FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Wednesday, November 14, 2018

8:00 a.m. to 4:04 p.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

MEMBERS (Voting)

Brian T. Bateman, MD, MSc

(Acting Chairperson)

Associate Professor, Harvard Medical School

Chief, Division of Obstetric Anesthesia

Department of Anesthesiology

Division of Pharmacoepidemiology and Pharmacoeconomics

Department of Medicine

Brigham and Women's Hospital

Boston, Massachusetts

Basavana G. Goudra, MD, FRCA, FCARSCI
Clinical Associate Professor of Anesthesiology
and Critical Care Medicine
Director of Endoscopy Anesthesia Services at the
Penn Presbyterian Medical Center
Perelman School of Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Mary Ellen McCann, MD, MPH
Associate Professor of Anesthesia
Harvard Medical School
Senior Associate in Anesthesia
Boston Children's Hospital
Boston, Massachusetts

Abigail B. Shoben, PhD
Associate Professor, Division of Biostatistics
College of Public Health
The Ohio State University
Columbus, Ohio

Lonnie Zeltzer, MD

Director, Pediatric Pain and Palliative Care Program
Distinguished Professor of Pediatrics, Anesthesiology, Psychiatry and Biobehavioral Sciences
David Geffen School of Medicine at UCLA
Los Angeles, California

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

W. Joseph Herring, MD, PhD

(Industry Representative)
Associate Vice President
Clinical Neuroscience
Merck Research Laboratories
North Wales, Pennsylvania

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

MEMBERS (Voting)

Sonia Hernandez-Diaz, MD, MPH, DrPH

Professor of Epidemiology

Department of Epidemiology

Harvard T.H. Chan School of Public Health

Boston, Massachusetts

Steven B. Meisel, PharmD, CPPS

System Director of Medication Safety

Fairview Health Services/Healtheast Care System

Minneapolis, Minnesota

Suzanne B. Robotti

(Consumer Representative)

Executive Director

DES Action USA

Founder and President

MedShadow Foundation

New York, New York

TEMPORARY MEMBERS (Voting)

Cynthia L. Arfken PhD

Professor Department of Psychiatry and Behavioral Neurosciences

Wayne State University

Detroit, Michigan

Michael Fischer, MD, MS

Associate Professor of Medicine

Harvard Medical School

Associate Professor of Epidemiology

Harvard T.H. Chan School of Public Health

Division of Pharmacoepidemiology & Pharmacoeconomics

Brigham & Women's Hospital

Boston, Massachusetts

Traci C. Green, PhD, MSc

Associate Professor, Emergency Medicine and Community Health Sciences
Boston University Schools of Medicine and Public Health
Deputy Director, Boston Medical Center Injury Prevention Center
Boston, Massachusetts
Adjunct Associate Professor
Emergency Medicine and Epidemiology
Brown University Schools of Medicine and Public Health
Providence, Rhode Island

Jennifer Higgins, PhD

(Acting Consumer Representative)
Director of Research & Policy
Association of Developmental Disabilities Providers
Framingham, Massachusetts

Brandon D.L. Marshall, PhD

Associate Professor of Epidemiology

Brown University School of Public Health

Providence, Rhode Island

Joseph O'Brien, MBA

(Patient Representative)

President & Chief Executive Officer

National Scoliosis Foundation

Stoughton, Massachusetts

Jeanmarie Perrone, MD, FACMT

Professor, Emergency Medicine

Director, Division of Medical Toxicology

Department of Emergency Medicine

Perelman School of Medicine at the University of Pennsylvania

Attending Physician, Emergency Department

Hospital of the University of Pennsylvania

Philadelphia, Pennsylvania

Thomas Prisinzano, PhD

Professor, Medicinal Chemistry

School of Pharmacy

University of Kansas

Lawrence, Kansas

Jon E. Zibbell, PhD

Senior Scientist

Behavioral Health Research Division

RTI International

Atlanta, Georgia

FDA PARTICIPANTS (Non-Voting)

Sharon Hertz, MD

Director

Division of Anesthesia, Analgesia and

Addiction Products (DAAAP)

Office of Drug Evaluation II (ODE-II)

Office of New Drugs (OND), CDER, FDA

Jennifer L. Nadel, MD

Medical Officer

DAAAP, ODE-II, OND, CDER, FDA

Judy Staffa, PhD, RPh

Associate Director for Public Health Initiatives

Office of Surveillance and Epidemiology (OSE)

CDER, FDA

Tamra Meyer, PhD, MPH

Team Lead Prescription Drug Abuse Team

Division of Epidemiology II

Office of Pharmacovigilance and Epidemiology

OSE, CDER, FDA

Dominic Chiapperino, PhD

Director

Controlled Substance Staff

Office of the Center Director, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. BATEMAN: Good morning. First I'd like to remind everyone to please silence your cell phones, smartphones, or any other devices if you've not already done so. I would also like to identify the FDA press contact Michael Felberbaum. If you're present, please stand.

My name is Brian Bateman, and I'm the acting chairperson for this meeting. I will now call the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. I'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table.

DR. HERTZ: Good morning. My name is Sharon Hertz. I'm the director for the Division of Anesthesia, Analgesia, and Addiction Products.

DR. NADEL: I'm Jennifer Nadel. I'm a

clinical reviewer in the Division of Anesthesia, Analgesia, and Addiction Products.

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

DR. MEYER: Hello. I'm Tamra Meyer. I'm the team lead for the prescription drug abuse team 1 in the Division of Epidemiology II, in the Office of Surveillance and Epidemiology in CDER.

DR. CHIAPPERINO: Good morning. I'm Dominic Chiapperino. I'm the director on the controlled substance staff, CDER.

DR. ARFKEN: I'm Cynthia Arfken. I'm an epidemiologist and professor at Wayne State University in Detroit, Michigan.

DR. MARSHALL: Good morning. I'm an epidemiologist and associate professor in epidemiology at the Brown School of public Health. My name is Brandon Marshall.

DR. GREEN: Hi. I'm Traci Green. I'm also an epidemiologist. I'm an associate professor of

emergency medicine and epidemiology at Community Health Sciences at Boston University Schools of Medicine and Public Health.

DR. ZELTZER: I'm going to assault you today. I'm Lonnie Zeltzer with laryngitis. I'm a distinguished professor of pediatrics, anesthesia, and psychiatry at University of California, Los Angeles.

DR. GOUDRA: Good morning. I'm Basavana Goudra. I'm an associate professor of anesthesiology at Penn Medicine.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. BATEMAN: Brian Bateman. I'm an anesthesiologist at Brigham and Women's Hospital and associate professor at Harvard Medical School.

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

DR. McCANN: Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's Hospital and associate professor of anesthesia at

Harvard Medical School.

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

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

DR. ZIBBELL: Hi, everybody. John Zibbell, senior scientist on the Behavioral Health Research program at RTI International and also professor of medical anthropology at Emory University.

DR. FISCHER: I'm Michael Fischer. I'm a primary care physician at Brigham & Women's Hospital in Boston and an associate professor in the Division of Pharmacoepidemiology at Brigham & Women's Hospital, Harvard Med school.

DR. PRISINZANO: I'm Tom Prisinzano. I'm a professor of medicinal chemistry in the school of pharmacy at the University of Kansas in Lawrence.

DR. PERRONE: Hi. I'm Jeanmarie Perrone. I'm an emergency physician and professor of emergency medicine and medical toxicology at the

Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

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

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

MR. O'BRIEN: Joseph O'Brien, president and CEO of the National Scoliosis Foundation. I'm the patient representative. I am also a patient with my sixth spinal surgery for scoliosis last December.

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

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

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now I'll pass it to the Moon Hee Choi who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management

Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employee or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflicts of interest laws, covered by but not limited to those found that 18 U.S.C. Section 208, is being provided to participants at 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 interest of their own as well as just imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts; grants; CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application NDA 209774 for an immediate-release oral tablet formulation of oxycodone, which is intended to resist common methods of physical or chemical manipulation and to

deter intravenous and intranasal abuse, submitted by SpecGx LLC for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

The committees will also be asked to determine whether the applicant adequately demonstrated that the abuse deterrent properties of the proposed product are sufficient enough to include this information in the product label and whether the product should be approved.

This is a particular matters meeting during which specific matters related to SpecGX's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary running 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 representative,

we would like to disclose that Dr. William Herring is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Herring's role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck & Company

We would like to remind members and temporary voting members that if the discussions involve any other product or firms not already on the agenda for which an FDA participant has a personal imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

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

FDA Opening Remarks - Sharon Hertz

DR. HERTZ: Good morning. Dr. Bateman,

members of the AADPAC and DSaRM committees, invited guests, thank you all for attending this joint meeting of these two advisory committees. We will be discussing an application for a new immediate-release formulation of oxycodone designed with properties intended to deter abuse by the nasal and intravenous routes using both physical chemical barriers to manipulation and the incorporation of aversive agents into the formulation.

The proposed indication is the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The term "inadequate treatments" is further defined in the labeling, in the limitations of use. And what we mean by that -- I just want to take a moment to discuss this because there seemed to be a little bit of confusion about the term at prior meetings.

The intent of the way the labeling is written and the way this language was developed is we're trying to encourage a stepped approach to the

use of opioid analgesics. So alternative treatments are inadequate means the use of a non-opioid is either not appropriate or not expected to be sufficient. And then the use of an opioid/non-opiod combination is either not going to be tolerated or not expected to be sufficient.

So the idea is to push progression or to describe a progression of the use of products for the management of pain. And it doesn't mean that every patient has to be run through a series of non-opioid combinations and then single-entity opioids, but that the judgment of which product to select when managing pain, that process should be undertaken by the prescriber.

One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids formulated to deter abuse, and we issued a final guidance describing the development of opioid products with these properties in 2015. We've had 10 products approved with labeling describing abuse deterrent properties, 9 extended-release and one

immediate-release product. Two of the extended-release products have been withdrawn from the market and two are listed as discontinued in the Orange Book.

For the most part, these products have not yet been widely adopted. This may reflect several factors, including cost and a sense by prescribers that it might be insulting to prescribe such a product to a trusted patient.

Another factor that's likely is the lack of evidence that abuse-deterrent opioid analgesic products have had the intended effect of reducing abuse. While there have been publications making a number of such assertions, no company has actually submitted the postmarketing data to support labeling statements that abuse deterrent formulations have the intended effect.

From our perspective, we're still hopeful that this is the case, but we have not had an opportunity to actually label a product with postmarketing data. It's not clear whether this arises from a failure to have an effect or a

failure to demonstrate an effect within the context of many, many factors also attempting to work at reducing the abuse of prescription opioid analgesics.

Current trends in prescriptions dispensed for opioids have been steadily declining over the past few years, making it even more difficult for these products to gain enough market share to demonstrate an effect. Anecdotal reports suggest that some practitioners misunderstand the term "abuse deterrent" to mean that these products are safer and less addictive to patients. This is a dangerous misunderstanding, as many of these products are still Schedule II opioids and retain all the warnings and contraindications as non-abuse-deterrent formulations.

Whether studies to support the presence of an abuse deterrent effect pass or fail, the results will be described in the labeling for all products upon approval. It's important for prescribers to understand the product performance to be able to make an informed decision about the role of the

product in their practice of pain management.

There is currently a product with labeling describing the negative results of studies that were conducted to assess properties of the formulation that were intended to deter abuse. The labeling includes negative study results from in vitro testing and human abuse potential studies that state the studies failed to demonstrate properties expected to deter abuse based on end points specified in the above-mentioned guidance. The label also includes language describing the results of additional secondary endpoints not described in the guidance and for which the clinical significance is unknown.

As you may recall from prior advisory committees, we have been improving our understanding about how to evaluate these products. Based on feedback from prior advisory committees, the agency is now requesting that applicants address the safety of excipients when administered by unintended routes that is abused by the IV or nasal route. And you'll hear a presentation by FDA

on this issue that discusses the safety of excipients and how this relates to the unintended routes that may be used in the context of abuse.

We've also learned that there can be unintended consequences when abusers find ways around the abuse-deterrent properties for these formulations. Opana ER was reformulated to have abuse-deterrent properties, however, abusers learned how to manipulate the product for IV abuse by a method that resulted in more sharing of needles, and local outbreaks of HIV and hepatitis infections ensued. Available data also suggest that there was some shifting from the nasal to the IV route of abuse, presenting greater risk of overdose and death.

The results of the applicant's in vitro and chemical manipulation assessments, and the in vivo intranasal human potential study will be presented during this meeting. You'll hear presentations from the applicant and the agency regarding these findings. However, for today's meeting, and potentially for future meetings where

abuse-deterrent formulations are presented, we have opted not to have a closed session.

This is not a decision based on the specifics of this application. This is a separate decision that we made. Having had a number of applications for ADFs, our review staff has gained a large amount of experience determining whether the methods studied by applicants are appropriate and adequate for the formulation. The mechanics of keeping proprietary information confidential limit the discussion of these methods in the context of the results. So today, we will focus on the results in the open session.

We will also have a presentation by FDA staff on prescribing patterns for oxycodone products and other opioid, as well as misuse and abuse patterns, and we will have discussion of some of the potential toxicities associated with some of the excipients.

There are critics of approval of new opioids, including ADFs when they are being evaluated for the management of pain. However, as

I've discussed at previous meetings, we know that there has been a steady decline in the number of prescriptions over many years now in spite of an increasing number of product approval, so the existence of new products does not appear to be increasing the market for opioids. They are just increasing the options for which opioid a prescriber may select.

This afternoon, we will ask you to discuss whether the applicant has provided adequate support for labeling abuse-deterrent properties for this product; whether the benefits of the product at issue outweigh its risks; and whether it should be approved. As always, your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern, and we're grateful that you've agreed to join us for this important discussion and taking time from your very busy schedules. Thank you very much.

DR. BATEMAN: Both the Food and Drug Administration and the public believe in a

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

For this reason, FDA encourages all participants, including the 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 a sponsor, including equity interest and those based on 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'll now proceed with SpecGx LLC's presentations.

Applicant Presentation - Martha Schlicher

DR. SCHLICHER: Good morning, everyone. My name is Martha Schlicher. I'm a vice president of research and development at Mallinckrodt Pharmaceuticals, and I'd like to thank the FDA and the advisory committee members here today for all the time you've already invested in preparing for today's meeting.

Let me start by describing why we're here today. Reducing opioid abuse is an important public health priority. One of FDA's initiatives to address the opioid crisis has been to encourage the development of opioid medications formulated to deter abuse. The FDA has recently stated that transitioning from the current market dominated by conventional opioids to one in which most opioids have abuse-deterrent properties holds significant promise for meaningful public health.

Mallinckrodt currently manufacturers approximately 15 percent of the immediate-release, single-entity oxycodone tablets that are dispensed to patients in the United States. This includes

both Roxicodone and its generic equivalent. In response to FDA's call for a market transition, we have developed an abuse-deterrent formulation to provide safeguards against both intranasal and intravenous abuse.

Based on the results of our development program, we are requesting approval for our proposed indication with abuse-deterrent labeling claims. If approved, with abuse-deterrent labeling, we will replace all of our oxycodone and generic immediate-release, single-entity oxycodone tablets with this new abuse-deterrent formulation, which we will call the ADF replacement for the rest of our presentation.

ADF replacement tablets are manufactured using a conventional, solid-dose manufacturing process and come in find strengths that are commercially available today. The tablets are hard and non-brittle, providing resistance to physical manipulation. Excipients produce a viscous solution when a tablet is dissolved in small volumes of aqueous solvents to deter IV abuse.

Aversive agents create nasal irritation to discourage intranasal abuse.

This slide provides an overview of the formulation components and their proposed functions. All excipients in ADF tablets are either generally regarded as safe or are used in other FDA approved oral drug products as listed in the inactive ingredient database.

I want to specifically mentioned polyethylene oxide, or PEO, which imparts hardness and gelling properties. It's really important to note that our ADF does not have any of the high molecular weight PEO that was used in Opana ER, which was associated with safety risks when injected. Our formulation contains less than 2 percent of a high molecular weight PEO, very similar to that used in commercially available OxyContin, but at over 20 times lower amounts.

The ADF replacement has been submitted for FDA approval as an NDA under the 505(b)(2) regulatory pathway. This pathway requires bioequivalence between the ADF and Roxicodone to

establish therapeutic equivalence of the two products. The FDA has concurred with our assessment that the ADF is bioequivalent to Roxicodone.

The ADF contained the same active ingredient and comes in the same oral dosage form as Roxicodone, therefore, if approved, it would receive the same indication, an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

What would separate the ADF replacement label from Roxicodone would be its nasal and IV abuse-deterrent designations. We have performed the full set of studies outlined in FDA's guidance for abuse-deterrent opioids and incorporated feedback from the agency throughout the development. Let me provide a brief summary of our findings.

In terms of intranasal abuse, our ADF tablets resist physical manipulation. In a human abuse potential study, the ADF reduced positive

effects at early time points such as liking and high. The aversive agents made the tablet difficult to snort and caused pain and burning, and subjects ultimately did not express willingness to snort the ADF again.

In terms of IV abuse, the ADF has multiple gelling agents to make syringeability difficult. It resisted all common methods for abuse, and a multistep procedure with advanced techniques was required to achieve an appreciable yield of syringes oxycodone. We have also conducted a series of excipient safety studies, and we have not found evidence of overt toxicity from injection of those extracts.

Overall, the findings from our program provide evidence that our ADF replacement can be expected to reduce intranasal and IV abuse compared to the products it would replace.

Mallinckrodt is committed to the opioid REMS requirements. These include the minimum requirements such as a medication guide; various elements to assure safe use, including training and

education activities; as well as providing regular REMS assessments to the FDA. While REMS are clearly necessary,
we think that we can and need to do more.

Mallinckrodt is committed to additional postmarket activities to provide important and meaningful information. We will perform enhanced pharmacovigilance with tailored adverse event questionnaires as well as web monitoring so that we can thoroughly evaluate any potential safety signals right away.

We're also proposing to collect additional data on both intended and unintended use. In terms of intended use, we want to understand how our transition impact prescribing patterns. And in terms of unintended use, we will monitor street price data, drug user chat rooms, and poison control center data to understand real-world abuse patterns.

We are currently conducting physician focus groups to understand knowledge gaps to find out how to better educate about ADFs and to ensure that the

limitations of these products are well understood. Our proposed transition also provides a unique opportunity to evaluate the public health benefits of a product with these safeguards.

We recognize that the lack of data on real-world impact has been a past frustration of this committee. Our proposed transition of a sizable proportion of the market could provide answers to many of the important outstanding questions in Category 4 postmarket studies.

Here is the agenda for the rest of our presentation today. Dr. Richard Dart will discuss the public health need for abuse-deterrent, immediate-release opioids. Dr. Ed Cone will review the results of our Category 1 studies. Dr. Mike Orr will present the results from our excipient safety studies, and Dr. Sandy Comer will review the results of our intranasal human abuse potential study. Lastly, Dr. Jeff Gudin will conclude the presentation with his clinical perspective. We also have Dr. Lynn Webster, another abuse-deterrent expert, here with us today to help answer

questions.

All of our external experts or their institutions have been compensated for their time and travel expenses, and none have an equity interest in today's outcome. I'll now invite Dr. Dart to the lectern.

Applicant Presentation - Richard Dart

DR. DART: Good morning. My name is Rick Dart. I'm the director of the Rocky Mountain Poison and Drug Center and a professor at the University of Colorado. I'm also executive director of the RADARS system, which studies prescription drug abuse and diversion in the United States. My presentation will discuss the public health need for effective abuse-deterrent, immediate-release opioids.

Let's start with a common view of opioid abuse and addiction. There are certainly other pathways, so please consider this diagram simply as a framework for discussion. As we would expect, a person's first exposure occurs when they receive a prescription for a pain medicine or a new

recreational user decides to abuse an opioid analgesic.

Most people start by swallowing intact tablets, but some individuals will go on to crush the drug in order to snort or inject it. It's important to realize that many users advance from oral to intranasal to injection, and then to injection abuse. Any of these abuse behaviors may lead to an adverse outcome, and to address abuse, several interventions have been implemented recent years. For example, prescriber guidelines, prescription drug monitoring programs, and law enforcement activities have all been employed as part of the effort.

Now, once an opioid is going to be prescribed, I think we can all agree that we want that drug to be as safe as possible. To that end, the FDA has promoted the development of opioids with abuse-deterrent properties. By physically resisting crushing, by releasing and antagonists, by adding excipients that make it unpleasant to snort, or by forming a gooey mess when mixed with

water, abuse-deterrent formulations make it much more difficult to abuse an opioid intranasally or intravenously.

It's critical that we set reasonable expectations about what ADFs can and what they can't do. ADFs can reduce intranasal or IV abuse of a specific product. They can make diversion less attractive, and if someone encounters and ADF early on, we hope that it will deter them from initiating abuse by snorting or injecting.

You may have heard this analogy in the past. If we think of opioids like a car, then ADFs are like airbags or seat belts. They can reduce injury and death, but they can't really completely prevent it. On the other hand, we have to think about what ADFs cannot do. They can't stop an individual from snorting or injecting an alternative drug or reduce oral over consumption.

ADFs impact misuse and abuse patterns differently for different individuals. For pain patients who need a prescription opioid to manage their pain, ADFs make their medicine less

attractive for misuse and diversion. For a novice user who is experimenting with opioids, an abuse-deterrent formulation may deter them from initiating the dangerous routes of intranasal and IV abuse.

For individuals with severe opioid-use disorder, an abuse-deterrent formulation may deter them from snorting or injecting that specific product, but it's not going to stop their underlying opioid abuse problem. They will likely switch to another drug or temporarily switch back to oral abuse. What these individuals need is treatment for their opioid-abuse disorder.

So an abuse deterrent product can't stop abuse, but it's very clear, from both quantitative data as well as chat rooms and blogs, that abuse-deterrent products do create significant barriers to risky routes of abuse. Now, let's take a look at some of that data.

Immediate-release opioids are frequently abused and diverted. In the RADARS Poison Center program, immediate-release opioids are involved in

abuse cases more than 4 times as often as extended-release products and are involved in diversion more than 6 times as often. The reason that immediate-release, single-entity products like Roxicodone are preferred over extended-release opioids is due to the immediacy of the high and the ease of snorting or injecting. When individuals are asked why abuse is easier, they cite the lack of abuse-deterrent properties like gelling or hardness, as well as the absence of other ingredients that they don't want to snort or inject, like acetaminophen.

The same profile we see for immediate-release and extended release opioids holds true for the specific case of oxycodone. Among individuals entering substance abuse treatment in the NAVIPPRO system, the rate of abuse of immediate-release, single-entity oxycodone is double the rate of abuse of extended-release oxycodone.

In terms of the route of abuse, approximately half of individuals who reported

abusing immediate-release, single-entity oxycodone abused it by the oral or intranasal routes and 25 percent reported IV abuse. So intranasal and IV abuse is certainly a problem with products like Roxicodone and all of the generic IR oxycodone products.

IV abuse is of particular concern because 6 percent of new HIV diagnoses and 9 percent of new AIDS diagnoses are attributed to IV drug abuse, and injecting an opioid also puts the user at risk for other bloodborne infections like hepatitis and endocarditis, but also blood clots and other adverse health effects.

In summary, the ultimate goal is to produce the safest product possible for each type of opioid analgesic. ADFs offer a mechanism to deter abuse by non-oral routes. Unfortunately to date, ADFs have claimed a tiny portion of the opioid market. The FDA has advocated for transitioning the opioid market to one where most products have abuse-deterrent properties, and they've clearly established a pathway for approval for formulations

with these significant safeguards against abuse.

I believe we should all be striving to get to a place where all opioid products have abuse-deterrent properties so that the user cannot simply switch back and forth between opioid products to snort or inject their drug.

Thank you, and I'll now turn the presentation over to Dr. Cone.

Applicant Presentation - Edward Cone

DR. CONE: Good morning. My name is Edward Cone. I'm a principal scientist at Pinney Associates. My expertise is in the chemistry, pharmacology, and the design and execution of Category 1 studies of abuse-deterrent opioids. Prior to joining Pinney Associates, I spent 26 years as a commissioned officer and chief of the chemistry section at the National Institute on Drug Abuse.

The Category 1 studies evaluated the physiochemical properties of the ADF replacement that makes intranasal and IV abuse more difficult. The studies were designed in accordance with the

FDA guidance document on abuse-deterrent opioids and in consultation with the agency.

Since the ADF is intended as a replacement for non-ADF products, Roxicodone was used as the comparator. Since this is an open meeting, the details of methodologies will not be discussed. I'll start with particle size reduction.

Unlike extended-release opioids, particle-size reduction does not substantially change the oral release profile of immediate-release opioids. Therefore, the main reasons an individual would try to reduce the particle size of an immediate-release opioid would be for snorting and injecting.

The goal of the particle-size reduction study was to identify the methods required to produce the smallest particle size. The ability to crush, cut, grate, grind, or mill Roxicodone and the ADF were evaluated using different levels of manipulation. Four levels were formally evaluated. The optimal time for manipulation was determined by testing until no further particle size reduction

occurred. The most effective manipulation for each product was then used in the human abuse potential study.

Let's look at the results. This graph will show the average percentage of particles that were less than 500 microns. That's a particle size which is considered amenable for snorting for each of the 4 levels of manipulation. Roxicodone was easily manipulated into small particles using the two lowest levels of manipulation. In contrast, neither of these were able to reduce the ADF replacement to small particles.

Because Roxicodone was easily manipulated in levels 1 and 2, it was not further evaluated at the higher levels. With the ADF, level 3 produced few small particles. Level 4 was the only manipulation that yielded a high percentage of small particles. However, this did not defeat its abuse-deterrent properties. As you'll see later in the presentation, the aversive agents made the ground product unpleasant to snort, and ground material was very difficult to syringe.

Next, I'll discuss the small volume extraction and syringeability studies. The rationale for these studies were to determine the conditions that are necessary to achieve a high-yield and syringeable oxycodone. Since ADF opioid medications must be available to treat pain, the abuse-deterrent properties of any ADF can be overcome with sufficient time, effort, materials, and knowledge. Given that any ADF can only be abuse deterrent and not abuse proof, the goal of the small volume extraction and syringeability testing was to determine the extent of the work required to overcome the abuse-deterrent properties and whether these barriers can be expected to deter IV abuse.

With that goal in mind, pretreatment conditions and advanced techniques were specifically selected to challenge the abuse-deterrent properties of the ADF. 1836 separate combinations of both common and advanced conditions were performed, and with more than 5,000 samples being tested. Testing was conducted in an

iterative fashion and in consultation with the FDA to ensure that the ADFs deterrents had been fully characterized.

288 combinations of common conditions were evaluated for both intact and ground ADF replacement and Roxicodone 30-milligram tablets. These studies used the most frequently used solvent for extraction and various temperatures, needles, agitation volumes, and extraction times.

1,548 combinations of advanced conditions with various pretreatments and other directly injectable solvents were further evaluated for the ADF only. This slide shows a summary of all common methods using ground tablets. For the ADF, common methods didn't work. Ninety-eight percent of conditions resulted in less than 5 percent syringeable oxycodone.

In contrast, Roxicodone could easily be prepared for injection with common methods. In most cases, the yield was substantial and could be done within minutes. Since little oxycodone could be recovered from the ADF with common methods,

scientists used advanced techniques to further challenge the abuse-deterrent properties.

Let's look at the results. The Y-axis shows the percent recovery of oxycodone for each pretreatment. The blue dots represent the median percent recovery and the bar show the range. IV pretreatments one and two did not increase yields beyond the common methods. The median yield for IV pretreatment 3 was 1 percent with a maximum recovery of 35 percent.

With IV pretreatment 4, the median yield was 10 percent with a maximum recovery of 60 percent. Advanced conditions were required to obtain the maximum yields from the ADF. It required a specific tool, tablet pretreatment, larger extraction volumes, long extraction times, elevated temperature, large needles, and a large injection volume. This extensive procedure would have taken an individual over an hour and considerable effort to perform. This information was used to inform the design of the nonclinical excipient safety studies, which will be presented next.

Overall, the results demonstrate that the ADF has physical and chemical barriers that would make intranasal and IV abuse much more difficult than the product it is intended to replace. The ADF was difficult to crush, and even if manipulated, particle-size reduction did not defeat the abuse-deterrent properties. Additionally, it formed a viscous gel that was difficult to draw into a syringe creating a substantial barrier for IV injection.

Thank you for your attention. I'll now turn the presentation over to Dr. Orr to present the results of the excipient safety study.

Applicant Presentation - Mike Orr

DR. ORR: Good morning. I'm Mike Orr. I'm a consultant pharmacologist and toxicologist. Prior to becoming a consultant three years ago, I spent 10 years at the FDA in various roles as a pharmacology and toxicology reviewer, team lead, and branch chief. I have reviewed all findings from the nonclinical excipient safety studies, and I'm here to provide my interpretation of the

results.

All of the excipients used in the ADF replacement are safe for oral use, the intended route of administration. Recently, there have been concerns about the safety of excipients and abuse-deterrent formulations when abused via the IV route. Studies have shown that repeated injection of the high molecular weight PEO and OPANA ER was associated with a variety of serious safety issues included in thrombotic microangiopathy.

PEO is an excipient used in many marketed ADFs to impart physical hardness and gelling properties to deter nasal and IV abuse. The molecular weight and amounts of PEO vary between products. As Dr. Schlicher mentioned earlier, the ADF replacement does not contain any of the high molecular weight PEO that was used in Opana ER. However, to ensure that the introduction of an ADF does not have unintended consequences, nonclinical studies are now performed to assess the risk of injection prior to marketing.

The sponsor performed a series of general

toxicology studies to understand the safety profile of the ADF when administered via the IV route. The nonclinical excipient safety studies were designed in consultation with the FDA. The in vitro blood compatibility studies evaluated hemolytic potential, plasma compatibility, platelet aggregation. The in vivo study evaluated multiple dose IV toxicity in rabbits.

All studies evaluated to test articles of the ADF, which were selected based on the conditions that achieved the highest yields of syringeable oxycodone using two different pretreatment methods. First, I'll start with the in vitro blood compatibility studies.

The ADF replacement extracts did not exhibit in vitro hemolysis. The hemoglobin levels for test articles 1 and 2 were low and similar to the negative control. A positive result for this assay was considered to be a hemoglobin concentration of 500 mgs per deciliter more than the negative control, so only the positive control met the prespecified definition for hemolysis.

The ADF replacement extracts did not exhibit any evidence of human plasma incompatibility. There are no macro or micro observations for test article 1. Following addition of test article 2 to human plasma, the sample was considered cloudy based on macroscopic appearance, and particles in the plasma were noted microscopically. This observation was likely due to the presence of finely suspended particles that were noted in the test article 2 prior to performing the assay. It was determined that test articles 1 and 2 were both negative for protein flocculation.

The addition of test article 1 or test article 2 to human platelet rich plasma did not increase platelet aggregation. Results were similar to the negative control and were within the normal reference range for healthy blood donors.

