FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Open Session

Wednesday, April 5, 2017

9:14 a.m. to 3:02 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Second Floor

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Stephanie Begansky, 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

Associate Professor of Anesthesia

Division of Pharmacoepidemiology and

Pharmacoeconomics

Department of Medicine

Brigham and Women's Hospital

Department of Anesthesia, Critical Care, and Pain

Medicine

Massachusetts General Hospital

Harvard Medical School

Boston, Massachusetts

Raeford E. Brown, Jr., MD, FAAP

(Chairperson)

Professor of Anesthesiology and Pediatrics

College of Medicine

University of Kentucky

Lexington, Kentucky

David S. Craig, PharmD

Clinical Pharmacy Specialist

Department of Pharmacy

H. Lee Moffitt Cancer Center & Research Institute

Tampa, Florida

Jeffrey Galinkin, MD, FAAP

Professor of Anesthesiology and Pediatrics

Co-Chairman, Colorado Multiple Institutional

Review Board

University of Colorado, AMC

Aurora, Colorado

Anita Gupta, DO, PharmD

Fellow, Princeton University

Woodrow Wilson School of Public & International Affairs

Princeton, NJ

Vice Chair, Associate Professor

Division of Pain Medicine

Department of Anesthesiology

Drexel University College of Medicine

Philadelphia, Pennsylvania

Jennifer G. Higgins, PhD

(Consumer Representative)

Research and Policy Manager

Association of Developmental Disabilities Providers (ADDP) Framingham, Massachusetts

Philadelphia, Pennsylvania

Ronald S. Litman, DO

Professor of Anesthesiology & Pediatrics

Perelman School of Medicine

University of Pennsylvania

Attending Anesthesiologist

The Children's Hospital of Philadelphia

Medical Director, Institute for Safe Medication Practices

Mary Ellen McCann, MD, MPH

Senior Associate in Anesthesia and Associate Professor

Department of Anesthesiology, Perioperative and Pain Medicine

Children's Hospital Boston

Boston, Massachusetts

Abigail B. Shoben, PhD

Associate Professor, Division of Biostatistics

College of Public Health

The Ohio State University

Columbus, Ohio

Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

Faculty and Clinical Instructor, Pain and Medical Ethics

State University of New York Stony Brook School of Medicine

Stony Brook, New York

Ethics Committee Chair

St. Catherine of Siena Medical Center

Smithtown, New York

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

W. Joseph Herring, MD, PhD

(Industry Representative)

Executive Director and Section Head

Neurology Clinical Neurosciences

Merck Research Laboratories

North Wales, Pennsylvania

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

MEMBERS (Voting)

Niteesh K. Choudhry, MD, PhD

Professor

Harvard Medical School

Associate Physician

Brigham and Women¹s Hospital

Boston, Massachusetts

Christopher H. Schmid, PhD

Professor of Biostatistics

Center for Evidence Based Medicine

Department of Biostatistics

Brown University School of Public Health

Providence, Rhode Island

Terri L. Warholak, PhD, RPh, FAPhA

Assistant Professor

Division of Health Promotion Sciences

College of Public Health

Adjunct Clinical Instructor

College of Nursing

Associate Professor with Tenure

Department of Pharmacy Practice and Science

College of Pharmacy

University of Arizona

Tucson, Arizona

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBER (Non-Voting

Linda Scarazzini, MD, RPh

(Industry Representative)

Vice President

Pharmacovigilance and Patient Safety

Abbvie

North Chicago, Illinois

TEMPORARY MEMBERS (Voting

Gregory E. Amidon, PhD
Research Professor of Pharmaceutical Sciences
College of Pharmacy, Department of Pharmaceutical Sciences
University of Michigan
Ann Arbor, Michigan

Charles W. Emala, Sr., MS, MD
Professor and Vice-Chair for Research
Department of Anesthesiology
Columbia University College of Physicians & Surgeons
New York, New York

Alan D. Kaye, MD, PhD
Professor and Chairman
Department of Anesthesia
Louisiana State University School of Medicine
New Orleans, Louisiana

Arthur H. Kibbe, RPh, PhD

Retired Professor of Pharmaceutical Sciences

Nesbitt School of Pharmacy

Wilkes University

Wilkes-Barre, Pennsylvania

Elaine H. Morrato, DrPH, MPH

Associate Dean for Public Health Practice

Associate Professor Department of Health Systems, Management and Policy

Colorado School of Public Health

University of Colorado Anschutz Medical Campus

Aurora, Colorado

Joseph O'Brien, MBA

(Patient Representative)

President and CEO National Scoliosis Foundation

Stoughton, Massachusetts

Sharon L. Walsh, PhD

Professor of Behavioral Science, Psychiatry,

Pharmacology and Pharmaceutical Sciences

Director, Center on Drug and Alcohol Research

University of Kentucky

Lexington, Kentucky

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

Judy Staffa, PhD, RPh

Associate Director for Public Health Initiatives

Office of Surveillance and Epidemiology (OSE)

CDER, FDA

Ellen Fields, MD, MPH

Deputy Director

DAAAP, ODE-II, OND, CDER, FDA

Joshua Lloyd, MD

Clinical Team Leader

DAAAP, ODE-II, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:14 a.m.)

