underscores the importance of moving this drug to greater access and also highlights the terrible risk of not acting in terms of making the drug more accessible.

I also just want to acknowledge there are

potential unintended consequences that were outside the scope of this meeting related to cost and potentially education around the use of naloxone that I hope all relevant parties will be attentive to.

Dr. Bicket, can you share your vote, please?

DR. BICKET: Good afternoon. My name is Mark Bicket at the University of Michigan and the Opioid Prescribing Engagement Network. I voted yes. I appreciate the presentations today by both the sponsor and the FDA and answering our questions. I was very impressed in hearing the voices of patients, clinicians, and others in support of over-the-counter naloxone.

We know that the crisis continues to grow, and we had a pretty unique consideration today, given the over-the-counter consideration for what would otherwise be a failed condition and its use by laypersons who aren't the recipient of the things that we've discussed.

I did find the safety profile to be very compelling, given the expansion of community and

harm reduction programs with very low documentation forms, I think, for users, and the steps that have been proposed about, including the packet. Potentially, the shift to having the one panel to optimize the recommendation steps would be welcomed. I do believe that we have a risk of not approving this product, and that is a major consideration in my vote today.

Then I'd just conclude by saying persons who are impacted by the crisis do have difficulties in accessing care and can experience stigma. So I think the hope is that by approving naloxone nasal spray, it would be one step to help reverse that part of the overdose crisis. Thank you.

DR. COYLE: Dr. McCann?

DR. McCANN: Hi. I voted yes also. I think there's a clear benefit and very little risk, so that's why I voted yes.

DR. COYLE: Dr. McAuliffe?

DR. McAULIFFE: Well, with the 100,000 deaths per year from opioid overdoses and six years of data with nasal naloxone, with minimal signals,

I think the benefit-to-risk ratio is very positive, and so I voted yes.

DR. COYLE: Dr. Sprintz?

DR. SPRINTZ: Hi. I'm Michael Sprintz, and I voted yes. In addition to being a pain doctor and an addiction doctor, I've also been in sobriety from opioid-use disorder for 22 years. The evidence is compelling that the benefits clearly outweigh the risks, and the urgency is definitely paramount right now. I actually had a friend who lost her 19 year old son about 4 days ago.

So I think this is a wonderful thing, what we did today, and while I agree that there are some incremental improvements, the bottom line is, overwhelmingly, the benefit outweighs the risk. Thank you.

DR. COYLE: Dr. Pisarik?

DR. PISARIK: Paul Pisarik, and I voted yes. It's a huge public health benefit, and it's way overdue. The next step will be to get those people who have opioid-use disorder into treatments for their issues.

DR. COYLE: Dr. Richmond?

DR. RICHMOND: Rebecca Richmond. I voted yes. Similar to other panel members' discussion and the information presented today greatly illustrates the need and the benefits of making this OTC, so I voted yes. Thank you.

DR. COYLE: Dr. Parker?

DR. PARKER: Ruth Parker. I voted yes, in line with [inaudible - audio gap].

DR. COYLE: I'm going to move on to Dr. Clement.

DR. CLEMENT: Yes. This is Steve Clement, INOVA Fairfax Hospital. I'm on the frontline for other conditions like diabetes, which has lots of first responders. I'm happy to be part of this panel and contribute to this discussion. I feel confident from the presentations of the sponsor that their heart's in the right spot, and they're going to be working with the FDA to come up with the best possible labeling, particularly the quick guide, so that there's less ambiguity, or as little ambiguity as possible going forward. Thank you

very much.

DR. COYLE: Thank you.

And last but not least, Dr. Ness?

DR. NESS: This is Tim Ness from Birmingham, Alabama. I voted yes because we need to get it out there. It is putting a lot of trust in the FDA to do the right thing, and I think they will. And since this is an advisory panel, I want to also encourage the FDA also to develop a REMS-like program that might also couple with the follow-up related to these things.

When you look at the statistics, 1 percent of the people who get this in their nose are going to be dead 30 days later from a repeat; 5 percent, 12 months later. So I think there's a moral imperative to set up some type of a system to do a follow-up. I know there's no regulatory thing for OTC right now, but there wasn't a REMS program either, and the FDA developed that. So I would encourage them to do a similar process to help with a connection to care so it doesn't have to be that high a mortality.

DR. COYLE: Thank you.

Thank you to all of the panel members. I'd just like to summarize again, for the record, that our vote was unanimous. All voting members are in favor of the vote to move naloxone nasal spray to OTC status. I'd just like to comment again on the appreciation that the panelists have expressed for both the FDA and the work of others, and this important public health step. Also, we look forward to additional measures to address the opioid crisis in our country.

Before we adjourn, are there any last comments from FDA?

DR. MICHELE: Hi. This is Theresa Michele, Office of Nonprescription Drugs. On behalf of FDA, and especially those of us in the nonprescription drug office, I just wanted to again express appreciation for the panel. You guys have a really hard job, and you've done us all proud today. We really appreciate all of the input. It's certainly invaluable and will be invaluable in our decision-making process going forward, so thank you

so much.

I also wanted to express appreciation for all of those in the community who stepped forward to provide comments both on the record today as part of this committee meeting, as well as those who submitted comments to the docket. Thank you.

DR. COYLE: Thank you, Dr. Michele.

It looks like we have some final comments from Dr. Ginsburg and Dr. Horrow, and then we will move to adjourn.

Go ahead, Dr. Ginsburg. Please state your name for the record.

DR. GINSBURG: Diane Ginsburg, and this is just more of a process question since this is my first advisory committee meeting.

What happens next? And if that's something that's better offline, that's fine. I just was curious as to what are the next steps in this process in terms of the decision getting out to the public and all of that. Thank you.

DR. COYLE: Dr. Michele, could you please address that question?

DR. MICHELE: Certainly. We have all been taking copious notes of all of the words of wisdom that you guys have provided today, and we will take that back as we finish up the review of this application. I'm sure they'll be additional discussions with the sponsor.

Traditionally, the information regarding this application is, of course, private to the sponsor, so FDA cannot comment further on it. If there is a drug approval, then we will, of course, have press surrounding that, and there will be open public availability of our reviews and so forth.

DR. COYLE: Dr. Horrow, I see you also have your hand raised. Would you like to speak?

DR. HORROW: Yes. Thank you. Jay Horrow. As a non-voting member of the panel, I would like to -- now that the vote is all in and tallied -- express that had I been solicited, I would have voted yes. I'm just curious as to whether or not there's any interest in other members of the panel even knowing that.

But regardless, I wanted to thank the FDA,

and also I want to thank you, Dr. Coyle, in particular, for the attention that you gave to the non-voting members and for the opportunity to contribute to the discussion. Thank you.

Adjournment

DR. COYLE: You're very welcome, and thank you for sharing that with all of us.

We will shortly move to adjourn the meeting, and I just want to thank all of you for participating. This has been a very full and intense day. There was a lot of information to consider, as well as a lot of uncharted territory for our respective advisory committees, so I thank you for your participation and your engagement, and for helping me out as a new person in this role.

So thank you very much, and then I will go ahead and adjourn the meeting, and send you all on your way. Thank you very much. Have a great evening.

(Whereupon, at 4:18 p.m., the meeting was adjourned.)