Next, I would like to summarize the results of the animal study, which evaluated the local and systemic effects of the ADF abstracts following daily IV injections. Twelve female rabbits were randomized equally to one of three dosing groups,

test article 1, test article 2, or the control article, which was 0.9 percent sodium chloride.

Each animal was administered dosage volume of 1 mL per kilogram by bolus in a marginally ear vein once daily for 3 days. The dose volume was selected based on the tolerability profile of oxycodone in this species. The dose volume in rabbits is approximately 10-fold higher relative to the humans based on body surface area or 58-fold higher based on mL per kilogram.

Each animal was monitored at least twice daily, and any abnormal findings -- mortality, pain, or distress -- were recorded. A full panel of clinical pathology tests were performed, including hematology, coagulation, clinical chemistry, and urinalysis. Standard panel of tissues were also collected and select organs were evaluated microscopically.

In vivo, there was no evidence of overt toxicity or tissue damage. The ADF test articles were not associated with signs or symptoms of thrombotic microangiopathy. Noteworthy

observations included statistically significant 1.5-fold increase in fibrinogen and a 50 percent increase in spleen weights only seen for test article 2. Neither the increase in fibrinogen nor the increase in spleen weight were considered adverse by an independent pathologist. And in terms of microscopic findings, minimal to slight microscopic pathology observations were seen, but the independent pathologist did not consider these minimal changes in the organs to be adverse in the context of the study findings.

Thank you. I'll now turn the lectern to Dr. Comer.

Applicant Presentation - Sandra Comer

DR. COMER: Thank you. Good morning. My Name is Sandy Comer. I'm a professor of neurobiology in the Department of Psychiatry at Columbia University. My research has focused on testing novel compounds for the treatment of opioid-use disorder and studying the relationship between pain and opioid abuse. Today, I will review the results from Mallinckrodt's intranasal

human abuse potential study.

Before we get started, I think it's important to understand why an individual would choose to snort an opioid tablet as opposed to simply taking it orally. By bypassing first-pass metabolism, snorting allows for faster entry of the opioid into the bloodstream and the brain. This leads to a faster onset of positive effects such as liking and high.

Intranasal and oral administration actually have similar maximum positive effects. The motivation for snorting and IR opioid is getting a faster onset of positive effects, therefore a major focus of my presentation will be the effects at early time points.

With this background in mind, let's talk about what abuse deterrence means in the context of intranasal abuse. On one hand, we have the positive effects like drug liking or drug high, and on the other hand, we have the potentially negative effects measured by the ease of snorting or other adverse nasal effects like pain or burning. Taken

together, we look at how subjects integrate the positive and negative effects in assessing the overall drug taking experience by asking them to rate their overall drug liking and how likely they would be to take the drug again.

ADFs can work by either reducing the positive effects, or by creating negative effects with aversive agents that make snorting unpleasant, or by a combination of these approaches. Regardless of the mechanism, what is most important is that the ADF makes individuals less likely to abuse by the intranasal route, which we measured directly by asking them whether they would take the drug again if given the opportunity.

The intranasal study was a randomized, double-blind, double-dummy, 4-period crossover study in non-dependent recreational opioid users with intranasal experience. In the qualification phase, subjects first underwent a naloxone challenge test to ensure that they were not physically dependent on opioids. Subjects then had to pass a drug discrimination test to ensure that

they can discriminate between an intranasal dose of 15 milligrams of Roxicodone and placebo. Ultimately, 38 subjects completed the study.

In the treatment phase, subjects received all four treatments in a random order with a 72-hour washout period. The three active treatments were intact oral ADF, intranasal ADF, and crushed intranasal Roxicodone. For the placebo treatment, subjects received both intranasal placebo powder as well as an oral placebo.

The primary endpoint of the study was drug-liking Emax. Emax is simply the maximum score for each subject regardless of the time it occurred anywhere between 15 minutes to 12 hours post-dose. Key secondary assessments included drug liking, drug high, the ease of snorting assessment, the nasal effects questionnaire, overall drug liking, and take drug again.

All secondary assessments were evaluated independently without any ranking assignment. Take drug again and overall drug liking are especially important because both measure the subject's whole

experience 12 and 24 hours after administration.

Let's move to the results starting with the pharmacokinetics. This figure will show the mean plasma concentrations over the first 2 hours, which is the most relevant time frame for intranasal abuse. When administered orally as intended, the ADF had a PK profile that was expected for an IR opioids.

Intranasal Roxicodone had a more rapid rise in plasma concentrations than oral administration. The intranasal ADF had significantly lower oxycodone concentrations than Roxicodone at many of the early time points, with concentrations similar to or lower than oral administration. As mentioned earlier, the Cmax or maximum concentrations of oxycodone were similar for the oral and intranasal treatments.

Let's turn now to the pharmacodynamic results. As described, the positive effects include measures of drug liking and drug high. The primary endpoint for this study was the same as for all prior ADFs, drug liking Emax or the maximum

drug liking at any time point. What's different about this study is that it's the first to use a superiority margin.

All abuse-deterrent formulations approved to date have needed to show that drug-liking Emax was significantly lower for the ADF than the non-abuse deterrent comparator. This is often referred to as superiority.

The FDA guidance document now requires that sponsors include a superiority margin. This means that drug-liking Emax for the ADF not only has to be statistically significantly less than the comparator, but it has to be significantly less by a specific margin. This is often referred to as super superiority.

In this study, the superiority margin was set at 10 percent. To measure drug liking, subjects were asked, "Do you like the drug effect you're feeling now?" A score of 50 represents a neutral response, 100 is strong liking, and 0 is strong disliking.

Based on FDA's analysis shown here, the

reduction in drug-liking Emax was not significantly lower than Roxicodone by the superiority margin. As you can see, the p-value for super superiority was point 014. However, drug-liking Emax was significantly lower for the ADF and Roxicodone using the standard analysis for superiority with a p-value of 0.0039. The important takeaway from this slide is that the maximum drug liking was relatively similar for all the active treatments but slightly lower for the intranasal ADFs.

Next, let's look at drug liking over time since the motivation for snorting is to achieve faster onset of positive effects in oral administration focusing on the first 2 hours. Drug liking for placebo remain neutral at approximately 50. The oral ADF showed a characteristic gradual rise in drug liking. Intranasal Roxicodone had a considerably more rapid increase in drug liking than oral administration. This difference at 15 minutes illustrates why people prefer snorting over taking a tablet orally.

The time to maximum drug liking was

significantly delayed by nearly an hour with the intranasal ADF compared to Roxicodone. Furthermore, if you look at just the two intranasal treatment arms, we can see that the ADF had significantly lower mean drug liking throughout the first hour and a half, which is the time frame users would expect to experience the most drug liking after insufflation.

Similar results were observed for drug high, which can be found in both FDA's and the sponsor's briefing books. The primary method of abuse deterrence for the ADF is the negative effects from the aversive agents. Ease of snorting was assessed within 5 minutes of insufflation using a unipolar visual analog scale where zero indicates very easy to snort and 100 is very difficult. The mean score for Roxicodone was 11, meaning it was easy to snort. In contrast, the mean score for the ADF was 84, indicating that the participants found it much more difficult to snort.

Another measure of negative effects is the Nasal Effects Questionnaire. This questionnaire

evaluates several different negative aspects of the intranasal drug-taking experience over time. Ninety five percent of subjects experienced at least one adverse nasal effect with the ADF, and 79 percent of subjects experienced an adverse effect that was moderate or severe.

Nearly half of the subjects rated moderate to severe effects for facial pain and pressure after snorting the ADF compared to 3 percent for oxycodone. This trend was consistent for all assessments, including nasal congestion, runny nose and nasal discharge, the need to blow one's nose, irritation, and burning.

So at early time points when individuals would be expecting a pleasurable experience, they're actually experiencing nasal pain, irritation, and burning.

To assess the overall drug-taking experience and predict future behavior, participants are asked 12 or 24 hours after administration how much they liked the drug overall and whether they would take the drug again. This slide will show overall drug

liking after 24 hours. This measure is different from the measure of at-the-moment drug liking or Emax, which I discussed earlier.

Not surprisingly, participants reported high overall liking to snorting Roxicodone with similar scores for the oral ADF replacement. Overall drug liking for placebo was neutral as expected. The intranasal ADF was associated with significantly lower overall drug-liking scores compared to intranasal Roxicodone with scores that were similar to placebo.

For the take drug again assessment, participants were asked, would you want to take the drug you just received again if given the opportunity? A score of 100 means they definitely would; 50 means that they didn't care one way or another; and zero means they definitely would not.

Participants reported high willingness to snort Roxicodone again with similar scores for the ADF taken orally. Willingness to take placebo again was neutral. The intranasal ADF was associated with a 30-point lower take drug again

score compared with Roxicodone, which was numerically lower than placebo. This is the most important finding of this study. Subjects had no greater willingness to snort the ADF again than they had to snort placebo powder.

To summarize, in terms of positive effects, the maximum drug-liking scores for the ADF were significantly lower than Roxicodone, but were not super superior at the prespecified margin. At early time points, which are the motivation for nasal abuse, drug Liking and high scores were significantly lower with the ADF.

In terms of negative effects, the ADF replacement was difficult to snort and aversive agents caused unpleasant sensations, including burning, irritation, and pain. When participants had the opportunity to reflect on the overall experience, their overall drug liking for the ADF replacement was similar to placebo. And when asked to predict their future behavior, they did not report wanting to snort the ADF again.

Thus, the data show that the ADF can be

expected to deter intranasal abuse relative to the products it would replace like Roxicodone. Despite not making the superiority margin for drug-liking Emax, take drug again contextualizes the positive and negative effects. When individuals were asked whether they would snort the ADF replacement again, they did not express a willingness to do so. This is the most important consideration for the deterrence of a drug. The totality of findings from this study provide important information to consider as we evaluate the abuse deterrence of new products in the future.

Thank you. I would now like to turn the lectern over to Dr. Gudin.

Applicant Presentation - Jeff Gudin

DR. GUDIN: Good morning. My Name is Dr. Jeff Gudin. I'm the director of pain management and palliative care at the Englewood Hospital and Medical Center in New Jersey and clinical associate professor of anesthesiology at the Rutgers New Jersey Medical School.

I've treated patients with pain as well as

addiction disorders for more than 20 years, and I've published throughout my career on safe prescribing and appropriate risk management for opioid analgesics. I'm here today to provide my clinical perspective on the ADF replacement and on the FDA's questions posed to you today.

Pain treatment guidelines, including those by the CDC, support opioids as an option for patients when other treatment options are inadequate. As a prescriber, I'm acutely aware of the dangers of opioids, not just to my patients but to their entire community. I usually feel comfortable evaluating the potential risk of abuse of the patient sitting in front of me, but I cannot control what happens to the medications once they are dispensed. We know that the end users of prescription opioids may not be our patients.

ADF safeguards, therefore, against abuse are not only for patients but for anyone with access to their medicine cabinet, and this is a major consideration when thinking about the role of abuse-deterrent formulations.

My goal for this meeting is to provide my clinical perspective on each of the questions under consideration today. First, can the ADF replacement be expected to deter abuse by the nasal or IV routes of administration? Next, what is the potential public health impact of the ADF replacement on misuse and abuse of opioids? And finally, should the ADF replacement receive FDA approval?

When answering these questions, I think it's important to remember that this is not another opioid that would simply be added to all of the currently available options. If approved, this would replace products without abuse deterrent properties that are already on the market today.

Starting with the first question, can the ADF replacement be expected to deter abuse by the nasal route of administration? I think we have three different approaches to assess this: the tablet's physical and chemical properties, the intranasal study, and the precedent set by RoxyBond, the only FDA-approved, immediate-release,

abuse-deterrent formulation, which this advisory committee recommended for approval last year.

RoxyBond set a high bar for abuse deterrence, so the results from their studies provide context for evaluating this ADF replacement. As you've heard, the ADF replacement has physical and chemical properties to deter intranasal abuse. In terms of physical properties, you saw ADF tablets were difficult to get into an abusable form for snorting. This is in contrast to Roxicodone, which was easily manipulated with simple tools.

For a young person experimenting with tampering, just this physical barrier alone may stop them from nasal abuse with the product. But even if they overcome the physical barrier, there is still the chemical barrier with aversive agents that cause nasal pain and burning during the time when those abusing would be expecting to feel the greatest high. This is in contrast to snorting Roxicodone, which is pleasurable within minutes and contains no agents to discourage intranasal abuse.

Next, the human abuse potential study also demonstrates that the ADF can be expected to deter nasal abuse. In terms of drug-liking Emax, the ADF had an average score that was 6 points lower than Roxicodone. Data from RoxyBond's intranasal study can also be used to provide perspective. We have to be careful about making cross-study comparisons, but RoxyBond does provide a relevant anchor for abuse-deterrent labeling.

RoxyBond's drug-liking Emax was 12 points lower than Roxicodone. This larger difference would be expected since RoxyBond's deterrence works by slowing and lowering drug levels, thereby reducing positive effects. In terms of take-drug-again Emax, where participants reported their willingness, the ADF replacement score was 31 points lower than Roxicodone. And recall, the mean score was less than 50, which is neutral. This lack of willingness to take again is consistent with the impact of the aversive agents.

For RoxyBond, the take-drug-again scores were 20 points lower than Roxicodone. This

difference is substantial but was somewhat less than the ADF, which may be due to the fact that RoxyBond does not contain aversive agents. Both of these products should be expected to successfully reduce intranasal abuse. The scores on the key endpoints were consistent with each formulation's primary mechanism of deterrence, either reducing positive effects in the case of RoxyBond or creating negative effects in the case of the ADF replacement.

Let's turn to the next question. Can the ADF be expected to deter abuse by the IV route of administration? Here, I think we also have three different approaches to assessing the question, the physical and chemical properties of the tablets; the sponsor's Category 1 studies; and the precedent relative to RoxyBond, which has an IV abuse-deterrence claim.

The physical barriers for IV deterrence are the same as we already presented for nasal deterrence. The ADF is clearly more difficult to get into an abusable form than the product it would

be replacing. In terms of chemical barriers, the ADF has multiple gelling agents that are intended to make injection difficult while Roxicodone and non-ADF products have no barriers to injection.

The Category 1 studies demonstrated that the ADF was difficult to syringe with low yields of oxycodone in the vast majority of conditions and required advanced conditions for IV abuse. Again, I look back to the RoxyBond data to put this ADF data in context. In the worst-case scenario, 60 percent yield could be achieved with the ADF replacement and a 66 percent yield could be achieved with RoxyBond.

Obviously, no formulation can be abused proof, but the fact that extensive multi-step processes were required to achieve these worst-case scenarios suggests that both RoxyBond and the ADF replacement can be expected to deter injection.

Next question is about concerns regarding the public health impact of the ADF replacement on misuse and abuse of opioids. I'd like to briefly walk through a benefit-risk analysis for some of

the common public health concerns that have been raised about abuse-deterrent formulations.

First, there is a concern that the uptake of ADFs will be low limiting their public health impact. If approved, this ADFs would replace the currently marketed branded and generic immediate-release, single-entity oxycodone tablets manufactured by Mallinckrodt. This would be a step towards FDA's goal of transitioning the prescription opioid market to one where most products have meaningful abuse-deterrent properties.

Second, there's been a concern that ADFs may send a false sense of security to prescribers. The approval of abuse-deterrent formulations has not led to an increase in opioid prescribing. Furthermore, Mallinckrodt has stated that they will not promote the ADF replacement.

Next, recent advisory committees have been concerned that ADFs cannot deter initiation into the dangerous non-oral routes of abuse. This product addresses that concern since it contains

aversive agents to actively discouraged intranasal abuse.

Another public health concern has been that ADFs should not push individuals from snorting a product to injecting it. While no product is abuse proof, it's reassuring that an extensive, multi-step, time-consuming process was required, supporting that the product is abuse deterrent.

Finally, we've all shared concerns about the potential risk of serious health consequences resulting from injection of excipients. The nonclinical studies showed no evidence of serious risks with repeated injection of the ADF. This does not mean that there is no risk, however, we have to remember that the most dangerous ingredient to inject from an oxycodone tablet, whether it's an ADF or non-ADF, is the oxycodone itself due to the risk of overdose and death. This underscores why deterring IV abuse is a public health priority and why the FDA continues to support the advancement of ADF technologies.

You've been tasked today with the question

should the ADF replacement be approved. I think we have to acknowledge that abuse-deterrent formulations are not the silver bullet that are going to solve our nation's opioid crisis. Making opioid medications more difficult to abuse is just one part of a more comprehensive plan to address our epidemic.

We need to use all of the strategies seen to their fullest extent to meaningfully address this unprecedented public health challenge. But to the issue before us today, the FDA has advocated for transitioning the opioid market to abuse-deterrent formulations because of the public health benefit that can be expected from providing meaningful safeguards against abuse. Unlike prior ADFs that have come before this committee, approval would not mean adding another opioid product to the market. Rather, approval would allow for an important transition.

Mallinckrodt's currently marketed immediate-release, single-entity oxycodone products without safeguards against abuse would no longer be

available, leading to a transition where millions of prescriptions would be replaced by a medication that is therapeutically equivalent to current products, but with meaningful safeguards against intranasal and intravenous abuse. This transition is in the interest of patients and of the public health.

Thank you for allowing me to share my perspective. I'll now turn the lectern back to the sponsor.

DR. SCHLICHER: Thank you, Dr. Gudin.

I'd be happy to take any questions.

Clarifying Questions

DR. BATEMAN: Are there any clarifying questions for SpecGx? Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter. Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I'm going to direct this question to Dr. Cone, but simultaneously Dr. Hertz because I'm not sure that I can ask this question.

What was the rationale used for choosing the manipulation techniques? Is that something that we could ask Dr. Hertz or is that too much more about methodology?

DR. HERTZ: This is Sharon Hertz. I can give you a general approach. What we basically ask companies to do is manipulate the product to defeat. We asked them to use a variety of solvents, different lipophilic, non-lipophilic; high pH, low pH; commonly available, not so commonly available; with heat, without heat; pretreat with heat, pretreat with -- whatever we think might be suitable to defeat, in this case, excipients intended to make the product difficult to manipulate.

DR. HIGGINS: Is it consistent with what's commonly done by abusers through bud chats or web-based --

DR. HERTZ: I can't swear that it's current to the absolute latest trend that might be surfacing, but overall, yes, it is. We have a controlled substances staff and a chemistry staff

that are very experienced in looking at this material at the methods. We interact with the companies during development. And if we don't think that the evaluation has been sufficiently robust, we request additional studies. And we've had circumstances with products that you all have never seen where we didn't even get to an advisory committee because we didn't think the methods were sufficient to even consider approval, so we didn't come here.

I know it's a little unsettling this time around because we haven't gone into the in-depth methodologies in the closed session, but if we think that there's a deficit along development or once an application has been submitted, we will ask for additional studies.

DR. HIGGINS: Thank you. And I have another question, actually two other questions for Dr. Comer, if I may ask.

With respect to the PK analysis, in the background materials, I found that there was a period of 8 hours to Tmax in one subject. And I

wondered if you might have an explanation for why that should have been.

DR. COMER: Yes. I think you're referring to the bioequivalence study.

DR. HIGGINS: Yes.

DR. COMER: Yes. I think I can help you with that. This was covered in the FDA briefing book as well as our briefing book, and I'd like to put up the slide of the three subjects.

So you're right. There was for 3 individuals, within the bioequivalent study and the fed study, they had a little bit longer time to the maximum plasma concentration. What we were reassured by is the fact, as you can see in this slide, in all 3 individuals, while their Tmaxes were at 4 hours -- I'm sorry, at 6 hours or at 8 hours, we actually saw that they achieved a maximum plasma concentration very close to their ultimate maximum plasma concentration within that dosing interval, really only differing by about a nanogram per mL.

DR. HIGGINS: Okay. My second question for

you, Dr. Comer, was with respect to the drug-liking study. Why was such a broad response scale used? 1 to 100 seems unnecessarily broad. Is it standard practice? Is there some standard method for using that scale?

DR. SCHLICHER: Yes. I think it's probably best to ask Dr. Webster to answer this since this study was conducted in his laboratory.

DR. WEBSTER: Lynn Webster, vice president of scientific affairs at PRA Health Sciences. Yes, this is a standard approach. This is something that we do for all human abuse liability with that typical scale. So this is a scale that standardized now for these studies.

DR. HIGGINS: Thank you. And one last question. It seemed to me that the N of 38 for study MNK48121013, with respect to the completer population of recreational opioid users, seems small. Is that also a standard number?

DR. SCHLICHER: I'll ask Dr. Webster to comment.

DR. WEBSTER: Lynn Webster. Yes, it's

evolved over time. When I first started doing these, we were looking at the lower 20's, but over the years, we've increased the number, and it appears to be a sufficient number in the mid 30's to low 40's for most of these studies. Yes.

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

DR. SCHLICHER: We actually designed this study for 34 completers, so we're pleased to see 38.

DR. BATEMAN: Dr. Zeltzer?

DR. ZELTZER: Thank you. I'll assault you again. This is a question for Dr. Comer. I must be missing something, but can people, if they break something into particles, while the particles may not be small enough for intranasal use, what about sublingual? Can people hold particles longer under their tongue to get sufficient absorption?

DR. SCHLICHER: Yes. So I think that's probably a question for me. This is an immediate-release drug products, so it needs to be immediately available upon being swallowed or taken. We don't expect any different release in

the drug product sublingually versus taken orally. We, again, want it to be immediately available.

DR. ZELTZER: Maybe I'm not being clear. If we talk about transmucosal -- intranasal is transmucosal absorption, so you get the first pass issue. You can get the first pass issue transmucosally and sublingually. So can people hold particles, that would otherwise be annoying, intranasally for a longer period of time to get more time for absorption sublingually?

DR. SCHLICHER: Great.

Dr. Gudin, can I ask you to comment?

DR. GUDIN: Jeff Gudin, pain management addiction medicine, palliative care. It's a great question, and especially in the palliative care world, we've tried with sublingual and other transmucosal routes of delivery. And what we've seen is that there's wide variability amongst the opioids and tends to have a lot to do with their lipid solubility profile, how lipophilic they are.

So hence, we see in even commercially marketed fentanyl products, which are

transmucosally delivered, tend to work very well and very rapidly; whereas the more hydrophilic drugs like morphine and oxycodone don't have enhanced absorption sublingually. So as Dr. Schlicher mentioned, simply taking it by mouth, it's so bioavailable and seems to give us a very comparable level as keeping it sublingual.

DR. SCHLICHER: Yes. I should probably also further articulate, while we're able through particle size reduction to dramatically reduce the tablet to fine particles, they still are formulated to a degree. So while we can get over 50 percent to be less than 250 microns, the size of the API is actually about 50 microns. So the product is still actually formulated when it's been insufflated. That's why you saw Dr. Comer's time delay to the high. So the product is still actually formulated, just not no longer in the tablet form.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Goudra. Penn Medicine. This question I guess is for Dr. Dart with reference to slide 13, 013. My question is, I was looking at

more recent literature in connection with pathways of opioid abuse, and there is literature out there which suggests, I don't know, what percentage, but some of these people who end up using it or abusing it would first find their opiates at home maybe prescribed for somebody else. And second, many of them start with a street drug.

My question is how significant -- rather what percentage this pathway contributes to overall opioid abuse, which we see now?

DR. SCHLICHER: Dr. Dart?

DR. DART: Rick Dart. That's a very good question, and unfortunately, we don't have an answer to it. It's something that I'm interested in and have looked at the literature repeatedly. The question I think you're asking is what relative proportions of people go through each pathway, and we really don't know the answer to that.

It gets complicated because some papers have looked at this but fail to take into account the patient's previous drug history. So they'll say, well, they started as a pain patient, but when you

actually drill down on that, they had previous experiences of abuse as well. So I think the honest answer is we don't know, but I would say that both are substantial. It's not 90 percent, one or the other, probably.

DR. SCHLICHER: And certainly what we're trying to do here is take a product that has no abuse-deterrent features, replace it with a product that we have demonstrated has significant abuse-deterrent features to prevent that progression under any route.

DR. GOUDRA: And the second question is, I guess you guys stated that you're going to replace the existing IR product with this one. Will the price be the same or it's going to be different?

DR. SCHLICHER: I think it's probably not appropriate to discuss pricing in this forum, but we certainly learned in the development of this drug product, when we were talking to individuals in the marketplace, to understand what could make this different, how could we get broader adoption and acceptance of ADF formulations that were going

to be critical to not only be bioequivalent but to be priced competitively with generic products. It is a generic marketplace; 99 percent of the drugs are generic. We need to make sure that that drug can be priced competitively.

DR. GOUDRA: Okay. And the last question is, I do see in the literature that immediate-release formulations are far more susceptible for abuse than extended release. Is there any reason for that?

DR. SCHLICHER: I'll ask Dr. Dart to come up. We'd agree with that concern. We think that's why it was so important and why we focused on the development of abuse deterrence for an IR formulation.

DR. DART: Yes. It's been a frustration of my whole career that since the beginning, the immediate-release opioids were actually much more abused than the extended release. But you know how the press is, and they get all the press time. So extended release became very well known for this even though the data never indicated that was the

case.

So there are multiple factors, but the main one is probably availability in that abusers, they always have a preferred drug, but they actually have to abuse what's available. They can't abuse a drug that they can't get their hands on. So the immediate-release products have always been more available. And when you ask the abusers themselves, it's always availability and ease of crushing and solubilizing, depending on which route you're going to use, snorting or IV.

Did that answer your question?

DR. GOUDRA: Are the extended-release tablets more prescribed than IR?

DR. DART: Oh, no. I don't know the exact number, and I don't know if we have a slide on that, but the IR's are the vast majority of the market.

DR. HERTZ: Excuse me. This is Sharon Hertz. We actually are going to present some of these numbers.

DR. DART: Oh, that's right.

DR. GOUDRA: Thank you.

DR. SCHLICHER: Dr. Gudin?

DR. GUDIN: Thank you. Jeff Gudin. A very important question. I can tell you as an active suboxone prescriber, seeing patients with substance-use and opioid-use disorders, that in the last few years, clearly the number one drug that patients come in with a problem is Roxicodone, immediate-release oxycodone.

It's been almost a decade that we would see patients come in with the extended release issues I think since those formulations have changed. So I'd have to say the number one commonly misused drug and the number one drug asked for by name on the street by the abusers is Roxy. They want the higher strength oxycodone IR products.

DR. SCHLICHER: And our understanding broadly is that would be about 20 million prescriptions on an annual basis, whole market, obviously, not ours.

DR. BATEMAN: Dr. Arfken?

DR. ARFKEN: Cynthia Arfken. I have a

question about the actual mechanics of replacing the generic. I monitor our prescription drug monitoring program, so I was wondering how it would appear. Would the physician just write a generic and the pharmacy would do it, or would they have to indicate a genetic ADF, and then that would appear on the monitoring program?

DR. SCHLICHER: Both of those we believe will be options, as well as the option to also write for Roxicodone. So it would be Roxicodone. It would be directly substitutable, the generic equivalence and bioequivalence. And yes, it would have these desired additional abuse-deterrent features.

We are actually currently conducting, as I indicated previously, focus groups with physicians to make sure we are understanding what the educational needs are, what the educational gaps are, and how to make certain we can do this in a seamless and effective transition. We understand that's going to take some time, and we're especially sensitive to it. Clearly, we can't have

very specific conversations along those lines without approval and without labeling, so much of that lies ahead.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Thank you. My question is for Dr. Dart and perhaps for Dr. Gudin, too.

Dr. Dart, on slide 13 again, I too had the questions but perhaps a little differently. I know there's a question or I think I've seen in the past the percentage of susceptible individuals. So the total, I believe, was estimated somewhere around 20 percent of that population. And then I think you just said you don't know what the breakout in terms of the pain patient or the recreational user is to that susceptible individual.

Is that what I just heard?

DR. SCHLICHER: Dr. Dart?

DR. DART: I think so, but could you restate that? Because I'm not sure I totally followed.

MR. O'BRIEN: My question is in terms of percentages, what we're talking about here to put it in context for my own self. What percent of

that susceptible individual comes from either the pain patient or the recreational user?

DR. DART: I may have missed literature, but I looked for this, and I really don't think we know that. I don't know how else to answer, but it's just that it gets very -- the concern I have is that when people try to predict this, they usually have not looked at the patient's previous history.

For example, let's say you are a pain patient who later recreationally abuses, and the investigator looks at the recreational phase of your career, if you will. If they don't tell me about that previous, then they've misrepresented what happened. I'm hoping to do this study myself, actually, but we're not there yet.

MR. O'BRIEN: And in terms of -- oh, I'm sorry. Go ahead.

DR. SCHLICHER: That's all right. What's especially important to us is to stop that progression at all. We want to make sure that the drug products we are producing are only going for their indicated route, and we can prevent that

progression for that individual or for any diversion, as Dr. Gudin is suggesting from the medicine cabinet.

MR. O'BRIEN: I understand that. I had another question for Dr. Dart, and again perhaps for Dr. Gudin. On that same slide, in terms of behavior, I tried to wrap myself around it coming mostly from representing pain patients, community, it seems to be anecdotally, I would say, that the behavior that first gets someone into trouble -- not the intended, but the unintended -- is alcohol. That's the first behavior, excessive alcohol. And in terms of anecdotally, whenever you see someone that is unintendedly death, there's always an empty bottle of alcohol that's in the car or in the thing.

So that seems to be the first real behavior, but yet I don't see that indicated as being a behavior. Is that not a behavior of those that abuse the drug, intended or otherwise?

DR. SCHLICHER: Dr. Dart?

DR. DART: You're absolutely right. There's

actually people around the table who could answer this better than me, but usually people start with alcohol and nicotine. It's not universal, but those are the most common predictors. And then there's a whole host of other factors such as abuse, physical abuse, trauma, isolation.

You can name a whole list of factors that the pain patients who end up with a problem have strong influences on that, including genetics. NIDA would say 60 percent of it is genetics. So there's probably 20, 30, maybe more factors that aren't shown on the slide, and alcohol is a big one. You're correct.

MR. O'BRIEN: More specifically I guess to Dr. Schlicher or Ms. Schlicher, I'm sorry, would there be any difference whether I took Roxicodone or ADF and drank a bottle of vodka?

DR. SCHLICHER: Yes. We certainly haven't done the study, but what we do know is that -- I'm sorry. Are you asking about their willingness to try to overcome the abuse-deterrent features or are you asking if alcohol has an effect on the drug?

MR. O'BRIEN: Overcome the abuse.

DR. SCHLICHER: That's what I thought. Okay. We do know what we've created is a progression of frustrations. Even just with the particle size reduction, the effort that they have to go to in order to be able to do that really needs, to some extent, to be predetermined. It isn't something that they can just do any place they are. They would have had a thought to have the right tool in place and to go through some elaborate actions in order to make it work.

Similarly, as Dr. Cone described, the process that they need to go through in order to be able to break that down into an abusable form takes over an hour and involves a number of steps. And in fact, if those steps are done a little differently or not in quite the right way, you saw that the yield differences are dramatic. Even though we saw a maximum yield of 60 percent, the median for that condition was actually 10.