Call to Order

Introduction of Committee

DR. BROWN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you have not already done so. I would also like to identify the FDA press contact, Sarah Peddicord, if you are present.

Hi, Sarah.

My name is Rae Brown. I am the chairperson of the Anesthetic and Analgesic Drug Products Advisory Committee, and I will be chairing 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.

We will start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. HERTZ: Hello. Sharon Hertz, director

for the Division of Anesthesia, Analgesia, and Addiction Products.

DR. FIELDS: Ellen Fields, deputy director in the same division.

DR. LLOYD: Josh Lloyd, lead medical officer, same division.

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

DR. KIBBE: Art Kibbe, emeritus professor of pharmaceutical sciences, Wilkes University.

DR. KAYE: Alan Kaye, anesthesiologist and pain expert, professor, program director, and chairman at LSU School of Medicine in New Orleans, Louisiana.

DR. SCHMID: Chris Schmid, professor of biostatistics, Brown University.

DR. EMALA: Charles Emala, professor of anesthesiology, vice chair for research at Columbia University.

DR. LITMAN: Ron Litman, professor of anesthesiology and pediatrics at University of

Pennsylvania and Children's Hospital of Philadelphia, and I am also the medical director of the Institute for Safe Medication Practice.

DR. GUPTA: Dr. Anita Gupta. I am currently a fellow at Princeton University at Woodrow Wilson Public Policy and International Affairs and also currently vice chair, associate professor at Drexel University College of Medicine in the Department of Anesthesiology and Pain Medicine.

DR. WARHOLAK: I am Terri Warholak from the University of Arizona College of Pharmacy, and my specialty is in quality and safety.

DR. CRAIG: David Craig. I'm a clinical pharmacist specialist at Moffitt Cancer Center.

LTC BEGANSKY: Stephanie Begansky. I'm the designated federal officer for today's meeting.

DR. BROWN: I'm Rae Brown. I'm professor of anesthesiology and pediatrics at the University of Kentucky.

DR. BATEMAN: Brian Bateman, associate professor of anesthesia at Brigham and Women's Hospital, Harvard Medical School.

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

DR. ZACHAROFF: Kevin Zacharoff, expertise in anesthesiology and pain medicine, faculty and clinical instructor at the Stony Brook School of Medicine.

DR. McCANN: Mary Ellen McCann. I'm an associate professor at Harvard University and Boston Children's Hospital.

DR. GALINKIN: I'm Jeff Galinkin. I'm a professor of anesthesiology and pediatrics at University of Colorado.

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

MR. O'BRIEN: Joe O'Brien, president and CEO of the National Scoliosis Foundation and patient representative.

DR. CHOUDHRY: Niteesh Choudhry, professor of medicine at Harvard Medical School and an internist at Brigham and Women's Hospital.

DR. MORRATO: Elaine Morrato, an

epidemiologist in the Department of Health Systems Management and Policy, and I'm serving as the interim dean for the Colorado School of Public Health at the University of Colorado.

DR. WALSH: I'm Sharon Walsh. I'm a professor of behavioral science, psychiatry, pharmacology, and pharmaceutical sciences at the University of Kentucky and also the director of the Center on Drug and Alcohol Research.

DR. AMIDON: Greg Amidon, research professor of pharmaceutical sciences at the University of Michigan.

DR. SCARAZZINI: Hi. Good morning. Linda Scarazzini. I'm the head of pharmacovigilance and patient safety at AbbVie, and I'm the industry rep for DSaRM.

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

DR. BROWN: I'd like to welcome everyone this morning.

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is

reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I will pass it to Lieutenant Commander Stephanie Begansky, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LTC BEGANSKY: Good morning. The Food and Drug Administration is convening today's joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

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

The following information on the status of the committees' compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the 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 particular individual'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 those imputed to them, including those of

their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of new drug application 209777 for oxycodone hydrochloride immediate-release oral tablets submitted by Inspirion Delivery Services with the proposed indication of management of moderate to severe pain where the use of an opioid analgesic is appropriate. This product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product.

The committees will be asked to discuss the overall risk-benefit profile of the product and whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling. This is a particular matters meeting during which specific matters

related to Inspirion's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Joseph Herring and Linda Scarazzini are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck & Co., and Dr. Scarazzini is employed by AbbVie.

We would like to remind members and temporary voting members that if the discussions

involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committees of any financial relationships that they may have with the firm at issue. Thank you.

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

FDA Introductory Remarks

DR. HERTZ: Good morning. I'd like to thank you all for coming this morning at this joint meeting of the AADPAC and DSaRM. We will be discussing an application from Inspirion for an abuse-deterrent, immediate-release oxycodone formulation under the trade name RoxyBond. This product has been designed with properties intended to deter abuse, and the proposed indication is for the treatment of moderate to severe pain where the

use of an opioid analgesic is appropriate.

Prescription opioid products are an important component of modern pain management, but we are well aware of the problems of abuse and misuse that have grown from the extensive use of opioids for pain management in this country.

To address the public health concern, FDA has announced a comprehensive action plan, and one element of this plan is to facilitate development of abuse-deterrent products. The goal is to keep the pharmaceutical armamentarium for analgesics broad so that prescribers have options that they need when they're managing their patients in pain.

With the development of products to deter abuse, we have issued a final guidance for industry to assist in this development. The guidance for industry for abuse-deterrent opioids evaluation and labeling was finalized in 2015, and it explains our current thinking regarding the studies that should be conducted to demonstrate that a formulation has abuse-deterrent properties, and makes recommendations for how those studies should be

performed and evaluated, and discusses how to describe those studies and their implications in product labeling.

We have got nine approved extended-release products with abuse-deterrent properties on the market at present. Many of you have been present for their advisory committees. This is going to be one of the first products evaluated, not the first but one of the first few evaluated that is an immediate-release product.

We currently don't have any immediate-release opioid analgesics on the market with abuse-deterrent language consistent with our current guidance, so this is a potential first. And that this is an immediate-release product raises some different issues than with some of the extended-release products. And you're going to see that in the data that will be presented, particularly relating to the results from the human abuse potential studies.

These are difficult questions. We are at the cutting edge of all of this development, and we

are hoping that we can benefit from your now somewhat extensive participation in these meetings and your expertise, and we greatly appreciate your presence.

Your advice and recommendations will be essential in assisting us with addressing the complex issues that we are presenting today, and once again, we are grateful you agreed to join us for this meeting. Thank you.

DR. BROWN: Thank you, Dr. Hertz.

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

For this reason, FDA encourages all participants, including the applicant's nonemployee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interests in a sponsor, including

equity interests, and those based upon the outcome of the meeting.

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

We will now proceed with Inspirion's presentation.

Applicant Presentation - Stefan Aigner

DR. AIGNER: Good morning. My name is Stefan Aigner. I am the cofounder and CEO of Inspirion. We started Inspirion in 2008 fully dedicated to the development of abuse-deterrent opioids in order to help address the epidemic of prescription opioid abuse in this country. I would like to thank the FDA and the members of the advisory committee meeting for the time you've spent reviewing our application on RoxyBond.

RoxyBond is an immediate-release,

single-entity oxycodone product for the treatment of pain severe enough to require the use of an opioid analgesic or for which alternative treatments are inadequate. RoxyBond is formulated using Inspirion's SentryBond technology, the same technology used in MorphaBond, which is an FDA-approved extended-release morphine with abuse-deterrent claims in the label.

RoxyBond has been formulated with physical and chemical barriers to deter intranasal and IV abuse. And like other abuse-deterrent products, RoxyBond is intended to be abuse-deterrent and not abuse-proof.

We acknowledge that some abusers dedicated will overcome any barriers provided by a formulation to abuse the product. The goal is to create significant improvements over non-abuse-deterrent products to make abuse more challenging and less rewarding.

As an immediate-release product, RoxyBond has to be rapidly bioavailable by the intended oral route of administration, therefore, it is not

expected to deter all abuse. RoxyBond is intended to replace easily abusable immediate-release single entity oxycodone products like Roxicodone.

Opioid analgesics are an important treatment option for pain. However, they are also at risk of diversion, misuse, and abuse. In response, as we heard, the FDA has encouraged the development of abuse-deterrent opioids as one component of a larger public health effort.

To date, the agency has approved nine extended-release long-acting opioids with abuse-deterrent label claims, but no abuse-deterrent, immediate-release has been approved. Developing any abuse-deterrent product is challenging, however, developing an abuse-deterrent immediate-release product has been particularly difficult.

Let's review why. Extended-release opioids release the drug slowly when taken orally as intended. By manipulating or extracting an extended-release opioid, an abuser's goal would be twofold. First, to convert the extended-release profile to an immediate-release to speed up their

high, and second, to transform the drug into an abusable form for snorting or injecting.

Most abuse-deterrent extended-release products work by resisting manipulation and conversion into an immediate-release form. The challenge with creating abuse deterrence for immediate-release opioids is because they already have the profile abusers want.

So the question has been what can we do to deter these products from being snorted or injected. With RoxyBond, we have been able to create a number of physical and chemical barriers specifically designed to deter those routes of abuse. As you will see throughout our presentation this morning, RoxyBond is difficult to manipulate or extract.