So I'm not suggesting they couldn't get any out, but if it's difficult to do when you're not

impaired, I would imagine that would go up by a significant factor if you are.

I'm going to extend my answer here for a minute because I think it's relevant, and we didn't provide it in the materials. So you could say to me, then, well, that's through small-volume extraction and an extensive procedure. What if I just drop that tablet in 30 mLs of water? What if I use large-volume extraction instead of small-volume extraction?

I want to make sure that distinction is really clear to the group here today because I think it was covered in the RoxyBond IR review a year ago, but that's been a year. So let me make sure I cover why large-volume extraction isn't relevant to an IR drug.

First of all, our drug has to be immediately available. By the guidance, we must be able to get the dissolution of 85 percent of that product within 15 minutes in water. That's a requirement for approval. So yes, you can absolutely achieve that, but I've now taken the highest dose, the

30-milligram tablet. I've dissolved in 30 mLs of water. I could drink it. That's not going to have any benefit over taking the tablets, certainly; or I could look to inject it, which was the concern with Opana.

But here again, I have an immediate-release drug that's an IR drug that's already readily vial available, 85 percent. So the satisfaction of injecting a milligram per mL, I'd have to inject 30 mLs in order to get to that same benefit, isn't likely to happen. But the real distinction with Opana is, again, that was an ER product, and it wasn't bioavailable, only about 10 percent bioavailable. So if I put that tablet in water, it provided a lot of bioactive material that individuals could share by IV; so absolutely no comparison to an IR drug that's readily bioavailable.

Sorry. I just wanted to make sure I explained why we didn't cover that.

MR. O'BRIEN: I just have one last question.

DR. BATEMAN: I'd like to move on to other

committee members.

MR. O'BRIEN: Sure.

DR. BATEMAN: Will come back to you if we have time later.

Dr. McCann?

DR. McCANN: Thank you. I have a couple of questions for Dr. Orr. I have questions about the validity of the toxicity studies in rabbits, and I think they're probably -- I guess I just don't understand the study.

On slide 40, it said dose volume selected based on tolerability profile of oxycodone. I'm presuming that is tolerability for the rabbits.

DR. SCHLICHER: Dr. Orr?

DR. ORR: Yes, that's correct. That's the tolerability of the rabbits. We actually had an antagonist on hand in case the rabbits went down, so pushed the dose to the dose that they can tolerate for the oxycodone.

DR. McCANN: Do they have similar tolerabilities to humans in terms of milligrams?

DR. ORR: Pretty similar. Then it says

58-fold higher dose for rabbits relative to humans based on mLs per kilo. So you gave the rabbits 1 mL per kilo. Right? So then you would say if you extrapolated that to humans, you would be giving them 70 mLs for a dose? And then if you back-figure that --

DR. ORR: Yes. The way we looked at this, it was 1 mL per kilogram for the rabbit dose, and for the human dose, it was 1 mL per 60 kilogram human. So it would be on a mL per kilogram basis, approximately a 59-fold greater dose than what a human would receive of the extract. Again, these are the test articles that were -- the most that there would be syringe or kind of a real-life test of what could somebody get out of the pill, and then use that extract to treat the animals.

DR. McCANN: Okay. So the presumption is that a human would not inject more than a mL at a time?

DR. ORR: That's what's been told to me is a reasonable dose for human.

DR. McCANN: Then to go to slide 42, test

article 2, statistically significant increases in fibrinogen and increases in spleen weight 50 percent. Does that mean that 50 percent of the rabbits had an increase in spleen weight or on average, the rabbits' spleens increased by 50 percent?

DR. ORR: It's the spleen weights for -- it's an average of the N of 4. So the spleen weights increased for test article 2 by 50 percent.

DR. McCANN: I think as a doctor of humans, if I gave a drug, an antibiotic, and the spleen increased by 50 percent, that would be of concern. But you said the independent pathologists didn't find it concerning. Is that because rabbits increase their spleens willy-nilly compared to humans?

DR. ORR: How about I put some clarity on this?

DR. McCANN: Sure. Absolutely.

DR. ORR: In a general toxicology study, we look at many different parameters. Test article 1,

many different parameters. We look at hematology, coagulation, many different endpoints of clinical chemistry, urinalysis. And then we actually take the tissues from the animals and then do a histopathological evaluation of those tissues to determine whether there's any overt damage to the tissue.

In this particular case, we did see, as indicated, and increase in spleen weights. There was a minimal and slight increase in congestion. However, if you look at all the parameters, we didn't see any evidence of overt toxicity. We didn't see red blood cell lysis, increase in plasma and hemoglobin. We didn't see the kidney damage, all of which was seen within 24 hours using the high molecular weight PEO.

So looking at all the information in context of the study and having very minimal effects and no obvious damage to the spleen, it was not considered adverse.

DR. McCANN: Thank you.

DR. ORR: You're welcome.

DR. BATEMAN: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I was going to start with a different question, but I wanted to follow up on Dr. McCann, and I need one more question after that. I too was interested in the in vivo testing of rabbits, 3 days of testing, once daily in 12 rabbits. The spleen weight seems incredible based on both volume and time.

What would happen if you did a more real-life test, like gave it to the rabbits once a day for 3 months? Would that spleen continue to grow? And how do you find a common side effect in this unique combination of ingredients when you've got 12 rabbits; when a common side effect is one that happens in 1 in a hundred humans? It just seems a ridiculously short period of time and an intensely small sample group. How can that tell me anything?

DR. SCHLICHER: So let me ask Dr. Orr to come, but I'll make a few comments while he's coming up to the podium. I think it's important to note that we did test two test articles. And the

test article that you're referring to was actually one that had significantly lower concentrations of oxycodone than test article 1.

So while we thought it was important to test two different thermal methods of heating, we don't think the likelihood is high that this would be a condition that users would actually use because the levels of oxycodone extracted are well under the 50 percent that we achieved in test article 1. So they might try at a time or two, but I think they would find it very unsatisfying in that they'd have to go through that multiple more than hour-long procedure, and then they would find the extraction amounts unrewarding and a significant reduction in the oxycodone that they paid for.

I'll now turn it over to Dr. Orr to provide some --

DR. ORR: Dr. Mike Orr, nonclinical consulting. Yes. If I understand you correctly, you're concerned about the number of animals in each cohort. The identical number of animals per cohort were used for the guinea pig study. They

were able to detect the overt toxicity, the TMA, within 24 hours in that particular study. The N of 4 for non-rodent species is a standard number for general toxicology studies attempting to identify the hazards with any test article.

MS. ROBOTTI: So you have no idea what would happen to the spleen over time, for example.

DR. ORR: At this point, we have 3 days of dosing, and we did look at the spleen. The spleen was taken out. They looked for any types of damage or evidence of red blood cell lysis occurring, and it was considered by the independent pathologists to be normal.

MS. ROBOTTI: Second question. I assume this would be to Dr. --

DR. SCHLICHER: Schlicher.

MS. ROBOTTI: -- Schlicher. Sorry. If the company receives approval for the formulation itself but does not receive ADF labeling, will you go ahead and be replacing all the products in any case? You did point out you would not be promoting the change in label.

DR. SCHLICHER: Correct. As I mentioned, we began this work in 2012, really in an effort to understand what was it going to take to be successful with an abuse-deterrent formulation, and we really learned it absolutely has to be bioequivalent. It actually absolutely has to compete in a generic market place, and it absolutely must have the IV and the IN labeling dose, both for educational purposes as well as -- as we talk to payers, and prescribers, and pharmacies, they don't see that there is value in providing that abuse-deterrent formulation unless they can actually show the stewardship and show the appropriateness of making that change and be able to have it preferentially prescribed.

So the answer is no. We would not be going forward without labeling.

MS. ROBOTTI: But if the original product is not available or if it's presented in this slight change in formulation to make it progressively more frustrating to abuse, you don't need the labeling; you've created a public good.

DR. SCHLICHER: We believe we very much are creating a public good, but we don't sell product to the marketplace. We must go through HMOs and retail pharmacies. And with a lack of willingness to put that product on formulary without abuse-deterrent labeling and features, we don't have a path forward to sell the product.

DR. BATEMAN: Dr. Zibbell?

DR. ZIBBELL: Thank you. John Zibbell, RTI International and Emory University. I think this is for Dr. Comer. I think I read this in the briefing, but can you tell me the reason for not conducting a human abuse potential study for the IV routes of administration?

DR. COMER: Yes. That would not be typical for the abuse-deterrent features that we are providing. That typically is done -- and I believe there have been previous abuse-deterrent committees on that -- when it's an artificial formulation created in order to be able to demonstrate abuse deterrence. So for us, that really wouldn't be relevant.

The other reason would be, once we've done the small-volume extraction work, once we've done the pretreatment, that is no longer the drug that is intended for oral use, so we don't have the specific details on the safety profile that we would be providing to those individuals, and clearly, that wouldn't be appropriate. It's all the more reason that the FDA suggested, and working with them, that we did the preclinical testing that Dr. Orr has described.

DR. HERTZ: This is Sharon Hertz. I just want to clarify this a step further. We probably wouldn't have allowed it. Because the excipients aren't approved for that route, it's not safe to study. And we think we have enough information from understanding the amount of oxycodone that can be achieved, and put into a syringe, and injected.

When we have products with an antagonist, what we do is have them simulate the amount of opioid, the amount of antagonist that we think would be available, just to make sure the antagonist is having the adequate effect on the

agonist. But here where it's just a single entity, we actually wouldn't allow it for safety reasons. And that is, as I said, why we've, on the advice of this committee, switched into pursuing more tox data in nonclinical models.

DR. ZIBBELL: Thanks, Sharon.

Can I do one quick follow-up?

I was also wondering what led you to choose aversion as your abuse-deterrent mechanism and just some sub-questions there. Is there a literature on the efficacy of physical-chemical aversion to deter the use of opioids? And the second one might be for FDA. Do other FDA-approved opioid medications include a chemical-based aversion mechanism?

DR. SCHLICHER: Yes. Working to develop an immediate-release, abuse-deterrent formulation is a difficult path to go down because you're trying to find a way to still make it immediately available but also abuse deterrent. So the effectiveness of the aversive agents is they actually work twofold. They're providing this aversion and they're also helping to facilitate the immediate release of the

drug to make sure that it can be bioavailable.

The thing that we're really encouraged by is the strong results on overall drug liking and take drug again. Nothing could be more reassuring to us than to have somebody willing to take placebo than willing to take our drug with aversive quantities that would get them high. So we're pleased that those aversive quantities are providing that lack of desire to take the drug again and yet be bioavailable for those who need it for pain.

DR. ZIBBELL: And those weren't physically dependent persons, right? They were recreational users without a physical dependency?

DR. SCHLICHER: That is correct.

DR. BATEMAN: Dr. Marshall?

DR. MARSHALL: Brandon Marshall, Brown School of Public Health. I have a question for the sponsor regarding the pharmacodynamic results. If we assume that the positive effects are independent from the negative effects, which seems to be the framework we're working from, I understand the mechanism of the negative effects is due to the

aversive agents that are added. But what is the hypothesized chemical or mechanism of action that delayed the drug liking and resulted in lower drug liking over time?

DR. SCHLICHER: Yes. As I mentioned, while we're able to get a particle size that's less than 500 microns; in fact, most of it under 250 micros, that's still a particle size greater than the API of 50 microns. So even though you have those fine particles, they're still formulated, so you're still experiencing those gelling properties on insufflation, which is delaying the release of the drug or delaying the time to high.

DR. BATEMAN: Dr. Green?

DR. GREEN: Hi. Traci Green. I have three questions. The first two are with respect to Dr. Comer's study. On slide 57, I was curious about the ADF replacement causing aversive nasal effects, the time points where statistical significance continued or did not during those time points.

DR. SCHLICHER: Yes. Really what we're

seeing here is that we immediately experience the adverse effects. In fact, if we actually show our adverse event details, we had a quarter of the individuals actually come forward spontaneously to report that nasal abuse and irritation right upon insufflation of the drug product. And then you see that these questions -- I'll ask Dr. Webster because he conducted the study and can speak to the questions asked over time were asked in a routine fashion over the course of the study.

DR. WEBSTER: So you're asking did we ask the same questions for longer than 2 hours? Lynn Webster.

DR. GREEN: The statistical significance at 1, 1 and a half, and 2 hours, did they overlap at that point? At what point -- clearly, the first half hour was significant and had a number of these --

DR. WEBSTER: I don't think that we have a great deal of significance after the 1 hour. Most of the impact, the aversive effect, occurs in the first quarter your and at the half hour. But we do

assess later. It's just not relevant.

DR. GREEN: Okay. Great. And the second question I have is --

DR. SCHLICHER: Sorry. So we were statistically significant at 1 hour, as Dr. Webster indicated, but post that time, we're absolutely not suggesting that that aversion is retained. We actually kind of like that. We don't want to be causing any kind of permanent nasal effect, but we really like the effect that even though it is gone after 2 hours, 12 and 24 hours later, when they're no longer high, they're saying, "No thank you. I don't want to take that thing again."

DR. GREEN: Great. And the related question, what's it taste like when it's insufflated, and how is that different from the current Roxicodone IN?

DR. SCHLICHER: What does it take like?

DR. GREEN: The nasal drip, that is, that people --

DR. SCHLICHER: Dr. Webster, would you have --

DR. WEBSTER: Lynn Webster. We didn't ask them, but some of them would spontaneously comment it was bitter. But that wasn't a survey question, and it would only be something that they would spontaneously report.

DR. SCHLICHER: Which they didn't, so we don't know.

DR. GREEN: Okay. And the last question I have is with respect to the emergent adverse offense. This is I guess part of table on MNK48121013. For how long did the respiratory and other effects continue in the patients as they were being monitored? And I ask this specifically in terms of the respiratory effects because of the contribution that many people who misuse, especially oxycodone but other opioids, use in the presence of a benzodiazepine, which of course contributes to the respiratory depression that brings on overdose.

So I'm wondering about these individuals who didn't otherwise have respiratory effects and irritation with the existing product, but now are

having it potentially in this experience and how we can maybe think about it down the line in actual use.

DR. SCHLICHER: Yes. My understanding it was one time. They reported it one time. It was transient, and they didn't continue to report that experience.

DR. GREEN: So the 21 patients who experienced some form of respiratory effects had it a very short period of time? Is that all 21 experienced it over --

DR. SCHLICHER: That is my understanding.

Dr. Webster, would you have anything to add there?

DR. WEBSTER: No. That was not a focus, I think, of my review, so I don't recall. If we can get back to you after the break, we'll take a look at that data.

DR. GREEN: Okay. Thank you.

DR. BATEMAN: Dr. Meisel, we have time for one short question.

DR. MEISEL: Steve Meisel. This I think will

be short. The agency I think is stipulating bioequivalency between this product and the original product. Could you put up a slide that shows the data on that? I don't think that's been presented here today.

DR. SCHLICHER: Yes. We're happy to pull up that slide. Let's pull up -- I think the forest plot are you asking for?

Yes. Here is the slide showing the bioequivalence in both the fed and fasted state. We agree with the agency that we meet the prespecified boundaries for being bioequivalent in that 80 to 125 percent range.

DR. MEISEL: But as I look at this, I remember this reading the briefing document, although it meets the agency's criteria, the confidence limits here -- clearly, the AUC is lower than the original, and the Cmax is lower than the original. I think Tmax is also slower.

Would that be accurate to say that they're statistically lower and slower -- although they meet the agency's criteria for bioequivalency, that

the actual AUC and Cmax are lower and the Tmax is slower?

DR. SCHLICHER: Yes. They're both over that 80 percent as you indicate. We actually see the same kind of variability here that we have traditionally seen with Roxicodone itself, and we discussed a little bit earlier in the fed state why we had that delayed Tmax for those 3 individuals.

DR. MEISEL: Okay. Thank you.

DR. BATEMAN: We'll now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We'll resume at 10:15.

(Whereupon, at 10:00 a.m., a recess was taken.)

DR. BATEMAN: We'll now proceed with FDA presentations.

FDA Presentation - Jennifer Nadel

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

Products. I'm going to provide you with a high-level review of the MNK-812 new drug application, NDA, and an overview of the agency's presentations.

The order of FDA presentations, as shown in the agenda, will be an introduction and overview of the application, which I will present. Dr. Amspacher will discuss the in vitro data. Dr. Mellon will discuss the nonclinical safety assessment. Dr. Tolliver will discuss the intranasal abuse potential of MNK-812. Dr. Meyer will discuss data on use, misuse, and abuse of oxycodone. Lastly, I will present a clinical summary of abuse deterrence and provide concluding remarks.

MNK-812 is an immediate-release oxycodone with reported abuse deterrence via the intranasal and intravenous routes. The abuse deterrence does not address the oral route, which is the most common route for abuse. This product is indicated for pain severe enough to require an opioid analgesic and for which alternative treatments are

inadequate.

The planned doses are 5, 10, 15, 20, and 30 milligrams. The efficacy and safety of this product was established by the applicant showing bioequivalence to Roxicodone in two PK studies, therefore, no further safety or efficacy studies were conducted or required.

The clinical development program for MNK-812 consisted of 2 pharmacokinetic studies to demonstrate bioequivalence to Roxicodone and one human abuse potential study, which evaluated the effect of the abuse-deterrent properties on the potential for intranasal abuse. Overall, the types of adverse events reported in the 2 pharmacokinetic studies were consistent with exposure to oral opioids.

The human abuse potential study also demonstrated adverse events that were typical of an oral opioid as well as findings that may be attributed to the abuse-deterrent properties of the product. This table depicts adverse events by system organ class, or SOC, a preferred term in the

HAP study. As shown in the table, adverse events showed a higher frequency occurring in the intact oral MNK-812 and the intranasal MNIK-812 groups as compared to the intranasal oxycodone and placebo groups.

These events were most commonly reported in the respiratory, thoracic, and mediastinal disorders, and gastrointestinal disorder SOCs. Within these SOCs, the most frequently reported preferred term for MNK-812 were cough, nasal discomfort, nasal congestion, nausea, vomiting, constipation, and retching. In general, most adverse events or AEs were mild in severity. Two AEs of moderate severity were reported for cough and nasal burning sensation.

Now, Dr. Amspacher will discuss the in vitro findings.

FDA Presentation - Valerie Amspacher

DR. AMSPACHER: Hello. My name is Valerie Amspacher. I'm a chemistry manufacturing and controls reviewer in the Office of Pharmaceutical Quality. Today I'm going to present on the

in vitro Category 1, abuse-deterrent studies of MNK-812.

MNK-812 is an immediate-release oxycodone tablet with intranasal and intravenous abuse-deterrent features. It is available in 5, 10, 15, 20, and 30-milligram strengths. Category 1 studies were performed by the sponsor and by FDA's internal labs according to the FDA guidance titled Abuse Deterrent Opioids:
Evaluation and Labeling Guidance for Industry.

Category 1 studies are in vitro studies performed to characterize the abuse-deterrent properties of a dosage form. Today, I will be discussing results of tests looking at physical manipulation, small-volume extraction, and large-volume extraction. Physical manipulation testing includes both manual manipulation using common household tools, as well as mechanical manipulation in which tablets are crushed or ground using electrically powered tools.

As I said, Category 1 tests include assessing the amount of drug that can be extracted

from a tablet with small-volume extraction and large-volume extraction. For this NDA, the sponsor chose 30 milliliters for the large volume extraction. The solvents used in the testing presented today are aqueous based and are frequently used for abuse.

When discussing the Category 1 studies, I will use the term "pretreatment." Pretreatment is the conditioning of a tablet at elevated temperatures in order to defeat abuse-deterrent properties. These Category 1 tests looked at 30-milligram MNK-812 tablets and 30-milligram Roxicodone tablets. Some 15-milligram tablets of both dosage forms were tested, but the results discussed today will be focused on 30-milligram tablets.

FDA labs repeated a select fraction of the studies performed by SpecGx. Our lab results are in general agreement with those of SpecGx, but this is not to say that our interpretation of those results is in agreement with SpecGx

The first Category 1 test presented today

will be physical manipulation. Generally, we consider particle sizes smaller than 500 microns to be insufflatable, which raises concerns of possible nasal abuse. In physical manipulation testing of MNK-812 with manual tools, the tablets tested were not pretreated, as I just discussed on an earlier slide.

A maximum of about 10 percent of particles smaller than 500 microns were obtained from MNK-812, 15 and 30-milligram tablets when physically manipulated with manual tools. A maximum of about 94 percent of particles smaller than 500 microns were obtained from Roxicodone 15 and 30-milligram tablets when physically manipulated with manual tools.

Please note that the FDA background document included the incorrect percentage of particles smaller than 500 microns for Roxicodone. The correct amount is about 94 percent as stated on this slide. As the sponsor stated, manual physical manipulation techniques were generally not successful with MNK-812. However, physical

manipulation with mechanical tools was successful.

With no pretreatment and with mechanical tools readily available from places such as Walmart and Amazon, about 90 percent of particles were found to be smaller than 500 microns when MNK-812 15 and 30-milligram tablets were physically manipulated with mechanical tools. Because more than 90 percent of particles smaller than 500 microns were obtained from Roxicodone using manual techniques, Roxicodone tablets were not tested with mechanical techniques.

To get the 90 percent of particles smaller than 500 microns for MNK-812 takes less than 5 minutes of physical manipulation with mechanical tools. In summary, the data shows MNK-812 is more difficult to physically alter then Roxicodone with manual tools but is readily manipulated with mechanical tools.

The second Category 1 test presented today will be small-volume extraction. This test is significant because it conveys information about the ease of abusing this drug via the intravenous

route as was seen with reformulated Opana ER. This is investigated by looking at tablets that are both pretreated and not pretreated.

These tablets were extracted at room and elevated temperatures with and without agitation for various time periods measured in minutes, not hours. The solvents used for extraction testing are frequently used by individuals who abuse. They are either ingestible, or injectable, or both. Syringeability was tested with three different needle sizes, also known as gauges.

We agree with the sponsor that for both pretreated and non-pretreated tablets, the syringeability was hindered by the gel-like consistency of the extract with small volumes of liquid. We also agree with the sponsor that of the more than 1800 variations tested, many yielded oxycodone recoveries of 10 to 15 percent or less. However, please focus on the table on the right, which lists the percent syringeable oxycodone recovered from 30-milligram tablets in 5 milliliters of solvent frequently used for abuse.

The text on the left lists the conditions that were varied during the testing.

This table shows that with pretreatment, there are multiple mild conditions that yield recoveries of greater than 50 percent oxycodone using a solvent frequently used for abuse, which is both ingestible and directly injectable. These physical manipulations, pretreatments, and extractions at elevated temperature will take about 1 hour for an individual who abuses to perform. Upon further discussion of data and retesting by the NDA sponsor, additional data on three conditions was submitted to the FDA that showed lower percent extraction of oxycodone. Note that some extractions could be syringed with the smallest needles tested.

With respect to MNK-812, up to 60 percent of the oxycodone dose can be recovered with pretreatment, physical manipulation, and elevated extraction temperatures with a specific solvent frequently used for abuse resulting in a syringeable dose in about 1 hour. For comparison

with Roxicodone, generally 70 to 80 percent of a dose could be recovered with manual manipulation and extraction and syringed in about 10 to 15 minutes.

To further clarify the data presented by the sponsor this morning, the 60 percent isolated from MNK-812 was extracted in 5 milliliters while the 66 percent pointed out by the sponsor in RoxyBond was extracted in 30 milliliters.

The final Category 1 test presented today will be large-volume extraction. This is investigated by looking only at non-pretreated tablets. These tablets were either intact or physically manipulated, extracted at room and elevated temperatures with and without agitation for up to 2 hours.

For the large-volume studies, the tablets were extracted in 30 milliliters of the solvent; 14 solvents of varying pH, polarity, and ionic strength were tested. Results showed the abuse-deterrent features are defeated in 30 milliliters of the most frequently used solvent for

IV abuse in 2 hours with no pretreatment of tablets. Even without pretreatment, recoveries greater than 80 percent are regularly achieved in solvents of low, neutral, and high pH, and recoveries greater than 90 percent are frequently seen, which may encourage multiple injections of shared solutions of the type scene with reformulated OPANA ER. Recoveries are achieved with intact or ground tablets extracted at any temperature.

From the provided data, our conclusions are up to 60 percent of oxycodone can be extracted and syringed from an MNK-812, 30-milligram pretreated tablet with a solvent frequently used for abuse under specific conditions. Greater than 80 percent of oxycodone can be extracted from an MNK-812, 30-milligram tablet in 30 milliliters of solvents frequently used for abuse from non-pretreated tablets. Thank you.

FDA Presentation - Daniel Mellon

DR. MELLON: Good morning. My name is Dan Mellon. I'm the pharmacology-toxicology supervisor

in the Division of Anesthesia, Analgesia, and Addiction Products. My goal this morning is to provide you with an overview of the nonclinical safety assessment of the excipients in MNK-812.

To preview, it's important to first note that the agency does not have any safety concerns with respect to the excipients used in MNK-812 when the product is used for the intended route, i.e., the oral route of administration. And in general, the agency is in agreement with the applicant's assessment of the toxicological studies conducted to date to assess the risk of misuse of the product via the intravenous route of administration.

The existing data, although limited, suggests that intravenous injection of extracts of MNK-812 did not result in clear evidence of thrombotic microangiopathy unlike the published nonclinical study that tested the excipients that were present in the reformulated Opana ER product. However, there are limitations to the existing data, and the FDA cannot rule out the possibility that adverse effects could occur with more frequent

or more prolonged administration of manipulated MNK-812 for IV use.

In terms of the safety assessment of excipients, the agency has a very consistent guideline for how we actually address the safety of products for the intended route and that's described in a guidance that really almost basically describes the same types of studies that you would use for a new molecular entity.

We actually also have a guidance that describes what one might do to justify the safety of a product if one were to intentionally try to reformulate a product from an oral route to an intravenous route of administration, and these studies typically would include some in vitro blood compatibility studies, as well as intravenous toxicology studies to try to understand both the local and the systemic safety of a product, and that's described in a guidance document as well.

In the past, as you know, the agency has not required an assessment of an oral drug product excipient for the safety of either the intravenous

route or any other unintended route. However, due to unanticipated outcomes with an introduction of an abuse-deterrent opioid formulation to the market, specifically Opana ER, our approaches had to shift.

As many of you realize, there were adverse events that resulted from manipulation of the reformulated Opana ER product that included evidence of anemia, thrombocytopenia, thrombotic microangiopathy, acute kidney injury, and even retinal damage and cardiac involvement. The data from that product also supported a shift from the intranasal route of administration to more dangerous intravenous routes of abuse that resulted in an increase in outbreaks of HIV and hepatitis C in drug users who were sharing manipulated, reformulated Opana ER.

Because of that, the current approach to the safety assessment of abuse-deterrent opioid excipients has changed. We do require sponsors to provide a risk assessment of the potential adverse effects and risks that are associated with abuse of

the final drug product, ideally based upon the results of their Category 1 studies. These types of studies should consist of an in vitro assessment for blood compatibility and perhaps an analysis of the Category 1 data with either a literature-based assessment or a nonclinical study to try to understand the risk profile.

We believe that an adequate assessment of the potential risks associated with the non-oral abuse of the final drug product is necessary to help inform the risk-benefit profile of the product. And ultimately, in many circumstances, we include the potential excipient related adverse events from abuse of opioid drug product in section 9.2 of the prescription information.

I think it's important to step back and remind ourselves a little bit about what some of the nonclinical investigations showed when they were trying to understand what was taking place with the reformulated Opana ER product, and these studies were actually published by Hunt, et al. in 2017 and previously presented to the advisory

committees that were discussing this particular product.

As many of you may recall, Hunt, et al. injected guinea pigs with a PEO-plus powder formulation, and this included basically the polyethylene oxide that was utilized to manufacture the reformulated OPANA ER product, which had a mean molecular weight of about 7 million daltons. It also included some smaller amounts of hypromellose, Macrogol, alpha tocopherol, and citric acid. These are kindly supplied by Endo, the manufacturer of that product. The doses that were utilized were intended to try to mimic the amount of material that humans were likely to be administering to themselves when they were manipulating the product for use.

It's important to note that the material tested was not subjected to any type of heat curing or other manufacturing processes. These studies were conducted with more of the raw materials. Hunt, et al. administered bolus doses of PEO-plus at doses of about 0.1 to 0.3-milligram per kilogram

either once or 5 times over a 1.5-hour interval. This did result in plasma levels of PEO that were approximately 3 to 5 microgram per mL after the single injection and rose up to 15 or 40 microgram per mL after repeated injections. This actually is pretty consistent with the estimated levels that were predicted to occur by individuals who were manipulating the product for intravenous use.

The results of this study did demonstrate very much the similar types of clinical signs that were noted in the public domain, and that includes anemia, thrombotic microangiopathy, and acute kidney injury. The investigators noted this was not due to a direct effect as the in vitro assessments did not reproduce any of the anemia, and that they hypothesized that it was likely an indirect effect due to perhaps increased shear stress in the microvasculature, and deposition of free hemoglobin from the lysed red blood cells into tissues.

So the big question today is does MNK-812 have the same risk for thrombotic microangiopathy

as the Opana ER reformulation. The sponsor, as you heard this morning, conducted some studies to try to address this exact question. And in particular, as you also heard, they conducted some toxicology studies with syringeable material from Category 1 manipulations of MNK-812.

They noted that there were no adverse effects the in vitro blood compatibility studies, very similar to the results noted by Hunt, et al. They noted as well that in rabbits that were injected once a day for 3 days with syringeable material from two different Category 1 conditions, the animals were ultimately sacrificed on day 4.

It's important to note that following IV administration of this material, there was evidence of oxycodone related clinical signs. There was approximately a 50 percent increase in spleen weight, and there were some slight increases, minimal to mixed-cell infiltrates in the eye, minimal to slight mix-cell infiltrates in the lung, and some spleen congestion that were noted. However, there was no clear evidence of thrombotic

microangiopathy or acute kidney injury the conditions tested.

The sponsor actually also submitted some additional studies, some studies that were conducted with two different compounds, PEO 200K, or 200,000, or PEO with a mean molecular weight of 2 million I'll refer to as 2000K. It's important to note that neither one of these excipients are present in MNK-812, but the data are actually very interesting because they do test raw material PEO at a molecular weight that is lower than the material that was tested by Hunt, et al. and present in the reformulated Opana ER product. It's also important to note that this material as well was not subjected to any heat curing or other manufacturing processes, but actually, these studies were conducted with the raw materials.

In the results of these studies, the animals that were dosed either singly or for 14 days with a 200,000 molecular weight mean PEO, there was no evidence of deaths, and there was predominantly vacuolation of tissues. Lymphocyte macrophage

infiltrates were noted in the heart, but there was no strong evidence of anemia or microangiopathy. It's important to note as well that one high-dose animal that was administered for 14 days with this material did show some minimal necrosis of the heart at recovery, although it's not clear whether or not it's completely treatment related or not.