Uniquely, we have also designed RoxyBond to have a lower and slower release for intranasal and IV abuse compared to simply taking the product orally as intended. This attribute of RoxyBond will be counterintuitive for abusers who associate snorting and injecting with faster absorption. In

addition, RoxyBond is also difficult to snort or prepare for IV abuse.

The development program for RoxyBond used a 505(b)(2) regulatory pathway with Roxicodone as a reference-listed drug. We are proposing three dosages for RoxyBond, 5, 15, and 30 milligrams. These are the same as currently available for Roxicodone.

In the clinical PK study, RoxyBond demonstrated comparable bioavailability to Roxicodone, which forms the scientific bridge to the well-established safety and efficacy profile of Roxicodone. A second PK study demonstrated that all dosages of RoxyBond were dose proportional.

Also, there was no clinically significant effect of food on the bioavailability of oxycodone, therefore, we can expect that RoxyBond will have the same safety and efficacy profile as Roxicodone but with the added public health benefit of abuse deterrence.

The abuse deterrence study for RoxyBond were designed in accordance with the FDA guidance for

abuse-deterrent opioids and in consultation with the FDA. The category 1 in vitro studies evaluated the effect of physical manipulation, chemical extraction, and syringeability on RoxyBond. A category 2/3 study evaluated the human abuse potential for RoxyBond when administered by the intranasal route.

Inspirion is also fully committed to fulfilling our post-approval requirements. This joint advisory committee recommended that immediate-release opioid products should be included in the existing opioid analgesics REMS program. Inspirion strongly supports all of those activities.

In addition, we look forward to working with the FDA to develop a series of category 4 studies that will be designed to assess the impact of RoxyBond's abuse-deterrent features in the real world. These category 4 studies will include monitoring utilization patterns, monitoring abuse patterns in a variety of settings, and conducting formal observational studies.

I will review our agenda and presenters for this morning. Dr. Rich Dart will discuss the public health need for abuse-deterrent, immediate-release opioids.

Robert Bianchi will review the results of our in vitro physical manipulation and chemical extraction studies.

Dr. Lynn Webster will review the results of our intranasal human abuse potential study.

Lastly, Dr. Jeffrey Gudin will conclude the presentation with his clinical perspective of RoxyBond and its abuse-deterrent features.

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 will now invite Dr. Dart to the podium.

Applicant Presentation - Richard Dart

DR. DART: Good morning. My name is Rick Dart, and I'm the director of the Rocky Mountain Poison and Drug Center. I'm also a professor at the University of Colorado, and I'm also executive

director of what is called the RADARS system, which studies prescription drug abuse and diversion in the United States.

Currently, all immediate-release opioid analgesics in the U.S. are easily abusable. 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 to abuse, 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 pain or a new recreational user decides to abuse an opioid analgesic.

Most people start by swallowing intact pills. Some people will go on to crush the drug in order to snort or inject it. It is extremely important to realize that users often switch back and forth between products and between routes of abuse. We see comments to this effect regularly on

websites and chat rooms that are frequented by substance abusers.

Any of these abuse behaviors can lead to adverse outcomes, and to address these outcomes, several interventions have been implemented in recent years.

For example, prescriber guidelines can reduce the number of prescriptions in the community while still providing appropriate access to patients who need them. Prescription drug monitoring programs have also been effective in quickly identifying patients who are doctor shopping.

Once an opioid is prescribed, I think we can all agree that we want that drug to be as safe as possible. To that end, FDA has promoted the development of opioids with abuse-deterrent properties.

An ADF is intended to interfere with extraction of the active drug from the tablet by physically resisting crushing, by releasing an antagonist, or by forming a gooey mess when mixed

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

This approach helps different types of abusers in different ways. For pain patients who are tempted to begin abusing the drug they have been prescribed, an abuse-deterrent formulation may deter them from crushing to increase the intensity of their high.

Assuming that a legitimate pain patient has not yet initiated intense abuse, ADFs present a barrier to intranasal and intravenous abuse because these patients haven't developed severe abuse behaviors and should be less committed to overcoming the ADF mechanism.

A novice abuser who is experimenting with opioids is similar. An effective abuse-deterrent product can create a barrier to snorting or injection, an important feature since these routes are inherently more dangerous than oral abuse.

For advanced abusers, an abuse-deterrent formulation may well deter them from snorting or

injecting that product, but it is not likely to stop their larger opioid abuse problem. They will likely switch to another drug or temporarily switch back to oral abuse. What these individuals really need is substance abuse treatment.

An abuse-deterrent product can't stop abuse, but it is very clear from both quantitative data as well as chat rooms and blogs that these products do create a significant barrier to risky routes of abuse.

Now, let's look at some of that data. Last year, there were 151 million prescriptions filled for immediate-release opioids, none of which are abuse-deterrent. This was compared to just 12 million prescriptions for extended-release opioids for which there are nine approved formulations. In fact, there was 17.9 million immediate-release prescriptions just for single entity oxycodone products, about 50 percent more than all extended-release prescriptions combined.

Immediate-release opioids are frequently abused and diverted. In our RADARS Poison Center

program, for example, immediate-release opioids are involved in abuse cases more than 4 times as often as extended-release products. Furthermore, the rate of diversion is six times greater with immediate-release than extended-release opioids.

Abusers also report actually preferring immediate-release over extended-release products. In a recent study of 300 opioid abusers entering treatment for substance abuse, 66 percent reported a preference for immediate-release opioids, and only 4 percent preferred extended release.

I would add that several studies have found that most individuals who abuse prescription opioids initiated their abuse with an immediate-release product.

Now let's focus on oxycodone. The abuse of single entity immediate-release oxycodone exceeds that of extended-release oxycodone among individuals entering substance abuse treatment programs as well, like those in the NAVIPPRO system. The number of individuals who reported abuse of the single entity immediate-release

oxycodone in the previous 30 days was over twice as high as the number reporting abuse of extended-release oxycodone.

Let's take a look at the route of abuse. This is also in the NAVIPPRO system. Approximately half of abusers reported abusing immediate-release, single-entity oxycodone by the intranasal route and similarly for oral. Twenty-eight percent reported intravenous abuse.

The relatively high prevalence rates of snorting and injecting are quite important because intranasal and intravenous abuse of opioids are associated with higher risk for serious outcomes. To illustrate this point, these data are from the RADARS Poison Center program, and they show the relative risk of death or a major adverse effect like an overdose for the intranasal and intravenous routes compared to the oral route. Point estimates to the right of the 1 indicate a greater risk compared to ingestion.

For each incident of abuse, the risk of death or a major adverse effect was 2 times greater

for intranasal abuse than oral abuse, and the risk is even higher for intravenous abuse, 2.6 times greater than oral abuse.

Of course, the intravenous abuse is of particular concern because, according to the CDC, in 2015, 6 percent of new HIV diagnoses and 10 percent of AIDS diagnoses were attributed to IV drug abuse. Injecting an opioid like oxycodone also puts the abuser at risk for other blood-borne infections like hepatitis C as well as serious infections like endocarditis, not to mention blood clots and other health effects.

In summary, I really think it is time to address the need for immediate-release opioids. We need abuse-deterrent properties. Immediate-release opioids are much more commonly prescribed, more commonly abused, and more commonly diverted than extended-release opioids.

Immediate-release single entity oxycodone in particular is commonly abused by high-risk intranasal and intravenous routes, which are associated with greater risk of death and other

serious health consequences.

Abuse-deterrent formulations are not intended to replace other important strategies to address the opioid epidemic such as prescribing guidelines and prescription drug monitoring programs, but they are designed to complement these other strategies and to replace easily abusable products.

Thank you. I'll turn the presentation over to Mr. Bianchi.

Applicant Presentation - Robert Bianchi

MR. BIANCHI: Good morning. My name is Robert Bianchi, and I'm the president and chief of scientific and technical affairs at the Prescription Drug Research Center in Bradenton, Florida.

I spent 34 years in federal service as a chemist at the FDA and DEA, including as chief of DEA's laboratory operations section and director of the DEA's special testing and research laboratory where in vitro studies were done more than 20 years ago.

For the last decade, I have conducted dozens of studies on abuse-deterrent opioid formulations. I assisted with the design of Inspirion's abuse-deterrent studies for RoxyBond, and I'm pleased to be able to present the results of those studies with you this morning.

Inspirion performed a comprehensive set of laboratory-based in vitro manipulation and extraction studies to evaluate the intranasal and intravenous abuse-deterrent properties of RoxyBond. The abuse-deterrent program was developed in accordance with the FDA guidance for abuse-deterrent opioids and in consultation with the FDA.

Inspirion took an iterative testing approach throughout the development and route process. Inspirion performed additional follow-up studies based on questions from the FDA to more fully characterize RoxyBond's physical and chemical abuse properties. Roxicodone was used as the non-abuse-deterrent comparator in all the studies.

Here is a general overview of the category 1 studies conducted. Particle size reduction

experiments were performed both with and without different pretreatments to determine the ability of various tools to get the products into an abusable form.

As part of the FDA guidance, large-volume extraction studies evaluated the resistance of the product to chemical extraction. Inspirion also performed several studies specific to the IV route of abuse, including small-volume extraction and syringeability.

First, I'll discuss particle-size reduction. There are differences in the rationale for reducing particle size of extended-release and immediate-release opioids. Reducing the particle size of an extended-release opioid does two things. First, it speeds up the release, converting the extended-release into an immediate-release profile allowing for dose dumping; and second, it transforms the drug into an abusable form that can be snorted or prepared for IV injection.

For an immediate-release opioid, particle-size reduction does not change the release

profile but can transform the drug into an abusable form for snorting or injection.

For RoxyBond specifically, the product is formulated to have a lower and slower release of oxycodone when manipulated for a non-oral route compared to intact oral administration. Therefore, reducing the particle size of RoxyBond does not defeat the abuse-deterrent properties.