In contrast, the animals that were dosed with the 2-million mean molecular weight PEO materials did show evidence of deaths, renal injury, anemia, myocardial degeneration, and necrosis, consistent with microangiopathy. So collectively, if we look at the data that we have available to us from the Hunt studies, as well as these particular studies, it's reasonable to conclude that higher molecular weight PEO does appear to perhaps produce significant toxicities if it were injected intravenously, and perhaps with either a greater or a faster onset, depending upon the molecular weight, although there's very limited data available to date.

It's important I think to step back and

realize that polyethylene oxide is not a single compound. It's actually a spectrum of compounds that is a polymeric material of vast amounts of different molecular weights. And from a chemistry perspective, anything over a molecular weight of about 100,000 is generally referred to as a polyethylene oxide, and anything below a molecular weight of about 100,000 chemically is referred to as a polyethylene glycol.

Polyethylene glycols of low molecular weight, approximately 600 daltons, are actually present in FDA-approved IV drug products. We noted today as well, and we've heard repeatedly, that the OPANA ER product actually contained a molecular weight polyethylene oxide of approximately mean 7 million daltons. In the public domain as well, it is known that the OxyContin product has a PEO in it as well, with a mean molecular weight of 4 million. And we just looked at some data with 2 million and 200,000 that also helped put into perspective some of the adverse events that could occur if this compound was actually able to be extracted from the

materials and administered to animals.

I think there are several conclusions and limitations that are worth pointing out in today's discussion. First, the data that we have available to us, although limited, does suggest that uncured higher molecular weight PEO, if injected intravenously, can be expected to result in thrombotic microangiopathy, acute kidney injury, cardiac damage, retinal damage, as we've seen before. It's certainly reasonable to conclude that if manipulation of an abuse-deterrent opioid for IV use could extract higher molecular weight PEO, we would expect similar toxicities would occur, likely in a dose- and duration-dependent manner, possibly molecular-weight dependent as well.

The IV toxicology data to date in rabbits with manipulated MNK-812 did not demonstrate the same degree of damage as reported by Hunt, et al. with PEO plus in guinea pigs or even in the 2 million molecular weight studies that were conducted in the rats. However, there are some key limitations that are worth noting.

First, the content of the syringeable material tested in MNK-812 IV tox studies is not known. We do not know if PEO was present in that material or not or at what doses. The MNK-812 studies also dosed once a day for 3 days, and the manipulations for the tablets were a single series of manipulations, and this may not necessarily reflect human abuse patterns.

There are a couple other key points that are also worth noting. First, it is recognized that there are other FDA approved opioids that also contain polyethylene oxide, including OxyContin, Hysingla, Arymo, and Zohydro. To date, these products do not appear to carry the same risk for thrombotic microangiopathy as reformulated Opana ER. We do note that there are three published reports of thrombotic microangiopathy with manipulated OxyContin, but these are published overseas, and to date we have not noted that in the United States.

It's also important to note that not all PEO-based abuse-deterrent opioid drug products are

the same. It's quite possible that there are differential risks that could be based on a variety of factors, including there may be very distinct differences in the manufacturing processes: the curing methods, the amount of heat and the duration of heat, and the additives that are present during the manufacturing of the products.

There very well may be differences in the molecular weight of the PEO used as well that can contribute to this differential profile noted to date. There may be differences in the methods used to prepare these products for abuse via the IV route, and it's also possible that there is just a very distinct different pattern of abuse for either the drug substance and/or the drug products themselves.

In terms of our overall assessment, specifically with respect to the thrombotic microangiopathy risk, the risk of PEO in various abuse-deterrent opioid drug products cannot be simply extrapolated across the class based upon reformulated Opana ER. Injecting any manipulated

oral drug product is likely to result in significant toxicity, including granulomas, thrombotic microangiopathy, and certainly the risk of spread of infectious disease.

The FDA cannot rule out the possibility that adverse effects could occur with more frequent and/or more prolonged administration of manipulated MNK-812 for intravenous use. However, if the PEO in the product is able to be extracted into an IV syringe and injected, we would expect similar results as noted with reformulated Opana ER, likely in a dose- and duration-dependent toxicity due to accumulation of the PEO in the system. And certainly, it's also worth noting that if this product is approved, it would likely include similar warnings in labeling with respect to the adverse event profile that could occur if manipulated through injection by the IV route as is concluded in many other opioid drug products.

FDA Presentation - James Tolliver

DR. TOLLIVER: Good morning. My name is James Tolliver. I'm a pharmacologist within the

controlled substance staff of the Office of the Director, Center for Drug Evaluation and Research within the FDA. MNK-812 two tablets are being developed as an abuse-deterrent formulation under NDA 209774.

According to sponsor, this formulation contains excipients intended to cause nasal irritation expected to deter intranasal abuse. In support of this claim, sponsor submitted intranasal human abuse potential study MNK48121013, which is a randomized, placebo-controlled, double-blind, double-dummy, 4-period crossover study, utilizing 38 non-dependent recreational opioid users with experience insufflating drugs. Treatments included oral intact, 30-milligrams MNK-812, as well as insufflated placebo manipulated MNK-812 30 milligrams and manipulated oxycodone hydrochloride IR milligrams as positive control.

I would like to briefly discuss the data of this study supporting the intranasal abuse-deterrent effect via an aversive mechanism. My focus will be on the primary comparison of

insufflated MNK-812 30 milligrams versus insufflated oxycodone IR 30 milligrams.

I will be using a number of terms defined in this slide. With regard to pharmacokinetic data, Cmax is the maximum achieved oxycodone plasma concentration. Tmax is the time to achieve Cmax. The area under the AUC is the area under the oxycodone plasma concentration versus time curve out at selected intervals indicative of cumulative oxycodone exposure.

With regard to pharmacodynamic measures and data, VAS stands for the 0 to 100 point Visual Analogue Scale. Emax is maximum or peak effect. Tmax is the time to Emax. And AUE stands for the area under the effect versus time curve at selected post-dosing, and reflecting cumulative experience for the subjective effect.

I will briefly discuss the following data generated in the intranasal study: percentage of dose insufflated pharmacokinetics of oxycodone following insufflated treatments, and the 0 to 100-millimeter VAS scales for the subjective

effects of ease of snorting, drug liking, high, take drug again, overall drug liking, and bad effects. I will also mention the subject rated nasal tolerability assessment.

The percentage of dose insufflated for placebo manipulated MNK-812 and oxycodone hydrochloride are provided in this slide. For all three treatments, the mean percentage of dose insufflated was at 98 percent or above. Three subjects insufflated 85 percent, 84 percent, and 92 percent of the MNK-812. All but one subject who insufflated 97 percent of dose insufflated the entire oxycodone hydrochloride IR dose. Neither the nasal aversive effect nor the size of the MNK-812 30-milligram tablet had much of an effect on insufflation of the entire dose.

The ease of snorting VAS is a subject rated assessment of difficulty in insufflating each treatment, which is taken at 5 minutes post-insufflation. Subjects used the 0 to 100-point VAS to complete the statement. Snorting the drug was: the anchors were zero, indicating

very easy, and 100 indicating very difficult. It was obvious from the histogram that subjects reported the insufflation of manipulated MNK-812 tablets to be more difficult compared to insufflation of manipulated oxycodone IR tablets. This greater difficulty could well be due to an initial aversive effect impacting nasal tolerability.

This slide pertains to the pharmacokinetics of plasma oxycodone following insufflation of MNK-812 and oxycodone IR. The graph presents the mean oxycodone plasma concentration as a function of time following insufflation of either drug. There was a fairly close overlap of oxycodone plasma levels for both treatments. Both treatments achieved a similar mean Emax of 55 nanograms per milliliter.

Although much of the rise in oxycodone plasma concentration occurred within the first hour, the Tmax occurred actually at 2 and 2.4 hours, respectively. As is evident in the graph, the area under the concentration curve from 0 to

1 hour was higher following oxycodone IR compared to following MNK-812.

The relevance of this limited greater oxycodone exposure over the first hour pharmacodynamic measures is not clear. Overall, this data suggests differences in oxycodone bioavailability may be at most of limited importance in contributing to differences in subjective measures between the two treatments.

The next couple of slides will pertain to the subjective measures of drug-liking VAS, the primary measure, and the high VAS. Both measures are taken at selected times post-dosing, beginning at 15 minutes and extending out to 12 hours. In addition, both measures assess at the moment subjective effects.

For assessing drug liking, subjects are asked do you like the drug effect you were feeling now? Subjects respond using a bipolar VAS anchored at zero, strong disliking; 50, neither like or dislike; and 100, strong liking. For high VAS, subjects are asked, do you feel high? Subjects

respond using a unipolar VAS anchored at zero equals none and 100 extremely.

The results of the drug-liking VAS are provided in this slide. The graph shows mean drug-liking scores as a function of time out to 4 hours. Insufflation of oxycodone IR resulted in a rapid rise in drug liking within the first 0.25 hours. By contrast, with insufflation of MNK-812 at the same early time point, there was actually a dip in mean drug liking into the negative range; that is into the mid 40's, possibly due to an aversive nasal effect.

Over the first hour, the mean drug liking following insufflated MNK-812 increased possibly due to a reduction in the severity of head aversive nasal effects. For insufflated MNK-812 and oxycodone IR, Emax of drug liking were 77.4 and 82.7, achieved with a median of 1.49 and 1 hour, respectively. When evaluating for at least a 10 percent reduction in Emax by insufflated MNK-812 compared to oxycodone IR, no significant difference was found between the two treatments, raising

question of clinical relevance.

As is also evident from the graph, when examining the cumulative drug-liking experience over the first half hour, as represented by AUE from 0 to 0.5, there was a significant reduction associated with insufflated MNK-812.

The results of the high VAS are provided in this slide. The graph shows mean high scores as a function of time out to 4 hours. Insufflation of oxycodone IR resulted in a rapid rise in high within the 0.25 to 0.5 hours. Following insufflation of MNK-812, the rise in high is slower, reaching most of its peak by 1 hour.

Insufflation of oxycodone IR and MNK-812 resulted in Emax values of 72.6 and 68.0, respectively, which were not statistically significantly different. Median TEmax values for both were 1 and 1.5 hours, respectively. Over the first hour, cumulative high experience, as represented by area under the effect curve, was lower following insufflation of MNK-812 compared to oxycodone hydrochloride IR.

Take drug again VAS is a global assessment administered at 12 hours and 24 hours post-insufflation where all of the drug effect has subsided. Subjects reflect back over the treatment experience in each period. Subjects are asked, would you want to take the drug you just received again if given the opportunity? The response is documented on a bipolar VAS anchored at zero by definitely would not; at 50 by do not care, and at 100 by definitely would.

The table provides the least square means for Emax take drug again for the three intranasal treatments. As might be expected, insufflation of placebo resulted in the mean score in the neutral range of 50. Subjects expressed a clear willingness to insufflate oxycodone IR again if given the opportunity, as reflected in a take-drug-again score of 77.

By contrast, as suggested from the mean score of 46.4, subjects did not care whether they insufflated manipulated MNK-812 again. This reduction in take drug again from 77 to 46.4 was

statistically significant and suggested a possible deterrent effect of this formulation to intranasal abuse.

It is noteworthy that the score for take drug again following insufflation of MNK-812 did not fall further into the negative range of the bipolar scale, indicating a stronger willingness not to take the treatment again.

The overall drug-liking VAS is another global assessment administered at 12 and 24 hours post-insufflation. Subjects reflect back over each treatment by considering this statement, "Overall, my liking for this drug is," the response is documented on a bipolar VAS anchored at zero by strong disliking; 50 by neither liked or disliked; and at 100 by strong liking.

As evident, from a score of 77.5, subjects documented a positive overall drug-liking experience following insufflation of oxycodone IR. With insufflation of MNK-812, there was a significant reduction to 49.8, close to that resulting from placebo insufflation, indicating a

lack of either liking or disliking the insufflated of MNK-812.

While aversive intranasal effect might have dampened any liking experience, it was not strong enough to push subjects to strongly dislike the overall experience of the insufflation of MNK-812. The result of overall drug-liking VAS still supports a possible deterrent effect of MNK-812 to intranasal abuse.

The bad effects VAS was conducted at selected times starting at 0.25 hours post-insufflation. Subjects responded to the question, does the drug have any bad effects? Using a bipolar VAS with anchors at zero of none and 100 of extremely. The graph is that of mean bad effect scores as a function of time post-insufflation.

Insufflation of placebo or oxycodone IR resulted in minimal bad effect scores. Insufflation of manipulated MNK-812 was associated with bad effects, which were highest at the earliest time point of 0.25 hours. Emax values for

bad effects following insufflation of MNK-812 and oxycodone IR were 38.5 and 18.5, respectively, and statistically significantly different.

Overall, this data suggests a limited adverse nasal effect associated with the insufflation of MNK-812, most evident at the earliest time point measured, which was 0.25 hours.

This table provides data from the subject rated nasal tolerability assessment following insufflation of MNK-812. I'm not providing the nasal tolerability assessment for insufflated oxycodone IR or placebo due to the very low levels of adverse nasal effects observed with these two treatments.

Looking at the table, the first column lists the 6 nasal symptoms that subjects were asked to assess, including burning; need to blow nose; runny nose/nasal discharge; facial pain/pressure; nasal congestion; and throat irritation. Severity assessment was conducted using a 4-point scale consisting of zero, no effect; 1 mild effect; 2, moderate effect; and 3, severe effect.

The second column denotes the time points of 0.25, 0.5, and 1 hour post-insufflation. The last four columns provide the percentage of the 38 subjects who rated the symptoms as none, mild, moderate, or severe. The columns denoting none and mild symptoms were color coded by time in shades of blue. Columns denoting moderate and severe nasal symptoms are coded in shades of orange.

The largest percentage of subjects reporting the severe or moderate adverse nasal symptoms was at the earliest measured time point of 0.25 hours as seen in the lightest shade of orange. For a rating of severe, the range was 15 to 30 percent. For a rating of moderate, the range was 27 to 37.5 percent.

Over the subsequent 45 minutes, the percentage of subjects reporting severe and moderate ratings of nasal symptoms dropped off substantially to ranges of 0 to 2.5 percent and 5 to 12.5 percent, as seen by the darkest shade of orange.

As can be seen from examining the 0.25-hour

time point, looking at the light blue area now, versus the 1-hour time point, which is the dark blue, over the first hour, there was an increase in the percentage of subjects documenting no nasal symptoms or mild nasal symptoms. By 1 hour, the percentage of subjects reporting none or mild nasal symptoms were in the range of 42 to 57 percent and 35 to 50 percent, respectively.

So by 1 hour, moderate and severe adverse nasal symptoms subsided substantially with the concomitant increase in reports of either no symptoms or mild adverse nasal affects.

Conclusions from this study. The overall findings suggest that MNK-812, 30-milligram tablets, in contrast to oxycodone hydrochloride IR 30-milligram tablets, may provide a deterrent effect to insufflation. This deterrent effect was most likely, not primarily, due to differences in oxycodone exposure. An alternative explanation would be that the insufflation of MNK-812 is associated with a limited degree of nasal irritation that is most intense over the first 0.25

hour and subsides over the first hour.

The slow rise in drug liking and high observed over the first hour post-insufflation may reflect, in part, the decline and the severity of the adverse nasal symptoms documented by subjects over this same period. However, following that period, following that delay, subjects did in fact experience both drug liking and high.

Last conclusion is that significant reductions in take drug again VAS and overall drug-liking VAS, following insufflation of MNK-812 compared to oxycodone hydrochloride IR, are consistent with a possible aversive effect associated with MNK-812. The two. The fact that both measures of these reductions did not extend substantially into the negative region of the bipolar scales may reflect the limited extent of the aversive effects and/or the fact that following the delay, subjects did experience significant levels of drug liking and high.

Thank you. The next speaker is Tamra Meyer, who will talk about the epidemiology of oxycodone

misuse and abuse.

FDA Presentation - Tamra Meyer

DR. MEYER: Good morning. I'm going to apologize in advance for my voice. It's not quite as bad as Dr. Zeltzer's, but sorry you have to listen to it for a while.

As Jim said, I'm Tamra Meyer. I'm the team lead for the prescription drug abuse team number 1 in the Division of Epidemiology II, in the Office of Surveillance and Epidemiology in CDER. I will be presenting recent epidemiologic data on use, misuse, and abuse of oxycodone products. The reason we're doing this is to provide context for the committee to consider the potential public health risk and benefits of approval of MNK-812.

FDA continues to consider public health risks throughout the life cycle of opioid products. We recently began presenting formal evaluations of trends in misuse, abuse, and related outcomes for similar marketed opioids at advisory committee meetings for new opioid approvals, and this is to help the committee weigh the potential public

health risks and benefits of a new opioid approval.

This practice is consistent with recommendations from a 2017 report released by the National Academies of Sciences, Engineering, and Medicine. Public health considerations should include both unintended consequences as well as use in non-target populations.

The purpose of this presentation is to provide you with a relevant public health framework to consider alongside other data. Our two objectives are first, to review the utilization of oxycodone products; and second, to review epidemiologic data on misuse and abuse of oxycodone-containing products and comparator drugs.

A special note is that many of the data sources that we reviewed do not distinguish well between extended-release and immediate-release formulation products, and neither do they distinguish well between brand products and generic products. So where possible, we will provide formulation-specific data, and then where it's not available, we will provide it combined.

We will not describe published studies of the association between abuse-deterrent formulations of opioids and reductions in misuse, abuse, and related outcomes, as we still await a complete submission of postmarket data under postmarket requirements that might demonstrate a meaningful effect on misuse, abuse, or related, adverse clinical outcomes in the community.

I'll begin by presenting data on utilization of oxycodone-containing products and comparator drugs, and these data are extracted from IQVIA National Prescription Audit. The specific questions that we sought to answer were which are the most frequently dispensed immediate-release opioid analgesic products; how frequently are specific oxycodone products dispensed in the U.S., and among products intended to deter abuse, which are the most frequently dispensed?

This slide shows the nationally estimated number of dispensed prescriptions in millions from 2013 to 2017 in outpatient retail settings, and this shows the top five immediate-release opioid

analgesics. The most commonly dispensed opioid analgesics during this time period were hydrocodone with acetaminophen, followed by tramadol, oxycodone with acetaminophen in the black dash line, and then single-entity oxycodone immediate-release products noted in the black solid line.

For reference, there were 14 million oxycodone immediate-release, single-entity prescriptions dispensed in 2013 and 17 million dispensed in 2017.

This figure shows the nationally estimated number of dispensed prescriptions for oxycodone-containing products only. Overall, dispensing of oxycodone prescriptions, shown in the gray boxes, peaked in 2015 at 56 million prescriptions dispensed, and it has subsequently decreased to 50 million prescriptions dispensed in 2017.

The vast majority of oxycodone prescriptions in 2017 were either for combination or single-entity oxycodone immediate-release products, while fewer than 8 percent were for an oxycodone

extended-release product, and these are mostly abuse-deterrent formulations like OxyContin.

This figure shows the yearly estimates of prescriptions dispensed for opioid analgesic products with labeling that they appear to deter abuse based on premarket testing. The active pharmaceutical ingredients in this figure include hydrocodone and morphine-containing products in addition to oxycodone-containing. RoxyBond is the only oxycodone immediate-release product that's currently approved with labeling that is expected to deter abuse. However, it does not appear in this slide because it was not marketed during this time period.

Reformulated OxyContin, an extended-release version of oxycodone, delineated by the solid black line at the top, accounted for 88 percent of abuse-deterrent products dispensed in 2017. There's been a downward trend in dispensing of reformulated OxyContin with 4.9 million prescriptions dispensed in 2013 and 3.4 million in 2017. Other abuse-deterrent opioids appear to be

increasing in market share during recent years.

The second part of this presentation describes misuse and abuse of oxycodone-containing products and comparator drugs. We will address the following questions.

What is the current scale of misuse and abuse of prescription opioids? Which are the most frequently abused opioids? What are common routes of abuse for oxycodone-containing products, including available abuse-deterrent formulations? And what is the magnitude of morbidity and mortality associated with oxycodone-containing products versus comparator drugs?

The definitions of misuse and abuse used for the majority of this talk are consistent with what FDA has previously issued in guidance to industry. Misuse is defined by FDA as the intentional therapeutic use of a drug product in an inappropriate way, and it specifically excludes the definition of abuse. Misuse will include things such as taking more than prescribed, taking more often than prescribed, or using someone else's

medication to treat pain or for sleep. Abuse is defined as the intentional non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect, and abuse would include use to get high.

We used a number of data sources that are described in detail in the background information provided, and as I go through the results, I'll provide a brief description about each of the relevant data sources. First, I will describe the scale of misuse and abuse for oxycodone-containing products and other opioids.

The data presented in this graph are from the National Survey on Drug Use and Health, also called NSDUH. It's a federally-funded general population survey of non-institutionalized individuals ages 12 years and older in the United States. The most frequently misused prescription opioid products in 2016 were hydrocodone and oxycodone, with misuse defined by NSDUH to include use of a drug in any manner, other than as medically directed, which would include misuse and

abuse as defined by FDA.

In this figure, the Y-axis on the left indicates the number of individuals in thousands who reported past year misuse of the drug, and the Y-axis on the right represents the percentage of the total population. There was no statistically significant change in levels of oxycodone misuse from 2015 to 2016, and the total number of individuals reporting misuse of oxycodone in 2016 was 3.9 million or approximately 1.5 percent of the total population.

This figure shows the number of calls to U.S. poison centers involving intentional exposure to selected opioids from 2012 to 2016, and these data come from the National Poison Data System. The National Poison Data System is a national network of poison centers receiving calls from the public or healthcare workers. One strength of this data source is that it collects information on formulation in a standardized way. In NPDS, intentional exposures include misuse, abuse, self harm, and unknown reasons for exposure, although

they assume that they are intentional.

This figure demonstrates that over 3,000 calls per year reported intentional exposures to an oxycodone-containing product over the period 2012 through 2016. Calls involving intentional exposure to immediate-release oxycodone products occurred much more frequently than those for extended-release oxycodone products. There were 50,000 calls involving intentional exposure to an oxycodone product over the entire time period, while by comparison, 75,000 calls involved intentional exposure to hydrocodone, 9500 calls for morphine, and 24,000 calls for heroin.

Now, I will discuss the relative frequency of abuse of specific products. This graph shows the percent of respondents reporting past month abuse of opioids within the RADARS Treatment Center Program by the active pharmaceutical ingredient or substance on the X-axis.

The RADARS Treatment Center Program is a surveillance program that includes surveys of individuals entering treatment for opioid-use

disorder. In this population, the oxycodone was the most frequently abused prescription opioid product at 35 percent of respondents, though heroin was the most frequently abused opioid overall.

Formulation-specific data suggest that there's more frequent abuse of immediate release than extended-release products, as Dr. Dart earlier noted. Twenty two percent of respondents reported past month abuse of oxycodone immediate-release products, and 15 percent reported past month abuse of an oxycodone extended-release product in this population.

However, after accounting for the prescription volume, the relative frequency of oxycodone abuse compared with other opioids changes. This chart shows rates of past month abuse per 100,000 dispensed dosage units by active pharmaceutical ingredient or substance. Note that heroin is not included on this chart since we do not have estimates of dosage units for heroin.

Here we see that some of the more potent agents, such as fentanyl and oxymorphone, are

abused more than other agents relative to their overall levels of availability. Oxycodone immediate-release products were abused less per the amount dispensed when compared to oxycodone extended-release products.

I will now discuss routes of abuse for oxycodone and for opioids with abuse-deterrent properties. This table shows the proportion of abuse by ingestion, nasal, and parenteral routes of abuse reported for single-substance abuse exposure calls involving oxycodone-containing products from the National Poison Data System from 2012 through 2016. The most common route of abuse is by ingestion across all formulations of oxycodone. 84.4 percent of calls involving abuse of immediate-release combination ingredient oxycodone products were via ingestion, while 74 percent were via ingestion for single-entity, immediate-release, and extended-release formulations of oxycodone.

About 12 to 14 percent of abuse calls involving single-entity, immediate, and extended-release oxycodone involved non-oral routes

of abuse. Non-oral routes of abuse were less common for combination immediate-release opioid formulations in the National Poison Data System.

The frequency of non-oral abuse of opioid analgesics depends on the population that you're looking at. This table shows the percent of respondents reporting specific routes of abuse in the past month for prescription opioid analgesics among patients entering or being assessed for treatment of substance-use disorder in the NAVIPPRO surveillance system that Dr. Dart presented earlier. This is just a different time period, so the numbers are a little bit different.

This population may be more enriched with people who abuse drugs via non-oral routes, and that is reflected in the frequency of routes of abuse seen in this table. These data come from a published study by Cassidy and colleagues and covers the period from 2012 through June 2015. From left to right, the columns for this table are the category of opioids assessed and specific routes of abuse assessed by the study, including

oral, snorting, and injection.

For combination oxycodone immediate-release products, 70 percent of respondents reported oral abuse, 40 percent reported snorting, and 10 percent reported injection. For single-entity, immediate-release oxycodone products, 40 percent of respondents reported oral abuse while 60 percent reported snorting, and 40 percent reported injection.

In addition to data on oxycodone immediate-release products, the Cassidy study reported routes of abuse for extended-release, long-acting products with properties intended to deter abuse. This included oxycodone as well as other opioid moieties. Extended-release, long-acting products with properties intended to deter abuse were commonly abused via non-oral routes, but less so than oxycodone immediate-release, single-entity products. We do not yet have data on the route-specific abuse patterns for RoxyBond, the only currently approved immediate-release oxycodone product with

abuse-deterrent labeling.

Finally, I will show some information on the contribution of oxycodone products to morbidity and mortality. This slide shows some data from the National Electronic Injury Surveillance System Cooperative Adverse Drug Events Surveillance or NEISS-CADES. This is a nationally representative sample of emergency department visits in the United States.

During 2016, there were nearly 300,000 estimated emergency department visits for harms from prescription opioid products. Of those, approximately 40 percent involved oxycodone-containing products specifically. Of the visits for harms attributed to oxycodone-containing products, 36 percent were attributed to therapeutic use of the products; 15 percent were attributed to self-harm attempts; and almost half were attributed to non-medical use of oxycodone products, which included misuse, abuse, or overdoses without a noted intent for the use.

Among the visits attributed to non-medical

use of oxycodone products, concurrent substance use was common. About 50 percent of visits involved more than one prescription opioid product; 32 percent involved oxycodone and a benzodiazepine; and 48 percent involved illicit drugs or alcohol.

This graph shows the proportion of the emergency department visits attributed to non-medical use of oxycodone products that were associated with specific categories of adverse outcomes. Nearly 20,000, or 40 percent, resulted in patients experiencing a serious adverse outcome such as cardiac arrest, unresponsiveness, or respiratory failure or distress, which is represented by the solid black section of this chart.

National data on drug involved mortality were made available to the agency by the National Center for Health Statistics Drug involved mortality data combine the cause of death, demographic, and geographic information from the National Vital Statistics System mortality files with information extracted from the death

certificate literal text, which allows for more granular analysis of specific drugs involved in the deaths.

In this figure, we see the number of deaths involving various opioids over time. Included on the graph are oxycodone, the solid black line; hydrocodone, the solid gray line; morphine, the darker dash line; and heroin, the gray dash line.

In a 6-year period from 2010 through 2015, oxycodone involved deaths remained relatively unchanged with between approximately 5[000] to 6,000 deaths per year. In contrast, there was a sharp increasing trend observed for heroin involved overdose deaths over the same time period rising from approximately 3000 in 2010 to over 13,000 deaths in 2015.

We provided detailed limitations of the data sources used in the background material, and I'll describe some of the key limitations here briefly. NSDUH IS affected by biases that are typical of most surveys such as recall, response, or social desirability bias. The National Poison Data System

likely under-captures exposures, particularly overdoses resulting in out-of-hospital death. That proportion of cases captured may vary over time as well as across drug substances.

Data on abuse patterns and routes of abuse patterns from the RADARS and NAVIPPRO Treatment Center Data may not be nationally representative, as they come from specialized populations with presumably more advanced opioid and substance-use disorders. Further, product misclassification can occur due to the self-report.

NEISS-CADES data do not include cases that result in death before or during emergency department evaluation. There's also a potential for misclassification of products here. These data only include acute opioid harms resulting in an emergency department visit. It does not include visits for opioid withdrawal, seeking treatment, detoxification, or inadequate therapy. For the drug involved mortality data, reliance on the literal text of death certificates is likely to miss a proportion of opioid-related deaths that do

not contain an ingredient or a product listed in the literal text.

In conclusion, oxycodone-containing products are frequently dispensed in the U.S. and combination-ingredient, immediate-release formulations constitute the majority of dispensed oxycodone prescriptions. Oxycodone-containing products are among the most frequently misused and abused prescription opioid products per population, but not after taking into account the prescription volume.

We had no data on routes of abuse for RoxyBond, the currently approved oxycodone, immediate-release product with abuse-deterrent labeling, but other available abuse-deterrent products are known to be abused by non-oral routes. And despite the growing popularity of illicit opioids, oxycodone-containing products continue to be involved with morbidity and mortality in the U.S.

I want to briefly acknowledge other members of the FDA review team. Each of you has

contributed substantially to either the analysis or the interpretation of the data presented. And now, I will turn the presentation back over to Dr. Nadel.

FDA Presentation - Jennifer Nadel

DR. NADEL: I will now present a clinical summary of the abuse-deterrent features. I will address the following in my presentation: the goals for abuse-deterrent opioid formulations, also known as ADFs, and the current experience; a brief summary of the abuse-deterrent testing results; a summary of the Category 1 testing; a summary of the excipients safety results; and lastly, I will briefly discuss the risks and benefits of abuse-deterrent products.

Prescription opioid products are an important component of pain management, however, abuse and misuse of these products have created a serious and growing health problem. The FDA developed a guidance for abuse-deterrent opioids in response to this problem. The guidance explains how we can evaluate and label abuse-deterrent

properties. It is important to remember that abuse-deterrent properties are designed to meaningfully deter abuse. They do not prevent abuse.

Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. Some of the most common approaches are outlined in the guidance. Physical and chemical barriers can limit drug released following mechanical manipulation or change the physical form of a drug, rendering it less amenable to abuse.

For aversion, substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or used at a higher dosage than directed. Lastly, an opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse.

Now we will discuss the goals for a successful ADF. They are twofold, consistent and effective delivery of an opioid dose when the ADF is used as labeled; and either an expectation of or

achievement of a reduction in abuse by making the ADF more difficult to abuse by one or more relevant routes.

While goals are useful, let's also discuss our current experience with ADFs. We know that ADFs are not abuse proof and do not prevent addiction. The FDA has approved 10 opioid analgesic products that are labeled with abuse-deterrent properties in accordance with the FDA guidance entitled Abuse-Deterrent Opioids: Evaluation and Labeling Guidance for Industry.

Abuse-deterrent labeling is based on data from premarket studies. There are three categories of premarket studies, Category 1, which are in vitro studies; Category 2, which are pharmacokinetic studies; and Category 3, which are clinical abuse-potential studies.

All approved ADFs have postmarketing requirements to conduct additional Category 4 studies. As stated in the FDA guidance, the goal of postmarket studies is to determine whether the marketing of a product with abuse-deterrent

properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. Published studies evaluating ADFs in the post-approval setting exist, however, to date, none of the sponsors of ADF opioid analgesics have completed and submitted all the required postmarketing studies.

Now, let's discuss the abuse-deterrence properties of MNK-812. It contains aversive agents that are intended to cause nasal irritation and potentially deter intranasal abuse. It is also purported to form a viscous solution when mixed with small quantities of liquid, potentially making it more difficult to inject. It has physical and chemical characteristics that are expected to make it more difficult to crush to a fine powder, making inhalation more difficult. Based on the abuse-deterrent features, the applicant concludes that MNK-812 is difficult to abuse by the intranasal and intravenous routes.

Now, I will summarize the abuse-deterrent

results from the MNK-812 by route of abuse. For the intranasal route, as discussed earlier during the review of the HAP study, subjects experienced less overall drug liking and less willingness to take drug again with MNK-812 as compared to the immediate-release comparator under the conditions tested.

With regard to the intravenous route under certain conditions, 50 to 60 percent and 80 to 90 percent of oxycodone present in a tablet could be isolated and potentially injected with small-volume and large-volume extraction, respectively. Based on an analysis of available epidemiological and in vitro data, we do not currently consider smoking a relevant route of abuse for oxycodone.

The implications of Category 1 testing are clear. Oxycodone suitable for IV use can be extracted from MNK-812. The amount of extracted oxycodone and the extraction volume may lead to sharing among persons who inject drugs. Given what occurred with reformulated Opana ER, other important public health consequences should be

considered.

Postmarket experience with ADFs has yielded some unanticipated outcomes when ADFs are abused by unintended routes. Based on the available data, some parallels can be drawn between reformulated Opana ER and MNK-812. Reformulated Opana ER, much like MNK-812, suggested some abuse deterrence by the nasal route.

In the case of reformulated Opana ER, data suggested that persons abusing the drug shifted from one route of abuse, nasal, to another more dangerous route of abuse, injection. This shift from non-parenteral to parenteral use of reformulated Opana ER was consequential. Some who abused via the IV route experienced thrombotic microangiopathy with use of manipulated, reformulated Opana ER, which an investigation suggested was related to tampering and injection of the PEO excipient.

Additionally, the method for preparation of reformulated Opana ER for injection resulted in a solution that could be shared. We saw an increase

in the transmission of bloodborne diseases, HIV and hepatitis C, in people who are sharing reformulated Opana ER. The existing limited nonclinical data suggests that IV injection of extracts of MNK-812 did not result in clear evidence of thrombotic microangiopathy, but the FDA cannot rule out an increased risk with more frequent and/or prolonged treatment, or manipulation using different conditions.

Now, I will discuss the risks and benefits of abuse-deterrent products in general. For risks, there are several concerns. Some of the risks of the excipients are unknown until the drug is more widely used. Postmarketing analysis found that OxyContin had the potential for GI risk with swelling and hydrogelling of the pill when taken by the intended oral route. There is the potential for excipient-related adverse events when abused by unintended routes. There is also the concern of possible shifting from the intranasal route to the more dangerous intravenous route or substitution of highly lethal illicit opioid such as heroin.

The benefits at this point have been less than straightforward. There is no real benefit to the individual intended patient when the drug is used as directed. There is the potential for improved product safety through reduced abuse of the drug by patients or others who may access the drug. However, the benefits to society are theoretical at this point and have not been supported by data.

The FDA continues to weigh the benefit-risk balance of ADF opioid analgesics. Currently, there is no data to show that ADFs slow progression of opioid-use disorder will reduce the risk of addiction. It is also important to remember for all ADFs that we cannot predict everything that could happen with the drug product once it is marketed.

In summary, the safety and efficacy of MNK-812 is based on demonstration of bioequivalence to Roxicodone. The abuse-deterrent data for MNK-812 show that there is some abuse deterrence by the intranasal route. Results of Category 1 studies

conducted demonstrate that oxycodone suitable for IV use can be extracted from MNK-812 under certain conditions.

Large volumes can be extracted and potentially result in solution sharing. If the PEO in this product is able to be extracted into a syringe and injected, we may see similar consequences to reformulated Opana ER.

Clarifying Questions

DR. BATEMAN: Are there any clarifying questions for the FDA or the speaker? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn Medicine. I've been following the deaths related to opioids for years, and it's clear that as the total number of prescriptions are going down, the number of deaths are going up, something like 60-plus thousand.

Two questions. One, what's the explanation of the FDA? And second, if approval of ADF

products is going to make it even worst, are we looking for answers in the wrong place with these ADF products?

DR. STAFFA: This is Judy Staffa. I'll try to address that. With regard to prescription volume going down and deaths going up, yes, that is correct. Many of the additional deaths are, we believe, the epidemic morphing toward heroin and fentanyl. So you can see that from the curves. But we acknowledge prescription opioids do still play a role in deaths, and many deaths are polysubstance.

With regard to the role of the abuse-deterrent formulations in that, I don't think we know yet. As we've mentioned, it's very complicated to try to assess the impact of one particular intervention, the introduction of these products, amidst a lot of interventions going on at the same time. So it's not clear to us exactly what the role of abuse-deterrent formulations has been or continues to be in driving those statistics. We don't know.

Dom, did you want to jump in?

DR. CHIAPPERINO: Yes, I wanted to add one thing to that. In the context of heroin and fentanyl abuse, we also know that there are a lot of new psychoactive substances, synthetics that are chemical analogs of those substances, and some of them are more potent than the known drugs substances fentanyl and heroin. So we don't know to what extent the far more potent fentanyl derivatives that are in the marketplace as illicits are playing in the rising death tolls.

DR. GOUDRA: Thank you.

DR. BATEMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. The first question is for Dr. Tolliver, and it's regarding the conclusions on slide 50 of his presentation. With respect to number 2, which offers contradictory kind of findings, I'm wondering -- and this is probably a question for the panel, which is probably how you'll respond. But is it your belief that a 1-hour delay in a positive experience for the abuser is sufficient

enough to deter abuse?

Your conclusions were a little contradictory, and I'm just trying to reconcile that.

DR. HERTZ: Could we get that slide up, please?

DR. TOLLIVER: That's slide 15?

DR. HIGGINS: Fifty, 5-0.

DR. TOLLIVER: 5-0.

DR. HIGGINS: And I'm referring to number 2.

DR. TOLLIVER: All right. We know that there was a rise. There was a correlation in the rise in drug liking and high over the first hour. And at the same time during that time period, there was a reduction in the nasal effects.

I'm doing two things here. Number one, I'm assuming that that rise and reduction are relevant to one another. And also, I'm assuming that the pharmacokinetics would provide, at most, a limited effect, based upon the previous slide that I provided.

DR. HIGGINS: So is it your sense that -- I

guess I'm trying to understand this better. So after that 1 hour, the 1-hour delay, there could easily be -- if someone got past that 1 hour, it could still be pleasurable and not a deterrent in a certain sense.

DR. TOLLIVER: Well, that's exactly what I'm getting at, yes.

DR. HIGGINS: Yes.

DR. TOLLIVER: I think the idea is that by 1 hour, most of the nasal effect is gone.

DR. HIGGINS: Right.

DR. TOLLIVER: There's a lingering effect there. I mean, it goes out. The sponsor went out quite a ways, so you have this very, very small amount of nasal tolerability, and it's by the mild effect, whatever that is. But at the same time, you've seen this rise. And in fact the Emax, the maximum effect, although it occurs later, you still have that effect out at somewhat a later time point.

What I'm doing is I'm thinking that in terms of looking at take drug again or overall drug

liking, keep in mind what they're doing here. These two measures are given at 12 and 24 hours after the dosing. The effect is already gone. You're no longer looking at, at the moment subjective effects.

People are asked to think back over their experience. So I'm assuming that they are going to be thinking of the good effects and the bad effects, both of them. Obviously, the bad effects were experienced early on, 5 minutes with the ease of snorting over the first hour. But that was followed by sniffing at levels of drug liking and high.

So I think that prevented these global effects, such as overall drug liking and take drug again, from really going into the very negative. If these nasal effects had lasted much longer, most likely, you wouldn't have had -- you would most likely have had a dip, a real dip, down into maybe the 30's, or 20's, or something like that, where you're, I definitely don't want to take this drug again --

DR. HIGGINS: Right.

DR. TOLLIVER: -- and I definitely think that this was a very unpleasant experience for me. They didn't say that, but it was enough to significantly, over that initial period of time, to serve as an aversive effect.

Does that help?

DR. HIGGINS: Yes, thank you. And just one other quick question.

DR. BATEMAN: Can I move on to other committee members? We'll come back to you if we have time.

DR. HIGGINS: Okay.

DR. BATEMAN: We don't have a lot of time for lunch.

Dr. Meisel?

DR. MEISEL: Steve Meisel. A question for Dr. Nadel. You said there were no Category 4 studies available yet. OxyContin reformulated has been on the market for 5, 6 years, something, 7. What's the expectation for timelines on the Category 4 studies if it's been that long, and we

still haven't seen it from that?

DR. HERTZ: Hi. This is Sharon Hertz. Our expectation is that this data would have been submitted to us years ago around the time they started publishing.

DR. MEISEL: But it's a requirement.

DR. HERTZ: It's a requirement to get additional labeling. It's not required to show your drug is really, really good. It's a requirement to report the problems that may be occurring over time postmarketing. And our postmarketing requirements are pretty much on a safety side; that's usually what we do. We don't require people to submit data to show they're having a good effect. And if they're satisfied with labeling that doesn't really demonstrate an effect, then it's hard for us to force submission of additional data.

DR. MEISEL: Well, then, I'm confused because on slide 85, it says, "All of these products have requirements to conduct additional studies to evaluate whether the postmarket data

supports a meaningful effect on reduction of abuse, misuse, or related outcomes in the community." I mean, that not what you're describing.

DR. HERTZ: Well, they have it, but it's hard for us to force them to submit it. They don't have to comply. We don't have a way of really going after that.

DR. MEISEL: Okay. So the requirement is really not a requirement.

DR. HERTZ: Well, it is a requirement.

DR. STAFFA: This is Judy Staffa. I can add to that. The science here is fairly new, and we've required these studies, but we also have to approve protocols and we have to approve the manner in which the studies are done. With a new scientific area, there's been a lot of back and forth with how we believe the studies should be done and how we could trust the results. So that has been part of the delay in getting the results. But we do not prevent companies -- we do not interfere with the publication process. That's not our purview.

Does that help?

DR. HERTZ: But you have to wonder what it means if they're busy publishing all this great stuff, but they haven't submitted a formal package for us to review. It always makes me wonder.

DR. BATEMAN: Dr. Fischer?

DR. FISCHER: Thanks. Mike Fischer, Boston, and I'll try to be quick given the time. This is for Dr. Amspacher, looking for a little bit of clarification on your slides 14 and 17 for context, the manipulation and the solubility. I'm less interested in how many thousands of variants were tried than if there is one or two that worked, that easily they'll be communicating.

If you can speak to it without getting into the stuff that's proprietary, you mentioned for the mechanical tools, it's something that's quick and easily available. If you could give some context, how similar is that to other manipulations that might commonly be done currently among communities of people who use prescription opioids or manipulate them for misuse?

Similarly, you mentioned mild relatively

simple solutions on slide 17. How similar is that to things that are commonly done?

DR. AMSPACHER: This is Valerie Amspacher. The methods that we're referring have historically been used for abuse. This is something that we know abusers do.

DR. FISCHER: So it would be a relatively straightforward adaptation of things that people are already doing to get it into that.

DR. AMSPACHER: It's something that's already been reported. We're just asking or performing testing according to what we've seen in literature that abusers are doing.

DR. BATEMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: My question's about the replacement. The applicant emphasized the replacement aspect, the intention of placement. And I wonder if there is any specific plan for it or an or an experience from FDA on the replacement for other drugs, or if there are specific steps that are going to be taken to ensure that replacement, or it's just a wish.

DR. HERTZ: There is a variety of processes that can occur. It depends in part on the sponsor's plans. If the sponsor submits a plan to discontinue marketing Roxicodone as it's currently formulated and to be replaced by this, then we would look at -- well, they have to factor in a variety of conditions: how much is on the market; how soon can they ramp up on the new product; all of these different things.

If they decided they didn't want to withdraw from the market, that's a more challenging question, and we'd have to explore a number of different options if we felt it was somehow necessary or important for that switch to occur.

DR. BATEMAN: Dr. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti; a quick question, although I have so many, but one.

To Dr. Hertz, does this applicant have any outstanding requirements to conduct follow-up studies on any drugs? Have they been submitted and completed?

DR. HERTZ: Off the top of my head, I don't

think so.

MS. ROBOTTI: There is no follow-up required?

DR. HERTZ: I think it might be easier to ask the sponsor if there were any outstanding commitments.

DR. SCHLICHER: I'm not aware of any outstanding commitments. I'll double check that with our regulatory staff and come back to you after lunch. The only outstanding commitments would be the ongoing work we're doing in seeking approval of this product; labeling, agreeing to what postmarketing would be, but no other outstanding study requirements.

DR. BATEMAN: I have a question for Dr. Tolliver. Can you describe the guidance that FDA gives sponsors regarding sample preparation for the inhalation abuse-potential studies? I would imagine that the PK and PD would be highly dependent on the particle size that's generated with the sample manipulation.

So is there guidance regarding a standardized process for grounding up the tablets, and measuring particle size, and doing some type of QC around that process?

DR. TOLLIVER: I think the closest thing that we have is that we ask the sponsors to try to manipulate the formulation to the lowest particle size possible, and that should be the manipulation that they use. They should also provide information on the particle-size distribution.

DR. AMSPACHER: This is Valerie Amspacher. The sponsor used a technique to specifically get down to a particle size that was insufflatable. Like Dr. Tolliver was saying, they characterized it and provided us with particle-size distribution, so we can trust that the particle sizes were of abusable use. They were very rigorous in their particle-size characterization, so we know the integrity of the data is excellent.

DR. BATEMAN: Great. Thank you.

Dr. Marshall?

DR. MARSHALL: Brandon Marshall, Brown

School of Public Health. I've got a question for the FDA. Much of the data here focuses on the impact of the ADF formulations on patients or users. I'm interested on the effect of these formulations on prescriber behavior. Are there any studies on the perceptions of these medications in the prescribing community? Might they increase particularly inappropriate prescribing for conditions where non-opioid medications would be appropriate?

So I guess my concern is that if we assume that these medications decrease the risk of diversion or abuse per prescription but we're just increasing the overall rate of inappropriate prescribing, those effects might be completely counterbalanced.

DR. HERTZ: I think that's a really good question, and it's something that we worry about and have some anecdotal data that makes us worry, not quite to the extent that you may be concerned. So we don't have any data right now that suggest increased prescribing of the existing

extended-release products that have abuse-deterrent properties over what had been happening prior to those. And in fact, in spite of a number of approved abuse-deterrent formulations, the prescribing numbers overall are dropping, including the prescribing numbers of abuse-deterrent formulations such as OxyContin.

The concerning part is we've done some preliminary work, and there is an ongoing study looking at what prescribers think ADF means, because we have heard concerns, actually from past committee members and from other sources, that prescribers somehow -- well, it's no surprise they don't read the labeling. I mean, we know that's an ongoing problem. But they're not reading the label, and for some reason, they are perceiving a Schedule II opioid as either not addictive anymore or that the formulation makes it abuse proof.

All these formulations are able to do at most, and we're waiting for the postmarketing data. But theoretically the idea is to impair the ability to abuse the product.

These products have to deliver the opioid, otherwise they're not analgesics. So at the end of the day, there's always going to be a way to get the opioid into the systemic circulation. And the idea is to make the products less amenable to ways to increase the yield from abuse, to deter the attempts because they're not as successful.

The focus that the sponsor described is about people who are on the early path to abuse; that when they get to oral, the next step is often nasal before they get to IV. And if you can make it not rewarding in a useful way, meaning aversive in this case, that perhaps they'll just give that up. We don't know yet if that's a true theory, a provable outcome, but that's what we're hoping might be the case.

I think I wandered from the question. But just to get back to the question, we have a formal study looking at what the extent of these misperceptions are, and then we're going to do some work to try and figure out if we need to change the terminology to something that can't be easily

assumed to do something that it's not meant to convey.

DR. BATEMAN: One last question before lunch. Dr. Zibbell?

DR. ZIBBELL: Thank you. John Zibbell, RTI International, Emory University. This is for FDA. I don't know who to address it to. Are chemically-based aversion mechanisms, like the one used here, meant to generate nasal discomfort used in any of the other 10 FDA-approved abuse-deterrent opioid products?

DR. HERTZ: The short answer is no. I will give you a more complete answer. There is a current immediate-release product on the market that has some aversive properties or purported aversive properties. It was evaluated before our current guidance clarified what was necessary or appropriate for the evaluation. But it's not counted in the 10 products that we described, and it doesn't have the type of abuse-deterrent language that the others have.

DR. ZIBBELL: Just a quick follow up; I know

we're doing lunch. Oh, take it.

DR. BATEMAN: All right. We will now break for lunch. We will reconvene in this room in one hour, at 1:00 p.m. Please take any personal belongings you may have with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any members of the audience. Thank you.

(Whereupon, at 11:59 a.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. BATEMAN: Good afternoon.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's 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 relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before then. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself?

(No response.)

DR. BATEMAN: Speaker number 1?

(No response.)

DR. BATEMAN: Okay. We'll move on to speaker number 2. Step up to the podium and introduce yourself. Please state your name and any organizations you are representing for the record.

DR. WOLFE: I'm Sidney Wolfe from the Public Citizen Health research group, and I have no financial conflicts of interest. Before getting into the small number of slides that I have time to show, a number of people -- I don't know how many on this committee -- were there at a meeting over a year and a half ago in March of 2017, when the topic was Opana ER, which was mentioned this morning. And the issue was that this drug had been approved by the FDA in the beginning of 2012, and it had made an attempt for abuse-deterrent labeling, but had never gotten it.

So one of the reasons for the hearing in March was to see whether it could get abuse-deterrent labeling. And the conclusion of the meeting was to take it off the market, so it became the first -- I mean, Dr. Hertz is absolutely

right that none of the ones on the market have really finished the studies that they said they would do and were required to do the so-called phase 4 to show that they actually deter abuse.

That drug, Opana ER, actually enhanced abuse. And the reason I mention it is because so many of the characteristics of that drug in the Category 1 studies were similar to the characteristic of MNK-812. So it's worth I think going over.

The data in the last couple of slides were in the approval package, which was put up on the internet at the beginning of 2012. So these are all data known to the FDA before it was put on the market. And I say FDA mistakes because the mistake I think was approving it, and we can talk more about that later. But we're talking mainly about this drug.

These are a couple slides just showing what they knew from the phase 1 studies. And the second thing, "New formulations have documented a minimal improvement in resistance to tampering by crushing,

and thereby limiting the likelihood of abuse by crushing." And then finally they say, "It is now rendered readily abusable by ingestion and intravenous injection, and possibly still by insufflation." So this was known at the time of approval, and it was approved, and we'll spend about 30 seconds at the end on that.

The second issue is a further statement by the FDA based on the Category 1 studies. "Can easily be prepared for injection despite -- and those claims of OPR tablets have resistance to aqueous extraction," et cetera -- "poor syringeability. In addition, certain data suggests OPR may be more easily prepared for injection then OP, the non-abuse-deterrent version of the extended-release oxymorphone."

This has been mentioned this morning, and this is just a quote from the briefing document. "Extraction time 2 hours less, variety of ingestible solvents of varying pH, approximately 80 to 90 percent of oxycodone hydrochloride will be released from intact. When testing using complex

extraction -- 87 percent."

Now, you heard different figures as a function of whether a small or large volume. I think the point is that this is an IV abuse non-deterrent formulation; the fact that Dr. Fischer's question earlier was what are the kinds of solvents that are used or can be used? Are they common solvents? And the answer was, "Yeah, they're common."

Opana ER, again, this difference from -- this is the difference between what's going on today. In the approval package for the drug, Opana ER, not taken to advisory committee because there were no unusual concerns regarding efficacy or safety. I mean, certainly it worked, and the normal safety concerns as opposed to abuse concerns weren't thought important enough to have an advisory committee meeting. Today, both the DSaRM and AADPAC are there. They should always be there for any meeting involving opioids.

So we get to the voting questions, can it be labeled as nasal route of abuse? I say no because

even though initially it has an effect, later on, it breaks through.

Should it be listed as abuse deterrent by the intravenous route? The answer is clearly no because the data are there with a small volume or large volume. The difference between the extended release and small is you just use more pills.

Finally, the approval question. Should oxycodone hydrochloride MNK-812 be approved for the management of pain severe enough to require an opioid analgesic for which alternative treatments are inadequate? No.

If I may take about 8 more seconds. If this would get approved, you would have the same kind of problem. You're deterring somewhat intranasal abuse and switching to intravenous. That's what happened in Opana ER, and if this is approved, we will have a repeat of that. Thank you.

DR. BATEMAN: Will speaker number 3 please step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MS. LITZ: Hello. My name is Stacy Litz, and I am an addict. I am not anonymous, and I am no longer living my life in shame of addiction. I am not being paid by any drug companies, but my travel expenses are being reimbursed.

I am currently in my 10th year of celebrating recovery, and I have learned to use my mistakes to create a message, a message that I am fortunately able to share with others inside and outside of gels on a daily basis.

As a state certified, peer recovery support specialist, working with community behavioral health services out of Hamilton, Ohio, I recently spoke on Capitol Hill earlier this year about non-opiates and using opiates when needed. And I still stick to my stop it where it starts message. But now I want to direct our attention to those individuals with chronic pain and acute post-op pain, to those individuals that need opiate. Yes, I believe that some individuals need opiates. We all know that not everyone prescribed opiates becomes addicted.

So until we're able to determine those who are susceptible to opiate addiction, then we must put in place an abuse-deterrent version on the opiates that are known to help these type of pain patients, instead of going through the whole process of creating new drugs.

A person in pain should not have to jump through hoops, or suffer just to obtain relief, or suffer from others' mistakes. I also don't think that pain patients should have to worry about their pain medications being stolen and abused by others. With an abuse-deterrent version, patients would have one less worry consuming their minds resulting in faster recovery. No one wants to deal with the excruciating pain from a surgical procedure, so the immediate release that this medication delivers will allow the acute post-op patient to heal more comfortably.

Now, I have heard countless versions of various addiction stories often where the addict has resorted to snorting them and breaking them down for IVs, and I'm no stranger to this method.

Even I had resorted to snorting my prescribed pain meds to receive a faster -- [audio break].

While my story of addiction isn't like other stories, my disease is. I was just fortunate enough, unlike numerous addicts, to receive help before my addiction had escalated to an unrecoverable or even fatal degree. I had endured long periods of pain due to a herniated disc that was discovered during my second trimester of pregnancy. I was then quickly referred to pain management after childbirth and received opiates before and after my back surgery for continual pain management. My pain meds increased in quantity or milligram with each returning visits, which brought on opiate-induced hyperalgesia.

We are aware of the effects and causes brought on by opiate abuse and the outcomes that have resulted. The opiate epidemic has brought on such a large degree of losses in every way, that words alone cannot do justice. We can't forget about those patients that are in pain. Do they deserve to suffer? Would you want to, if it was

you? Thank you.

DR. BATEMAN: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MR. THOMPSON: Good afternoon. My name is Edwin Thompson. I'm the president of Pharmaceutical Manufacturing Research Services. Today, Mallinckrodt's asking you to approve their drug without submitting clinical studies for substantial evidence of efficacy. Instead, they're relying on Roxicodone to supply clinical evidence of substantial evidence of efficacy. The problem is Roxicodone didn't submit any clinical studies for substantial evidence of efficacy.

Let's look at the data. Oxycodone 5 milligram was approved in May 2009. Dr. Hertz approved it. And you can see it's a supplement that had as an addition the 5-milligram tablet. In addition to what? The 15- and -0 milligram tablet. So let's look at the 15- and 30-milligram approval.

This is Dr. McCormick's notes in reviewing the 15- and 30-milligram approval. "Currently, oxycodone exists in the marketplace in many forms by virtue of DESI evaluation for the immediate-release product, 5 milligrams in combination" -- critical -- "in combination with aspirin." That's Percodan.

"The currently available oxycodone IR 5-milligram product that is being marketed as a single entity analgesic has no historic basis for approval. This NDA contains no efficacy data." So the 5 milligram has no efficacy data and the 15 and the 30 have no efficacy data. "It presents a problem." It sure does, the root cause of which is the basis for the determination of efficacy of single-entity oxycodone immediate release.

You have no evidence of efficacy in studies, and you have no reference-listed drugs. How did 5, 15, and 30-milligram Roxicodone ever get approval? How can you support approval of a drug that uses it as a reference-listed of drug?

Let's go on. This is the letter to Roxane

written by the FDA.

"There are no data submitted in support of the effectiveness of immediate release 15 and 30 milligram oxycodone in this application. There is also no link to any product for which the FDA has made the finding of efficacy. Clinical safety in the higher doses, 15 to 30 milligram, has not been adequately established with the database submitted."

So not only don't you have efficacy; you don't have safety data. And "there is no link to any product for which the FDA has made the findings of safety in higher doses." It doesn't look like this is getting approved, does it? But it does.

Let's go on. The review says, "A bridging study or studies will be required from which the agency can link its prior findings of efficacy for immediate release oxycodone to your product seeking approval. Such a bridging study is" going to be a biopharmaceutic study.

"An adequate rationale will we required for the extension of the dosage form." What extension?

Five milligrams not approved. What are you extending from? "For 15 and 30 milligram without having provided clinical studies demonstrating efficacy at higher doses."

So let's look. NDA 21-011 for oxycodone 15 and 30 milligrams was originally submitted in September 1998. Application requested approval of 15-30 milligrams -- the sponsor's marketed, although unapproved, 5-milligram oxycodone.

"No data to support effectiveness were included in the NDA as comparative studies included only the subject of this application and/or unapproved 5-milligram tablets. The application has been filed as a 505(b)(1), although it's provided no clinical useful effectiveness data."

So what happens? The agency recommends performing a relative bioavailability study for their product or previously-approved product, but there is none. You don't have single-entity oxycodone approved in the United States; providing adequate rationale for extension. Again, extension from what? To approve 15-and 30-milligram tablets

in the absence of clinical evidence of efficacy.

This submission included the results of a bioequivalence study to Percodan, a combination drug. Right? Is it also a line extension of the 5 -- it's not a line extension of an unapproved drug.

So what happens? In 1975, the federal government passes a law, the Code of Federal Regulations, 300.50. It requires that two or more drugs, a combination drug, which applies to Percodan, when combined in a single dose, each component must make a contribution. That says "Percodan." Oxycodone and aspirin must be statistically significantly more effective than oxycodone alone, or it violates the law. So you can't use Percodan as your reference-listed drug, but the FDA approves this drug on Percodan.

DR. BATEMAN: Please conclude your remarks.

MR. THOMPSON: I will.

Finally, on your page background 105, you can see that the sponsor informs you that oral MNK-812 always exceeds intranasal use here. The oral

always beats the intranasal. You're trying to protect something that doesn't need protecting. Passing labeling that provides intranasal abuse labeling is a scam. It's a fraud, on physicians and on patients. Tmax is always smaller; Cmax is always larger for oral over any form of intranasal use. Your answer should be vote no. Thank you.

DR. BATEMAN: Thank you.

Will speaker number 5 please step up to the podium and introduce yourself? Please state your name and any organizations you are representing for the record.

MR. CICHON: Good afternoon. I'm Charlie Cichon, the executive director of the National Association of Drug Diversion Investigators, NADDI. I have nothing to declare.

With 25 chapters in 31 states and over 4,000 members, NADDI is the leading drug diversion training organization in the U.S. with the largest networking platform of professionals involved in the field of pharmaceutical drug diversion. The NADDI networking platform provides the opportunity

to bring diverse viewpoints, education, supports, and resources to the individuals facing the challenges in the fight against the misuse and abuse of pharmaceutical drugs.

Prescription drug abuse does not discriminate by region, socioeconomic status, or age. The Centers of Disease Control and Prevention have identified prescription drug abuse as an epidemic reporting more than 15,000 American deaths each year from prescription painkillers. An important step in the abuse-deterrent prevention process for both new and chronic pain sufferers is the development of abuse-deterrent technologies for opioids.

NADDI's a nonprofit organization that works to develop and implement solutions to the problems of prescription drug abuse and diversion. NADDI advocates for the responsible use of prescription drugs by people who need them, and at the same time, we work with law enforcement and regulators to pursue those involved in related criminal activity.

Continuing progress in the field of pain management involves a juggling act that balances the needs and interests of those involved. The development process involves all the stakeholders in the medical treatment of pain: clinical, legal, regulatory, law enforcement, and industry. NADDI recognizes that no one approach to maintaining this critical balance will succeed unilaterally. Therefore, we support ongoing interaction and cooperation among all who can impact the access to competent health care, and who can effect diversion and abuse of medications.

A scientific approach was taken to reduce illegal street activity. And speaking with and surveying our members at our trainings throughout the country, it appears likely that the rates of diversion decreased dramatically after the introduction of reformulated abuse-deterrent opioids.

This new drug application under review for an immediate-release oral tablet formulation of oxycodone has been formulated with the intent to

deter abuse. Adding new physical and chemical features to prescription opioids to deter abuse could also reduce misuse of these drugs, and at the same time the deadly consequences.

These products can be part of a comprehensive approach, which should include prevention, interdiction, prosecution, and substance abuse treatment. While the first generation of abuse-deterrent formulations have reduced abuse and diversion, any advances of the technology that would further erode the street value of opioids and maintain access to the individuals who benefit from their relief would be welcomed.

In short, NADDI believes that abuse-deterrent formulations of opioids can interrupt the abuse trajectory for these medications by preventing manipulation for nasal and intravenous abuse. This is true whether the drug is obtained by prescription or is diverted to an unintended user.

NADDI supports expanding access to ADFs in

order to reduce prescription drug abuse and diversion, and we continue to be a strong proponent of new abuse-deterrent medicines that make it more difficult for the abuser and reduce law enforcement involvement in health care. Thank you.

DR. BATEMAN: Thank you. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organizations that you are representing for the record.

MAJ-GEN PRICE: Good afternoon. My name is Major-General Barry Price, U.S. Army retired. I serve as the executive vice president and chief operating officer of the Community Anti-Drug Coalitions of America, better known as CADCA. located in Alexandria, Virginia.

CADCA supports prodrug technology such as abuse-deterrent formulations that make opioids harder to abuse. As you know all too well, our nation is in the grips of a major opioid crisis every day. Countless lives are lost to drug overdoses related to prescription opioid and heroin

abuse, and many communities and states continue to be burdened by this complex problem.