With this in mind, let's turn to the results, starting with Roxicodone. Roxicodone is a non-abuse-deterrent and offers no resistance to particle-size reduction. Therefore, it was easily manipulated with mechanical tool E and reduced 100 percent of the particles to less than 2000 microns. Because Roxicodone was defeated with this simple tool and procedure, no further tools were evaluated.

We concluded from this experiment that Roxicodone is very easy to get into an abusable form, which is a fine powder that could be snorted or prepared for IV abuse.

For RoxyBond, we evaluated 7 different

tools, representative of cutting, crushing, grating, and grinding with both mechanical and electrical tools.

This table shows the amount of manipulation time, manipulation difficulty, and yield of small particles for each tool. This row shows the median time in seconds that it took to adulterate the tablet. The maximum time allowed in the protocol was 300 seconds.

This row shows the manipulation difficulty. Laboratory technicians rated the difficulty of each manipulation on a scale of 1 to 10 where the 1 meant very easy and 10 meant impossible. This row shows the percentage of particles smaller than 2000 microns.

Only tool G, which was an electric tool, was able to reduce more than 90 percent of the particles smaller than 2000 microns with a low level of difficulty.

Pretreatment did not substantially increase the yield of small particles, and we concluded from these experiments that RoxyBond was difficult to

get into an abusable form for intranasal or IV abuse with most tools.

The most effective tool for particle-size reduction of each product was used as the method of manipulation for all the other experiments. This was tool E for Roxicodone and tool G for RoxyBond.

Next, I'll discuss the large-volume extraction experiments. Large-volume extraction is important to evaluate for extended-release opioids that have the potential to dose dump in the presence of certain solvents. However, there was no practical advantage for large-volume extraction of an immediate-release opioid.

Let me illustrate this with data from the Roxicodone prescribing information for both intact tablets and liquid oral solution. Essentially, you can think of the oral Roxicodone solution as a large-volume extraction of a crushed Roxicodone tablet.

As you can see, the Cmax values or maximum concentrations are very similar between the intact tablet and the oral solution as were the times to

maximum concentration or Tmax. Therefore, a large-volume extraction of an immediate-release oxycodone product does not speed the oral absorption over intact oral administration. The drug comes out in the body just as fast intact as it does in a fully extracted liquid solution.

An immediate-release product that is resistant to physical manipulation and extraction would not be expected to deter oral abuse. Nevertheless, let's review the top line large-volume extraction results.

This slide will compare the extraction of oxycodone from Roxicodone and RoxyBond in ingestible and non-ingestible solvents using agitation B. The Y-axis is the percent of oxycodone released, and the X-axis shows the solvent code.

Roxicodone was easily defeated in 1 minute. One hundred percent of the oxycodone was released in solvent A, which is ingestible and widely used by abusers. Almost no oxycodone was released by RoxyBond at 1 minute, so I'll be showing results

after 30 minutes of extraction with agitation B.

The solid blue bars show the percent of oxycodone released from intact RoxyBond tablets. None of the solvents released an appreciable amount of oxycodone. Manipulation of RoxyBond with tool G is shown in the dashed blue bars. As you can see, manipulating RoxyBond even with the most effective tool did not have a meaningful impact on extraction.

The briefing documents provide detail on more extreme large-volume extraction conditions that released significantly higher amounts of oxycodone. However, as I mentioned earlier, extractability in large volumes does not increase the abuse potential for the oral route.

Next, I'll discuss the route-specific manipulations we performed for intravenous injection, including a small-volume injection and syringeability. For each experiment, we performed a small-volume extraction in an injectable amount of solvent, and then used the smallest needle gauge that was able to syringe the liquid. Laboratory

technicians performing these experiments rated each condition on a 1 to 10 scale where 1 meant it was very easy to syringe and 10 meant it was impossible.

We used 3 different needle gauges to evaluate syringeability. This figure shows all 3 needle gauges along with a dime to give you a sense of the scale. Needle gauges A and B are typically needles that might be used for IV drug abuse. Needle gauge C, which is commonly used for blood transfusions, was evaluated as an extreme case. This needle size is not preferred for IV abuse.

Here we see the resulting IV preparations when both Roxicodone and RoxyBond were manipulated and subjected to volume A of solvent A. On the left, the vial of Roxicodone shows the resulting syringeable liquid.

This contrasts with the highly viscous material formed when RoxyBond was subjected to the same conditions. It formed a material that was difficult to syringe and only produced a small amount of syringeable liquid, and even with the

vial turned upside down, most of the material sticks to the bottom of the vial.

The next slide will show the amount of oxycodone recovered from the syringe following small-volume extraction in solvent A at temperature A with agitation A. The Y-axis is the percent of oxycodone recovered, and the X-axis shows the extraction time.