We know that the Centers of Disease Control recently announced that more than 72,000 people died from overdose deaths in 2017, up from 64,000 in 2016. To address this epidemic, CADCA believes we must utilize a comprehensive approach, which encompasses evidence-based prevention, treatment and intervention, and recovery support services.

CADCA supports enhancing medical training and proper prescribing of powerful prescription opioids and requiring drug manufacturers to create abuse-deterrent formulations for prescription opioids to make it more difficult for people to abuse these medications. While abuse-deterrent formulations are not without limits, they are another step in thwarting abuse of these powerful and highly addictive medications.

In 2013, CADCA supported the tampering of prescription pills, Stop Act, which directs pharmaceutical manufacturers to invest in research and production to formulate tamper-resistant drugs

in order to compete with drugs of a similar nature that already employ tamper-resistant technologies.

At the end of the day, CADCA knows that primary prevention, stopping drug abuse before it starts, will be the key to our nation's opioid and heroin crisis. Centers of Disease Control data shows that addiction to alcohol, marijuana, or cocaine all increase the probability of heroin use. Not surprisingly, those addicted to prescription opiates are 40 times more likely to use heroin.

Mallinckrodt's new drug application for an abuse-deterrent reformulation of Roxicodone appears to represent a medication that when properly prescribed may be of great benefit to help deter the abuse of opioids. CADCA supports their application from this viewpoint.

As required by the FDA rules, Mallinckrodt Pharmaceutical is a corporate partner of CADCA and has provided a discretionary grant to assist CADCA in their mission of building healthy, safe, and drug-free communities globally. If the panel has any questions of me or CADCA, please contact me at

703-706-0560, extension 222, or to email bprice@cadca.org. Thank you for this opportunity to appear before your hearing.

DR. BATEMAN: Thank you. Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MR. MULLENIX: Good afternoon. My name is Steve Mullenix. I have been asked to provide the testimony of Mr. Dan Cohen in his absence, and I have agreed to do that.

"Thank you for the opportunity to offer comments this afternoon, and I appreciate the reader of my remarks due to an unavoidable schedule conflict.

"My name is Dan Cohen, and I am the chair of the Abuse Deterrent Coalition. The ADC is a talk forum comprised of ADF innovators, patients and issue advocates, and research groups dedicated to educating the public policymakers and the FDA on the importance of developing and expanding access

to the most current ADF technologies.

"Today my comments are in support of Mallinckrodt and its immediate-release, single-entity oxycodone product designated as MNK-812, which incorporates an abuse-deterrent technology and with the proposed indication for the management of pain severe enough to require an opioid analgesic for which alternative treatments are inadequate.

"MNK-812 is bioequivalent to Roxicodone and will be available in strengths of five, 10, 15, 20 and 30 milligram for oral administration. MNK-812 incorporates Mallinckrodt's immediate-release, abuse-deterrent technology, which is a formulation based on physical and chemical barriers and aversive agents that impart a meaningful deterrence to intranasal and intravenous abuse.

"What is particularly exciting is the plan of Mallinckrodt to eventually replace its currently approved, non-abuse deterrent, immediate-release oxycodone product with the new MNK-812 formulation. My understanding is that Mallinckrodt will work

with trade pharmacy partners, distributors, and payers to stock, dispense, and reimburse its new abuse-deterrent formulation, a pure market replacement strategy that offers the potential benefit of abuse deterrence without a single solitary risk to appropriate patient treatment.

"So the primary question before the advisory committee today is, is it reasonable to approve MNK-812 ADF formulation as safe and effective, and does it have the potential to discourage intranasal and intravenous abuse? As the panel prepares to answer this fundamental question, it is important to ensure we are using similar terms for this discussion. MNK-812 is designed to offer the same treatment benefit as its comparator for a patient requiring analgesia, but with a expected reduced risk of abuse and misuse. That is an ideal and pure definition of ADF.

"Do not fall into the trap by considering what is not under review today, and that is whether MNK-812 is an abuse-prevention formulation or ADF. That is because there is no abuse-proof

formulations. Products with ADF technology do not and are not expected to be abuse proof. They are designed only to lower, through deterrence, the abuse potential of the products.

"Is this deterrence perfect? In a word, no. There is no such thing as a perfect deterrence, but this is clearly state-of-the-art abuse-deterrence technology and can be expected to deter and intranasal and intravenous abuse. Innovators in ADF technology do want ADF technologies that do more, but your question for this advisory committee is, will we adopt the science that is possible today and not wait for what we hope will be a technology of tomorrow?

"Keep in mind that technological feasibility is why intranasal and intravenous abuse deterrence is a consideration and oral abuse deterrence is but an aspiration. The development of abuse-deterrent formulation is part of a multifactorial approach to reduce risk and abuse and diversion. Nothing is abuse proof and oral ADF is not technically feasible today, even as both aspirations remain the

goal of innovators.

"ADF is getting more effective, but we cannot get future innovation by failing to approve current discovery. But to give full meaning to ADF, it is important to agree on another term. Who is the customer for deterrence technology? We believe that ADF will ultimately reduce the number of addicts and highly experienced abusers in the future by reducing abuse progression at its early stages. Abusers that are deterred from progressing to ever more aggressive forms of abuse, such as intranasal and intravenous use, is the goal of ADF.

"Lastly, the population adjusted rate of abuse of immediate-release opioid products is over 4 times greater than extended-release products. Over 220 million immediate-release opiate prescriptions were issued in 2017, yet there is only one abuse-deterrent, immediate-release opioid product approved and waiting market commercialization. These are the entry level opioids that need deterrence properties.

"My ask of this panel is do not make the

perfect the enemy of the good. Immediate-release oxycodone is a common target of abuse and relatively high rates of intranasal and intravenous abuse. The data presented by the sponsor this morning demonstrated that MNK-812 offers and abuse-deterrent replacement IR, an immediate-release oxycodone product that provides similar safety and efficacy to comparator products, but at a reduced risk of abuse and misuse."

DR. BATEMAN: Can you conclude your comments, please?

MR. MULLENIX: Yes.

"Overall, the results of the in vitro and clinical studies leave this panel with but one question. What more would you need to see to vote yes?" Thank you.

DR. BATEMAN: Thank you. Will speaker number 8 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. BRASON: Good afternoon. My name is Fred Brason. I represented Project Lazarus. I

have no disclosures today. I'm here to not share more about what we've been doing in the United States to address the issues of prescription drugs and opioids and heroin and fentanyl. I will say that I no longer see this as an opioid crisis epidemic. I see this as a substance-use epidemic because of the amount of polypharmacy that is hitting our communities.

I found myself involved in this entire issue back in 2004 and '05 as a chaplain and a director for hospice. In doing so, I kept my chaplain charge with me in all that I've been doing. And that charge is to do no harm, to make sure that we prevent, reduce, and help those in harm.

So all we do and all we've looked at doing from prescriber education to emergency department and hospital system policies, to working with people with pain that deal with substance-use disorder, and community education and the like, we have made sure that we do no harm to anybody and have no adverse events or effects with them. In order to do that, we had to make sure that we were

preventing overdoses, but at the same time presenting safe and effective, and responsible pain management and also promoting substance use treatment and support services.

Through my process as that charge as a chaplain to do no harm and to meet that need of help for any person that I come before or comes before me, we needed to make sure that we addressed it in ways that we help them and not harm them. In doing so, I have had a series of tipping points through my process and journey regarding this, and those tipping points started as a hospice chaplain when the providers started to call me and say, "I can no longer safely write a prescription to that terminally ill patient in that home" because that medication was being diverted in less than a 2-week time frame every time that prescription was written.

So I had a care issue of what do I do with the patient? How do I help that? How do we change that? So obviously, we had diversion issues and had to work on making sure that we kept the patients

safe in their home with the right medication and did not have it robbed, stolen, or not.

I also learned in a tipping point when we started addressing it and bringing awareness, we went from people who felt that, oh, I don't want to be on that medication because I might become addicted, to one patient that I met for the first time, when he had been notified that he was terminally ill and had less than 6 months, when he said to me, "I'm afraid of that medication because if people find out, I'll be robbed." That was another tipping point.

Then another tipping point was when the North Carolina medical board said yes to take home naloxone to make sure that those who are at risk have it, in any way, shape, or form, within their home, within their person. Another one was when we had that first rescue of the first time we dispensed and distributed naloxone; that emotional event when you get that call and find out a brother saved a sister's life because of her adverse use of prescription medications.

Then we realized another tipping point when the Chronic Pain Initiative that was started within our county at Wilkes County, North Carolina in the Appalachian region for the state of North Carolina, that we could safely and responsibly prescribe reduce overdoses, reduce emergency department events, but also make sure that the person who does have pain can receive the care and the prescription that they need and have it in a safe and responsible manner.

But I have a new tipping point. As I criss-cross the country and work with communities to mobilize them, doing forums and workshops around a whole comprehensive approach to addressing this issue, I used to have, and always do still have, patients, families, members of the community coming to speak about their issue.

The new issue that I'm hearing is from people with pain coming to my forums and saying, "I can't get care. My doctor is denying me anymore prescriptions and referring me to a provider and another area, in another way, out of town, an hour

away." I have an entire community in Louisiana that no longer has prescriptions for opioids unless it's the emergency department. If you are in a chronic pain situation, you are being sent an hour away in order to receive that treatment.

We are causing harm if we don't find a way to have the reason to prescribe and to treat because all of the headlines and everything else in the fear factor is giving prescribers a reason not to treat. When we fail to treat, we call that mistreatment. Abuse-deterrent formulations give doctors the encouragement to be safe and responsible with the prescribing that's necessary to treat that individual.

So I encourage you. You are looking at the science and the efficacy of that. I'm talking about abuse-deterrent formulations overall, whether it is nasal and/or intravenous aberrant protection. And I encourage you to look at it from the perspective of the person so that we do no harm and we provide the treatment that's necessary. Thank you.

DR. BATEMAN: Thank you. Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MR. MULLINEX: Thank you for the opportunity to offer comments regarding this important topic. My name is Steve Mullinex. I am senior vice president of public policy and industry relations at the National Council for Prescription Drug Programs. I'm also a pharmacist by training with lengthy professional practice experience in nearly all facets of pharmacy, spanning community, hospital, health system, pharmacy administration, pharmaceutical manufacturing, and addiction treatment to name a few.

My comments today are in support of Mallinckrodt and its efforts in incorporating abuse deterrent technology into its immediate-release oxycodone product designated as MNK-812. And while NCPDP defers to the manufacturing and product evaluation expertise of Mallinckrodt and FDA,

respectively, we believe strongly in the development and application of abuse-deterrent technology as an important factor and a more comprehensive effort to assure safe use of these important medications, while at the same time maintaining access for those with legitimate need.

As a means of providing additional perspective, NCPDP is a not-for-profit, ANSI accredited standards development organization located in Scottsdale, Arizona. It's stated vision and purpose are to lead the industry in creating healthcare standards for the common good and to standardize the exchange of healthcare information to improve outcomes.

Membership is comprised of representatives in all sectors of the healthcare industry. Decisions are made using a consensus-building approach with an obligation to be non-biased. For the over 40 years of NCPDP's existence, it has been using this very defined process in serving as a problem-solving forum for the healthcare industry.

Results include various published solutions,

industry guidance, and maybe most significantly has been the development of several interoperable electronic communication standards used in healthcare, many of which have been named in various federal legislation and/or regulation.

Two of the most prominent examples are the telecommunication standard. Telecom is a real-time bidirectional communication standard that connects the community pharmacy with the payer and other entities. And SCRIPT, SCRIPT is the second example authored by NCPDP and is the communication standard in which all outpatient electronic prescribing is based. This standard is also real time and bidirectional and connects the prescriber to the pharmacy. The advantages of utilizing electronic prescribing are many and serve as a basis for why many states either have or are strongly considering mandating its use.

As I mentioned earlier, NCPDP has long considered itself as a problem-solving forum, and in the case of prescribed opioids, several of our members came to us over 6 years ago and asked if we

would examine this issue in more detail. Our response since has largely been focused on how prescribers and pharmacists can best obtain the information they need to support good clinical decision-making.

The result was the creation of a white paper that outlined the perceived challenges, existing state monitoring programs, and propose solutions. That document is now in its 4th edition. It is entitled NCPDP Standards Based Facilitator Model for PDMP: An Interoperable Solution for Patient Safety. The document was just approved for publication last week and will soon be available on NCPDP's website at www.ncpdp.org.

In short, this solution utilizes existing infrastructure and connects prescribers and pharmacists to a national facilitator via two real-time, bidirectional, HIPAA compliance standards as a means of providing those entrusted with the care of patients with complete timely and accurate information on which to base their clinical decisions.

While NCPDP believes strongly that utilizing this approach will go far and helping to assure safe use of these important medications, we recognize also the complexity of the opioid misuse and abuse issue and a need for a comprehensive approach and a commitment from all stakeholders.

The abuse-deterrent technology suggested by Mallinckrodt via MNK-812 is in our minds another important piece to the puzzle of assuring safe and effective use of these important and effective medications, and NCPDP commends Mallinckrodt for their efforts. Thank you again for your attention and for allowing NCPDP to provide comments regarding this important topic. Thank you.

DR. BATEMAN: Thank you. Will speaker number 10 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. ZOOK: Good afternoon, Mr. Chairman and members of the committee. My name is Dave Zook, and I am pleased to appear today in support of providing patients and their healthcare providers

improved access to safer abuse-deterrent versions of prescription opioids. I'm speaking today as chair of Faegre Baker Daniels Consulting and our health practice. For the record, our team has had the opportunity to work with Mallinckrodt in over 80 organizations on the broader efforts of the collaborative for effective prescription opioid policies.

As the committee and the FDA consider the merits of novel ADF medications, it's critical these newer entities be shown to provide patients with adequate pain relief while reducing, to the greatest extent possible, the misuse of these products. This review also should consider the effects of marketed non-ADF opioids on our nation's substance abuse epidemic as it relates to their misuse, abuse, and diversion.

We've seen this approach work across other categories with the replacement of older therapies when innovation proves more effective or can be dosed through an improved route of administration. Effective ADF opioids present an equally compelling

opportunity.

At the same time, our policy work has examined how to address the real complexities of quantifying the non-therapeutic benefits of ADF medications and what they can deliver to individuals, health systems, and communities struggling with the burdens of prescription and illicit drug abuse. We do know, however, that the trajectory of abuse, from oral to nasal or intravenous, is a deadly pathway, and any measures that can interrupt it should be pursued to their fullest extent.

We also know that countless unused and unwanted doses are and will be available to misuse, abuse, or diversion in medicine cabinets across the nation. Again, safer medications that are less prone to tampering should play an important role in impacting the broader complex epidemic.

From an economic standpoint, the rationale for action is equally persuasive. Estimates around the impact of the opioid epidemic to the U.S. economy average well over $100 billion per year

from the combined cost of treating substance-use disorders, as well as the lost productivity and workforce struggles. The impact on communities due to our emergency care, hospitalizations, workplace absence and distraction, recidivism, and many other risks are clearly correlated with the rise of opioid misuse, abuse, and diversion. We also must acknowledge that appropriately treated pain, sometimes through the use of prescription opioids, can have a net positive impact in improving productivity.

The data at the individual level are equally compelling. The White House Council of Economic Advisors [indiscernible] note the significant impact that each overdose related death has on our economy. With the average age of an opioid overdose victim now 41 and in the prime of their working years, the tragic impact per life is upwards of $10 million. We must find reliable ways to factor improvements that ADF medications can generate in curtailing these losses and their devastating human impact into both the regulatory

and reimbursement processes.

There are bright spots in the otherwise chilling statistics around prescription drug abuse. Appropriate prescribing levels are improving. Major policy changes have recently been enacted around several core issues such as safe disposal, and some advanced ADF medications are gaining acceptance with payers who recognize their broader value.

I believe this committee has the opportunity to add one more important element to balanced efforts to reduce abuse while appropriately treating pain by recommending approval of MNK-812. Once again, thank you for the opportunity to provide this perspective.

DR. BATEMAN: Thank you. Will speaker number 11 step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record.

MR. LEWIS: Hello. My name is Joshua Lewis, and I requested to speak here today as an addict that is seeking long-term recovery from opiate

abuse. I am not paid by any drug company by travel, but my travel expenses are being reimbursed. I am here because part of my recovery involves sharing my story.

I abused opiates. I snorted them I injected them. I believe replacing opiates with medications that try to prevent these types of abuse is important and can benefit people like me.

I would like to start off with walking you through the chaos of my addiction. I started using opiates at the early age of 13. I remember my mother being prescribed opiates for a broken leg, which led her to her addictions as she began breaking them down to snort them, which led me to doing the same.

I recall the younger version of me stealing them from my mother out of the household medicine cabinet. I truly believe that if the doctors would have prescribed an abuse-deterrent version of opiates, then we would have never gone down this deep, dark path of addiction.

My addictions have led me to snorting and

breaking down several different types of drugs into IV use. I was continuously chasing that temporary high. This disease eventually led to overdoses and deaths of many loved ones in my life, including my mother.

I have caused a lot of pain in the 19-year relationship with my significant other and with my 17-yea- old son, leaving them both with depression and fears that I am going to overdose on a relapse the rest of our lives, just like the rest of our family and friends. Even after 16 months clean from all substance, I still struggle with scores and images that cloud my mind, reminding me of the shame and the guilt I have from being in active addiction.

Addiction truly is like going to war. You'll never come back and be the same. Some don't even make it back at all. I have had to start completely over in life with little education, no computer skills, and a criminal background that has prevented me from providing for my family and living a normal life. I've been in and out of

jails and institutions along with 12 attempts in rehab before finally getting to an area of active recovery in my life.

Standing here today sharing my testimony is rewarding because I know that each time that I share, I am healing on the inside. I can't undo or change my mistakes, and I can't bring my loved ones back from all of the grief. But I can speak up and not allow their memories to be lost in vain of this tragic disease.

With this being said, it is time that we take a different approach and have a different view so that millions more don't fall victim to this same pathway and into this disease of addiction. Thank you.

Clarifying Questions (continued)

DR. BATEMAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we'll no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the

committee as well as the public comments. But before we do that, the sponsor has a couple of answers for questions that were raised this morning.

DR. SCHLICHER: I'll quickly follow up on a few questions from this morning. The first was the question on whether we were compliant without any outstanding regulatory requirements, and I just wanted to make sure that I was accurate. So I checked with our specialty generics regulatory team, and we are compliant with all outstanding postmarket requirements.

I was a little surprised by Dr. Hertz's comment about the compliance or interest in postmarketing for the abuse-deterrent formulations and for us that's something we are very interested in really quickly pursuing. We're working with Dr. Dart and outlined to you this morning some of the things that we are proposing doing right away, because I think for all of us, we really need to know if these ADFs are working on not and which HAP study endpoints are meaningful to guide all of us

our work. So we are committed to being very quick in putting in place the appropriate studies that can help us in that postmarketing effort.

The second question that came up was around the adverse events around the HAP study, and I apologize for my confusion on that respiratory category. So I'm going to ask Dr. Webster to get up and share the table that was in the FDA briefing book and help provide some clarity there.

DR. WEBSTER: Dr. Lynn Webster, vice president of scientific affairs at PRA Health Sciences. Here we go. Can I put that up? This is what, Dr. Green, I think you were referring to. Yes.

Well, what happened is we had to code all of those adverse events that the subjects were experiencing during the snorting event: cough, nasal discomfort, nasal congestion. And they're coded under respiratory. There are really no pulmonary symptoms or signs. I even went back and took a look, and we saw no desaturations, mild respiratory rate decreases, but nothing outside of

the normal range.

DR. SCHLICHER: And I would just ask Dr. Webster to remain at the podium to try to clear up one last confusion; I think it's really important to note. As I mentioned, we are replacing a product with no abuse-deterrent features with one that has significant abuse-deterrent features, intravenously and intranasally, where people would rather take placebo than to take our drug again.

We need to be able to demonstrate value of this product. We're taking another product off the market. And that means it absolutely has to be safe. So we were very careful in the development of this formulation, and we're sensitive to concerns that were arising around PEO.

So to be very, very clear, we have absolutely none of the high molecular weight PEO that was present in the Opana product that was taken off of the market at a molecular weight of 7 million. The much more comparable product to compare us to is OxyContin, which has been on the

market since 2010 and has a molecular weight PEO of 4 million. We also have an amount of that high molecular weight at very substantially reduced amounts than either of the Opana product or the OxyContin product, less than 2 percent of our formulation while greater than 60 or 65 percent in either of the other products.

I'll now ask Dr. Webster to comment on why we wouldn't expect the same kind of treatment as Opana; same kind of uses as Opana.

DR. WEBSTER: So if I can draw your attention to the APIs up here, you've got oxycodone and then oxymorphone. These are not comparable. So you've got the oral bioavailability of 85 percent for oxycodone, but only 10 to 15 percent oral viability. That means that very little of that drug is going to be effective. But if you then dilute into a syringe and inject it, you get 100 percent of that only 10 to 15 percent viability. That means it's 10 to 20 times more potent than the oxycodone.

So that's why you can take a syringe of

30 ccs and draw out 1 cc and get enough to be rewarding with oxymorphone that would be comparable to 1 or 2 milligrams of an oxycodone, which for most people who are injecting is not rewarding.

DR. BATEMAN: Okay. Thank you.

We're now going to move on to Dr. Hertz providing us with the charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: We have to be careful as we, as an agency and as a society, seek to address serious problems with prescription opioid analgesic abuse that we don't end up denying patients adequate pain management. I think we all agree that the goal here is not to do that.

We do need to work to change the type of products that are available and the way currently available products are used. In particular, we need to work to change the way opioids are used in the management of pain so that they're not used when not necessary and when opioid analgesics are not appropriate

When they are used in an appropriate

context, we need to ensure or work toward these products being used in the context of a fully informed prescriber and a fully informed patient. Efforts to assist the medical community to prescribe opioids appropriately and safely are a top priority of this agency, and the different ways we're approaching that have been discussed in many settings and are also present on our website. We support the development of products that may deter abuse.

Today, you've heard the applicant's and the agency's presentations of the data from the assessment of the abuse-deterrent properties of this immediate-release formulation of oxycodone with the intent of deterring nasal and IV routes. We agree with some but not all of the applicant's conclusions.

In particular, we are worried about unintended consequences that can be associated with well meaning products such as this, and we'd now like to hear what you have to think about these data and whether they support labeling to describe

that the properties of this product can be expected to deter abuse by the nasal and IV routes, as well as the impact of this product on the public health. And then finally, if it should be approved.

Your advice and recommendations really will be essential in assisting us with addressing the questions we have about this product and in how we look at it in the broader context of public health. Thank you for your time and attention to this today.

Questions to the Committee and Discussion

DR. BATEMAN: We will now proceed with the questions to the committee and panel discussions. I'd 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.

We're going to start with question 1, and we'll take this in part. So we'll start off with discussing the nasal route and then the intravenous route. The discussion question is, please discuss whether there are sufficient data to support a

finding that oxycodone hydrochloride immediate-release tablets, MNK-812, has properties that can be expected to deter abuse, commenting on the support for abuse-deterrent effects for each of the following routes of abuse. We'll start with nasal and then intravenous.

Are there any questions regarding the discussion question, any clarifications that are needed?

(No response.)

DR. BATEMAN: So if there are no questions or comments concerning the wording of the question, we will now open the question to discussion. Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn Medicine. The question or the discussion point is whether the new drug MNK-812 has properties that can be expected to deter abuse. I think my gut feeling is yes because we're not asked to address as to how much or the degree of deterrence it causes. If it is yes or no, maybe it does better in terms of intravenous than nasal. Yes, I think the answer

has to be yes.

DR. BATEMAN: Dr. Meisel?

DR. MEISEL: Steve Meisel. I have a really hard time with the question. I understand the question, but I have a hard time answering the question because we don't have a frame of reference or definition of sufficient data. "Expected to deter" those are terms that are very subjective, and I think we implicitly get that.

I've been on several of these committee meetings over the last year or two where we've been evaluating some of these products, and it seems like the frame of reference is always a little bit different with every discussion. The dynamics of the committee are a little different. The data are a little different. The questions that are posed a little different.

If we were to go back to OxyContin and we had the same conversations today, we probably wouldn't approve it because we think about it differently. But the fact that OxyContin has been available for 7 or 8 years, and we still don't have

any data to know whether it does any good whatsoever, I think it's impossible to answer the question as to whether we would expect this product to do any good in terms of deterring abuse, whether it's nasal or IV.

I think there are some intriguing data points that the applicant has submitted, and you'd like to think it might. But without any data to know whether that's just feel-good supposition or reality, we just don't know. And without the guidance from the agency on what the term "expected to deter abuse" means, sufficient data is supposed to mean, I think we run the risk of saying yes to product A and no to product B, but product B may be better than product A.

DR. BATEMAN: Dr. Fischer?

DR. FISCHER: Thanks. Mike Fischer, Boston. I'll try to maybe outline some thoughts on this question, and hopefully frame it to get some additional feedback from other members of the panel to get it documented. I was concerned about what exactly we mean here. I'm trying to unpack

the -- when we're talking about sufficient data for the expectation to deter abuse, what we really saw in the data presented today was evidence from the study with a relatively limited number of patients who were recreational users of opioids.

In that setting, we certainly saw the unpleasant effects and the idea that their willingness to use it again was similar to placebo, and to me, when I think about how does that apply for deterring abuse longer term, that might apply to the sort of patient who has perhaps used an oral formulation of an opioid and perhaps is using the medication nasally for the first time. We're focusing just on nasal here of course.

We didn't have information on the patients who already have physical dependence on opioids. There was the naloxone screening and so on. So to me, where I struggle with whether there is sufficient data for deterring the ongoing abuse and the ongoing potentially harmful use of opioids by unintended roots, by patients who already have become dependent is, what happens when a patient

with dependence uses this medication nasally?

There's certainly an initial unpleasant nasal sensation, but the data that we have doesn't apply to patients who, for example, are essentially treating their withdrawal symptoms when they use. And I would think that has the potential to really shift where someone would rate their likelihood to use again, and we just don't have information on that.

So I'm left feeling like we have a fairly narrow window in terms of this deter abuse question. As Dr. Goudra said, yes, in the study it was done. For somebody who the very first time is exposed to this, it's unpleasant, and they said they wouldn't want to use again. But that's a very specific niche of the patients who might take an opiate medication like this and use it other than how it's intended. For the larger population of patients, I'm not sure we have the data we would really want to answer that question.

That's what I'm grappling with and would love to hear insights of how others in the

committee interpreted the data.

DR. BATEMAN: Does anyone want to respond to Dr. Fischer's comments about the interpretation of the intranasal abuse studies on the population that was studied? Mr. O'Brien?

MR. O'BRIEN: I share Dr. Fletcher's [sic] concern about the narrowness and what we're being asked to do, but it's always difficult with these because the question was did the sponsor provide the data? Well, as I look at all the background material and as I read the material, they provided the data that it seems they're required to provide. And in fact for nasal, it looked like they did in fact -- I agree; 38 recreational abusers, I don't know where that comes from.

However, as I read their material and read the requirements from the FDA, that's what's required. You have to provide that type of material. It has to be recreational users. It has to be screened with naloxone, et cetera, et cetera. That's what it says to do, if I understand it correctly, to do it.

In terms of interpreting the question, it seems to me, yes, they provided the data that was necessary for them to provide. The FDA agreed that there was abuse deterrence for nasal. The question became the timeframe and that it only lasted for an hour. So the question is, is that enough? And there is no definition. It said it had to be 2 hours, or 4 hours, or 24 hours. So we're left with this quandary that's there.

That being said, my concern really is from a patient care perspective, and I do think that the nasal portion of interference is extremely important to interrupt that next trail that someone's going to take from an oral process to a nasal and diversion. And I'm not concerned for myself, but I am concerned for whoever in my family may get a hold of the drug, or if I'm in a hotel room and my drug's in my underwear draw, whether that clerk gets a hold of that. That being the case, I have great concern in that area.

I didn't get to ask the question before lunch of Dr. Nadel. When I looked at the

conclusions that were there and in reading the background material, I just want to know the basic. Do we currently have an opioid IR SE on the market that is abuse deterrent? I understand we have one that was approved by the FDA, but that it is not marketed in the United States.

Is that correct?

DR. MEISEL: RoxyBond is on the market.

MR. O'BRIEN: But RoxyBond is not marketed the United States. It's only in the --

DR. MEISEL: No, no. It's available.

DR. HERTZ: No. It's approved -- at the time the data were collected, it hadn't reached the market yet.

MR. O'BRIEN: Oh. My background material says it was not marketed in the United States.

DR. HERTZ: Yet, as of October.

DR. STAFF: Right. This is Judy Staffa. As of October 17th of this year, which is when we looked at dispensed prescriptions, there were none for RoxyBond.

MR. O'BRIEN: Okay. As of October 17th

still. It's still not in the United States.

DR. STAFFA: Correct.

MR. O'BRIEN: So as we know, we currently do not have a similar type product in the United States for patients. Is that correct?

DR. HERTZ: Yes, in this context.

MR. O'BRIEN: All right. Thank you.

DR. BATEMAN: Additional comments on the interpretation of the human abuse studies via the intranasal route. Dr. Zibbell?

DR. ZIBBELL: John Zibbell, RTI, Emory. This is complicated stuff. I'm going to try to put my thoughts out here. In my career, I actually do research among people who misuse drugs and abuse drugs, mostly opioids and illicit medications, but also prescription medications. And I've spent the most of my career hanging out with social networks of people using drugs. I feel like I have a pretty good grasp of the motivations and the behavioral aspects of the dynamics of misuse and abuse.

I'm coming at this from a public health point of view and not a clinical point of view, and

I kind of want to put some terms out. In the public health world, we often think about primary prevention versus secondary prevention. And if you think about that with addiction, primary prevention would be stopping someone from starting in the first place. You don't want them to start; that's the primary prevention.

Secondary prevention is if they're already started, and they're already dependent, and they're already addicted, how do you prevent all the other stuff to kind of come downstream, all the harms, infectious disease, overdose, stuff like that?

So it seems to me that the majority of people's initiation to opioids are oral, and I think the data is pretty clear on that. This medication wouldn't prevent that at all. It has nothing to do with primary prevention, so for me, the question is secondary prevention. What are people who are already dependent on these drugs, getting these drugs and misusing them?

I was part of the Scott County HIV investigation, and a 100 percent of those people

using were all physically dependent and were using for a long time. I didn't meet any recreational users that were just using, so that's the population.

The other part of my research is looking at transitions from oral use, to insufflation, to injection. And what we find is that people take oral medications, and then they become tolerant. And that's what opioids do; they create a tolerance, and then you don't get the same feeling that you do with repetitive use. So you kind of have to take more and more to get the same effect, and there's no ceiling there. That's why opioids are so dangerous.

So what happens is people orally take these medications, and then they have to get a tolerance, and they get a physical dependence. So there's an incentive to switch a route of administration. It's not that I just want to switch; it's that I have an incentive. I'm going to get 40 percent bioavailability from oral use, and I'm going to get 80 percent from snorting, so I'm going to snort

them.

By this point, I'm usually physically dependent. So echoing Dr. Fischer, I'm already dependent, so I have an incentive to transition. And then I'm going to be insufflating for a while, and I got the tolerance there as well. And then some people will transition to injection because you're going to get a hundred percent of the drug now and there's incentive to do that.

So my concern here is that the population that I know, in a large population of people that are going to misuse and abuse this population, if they're physically dependent, I do not think that irritation of the nasal is going to prevent that use. That's my concern. I think in recreational users, if you feel bad, and you don't have a habit, and you just use for fun, and it's not a big deal, then you can be like, "Oh, that feels bad." But if you're physically dependent, if you're addicted to opioids, you are going to use over a nasal irritant. And the best evidence for that is the strong literature that shows people using in the

face of harm.

We know that people use drugs with abscesses. They'll let abscesses on their arms until their arm's falling off, and they're still going to use because you're addicted, you're in withdrawal, et cetera. So the drive to use and insufflate and inject is really great. So my concern is that the majority of people that are going to misuse are a large population we have in the United States who are physically dependent on opioids, and the nasal is not going to prevent that transition.

I just wanted to kind of put a public health thing on that and address your concern.

DR. BATEMAN: Okay. Other comments? Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. It was concerning to me that the data presented by the applicant, or the sponsor, and the FDA came to such, to me, startling different conclusions. I noted it in the background information, but it was even more clear today. There are a lot of reasons

to argue about the nasal, that I would say that it's not abuse deterrent for either nasal or intravenous.

But what I'd really like to say is that given that there is no abuse deterrent in this drug when abused by the oral route, and that the oral route is by far the most likely route for accidental misuse and/or entry level recreational use leading to addiction, I'm not impressed that it may or may not abuse with the nasal or intravenous route.

Addiction starts at the oral routes. And until it's managed by some means, we're not getting anywhere. We need to manage it by adding an aversive agent that accumulates if you take too many pills: limitation of availability; addressing mis-prescribing; shared dispensing records; Smart Caps. There are ideas out there, and those are abuse deterrent, and they are never presented.

This is my seventh meeting on abuse deterrent, and never have I heard anything significant about stopping abuse at the oral level.

So that's why I think. There you go.

One more thing. Sorry. The testing I thought was very thin and unconvincing, a cohort of 32, a cohort or a 12. I don't care if the FDA has set the bar too low, we don't have to accept that. So I don't mean to get overly passionate here, but I think that we've been accepting research that just isn't stringent enough. And if we don't speak up and say that we need better, better information, higher bars, new ideas -- all through the FDA guidelines, it says people are not to be held to the standard that approved the last drug. They're to be making progress in ADF formulations, so let's see some progress.

DR. BATEMAN: Thank you. I think several people on the committee have raised the question of whether the abuse liability study is relevant to opioid-dependent patients, maybe the population that's most likely to insufflate. But they did show data that suggests that take drug again and overall drug liking was significantly reduced amongst recreational users.

So maybe people can comment on the relevance of that. Is that a target population that's relevant to this question of abuse deterrence? Dr. Shoben?

DR. SHOBEN: Thanks. So that is actually quite timely since that's what I was hoping you talked about before. A couple comments; one is like, yes, we need better products, and, yes, like I think everyone wants to reduce the -- stating the obvious, but everyone wants to reduce this risk of opioid addiction and the consequences of opioid addiction, but I think that we need to step back and think about these incremental improvements and can this be, at least potentially -- I think the wording is actually quite relevant to say, can it be expected to deter abuse; is there sufficient data to go forward without doing the kinds of large really postmarketing type studies that would allow us to determine that more definitively.

The abuse potential studies I think actually are quite relevant, particularly for nasal since this is potentially a population that would benefit

from the kind of abuse-deterrent formulations. So these who use them for fun, and maybe they heard that using a nasal, the insufflation would be more exciting and better and produce a better high. And if that is going to deter them, as we saw with the take drug again and the overall drug liking, then that would perhaps meaningfully deter abuse in that small population.

I certainly agree that people who are already opioid dependent, probably not that relevant; a half an hour of nasal irritation is going to deter them, but that's not necessarily the population that we should actually be most focused on in terms of at least initial deterring abuse.

DR. BATEMAN: Dr. Arfken?

DR. ARFKEN: I am concerned about the public health aspects of it. I agree about the human abuse potential and using recreational. I've seen it done multiple times. It's the first step in assessing it. My concern is the FDA finding that it would be possible to inject it, and I am very nervous about supporting any application --

DR. BATEMAN: We're going to talk about intravenous in the next phase, but additional comments on the nasal route of abuse.

DR. ZIBBELL: I've got one more. Sorry.

DR. BATEMAN: Sure, go ahead.

DR. ZIBBELL: I think there's someone down there what was before me. John Zibbell, RTI, Emory. I was kind of struck that we have a group of recreational drug users, but no one was like, "Oh my gosh, I would never do this again." So when I look at the data, it seems like, yeah, it's an irritant, and people are like, "Um," they were kind of neutral on it.

So it seems to me that the irritant is a weak abuse-deterrent choice, and I think maybe it should be re-thought to be -- and this is beyond the scope of the panel probably, but to be an agonist/antagonist model or thinking of another form. Because like I said, if people that are recreational users are neutral -- and it was that first 25 minutes, which makes sense -- it doesn't feel bad -- but then you get the same kind of high,

seems to me that's not really going to deter; maybe that small group that Dr. Shoben talks about, but I'm thinking of the large public health effects, and that's a small group.

So I just think it's weak as an abuse deterrent, and I think the data kind of shows that, in my opinion.

DR. BATEMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I agree with Dr. Goudra. I find the data convincing, and I feel like it is demonstrated to be just too difficult to physically and chemically abuse. I appreciate the 1-hour delay. I can't speak to what Dr. Seibel has -- with respect to his knowledge of abusers and whether that would be a deterrent, but to my mind, it seems very daunting to work really hard for at least an hour to achieve some sort of result. So I believe it's likely to deter, and I find that data convincing and sufficient.

DR. BATEMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: The way I was thinking about this question is that it would probably deter

abuse for this particular product. And I think because of the short-term effects, probably it could deter from abuse of this particular product. But I think we are trying to now answer a different question; is this going to deter abuse for opioids overall, and is it going to reverse the opioid epidemic or help to do that? And that I think is speculation on our side because we don't have the data.

So that's where I'm struggling answering the question. I think there is data to support that because of that initial adverse event is going to deter abuse for this particular, for the nasal route. Is it going to deter abuse from opioids overall, from erring? Probably, we don't know.

DR. ZIBBELL: I'm going above protocol, but I wasn't arguing that. I was arguing this product. Yeah, I don't think it will. I think it's a weak nasal.

DR. BATEMAN: Dr. McCann?

DR. McCANN: I think what I got from the data is that if you really want to get high

quickly, you should just chew a couple of tablets. And that if you contrast that with taking it nasally, from my review of the data, I'd much rather just chew a couple of tablets.

So to me, it really is a deterrent because it's unpleasant, and I would go with Abby, that a dependent person, whether you're dependent on alcohol or whatever, if they can't get ethyl alcohol, they'll go to isopropyl or methyl alcohol. I mean, they have to get their drug no matter how many hoops or frustrations you put in front of them. So I do think that the formulation, both nasally -- and we're jumping to intravenous, but that they really have shown that this would be a deterrent.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: Just a quick note of about how weak is this nasal irritant. If you look in the labeling -- actually it was included in the FDA briefing document -- we've actually approved -- not to say this should be the standard, but certainly there have been approvals for drugs on abuse

deterrent by the nasal route with sufficiently higher drug liking and take drug again compared to placebo.

So the fact that this was numerically less and certainly statistically much more similar to the placebo gives me actually confidence this is probably a stronger nasal deterrent than some of the ones that have been previously approved.

DR. BATEMAN: Dr. Green?

DR. GREEN: I have concerns about repeated use by nasal route of the medication with aversive agents; that we lack data from RoxyBond in humans in this country with information about that. And the current Roxicodone product does not have this addition in it, so we lack the ability to know on a population level what that would do to the health consequences of people who are using by insufflation. So I think that's a concern.

But I think also looking at the data presented today, that I do think that with the folks who were using primarily by oral routes, they'll continue to chew or to swallow, to crush,

and to take orally, and they'll just hover there. But the folks who are currently snorting with a push towards -- they won't wait the half hour. They'll move more to the solubility and syringeability data that we saw, very strongly suggesting that injection of this medication is viable.

So if you can get through that first 15 to 30 minutes, the reinforcing effects of Roxicodone, which is incredibly pleasurable, will be placed into the brain and propel continued use towards dependence. So this is a concern, especially with the aversive agents not knowing on a population level what would happen to -- and given the lack of negative attributes associated with the overall effect of this drug, that the calculus is leaning towards concern about the nasal route for me.

DR. BATEMAN: Dr. Prisinzano? Is that right? How did I do?

DR. PRISINZANO: Now you know the other reason I didn't put my thing up faster in terms of the last name.

(Laughter.)

DR. PRISINZANO: So it's Prisinzano, like the place you don't want to go.

(Laughter.)

DR. PRISINZANO: I guess at least in terms of my thinking about this particular aspect, I'll use an analogy. I think we would all argue that a home run is more fun than a single in this particular case, and I don't think we necessarily have to have a home run the first time out of the gate or a single would be acceptable. And I think from the data that's presented at this particular point, it provides an advance from the abuse-deterrent possibilities for some population, which is better than what we have now.

DR. BATEMAN: Other comments?

(No response.)

DR. BATEMAN: Okay. So I'll summarize our discussion briefly on this point. I think several on the committee thought that there was an expectation that MNK-812 12 does have some properties expected to deter abuse via the nasal

route based on the human abuse studies that were performed, particularly the data regarding take drug again, the delayed time to Emax, and nasal irritant effects that were reported by users.

There were some concerns voiced that people who are highly dependent on opioids or that are seasoned abusers may be willing to tolerate these aversive effects and continue to use it via the nasal route. But several on the committee voiced the opinion that although this is an incremental improvement, it's not a home run and it's not going to eliminate a nasal abuse, it was a step in the right direction.

Is that a fair enough summary? Any comments to add?

(No response.)

DR. BATEMAN: Okay. So we'll move on now and talk about the intravenous route. Comments regarding whether MNK-812 is expected to deter abuse via the intravenous route. Mr. O'Brien?

MR. O'BRIEN: Well, it seems clear to me, with that evidence that the FDA gave, which I still

don't know, it's kind of secretive, but they have brought something and done something, that it says they clearly can get 90 percent out. So to my mind, no, it doesn't deter intravenous if that's the case.

I haven't heard anything from the sponsor refuting that, so I have to go on that. And based on that tells me -- I see the other data that tells me with an hour's work, yes, it can be done, but it's going to take an hour, but they seem to have something that's relatively quicker and easier.

DR. BATEMAN: I think the data the FDA presented suggested that it was about an hour long process to thermally treat the medication, dissolve it solvents; several stops in order to extract 60 to 80 percent; whereas Roxicodone could be extracted in 10 to 15 minutes. So there was a difference there. Maybe people can comment on those data.

MR. O'BRIEN: Just to that end, I would switch it, both nasal and intravenous. There is clearly evidence that Roxicodone is not better than

what's being presented; so if I reverse the question.

DR. BATEMAN: Okay. Dr. Meisel?

DR. MEISEL: Steve Meisel. I'm going to agree that the data on intravenous deterrence is weak at best. And if somebody is intending to do this -- the FDA was able to do this within an hour in 30 mLs -- it sounds relatively easy -- I can guarantee you within 3 months there will be websites with techniques that are a lot more efficient than that. If it's somebody's intent to do, they're going to do it. If you're the 16 year old stealing mom's oxycodone and trying to do it at home for the first time, is it going to be harder? Yeah, but they'll figure it out. I think the deterrence here is going to be temporal and not in terms of magnitude.

DR. BATEMAN: Dr. Zibbell?

DR. ZIBBELL: John Zibbell, RTI, Emory University. Yes, FDA does say 15 minutes for Roxicodone, but I've seen someone do it in 2 minutes, and it's actually pretty easy to do, so

an hour might be questionable. But I agree. I think the intravenous data is weak. And when you combine the two -- and maybe I have a little PTSD from Scott County, Indiana, but when you combine the two, it kind of sets up jumping the nasal route and going right to intravenous, like we did see with Opana ER.

So if it is an irritant and you're already down that kind of physical dependency abuse teleology, then I could see the intravenous risk being heightened because of that, and with that, the public health effects of all the injection-related harms. So I think when you take the weak intravenous data and you combine it with what I believe is a weak deterrent for nasal, even so, if we take people's argument that it is as strong, then there's an incentive for me to jump to intravenous because you're able to at least do it. It might take a little time, but there's de facto chemists out there on the street that can do it pretty quickly, according to Dr. Meisel. Those are my comments.

DR. BATEMAN: I think it's pretty clear that it's harder to extract the drug and turn it into a syringeable form compared to Roxicodone. I guess the question is how much harder does it need to be to truly be an abuse deterrent? So maybe that's something we can comment on. Where does that bar need to be set? Dr. Fischer?

DR. FISCHER: I think if we think forward on the consequences, I think your point's well taken. But at least if I understand the plans that are being put forward, that's actually not a choice that patients in real life will face. If we approve this, it will replace the existing Roxicodone. So if it is extractable in a reasonably straightforward way, and once it's way out there, it will be on the internet. And if it's something you can do with a tool, you can get at Walmart in solvents that are relatively easy, and it will be out there.

I completely agree that compared to Roxicodone, this is harder to do, but this would presumably -- and I know there are other generic

immediate-release, single-agent Roxicodone out there. But this would replace it.

So I think your point is accurate, but I don't know whether that's the right question in terms of whether this deters abuse well enough given how quickly information spreads about those kind of things. I think the direct answer to your question is, yes, it's harder, but is that the comparison that an individual sitting out in the community who has acquired some MNK-812 and is trying to figure out how they might use it, that's probably not the minute-to-minute decision they're facing.

DR. BATEMAN: Dr. Marshall?

DR. MARSHALL: Yes. Dr. Bateman, Brandon Marshall, Brown School of Public Health. I think the answer to that question depends on the context of what else is available in the drug market in that environment. If you're looking at a situation where heroin and synthetic opioids are freely available and can be cooked up and injected quite quickly, people may not choose to inject this

because it does take an hour to do so, or half an hour.

But if you're in a situation in a rural county with poor availability of heroin or other illicit drugs, I feel like the abuse adherence of this formulation is a lot weaker, and people may take these steps to get through that and do so.

DR. BATEMAN: Dr. Zeltzer?

DR. ZELTZER? Sorry. If I whisper, can you hear me? One of the concerns I heard was that in the 30-milligram dose, that even though it took an hour for breaking it down for IV use, that there would be a public health concern because it would group people together to share a dose. Some might spread HIV or hep C, et cetera. In fact, from other drugs, are there data to support that fear?

DR. BATEMAN: Does someone from the FDA want to comment on that? I guess the question is, does the fact that large volumes are required to easily extract the medication raised the concern that it's going to be something that's shared between intravenous drug users, and are there data to

suggest that pattern for other medications?

DR. HERTZ: This is Sharon Hertz. The Opana ER experience has given us pause when we see a product that may have nasal deterrent effects but may be suitable for injection even with some effort. And then if it takes either a greater volume -- well, if it takes a greater volume to get the product into the right form, yes -- and that's what we saw with Opana -- then there may be sharing behaviors that then lead to outbreaks of infection.

Everyone wants these absolute standards, and that's very hard for us to do. We don't know what the right answer is. Is good enough? How much do we have to worry about the unintended consequences that we saw with Opana, and are we going to be driving that kind of behavior here? These are the reasons why we need your help.

DR. BATEMAN: Dr. Fischer?

DR. FISCHER: Just to try to clarify, this is more just a quick clarifying question. Am I understanding the analysis right that the small volume, the data that was presented an hour or so

with some kind of mechanical assistance to crush it, and the 60 percent availability, that was a small volume. And then the larger percentages was the large volume. But it is possible to extract this with the small volume as well, just because I think we're conflating the two. And I wanted to be clear that I'm understanding which data are which is as we discuss this.

DR. HERTZ: Yes. And I'm looking at Valerie Amspacher.

Valerie, do you want to speak to that?

DR. AMSPACHER: Hi. This is Valerie Amspacher. So what we saw with the small-volume extraction was we could get 60 percent extracted. That was the maximum we saw. But there were probably 5 conditions that we saw at least 50 percent extracted. So then when you move to the large volume, the 30-mL volume, 14 different solvents were tested, and these are common solvents that you're going to see frequently used for abuse. We would regularly see 80 to 90 percent extracted with the 30 mLs, the large volume.

MALE SPEAKER: [Inaudible - off mic].

DR. BATEMAN: I guess not, not at this point.

Other comments on intravenous? Dr. McCann?

DR. McCANN: I don't know if I'm going to be clarifying your point for you, but I thought the point that was made was that this drug is fairly bioavailable orally, so that if you took a pill and you put it in a large volume, you really wouldn't get much benefit at all if you shared it. You'd want it all for yourself, whereas with Opana, it was not particularly orally bioavailable. So once you got it into an intravenous form, you actually had extra to share.

So I think there's a different behavioral dynamic that we have to consider when we're looking at large volumes. And yes, somebody might share, but I don't think there would be the word out in the street that you've got so much stuff here you can share with your buddies.

Am I right?

DR. HERTZ: This is Sharon Hertz. I would

like to see if anyone on the committee would like to comment further on whether there is potential for sharing a 30-milligram dose. I think if it was just available as a 5, perhaps that's not really suitable for sharing, but I'm not sure about the 30.

DR. ZIBBELL: John Zibbell, RTI, Emory University. How I see it, it wouldn't be you would take one pill and you would put it in a 30-mL solution, and you get 1-milligram per mL. I think my fear would be you would put multiple pills in there. So what you can do is you put multiple pills, and now you're getting a 30-mL solution. The equivalent would be if you had a 5-mL solution and there was 60 percent, and everybody had a 1-mL syringe, you could share, and everybody would get 8 mLs; wouldn't you think?

DR. BATEMAN: But if you're extracting more pills, you probably need more solvent, just proportion it.

DR. McCANN: You'd need 150 mLs, right?

DR. ZIBBELL: I don't know.

DR. McCANN: But isn't that what large-volume extraction is? You need X amount of volume per pill? So if you put 10 pills in, you need 10 times the volume. But people could do that. They can make a pitcher up -- I mean, I didn't think of that. But they could make a pitcher of it up, and then share that.

DR. ZIBBELL: But if you took a 30-mL pill and you put it in 5-mL solution -- this is what happened in Scott County. They were using Opana ER, and instead of 1-mL syringes, they used 2 mLs of water, let's say. But they were using 1-mL syringes to inject. So now you had a 2-mL solution, and they would split the solution, and that's the sharing. So I think the concern is if you have a larger solution, there's more available to share. And people will share even if it's just 5 mLs.

DR. BATEMAN: But of course the same could be said of the generic formulation, right?

DR. ZIBBELL: Yes.

DR. HERTZ: Wait. I don't think it was the

same for the generic formulation. And by generic, I'm going to qualify for the non-abuse-deterrent formulations that are currently marketed. Valerie is here to clarify some of this, but also could you please clarify what the volume used for the comparator was to get the 60 percent or more out?

DR. AMSPACHER: Hi. This is Valerie Amspacher. I just wanted to make one point about 30 mLS of solvent. Technically the testing that was done was one 1 tablet in 30 mLs of solvent. There was no testing done on 2 tablets per 30 mLS, or 3, or 4, or 5 tablets per 30 mLs. So technically, we don't know the answer to that question. I'm sorry, but there's nothing to suggest that you can't put 5 pills in 30 mLs and extract a lot of oxycodone.

As far as the Roxicodone, that extractability was 90 -- actually, it was probably 80 percent in the small volume. And I'm drawing a blank on the large volume, but I would go with 90 percent.

Oh, actually for the large volume -- sorry,

it came back. I would say for the large volume, you would get a 10 or 20 percent higher recovery from Roxicodone versus MNK-812 in the 30-mL volume. So it would depend on the solvent. Sometimes you'd get 10 percent more Roxicodone. Sometimes you'd get 20 percent more Roxicodone because the extractability for the MNK-812 was already 80 to 90 percent for many of the solvents and 30 milliliters of volume.

Does that make sense?

DR. BATEMAN: Just to clarify, when you add more tablets, for example, to a 30-mL solution, you're starting to approach the proportions used for the small-volume extraction study. Am I understanding that incorrectly?

DR. AMSPACHER: I would say we can't answer how many tablets you can add before you start limiting solubility because we didn't test it. I apologize. I don't have a better answer.

DR. BATEMAN: We'll get some clarification there, and then the sponsor wanted to clarify this particular question.

DR. PINTO: Hi. This is Julia Pinto, FDA. To put it into perspective, with the small-volume extraction, it was a 30-milligram tablet that was extracted with 5 mLs. So we got 60 percent of 30 milligrams out in 5 mLs, which is about 18 milligrams. So if you compare that to 30 milligrams, in 30 mLs, that would imply that you can definitely solubilize more than 1 tablet in 30 mLs. But to your point, yes, at some point you will reach a saturation. We don't know what that point is, but from the comparison of the 5 mL to the 30 mL, it's definitely more than 1 tablet.

DR. BATEMAN: And the sponsor wanted to provide some clarification on this.

DR. SCHLICHER: Appreciate the opportunity to clarify. So the distinction there in the case of the small-volume extraction is that's undergone thermal treatment to break down the excipients to allow it to be extractable. In the case of the 30 mLs, remember that's the requirement an IR opioid must meet in order to be immediately available.

So we are able to -- as Dr. Bateman said, is we add a second tablet, you now have to increase that volume or you're going to get the gelling properties because we haven't broken down the excipients. So you can't just keep adding tablets to the 30 mLs, you need to double the solution in order to be able to do that. So that concentration largely remains the same, of about a milligram per mL for an injection in contrast to what was discussed here, where today with the current Roxicodone, that would be 30 milligrams in a mL or two.

So 30 milligrams in a mL or two, we're comparing to 1 milligram per mL in the large-volume extractions. To me that's clearly deterrent.

DR. HERTZ: This is Sharon Hertz. But my understanding is our experience with Opana shows us that people quite readily will heat-treat or pretreat. And I'm looking at Dr. Zibbell based on his experience.

DR. ZIBBELL: John Zibbell. Yes, they will. They actually bake it, and cook it, heat it up, and

then they actually heat the solution as well; so heats from soup to nuts.

DR. SCHLICHER: Yes. And I think that takes us back to the small-volume extraction conditions and also the reminder, the motivations are very different because the differences of bioavailability of the two, where oxycodone is readily bioavailable in the tablet form, and there's not that motivation.

DR. BATEMAN: Okay. Thank you. Dr. Zibbell?

DR. ZIBBELL: I'll follow up there. Thank you for that, that's really helpful.

I also just want to state that the gelling mechanism is the reason why you need the solution. So if you crush up a pill and you add 1 mL of water, it just turns goopy, with the hydroxyethyl cellulose. It's kind of like stuff in a diaper, so it turns into a gel.

All you have to do is over-hydrate the cellulose, and you don't need 30 mLs of water to over-hydrate the cellulose in 1 pill. You could

absolutely put 2, 3, 4 pills in there because 30 mLs of water is a lot of water. So it's very easy to over-hydrate cellulose. So I just want to make that clear that from my experience, you could put many pills in the 30 mL and make a solution if you wanted to.

DR. BATEMAN: Dr. Fischer?

DR. FISCHER: At the risk of being a little pedantic about which thing we're discussing, it seems like the smaller volume piece and some of the -- maybe if you do a larger volume but don't get as much concentration of drug per mL, it sort of speaks to this question about -- but the smaller volume really speaks to this abuse deterrent. I think we're supposed to in a minute turn to the public health impact. I think it's where the Opana example comes up. If you get a very concentrated solution, that people are going to share, and that might have sort of a knock on public health effect with all those other consequences.

I think that's a distinction here. We're thinking about does it deter abuse for which can

you extract it into a small volume is really important versus if there's the potential for these public health disasters that you can get when you can make a very concentrated solution. I think those are actually two different questions, which is why I was asking for that clarification before.

DR. BATEMAN: Okay. Any other comments about the intravenous route of abuse?

(No response.)

DR. BATEMAN: I think the committee's discussion regarding the intravenous abuse potential pointed to the fact that there's concern that the abuse-deterrent properties can be overcome with readily available methods and solvents. There's perhaps some disagreement regarding where the bar should sit in order to label something as abuse deterrent via the intravenous route. There was some concern voiced that if people move towards larger volumes for extraction, that may lead to sharing that may have important public health consequences.

Any other points to make on this issue?

Dr. Perrone?

DR. PERRONE: Jeanmarie Perrone. We're doing a lot of research with social media, and it does seem that even today, you can quickly look on Reddit for the exact recipe of all those different solvents and all those different ways of solubilizing and overcoming all of these barriers. So the fact is, whatever the abuse-deterrent formulation might be that can get as close to 80 or 90 percent extraction, that's the one that's going to be out there when it's released.

DR. BATEMAN: Thank you.

So we'll move on to discussion question number 2. The applicant is requesting approval of oxycodone hydrochloride, immediate-release tablets. MNK-812 is an analgesic with properties expected to deter abuse by the intravenous and intranasal routes.

Discuss whether you have concerns regarding the impact of this oxycodone hydrochloride, immediate-release product on public health. Take into consideration its potential effects on the

abuse of opioids, including oxycodone, as well as potential consequences of administration of this product by unintended routes.

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

DR. GREEN: I have a question.

DR. BATEMAN: Okay. Dr. Green?

DR. GREEN: Just with respect to the word "abuse of opioids" is that inclusive of illicit opioids or just the prescribed medications and compounds?

DR. BATEMAN: So I'd say maybe start with the prescribed medications, but then if you have comments regarding opioid abuse overall, we can take that into consideration. Dr. Zibbell?

DR. ZIBBELL: Sorry. I was going to wait, but no one else did, so I'll go. Yes, I have two concerns. One would be we know from the literature that the sharing of paraphernalia equipment for insufflation can lead to the transmission of bloodborne pathogens, specifically with the

irritation of the nose and blood. So people are using straws or tubes to snort medication. If this is irritable, I'm not sure if repeated use does compromise the nasal mucous membranes and lead to blood being there, and then the sharing of a straw or something to exchange blood. That's my first with the nasal.

For the intravenous, I have a concern that's analogous to Opana ER, that if you have a larger volume solution, it sets up so people can share the solution. In a lot of areas, people are really poor and really struggling, and they often pool money together to buy drugs. And when pool money together to buy drugs, you share drugs.

So the sharing of the drugs, so having a larger volume solution rather than a half a mL, 50 ccs or 100 ccs for one injection, having 5 mLs allows potentially 2, 3, 4 people to share, even if each dose is 3 milligrams, because people are sick and people are going to do it. So I have the infectious disease issue with both the nasal and the intravenous.

DR. BATEMAN: Dr. Fischer?

DR. FISCHER: On the public health point, on Dr. Zibbell's point, it seems like that concern that was raised about sharing or people pooling their resources isn't any different than what could happen right now with any of the formulations that are available. That seems like it's one where it's not necessarily any better or worse; whereas Opana, as I understand it, allowed for much more concentrated solutions, this would be similar to a lot of what is out there, from a public health lens as opposed to the individual patient lens that we were talking about in question 1.

But for the actual public health comment I wanted to make is my concern about this in terms of the public health is what might happen if we take a -- and it goes to some of the misperception concerns, recognizing that it's stated in documents, the company says they're not going to go out and promote it to clinicians as sort of the non-addictive oxycodone.

Nonetheless, if we replace a big fraction of

the market share of the immediate-release oxycodone with this agent, I do have a concern about how the perception will spread in a clinician population that are all looking for a quick and easy solution to what do we do about prescribing opioids in the current environment, that there will be a perception of this is the safe one; we can just go ahead without thinking about it too much. And that's a public health concern that we need to weigh.

DR. BATEMAN: But oxycodone is very widely prescribed, so what's being discussed here is replacing an oxycodone preparation that has no abuse-deterrent properties with one that has perhaps some. So I think that's something we have to weigh and maybe people can comment on.

DR. ZIBBELL: There is a difference between the Roxicodone instant release and this one, and it's the volume of water. And for me, that's the public health risk because the instant-release Roxicodone, you can use a mL of water for a 30-milligram pill, and the water sits on top of it;

it doesn't turn gel. That's the instant release. That's why injectors like it because you can crush it. You put water on it, and it's really easy, and in their words, beautiful to pull up; whereas the gelling, you need more water to override the hydroxy cellulose, and that leads to a bigger solution, which it allows 3 or 4 people to share.

So I just wanted to clarify that there is a difference between the two.

DR. BATEMAN: Okay. Other comments? Dr. Meisel?

DR. MEISEL: Steve Meisel. I'm going to take this in a different tact. We saw earlier today the bioavailability data, that although it's, by the book, bioequivalent based FDA's standards, it's about 10 percent less bioavailable than the reference product of Roxicodone. I don't know if that's clinically relevant or not. And as one of the public speakers mentioned, there's been no efficacy data at all on oral oxycodone going back for 30 years.

But if it were clinically relatively

different, from a therapeutic point of view, a patient is going to -- instead of taking 10 milligrams, they think they're getting 10 but they're really getting 9. And now it doesn't work as well, and when it does work, it's going to be a half an hour later in terms of a peak, they may be more inclined to take more. And if they end up taking more, that could increase the number of milligram equivalents that are consumed, which then adds to the opioid problems in a different way.

That's something that's strictly speculation; we just don't know. But I think assuming that these are bioequivalent because they meet the 80 percent rule, even though they're statistically less bioavailable than the reference product, may have unintended consequences that we haven't thought of and we're not prepared to study whatsoever.

So I just want to keep that in mind, that there may be some impact on the number of milligrams consumed therapeutically, which then of course has impact for abuse and misuse down the

road.

DR. HERTZ: This is Sharon. I just want to point out that those are the criteria that are established and used for generics as well. So it's a standard that's out there and used. Even if the company itself was going to make changes internally and needed to conduct a new study, that would be the same set of criteria for showing that the product could still continue.

DR. MEISEL: Oh, I understand that, and that's true with blood pressure medicine and all sorts of other things as well; I get that. But just because those criteria are there doesn't mean that they don't have clinical impact.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Dr. Goudra, Penn Medicine. I made some points. One, think Dr. Fischer mentioned it that clinicians might be drawn into a false sense of security with this and might start over-prescribing. So there is always that risk.

Second, if the drug is as effective in terms of deterrence, people might start looking for

street portions, which could be a much worse thing.

Third, people might start working ways to decrease the nasal irritation. I don't know. For example, if they just institute some local anesthetic drops, would it be just a simple method enough to decrease the irritation? What will happen if you use a vasodilator, a nasal vasodilator or just a vasodilator in general? Then is the nasal -- would it increase the absorption?