With manipulated Roxicodone at 1 minute, 98 percent of the oxycodone was recovered from a syringe with the smallest needle gauge evaluated. The median difficulty of syringing the material was rated as a 1, so the material was very easy to syringe.

At 1 minute, no oxycodone could be recovered from RoxyBond in the intact condition. A very low yield was recovered from manipulated tablets using the largest needle gauge evaluated. The mean difficulty score was rated as 9 on a 1 to 10 scale, indicating the considerable challenge of syringing this viscous material. Even at 30 minutes, the recovery of oxycodone from RoxyBond was very low.

In addition to performing small-volume extractions at temperature A, we also performed the experiments using temperature B. Manipulated Roxicodone released 89 percent of oxycodone in 1 minute. The yield of oxycodone from RoxyBond at 1 minute ranged between 1 and 18 percent. Even after 30 minutes, the yield did not exceed 22 percent for any condition.

Overall, these experiments showed that RoxyBond is highly resistant to being prepared for injection with solvent A, which is by far the most common solvent used for IV abuse.

In order to test RoxyBond to failure, we evaluated extreme small-volume conditions for intact and manipulated tablets. These conditions included solvent H, which is an extreme solvent for injection. The solution was subjected to pretreatment D followed by agitation B for 30 minutes. The physical manipulation of the tablet resulted in lower oxycodone release compared to the Roxicodone intact.

In solvent H under agitation B after

pretreatment D and 30 minutes of extraction, 66 percent of the oxycodone recovered from the intact RoxyBond. The fact that a condition was identified in category 1 testing that released this amount of oxycodone was not surprising.

RoxyBond is abuse-deterrent and is not abuse-proof. But what is important to take away here is that the only condition identified that released this amount of oxycodone was extreme and required a complex multistep process. This particular extraction required pretreatment D, a large intravenous volume, an extreme solvent, agitation B at an extended time point, and even despite all of these steps, the product is still not in an easily abusable form.

In order to make solution A acceptable for injection for most abusers, they would need to perform additional back extractions and neutralizations that's on top of the 30 minutes already spent to prepare the formulation.

These barriers to IV abuse are considerable in comparison to Roxicodone, which can be

completely and easily extracted for IV abuse in a common solvent in just 1 minute. Overall, we concluded that RoxyBond makes IV abuse considerably more difficult and less attractive than Roxicodone.

In conclusion, the abuse-deterrent studies for RoxyBond have demonstrated its physical and chemical barriers to snorting and injection. RoxyBond is difficult to convert into an abusable form for IV and intranasal abuse. And even if manipulated, particle-size reduction did not defeat the abuse-deterrent properties.

Importantly, across every extraction experiment conducted involving different solvents, different temperatures, different agitation conditions, pretreatments, different volumes, with and without manipulations, RoxyBond had considerably lower and slower oxycodone release than Roxicodone.

Finally, the manipulated RoxyBond formed a viscous material that was very difficult to draw into a syringe. It created a considerable barrier to IV abuse.

I thank you for your attention, and I will now turn the lectern over to Dr. Lynn Webster to present the results of the human abuse potential study.

Applicant Presentation - Lynn Webster

DR. WEBSTER: Thank you, Bob.

Good morning. My name is Lynn Webster. I'm vice president of scientific affairs at PRA Health Sciences. My board certifications include anesthesia, pain medicine, and addiction medicine. Over the last 20 years, I've led dozens of research programs for the development of safer and more effective treatments for pain. I was also the principal investigator for the intranasal human abuse potential study for RoxyBond.

This study was a randomized double-blind, double-dummy, placebo-controlled, 4-period crossover study. The study enrolled recreational, nondependent opioid users who were experienced with nasal insufflation of opioids. Twenty-one subjects met inclusion criteria for this study and entered the treatment phase. Twenty-nine subjects

completed the study.

There were 4 treatment arms. The intranasal Roxicodone arm used Roxicodone manipulated with tool E. The intranasal RoxyBond arm used RoxyBond manipulated with tool G. The study also included arms for intact oral RoxyBond as well as placebo. All the active treatments in the study used the 30-milligram dosage strengths.

The primary endpoint of the study was drug-liking Emax, which is the maximum drug liking at any time after administration. Key secondary endpoints included take drug again, overall drug liking, the drug effects questionnaire, and the ease of snorting assessment.

With this background in mind, let's turn to the PK results. This slide will show the mean oxycodone plasma concentration on the Y-axis and the time in hours post-dose on the X-axis. Intranasal Roxicodone, shown by the red line, has plasma concentrations characteristic of a snorted, immediate-release opioid, a very rapid rise in blood levels with a high Cmax.

When we compared this to intranasal RoxyBond, shown by the blue line, we see that concentrations were consistently lower than Roxicodone through the first 3 hours. The light blue line shows RoxyBond when taken orally as intended.

Just looking at intact oral and snorted RoxyBond, it's important to note that intranasal administration actually resulted in a lower Cmax and slower absorption of oxycodone compared to oral administration.