So as a result, it's kind of unknown what exactly it's going to be. In fact, I think the one which I'm most concerned about is the very fact it decreases the chances -- used nasally or intravenous might just increase people to seek drugs, which I think are available and plenty by unscrupulous traders. Thank you.

DR. BATEMAN: Ms. Robotti?

MS. ROBOTTI: Most of the specific points I wanted to make were made better already by others. I would just like to say that I feel like without addressing the primary route of abuse, we're trying to hold a tiger by its tail. And I would like in

future meetings to have some address of oral abuse addressed in some way. And I say that again so that maybe it will make into the comments this time. Thanks. Bye.

DR. BATEMAN: Dr. Green?

DR. GREEN: Traci Green, Boston University. I think I'm looking to our recent history and also my work with the high intensity drug trafficking area and CDC, and some of the data, the DEA drug threat assessments that have been placed into the public literature, to think about the important complications of fentanyl and earlier on, on heroin, and specifically with respect to counterfeit medications and the rise of counterfeit pain pills that contain fentanyl.

When we look to the history of OxyContin and its abuse-deterrent formulation change, we saw counterfeit OxyContin pills, the OC, created pressed with heroin, and then very quickly soon thereafter pressed with fentanyl. In my neck of the country in New England, the most commonly obtained and recognized counterfeit medication is

the Mallinckrodt 30, the oxycodone single-entity immediate release, and it has a very important place in the community currently of people who use drugs and the people that I research and work with.

So I think that we should consider not just the implications on the people who have pain, and the people who use drugs, and the providers, but also perhaps on the illicit marketplace as part of the conversation of the public health impact and what it may mean.

By this, one of my concerns may be is the already established counterfeit market for oxycodone single-entity, immediate-release counterfeits with fentanyl may actually increase as people seek those that actually can be crushed and snorted as opposed to those that are not currently soluble or may be hard to -- and create an irritant; so to consider those possible complications.

The other thing I think that we see in conversations with people who use drugs is the important place, ironically, that the current

Roxicodone products are playing, those that can be obtained either through the prescriber or on the street, in terms of protecting people from fentanyl exposure.

There's actually kind of a renaissance, in many respects, to try to avoid fentanyl, and of course, we don't have enough treatment slots. We don't have enough beds and chairs to care for people with opioid-use disorder further along in their severity of addiction; but the importance of thinking about the current marketplace as also one that has its protective features, both from counterfeits and from further fentanylyzing, if you will, in rural places in particular and suburban locations that don't yet have a fentanyl or heroin presence but that may have a reason to switch in this instance, lacking the ability to continue to snort or protect themselves from fentanyl That's a concern I have.

DR. BATEMAN: Okay. Other comments?

(No response.)

DR. BATEMAN: I think the committee, there

seemed to be some agreement that medication does have an impact on intranasal, or has the potential to have an impact on intranasal abuse; perhaps less so with intravenous. So are we concerned about a shifting in utilization patterns away from intranasal towards intravenous? And that was raised in some of the comments during the public session as well and as part of the story around Opana, that it's more difficult to adjust nasally, so people switched to using them intravenously.

Is that a concern? Do people want to comment on that? Mr. O'Brien?

MR. O'BRIEN: Well, I guess it's just the -- I'm sitting here thinking, it's just the opposite. We don't know -- you're only dealing with one side of the equation. Yes, there may be more people that switch, but we don't know how many people do not go to that next level, and do not have an overdose, or do not have a death. We don't know the positive side. We're looking at all the potential negatives that may in fact happen, but we don't have any data or any discussion around the

potential positives that in fact we heard in some of the public discussion that's there.

There are clearly a lot of positives by doing it and taking a current product that is very easily adaptable, a hundred percent, and you could do this and do that. And now you're going to provide an abuse deterrent, at least as a beginning product, but we have no data to do that.

So the conversation seems to be a one-sided type effect. In terms of the positive benefits in public health, the positive benefits, if there's one life saved and if that's my family, I'm very happy with that, and that's a good positive public health.

DR. BATEMAN: Does anyone else want to comment on the potential benefits of the substitution of this formulation?

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Other than the concern about the potential move from nasal to intravenous routes, I think we are discussing in general whether deterrence of abuse are going to

potentially improve the situation. I think we should be using in the country a tenth of the opiates we are prescribing. I'm not promoting opioid use, but within the current context, do we think that having abuse deterrents in our product is going to improve, or are we concerned from a public health point of view that things are going to get worse?

Other than the specific problem with perhaps going into intravenous use, we are putting into question that using the deterrents might actually make things better. Do we think that's the way to go? I think, looking for consistency, if we have more committees, I think we are questioning that.

DR. BATEMAN: Dr. Marshall?

DR. MARSHALL: Brandon Marshall, Brown School of Public Health. My primary concern with these products -- and this is where I think we need studies so desperately to inform this, is the effect of these formulations on prescribing behavior. We can imagine maybe a 20 percent reduction in diversion and abuse due to this

formulation that could be completely offset by a 25 percent increase in inappropriate prescribing due to misperceptions of the safety of the ADF formulation in the prescribing community.

So without seeing that data, I suppose it's speculation. So that's I suppose a call for those studies. That's what I would like to see.

DR. BATEMAN: Dr. Perrone?

DR. PERRONE: Jeanmarie Perrone. Well, I'm going to definitely agree with Dr. Marshall because that was part of my point. But a lot of the literature just shows how incredibly variable opioid prescribing is, and there's a recent study that we published about opioids for ankle sprains.

I think most of us would think that that's a ghastly idea. But the variability in patients being seen for ankle sprains was 2 to 40 percent of patients getting opioid prescriptions. And that's just exactly where you would tip the iceberg, where someone's facing a patient where they could have the difficult question of an NSAID versus an opioid, but then they think, oh, let me go for that

safer opioid, and if the patient has insurance, maybe it's not an issue of cost even if it's a higher priced item.

So I think we haven't really capitalized on the subjectivity of opioid prescribing yet and the face to face a clinician is coming up with in every single patient when we have this. We have vague guidelines. Everything is so variable that I really just want to overemphasize Dr. Marshall's point and some of the other people's points, that there is absolutely a huge risk of increasing opioid prescribing.

While Dr. Diaz and I would definitely agree that we should be prescribing 10 percent of what we're prescribing, this really might cause a crazy shift in the other direction, including people who routinely prescribe hydrocodone may be shifting to this product as well because of this perhaps labeling.

DR. BATEMAN: Just to clarify your comment, is it a question of the way these medications are labeled and the term "abuse deterrence" or is it

the fact that they have these properties? What are the --

DR. PERRONE: I think it's the doctors reading headlines problem, that these things seem like they're safer. And while they might be abuse deterrent, they're not addiction-proof and they're not abuse-proof by the oral route. So clumping them all together into the idea that they're safer is exactly the misperception that's going to get exploded, escalated, all throughout clinical practice.

It's the people who read the subtext who may understand that these are not any safer or maybe a fraction safer, but not to the risk of overprescribing. We have not really clarified our prescribing goals or diagnosis-based prescribing. There's no standards for virtually every diagnosis that gets opioids, maybe excluding cancer.

I'm a frontline emergency clinician. I see every disease, I see every disorder, and if you looked at me and lined up a bunch of my colleagues, everyone would feel a little bit differently about

when we should try other drugs first. So that's what worries me.

DR. BATEMAN: Dr. Zibbell?

DR. ZIBBELL: John Zibbell. I think one of the things that's hard to wrap our heads around, too, is the population. So when we're asking is it going deter abuse, I guess it would be like among what population, because all opioid users aren't the same.

The sponsor did it among recreational users, so we're trying to weigh the risks and benefits. Are we going to say, okay, this might have a deterrent effect among a small number of recreational users who might not want that, who might not like the nasal irritant, and they might not transition, and weighing that against the million people we have in the United States who are physically dependent on opioids, and whether this will create health outcomes down the road that outweigh -- and it's hard to -- I'm even having a hard time comparing both groups because they're both important.

Back to the Mr. O'Brien's comment before, I think this is still orally taken. So it doesn't prevent someone from initiating an opioid. It prevents going down routes of administration. So that's my thing. I'm looking at the population, so I'm trying to weigh what I think might be a small benefit for a small group; does that outweigh all the health effects that we've seen with previous medications, Opana being one.

I just wanted to share with the group, I think it's important to think of what population we're talking about to deter abuse because it's not going to deter abuse for everybody, and who do we mean? This study is a small group, and can you extrapolate? And that's why I appreciate FDA allowing us to talk about public health effects, and that's new. We weren't able to talk about that before.

So they're so big, and they're so large, and in terms of costs, there are way more costs than the group we're protecting, but it's hard to

compare lives.

DR. BATEMAN: Dr. Meisel?

DR. MEISEL: On that point, just going back to a bigger picture here, we've got guidelines for industry on abuse-deterrent formulations, but we haven't defined the population. We haven't defined the term "deter abuse." We haven't defined the term "sufficient data."

I think more clarity needs to be had, and the agency needs to go back and rethink the model, and the strategy, and all that as to what exactly is it that is intended to be accomplished because every applicant will have a different frame of reference for what we mean or what the agency means by deter abuse, in what population, what situation, in what settings.

I think as we've heard here, the populations and situations are so variant, that you might deter here, but in doing so, you increase it there. So I think it's a good idea that was developed three years ago for the guidance, but I think a lot more work needs to go into rethinking that document and

providing a whole lot more specificity for what the goal is.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: I just want to echo a couple of comments. One is to say that -- well, yes, echo a couple comments, and then give my thoughts on this subject, which is to say we definitely need data at the public health level.

This is the point that I made long time ago, where we were discussing how to evaluate these abuse-deterrent formulations, which is I think the question is really what Dr. Marshall I think was the first one to allude to, which is if you were to implement a scenario where all of the IR single-entity oxycodone was this abuse-deterrent formulation, what sort of impact does that have on that population and how do you compare that to the similar population where everything is not the abuse-deterrent formulation?

That's the question that would really give you this answer about public health concerns and how do you weigh the benefits and the risks at a

public health level. So I would hope that maybe someday we could have data on that exact topic, but until you have that, there's a lot of speculation.

There are high profile examples of where this has led to unintended consequences, Opana being the most obvious, but there's not that same anecdote about the person who was deterred because they tried to crush the pill, and it didn't work, so they gave up. We just don't have that data.

So it's really hard to know how to weigh those two things when one is like this high profile, everybody's talking about it, and the other is you don't even know that it didn't happen because they're not telling you in the newspaper about, hey, I tried to crush the pill and it didn't work, so, hey, I didn't become an opioid user. That's a weird sort of story.

So I don't know how to weigh all those things and try to determine what the future is for abuse-deterrent formulations.

DR. BATEMAN: Dr. Perrone?

DR. PERRONE: Just to echo one more thing,

When we're at that junction of I've tried oral for a little bit and now I want to try nasal, and I only have this ADF product, in places like Philadelphia where fentanyl is ubiquitous, the leap from oral to fentanyl could happen in half an hour stepping outside of your apartment building.

So there's no question that that has to be part of our public health study and likely is already consequence of some ADF formulations that may already be out there.

DR. BATEMAN: I'll try to summarize our discussion of this question. I think the committee was in agreement that it's very difficult to assess the public health impact of a reformulation of oxycodone that's proposed. On the one hand, it may deter some abuse, and it may deter some people who are using the medications orally to switching to insufflating the medication or even injecting it intravenously. But by changing the label, that there may be unintended effects of physicians feeling reassured that the medication is safer than it may be.

Several people pointed out the highly subjective aspect of prescribing opioids the way in which that's at the discretion of the clinician. So by labeling something as an abuse deterrent or having a headline that this is a safer formulation, it may lead to more prescribing.

There was also several people that brought up the point that the public health impact will really depend on the population, and it's going to be highly context specific. There's going to be an essentially different effect on recreational users than on populations that are already opioid dependent, where the changes in behavior associated with the replacement of a non-abuse deterrent formulation with this product may have an impact.

There's also some concern raised about this question around large volumes needed to create an injectable form could lead to some drug sharing. Some people raised the point around the fact that the drug has pretty substantial adverse effects when adjusted via the intranasal route, that that may tip the use towards the intravenous route in

some people.

Any other comments on this point to include?

(No response.)

DR. BATEMAN: Okay. So we'll now take a 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with members of the audience. We'll resume at 3:15.

(Whereupon, at 3:14 p.m., a recess was taken.)

DR. BATEMAN: We'll now move on to the voting questions. We'll be using an electronic voting system for the meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the

vote from the screen into the record. Next, we'll go around the room, and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

Question 3. If approved, should oxycodone hydrochloride immediate-release tablets, MNK-812, be labeled as an abuse-deterrent product by the nasal route of abuse? Are there any clarifying questions or comments?

(No response.)

DR. BATEMAN: Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed. So we'll now move on to the vote.

(Voting.)

DR. BATEMAN: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 12 yes; 5 no; zero abstentions.

DR. BATEMAN: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start on the left with Dr. Arfken.

DR. ARFKEN: I was convinced by the evidence that there is a difference, so I'm not saying it would be the best thing in the world. I like the analogy of it. It's not a home run, but getting to first -- it's not a home run. I'll leave it there.

(Laughter.)

DR. MARSHALL: Brandon Marshall, Brown School of public health. I voted yes. This was an equivocal yes. I was convinced that for a small group of individuals, this may prevent insufflation

of the substance. So therefore, it may have some degree of abuse deterrence by the nasal route.

DR. GREEN: This is Traci Green from Boston University. I voted no. I did not see that there was sufficient data to suggest that it would not be manipulated or insufflated, and that the overall 30-minute effect for irritation was sufficient to reduce and meet the abuse potential concern.

DR. ZELTZER: Hi. Lonnie Zeltzer. I voted yes because I think the questions that were raised of concern are broader questions that the committee and the FDA need to address. And I didn't feel like there was enough negative to penalize this particular product because of the questions that we raised that I think are broader implications in our voting moving forward.

DR. GOUDRA: I voted yes for similar reasons. The question is not one of degree; the question is yes or no. Thank you.

DR. BATEMAN: Brian Bateman. I voted yes based primarily on data from the intranasal human abuse potential studies showing a decrease in

overall drug liking and take drug again. This is not a perfectly deterrent formula, but it's definitely a step in the right direction based on my interpretation of the data.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes because the question was not whether it's going to prevent abuse but whether it is a deterrent. And I think it is less likely that oxycodone alone, without the abuse-deterrent formulation, to be used nasally -- there will be adverse effects at the beginning that I think will make it more likely for the users to take 2 or 3 pills orally given the bioavailability than to use it through this route.

So that's why I thought it was within the deterrent definition.

DR. McCANN: Mary Ellen McCann. I voted yes for similar reasons. I think in some ways, this company had an easy bar because the oral route is so bioavailable that almost any deterrence that they put on it would be truly a deterrent because you could get what you needed taking the drug

orally.

DR. SHOBEN: Abby Shoben. I voted yes primarily based on the take drug again and overall drug liking from the human abuse potential study.

DR. MEISEL: Steve Meisel. I voted no, although if the question were phrased differently, I might have been convinced to vote yes. But the reason I voted no is because I think, although it does have what others have described, some abuse deterrence in some populations, I don't know that it's got an abuse deterrence in the broader population.

The labeling is not going to be that specific. The labeling would not be -- well, in this group, it could be abuse deterrent, but in this other group it may not be. You're not going to get to that kind of fine tuning on a labeling, and even if you did, nobody would read it. But if we were, I do think it does have some abuse-deterrent properties for intranasal use, but only in a small population of potential users.

DR. ZIBBELL: John Zibbell. I voted no. My

biggest concern was the small population, and I thought the risks outweigh the benefits to that small population. I was also not inclined on the data of recreational users disliking the drug. I thought those results weren't that strong, particularly for a recreational population.

DR. FISCHER: Mike Fischer. I voted yes. My interpretation of the data was actually very similar to a couple of members of the committee who just spoke. But I felt like looking at the study that was done, even though it is a relatively narrow population, it is, compared to the other alternatives, less abusable. And the way the question was set up, that left me to yes.

DR. PRISINZANO: Tom Prisinzano, University of Kansas. I voted yes for the reasons that have been stated previously.

DR. PERRONE: Jeanmarie Perrone. I voted no. I'm concerned that the intranasal deterrents wears off, and for committed users, that's probably going to lead to other problems.

MS. ROBOTTI: Suzanne Robotti. I voted no

because it was not tested. In conjunction with products that could block or stop the discomfort, the group upon which it was tested was too small to identify unanticipated adverse events for me. It certainly wasn't tested against any subpopulations. The unknown risks outweigh the theoretical benefits.

DR. HIGGINS: Jennifer Higgins. I voted yes.

MR. O'BRIEN: Joe O'Brien. I voted yes.

DR. BATEMAN: Okay. We'll now move on to voting question 4. The question is, if approved, should oxycodone hydrochloride immediate-release tablets, MNK-812, be labeled as an abuse-deterrent product by the intravenous route of abuse? Are there any clarifying questions or comments?

(No response.)

DR. BATEMAN: Okay. So if there are no further questions or discussion on this question, we'll now begin the voting process. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to

vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. BATEMAN: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 7 yes; 10 no; zero abstentions.

DR. BATEMAN: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did for the record, starting with Dr. Arfken.

DR. ARFKEN: Cynthia Arfken. I voted no. I was very concerned about the long-term safety, and I wasn't as convinced of the abuse deterrent.

DR. MARSHALL: Brandon Marshall. I voted no. I wasn't convinced by the data around the prevention of parenteral consumption of this substance. It just seemed like we needed more to

truly evaluate whether there would be truly deterrence to injection of this ADF formulation.

DR. GREEN: Traci Green from Boston University. I voted no based on the data presented from both the company itself and also from the FDA suggesting the syringeability and abuse potential via parenteral routes

DR. ZELTZER: Lonnie Zeltzer. I voted yes because I felt like the data certainly in this smaller dose was convincing, and I wasn't convinced that the larger dose could be divided up; at least the data weren't there to convince me of that.

DR. GOUDRA: Goudra from Penn Medicine, and I voted yes. In fact, this one is more robust to yes compared to question 3. Thank you.

DR. BATEMAN: Brian Bateman. I voted yes. I think any formulation's, the abuse-deterrent properties are going to be able to be overcome with sophisticated enough methods and time. But I think there were compelling data presented that it's more difficult to extract the oxycodone from this formulation than Roxicodone, and thus would expect

that there's some barrier to intravenous abuse.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes, although it was a weaker yes in this case because I think it depends on where we put the bar for deterrence, but still there was some deterrence from parenteral use compared to using it it orally with just higher doses given the bioavailability.

DR. McCANN: Mary Ellen McCann. I voted yes. My yes maybe was a little bit weaker. What concerns I had were about the excipients. I think we just don't have a huge amount of data about long-term use of these excipients being injected. That being said, I still voted yes.

DR. SHOBEN: Abby Shoben. I voted yes. I agree that I think the data were a little weaker for prevention of intravenous abuse, but that there was still some evidence that there'd be a barrier to intravenous abuse compared to intact Roxicodone.

DR. MEISEL: Steve Meisel. I voted no. While there may be a barrier, I think that barrier is pretty flimsy and easily overcomable. Perhaps

the 16 year old who's trying his mom's oxycodone for the first time, it's a barrier, but anybody who wants to dissolve this stuff and inject well, I don't think it's going to be a deterrence to real abuse.

DR. ZIBBELL: John Zibbell. I voted no. I thought that the evidence showed that it could be extracted and suspended in solution, albeit with some effect. I thus believe it will be injected and shared, and I therefore believe infectious disease risk is significantly increased with this medication.

DR. FISCHER: Mike Fischer. I voted no. I felt like looking at the data that were presented, this was a somewhat more difficult to abuse formulation, but there wasn't anything that to me rose to the level of actually deterring the use of this product intravenously given that once there is a method that works, it will disseminate rapidly.

DR. PRISINZANO: Tom Prisinzano. I voted no as well. I guess I had difficulty looking at the difference between the FDA data versus that of the

sponsor's data, and in this particular case, looking and ultimately coming down to voting on the side of no, based upon my difficulty in relating that information between the two.

DR. PERRONE: Jeanmarie Perrone. I voted no. I would ask the FDA to clarify maybe in the future the idea of is it a qualitative or quantitative assessment of abuse deterrence. And I think quantitatively, we can conclude that there will be a way to overcome that gap in abusability and syringeability, and that that one recipe that will get us to 90 percent of the product or 80 percent of the product will be widespread once disseminated.

MS. ROBOTTI: Suzanne Robotti. I voted no for many of the reasons already mentioned, but I'd like to say that, again, the test was on very small groups of rabbits and guinea pigs, or on other small animals. It does not give us enough data to convince me that there wasn't even an exploration of unanticipated adverse events from the ingredients or from the various uses of the drug.

DR. HIGGINS: Jennifer Higgins. I voted yes for the reasons I previously stated.

MR. O'BRIEN: Joe O'Brien. I flipped on this one. I voted no. I probably could abstain. But I wasn't as convinced with previous panels. And with Dr. Fischer and Dr. Prisinzano, I thought there were some questions that were left in my mind at the end of our discussion going around.

DR. BATEMAN: Okay. Thank you. So we'll now move on to voting question 5. The question is, should oxycodone hydrochloride immediate-release tablets, MNK-812, be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate? Are there any clarifying questions or comments regarding this question?

(No response.)

DR. BATEMAN: Okay. In the absence of clarifying questions, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please

press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. BATEMAN: Everyone has voted. The voting is now complete. Now that the vote is complete, we'll go around the table and everyone -- oh, excuse me. Sorry.

(Laughter.)

DR. CHOI: For the record, we have 10 yes; 7 no; zero abstentions.

DR. BATEMAN: Okay. Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. And this time let's start on the right, so that's Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien. I voted yes. I do think it's an important drug. I think it is an important step. I do think for the population of

patients that I'm thinking about, who don't even know what drug they're taking necessarily, what name it is, or whatever -- but in the case of where there may be diverted, I think it is important to have something that has the provided benefits that are given.

DR. HIGGINS: Jennifer Higgins. I voted yes. I think it's a step in the right direction. I also was persuaded by several points that were made today; specifically the fact that there are fewer IR single-entity products being prescribed, which means to me there's less readily available product for diversion. I also found that the data on the global assessment of taking drug again, I found that highly persuasive. So those were several things that stood out for me.

MS. ROBOTTI: Suzanne Robotti. I voted no. If the distribution of the drug can be limited to those who are prescribed it appropriately and use it appropriately, I would feel differently, but there's a very predictable expectation that there will be illegal use, abusive use. Because we can

predict that and the concerns I have over that, I had to vote no. I don't believe this drug is a big enough step forward to warrant the risk that it causes.

DR. PERRONE: Jeanmarie Perrone. I voted no. I'd like to restate that I was here about 5 years ago maybe when we voted no for Zohydro, and the FDA committee went ahead and approved it 7 or 8 months later. That was the tip of the beginning of our knowledge of the worst public health crisis of our time. And now 5 or 6 years later, I don't want to be misguided into thinking that the goal of the sponsor here is particularly aimed at making a safer product.

The economic review of abuse-deterrent products suggests that there will be $2 billion spent to save one life, so I'm just a little bit -- I want to just reshape the idea that it's a little misguided to head in that direction and that I think it's time that we actually regulate rather than go along with the goals of our sponsors.

So for all the unintended consequences, for

the real clinical spectrum of patients that I see, and for the really biggest concern that people might think that an abuse-deterrent formulation is an addiction-proof or abuse-proof formulation really raises great concerns in my mind.

DR. PRISINZANO: Tom Prisinzano, University of Kansas. I voted yes. I thought that the sponsor put together a convincing argument for the abuse-deterrent formulation.

DR. FISCHER: Mike Fischer, Boston. I voted no. When I weighed the risks and benefits, to me there is an argument for abuse deterrence in the narrow window of individuals who are relatively new to misusing the drug by the nasal form, but for experience users, we don't really have data. And panelists spoke convincingly about the idea that indeed using an opioid despite aversive effects is kind of the definition of an opioid-use disorder, and that for intravenous, it didn't, to me, meet the bar for abuse deterrent.

Then weighing the risks, the public health risk of having the first immediate release, what

would likely be massively available abuse-deterrent opioids, the possibility of misperceptions just at a time when we are starting to see a decrease in the extent to which prescription opioids are part of the crisis, there's plenty of other elements that strike me as potentially a step in the wrong direction in terms of overall prescribing safety for patients. So putting those risks and benefits together left me at a no.

DR. ZIBBELL: John Zibbell. I voted no, but this is not because I don't think we need good opioid medications for pain. We absolutely do, and I believe there are already drugs on the market for pain patients. That question said nothing about diversion or abuse deterrence at all. So I think we already have instant-release medications for pain patients, and I support that. And I actually think the pendulum has swung, so we have real pain patients that aren't getting the medications they need. That does concern me, and they need those medications.

I do want FDA to consider the whole

abuse-deterrent framework. From what I've seen both on the street, in these halls, and in my own research, I'm just not convinced, at least where the science is now, that they're better than non-abuse deterrence. I think the population that we're trying to protect here is really small compared to the greatest risk. And I think we really need to focus on prescribing anti-diversion practices and responsible prescribing rather than going around the back end and trying to do abuse deterrence, at least with the status of the sciences now for abuse deterrence. And maybe that will change in the future, but until then, I think it's really problematic.

DR. MEISEL: Steve Meisel. I voted yes even though I voted no for the first two questions, and it requires some explanation here. The question here is whether the drug should be approved for the management of pain. This is a bioequivalent analgesic. So if the labeling were indeed limited to just that; and the applicant is indeed serious about following through on taking off the original

product and replacing it this as the standard rapid-release oxycodone; and as long as it didn't have the labeling for abuse deterrence, I'm fine with that. It's bioequivalent. It works. I've got no issue with that. But I don't believe that the labeling should include abuse deterrence. I think that's problematic.

As long as I've got the microphone -- I mentioned this before and I'll mention this again -- the agency requires Category 4 studies as a condition for approval, yet we've heard today that the agency has no power to enforce that once the drug is actually on the market and doesn't enforce it. We've got the OxyContin that's been on the market since 2010-2011, and we're still waiting for data, and that's eight years.

I think that's indefensible. I think if indeed the drug were approved and if there was a requirement for Category 4 studies, the requirement has to include a time certain by which data and studies are submitted and deemed to be acceptable or the approval is withdrawn. But this open-ended,

we'll wait until they send us data, or we'll wait until they come up with a study that we'll approve and we'll just see what happens, I don't think that's defensible.

DR. SHOBEN: Abby Shoben. I voted yes. I do think it's an incremental step forward as an abuse-deterrent formulation of the IR oxycodone. I agree actually with Dr. Meisel about the importance of the Category 4 studies going forward postmarketing.

DR. McCANN: Mary Ellen McCann. I voted yes. I actually took the question at face value, and since it's bioequivalent to the alternative, I voted yes.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes because I thought that [indiscernible] versus oxycodone without formulation may affect the proportion of the population not going down the path, but this is based on no data. So I totally agree that we need to base our decision on data, hopefully.

But I would like to highlight that I'm all

for regulation of all opioids and for responsible prescribing and reducing the use in the population. And I was just hoping, based on the literature, that that can take us into that direction, but I might be wrong.

DR. BATEMAN: Brian Bateman. I voted yes, first based on the bioequivalence of the drug to Roxicodone. And second, we saw data that immediate-release oxycodone is widely abused, so there's a clear need for abuse-deterrent formulations of immediate-release oxycodone. And while the abuse-deterrent properties of this medication are perhaps not as robust as we might like, it is an important advance over the existing formulations.

I agree with members of the committee that it's hard to fully evaluate the public health impact of introducing this medication, so I think there will be a real need for close surveillance in the postmarketing period to detect any unintended consequences.

DR. GOUDRA: Dr. Goudra. I did vote yes for

a few reasons. One, there's no debate that opiates are indispensable for many types of pain, and there is always this risk of increased prescription because clinicians may read the label, but that's not fault of the manufacturer. And the results increase risk of street use, but again, there are other ways of tackling it. The opioid crisis requires a multi-prong attack, and this is one of them. Thank you.

DR. ZELTZER: Hi. Lonnie Zeltzer, and I voted yes, basically because I feel like IR oxycodone is out there. It's used. It's abused. So even if a small percent of patients -- if it provides some abuse deterrence to even a small percentage given that it's very widely used and abused, then it's worth it. And I just want to say ditto to what Steven or Dr. Meisel said in terms of something I think FDA needs to tackle in the future in terms of this, how to enforce this phase 4 because that's the big missing black box right now.

DR. GREEN: Traci Green from Boston University. I voted no in consistency with my

prior two vote. We already know that the current medication that's approved is already an important drug and that we have opportunities to work through prescribing efforts and other guideline-based efforts to reduce prescribing and reduce the impact of misuse and diversion.

We are continuing to see that the trends for oxycodone IR are reducing over time, and we're starting to see a change in our national epidemic to indicate that. So I see the incremental effect of this introduction of an approval for this vote is too incremental. The insignificant advances that it would put into the marketplace do not counterbalance the risks that it may introduce in the introduction of more potential effects on the public health impacts, as well as on the marketplace itself. We cannot underestimate the impact of having multiple abuse-deterrent formulation or formulations such as the one we're considering, especially focused on oxycodone products.

Finally, I think it's important to think

about the large market share that oxycodone immediate release has. So it's not a small tinkering; it's a very large one by approving this particular product. And that is a concern of mine.

DR. MARSHALL: Brandon Marshall. I voted no for reasons similar to Dr. Green. I've weighed the risks and benefits. Even against the currently approved medication, it seems like there may be some incremental benefit. Maybe a small group of recreational users may cease to insufflate the drug and use it orally instead, in which there is still some risk of dependence through that mode of transmission.

I just felt like those incremental benefits were outweighed by the risks that I heard around the table, Dr. Zibbell mentioning increased infectious disease risk through sharing; Dr. Perrone mentioning the subjectivity of opioid prescribing and how this may induce misperceptions in the prescribing community. I understand those risks are conjectural, but until I see that data, it just seemed to me like those are present and

real outweighed the marginal benefit of this medication.

DR. ARFKEN: Cynthia Arfken. I voted no. I thought it had nasal abuse-deterrent properties, but not IV. And because of that, I would not want to switch the abuse to IV, and therefore voted no.

DR. BATEMAN: Thank you. Before we adjourn, are there any last comments from the FDA?

DR. HERTZ: I just want to thank everybody for their thoughtful deliberations and for taking time from their busy schedules.

Adjournment

DR. BATEMAN: Okay. Panel members that are returning for tomorrow's meeting, please monitor your emails early tomorrow in case there's a federal government delay due to potentially inclement weather in the morning.

Panel members, please take all your personal belongings with you, as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table

on your way out so it may be recycled. We will now adjourn the meeting. Thank you.

(Whereupon, at 4:04 p.m., the meeting was adjourned.)