Let's turn now to the pharmacodynamic results. This graph shows the results of the primary endpoint Emax or maximum drug liking. The bipolar 100-point drug liking visual analog scale is plotted on the Y-axis. As indicated on the right, a score of 50 represents a neutral response. 100 is strong liking, and zero is strong disliking.

The primary endpoint was met. The 12-point reduction in Emax between intranasal Roxicodone and RoxyBond was statistically significant with a p-value of less 0.0001. And consistent with the

pharmacokinetic results, subjects reported significantly lower maximum drug liking when RoxyBond was taken intranasally compared to intact oral administration.

These are the results from all the treatment arms. On this slide, I'll be plotting the mean drug liking over the first 4 hours. The light blue line shows RoxyBond when dose intact orally, which increases gradually over the course of the first hour and a half.

The red line shows snorted oxycodone, which increased considerably faster than the oral RoxyBond. This more rapid onset of drug liking is why many abusers prefer snorting opioids over taking them orally.

Adding in intranasal RoxyBond versus Roxicodone, we see that drug liking was lower for RoxyBond at all time points through 4 hours.

This slide shows take-drug-again Emax. A score of 100 means they definitely would take the drug again, 50 means they didn't care one way or another, and zero means they definitely would not

take it again. Subjects reported they would be very willing to snort Roxicodone again with a mean score of 82. The take-drug-again score for snorted RoxyBond was 20 points lower, which was statistically significant.

This slide shows overall drug liking, which is measured after 12 and 24 hours when subjects have had a chance to reflect on the entire drug taking experience. Consistent with the other endpoints in the study, the overall drug liking Emax of intranasal RoxyBond was 17 millimeters lower than Roxicodone, which was statistically significant.

We measured drug high on a unipolar scale where a score of 100 meant extremely high and a score of zero meant not at all high. Intranasal RoxyBond was associated with a significantly lower high than intranasal Roxicodone. The maximum drug high for RoxyBond was 28 points lower than Roxicodone.

We also assessed the ease of snorting Roxicodone and RoxyBond on a unipolar scale where

zero means very easy to snort and 100 means very difficult. Roxicodone had an average score of 9, indicating that participants rated it as easy to snort. RoxyBond received a score of 72, indicating that participants found it significantly more difficult.

There are two published studies in peer-reviewed literature that have attempted to determine the clinical relevance of findings from human abuse potential studies. Before I review them, I think it's important to acknowledge that the science of abuse deterrence is relatively new.

We have really just started to learn how human abuse potential studies can predict real-world reductions in abuse. I consider these studies as a useful anchor to evaluate the clinical relevance rather than a definitive answer.

In the first study, a meta-analysis approach was used to evaluate the association between human abuse potential study endpoints with potential reductions in real-world rates of nonmedical use. Since there are no approved immediate-release

abuse-deterrent formulations, we applied the model for extended-release, abuse-deterrent oxycodone.

In their meta-analysis, a 5-millimeter difference in overall drug liking was associated with an approximate 10 percent reduction in the rate of nonmedical use for abuse-deterrent formulations of ER products. The results from this meta-analysis suggests that the 17-millimeter reduction in overall drug liking with RoxyBond is likely to lead to reductions in abuse.

The second study determined the clinically important difference in drug-high Emax. Using a variety of statistical methods, the researchers determined that differences between products of 8 to 10 millimeters in drug-high Emax led to clinically significant changes in drug-taking behavior.

RoxyBond's 28-millimeter difference in drug-high Emax, compared to Roxicodone, supports the conclusion that RoxyBond has a lower abuse potential than Roxicodone for the intranasal route of abuse.

In summary, RoxyBond met its primary endpoint with significantly lower maximum drug liking for intranasal administration compared to Roxicodone. RoxyBond also met its secondary endpoints. Compared to Roxicodone, RoxyBond was less likely to be taken again, had a lower overall drug liking, had a lower drug high, and was more difficult to snort.

The pharmacokinetics were consistent with the pharmacodynamics, and the PD findings are consistent with the clinical significance we found in the literature.

In conclusion, the findings from the intranasal human abuse potential study strongly suggest that RoxyBond can lead to a real-world reduction in intranasal abuse.

I would now like to turn the lectern over to Dr. Gudin to give his clinical perspective on RoxyBond.

Applicant Presentation - Jeffrey Gudin

DR. GUDIN: Good morning. My name is Jeff Gudin. I'm the director of pain management and

palliative care at the Englewood Hospital and Medical Center in New Jersey. My board certifications include anesthesiology, pain medicine, addiction medicine, and hospice and palliative care.

After more than 20 years of treating patients with pain as well as addiction disorders, I'm able to offer a unique perspective on the challenges associated with opioid use in both of these populations.

I have published throughout my career on safe prescribing and appropriate risk management for opioid analgesics, and I'm here to provide my clinical perspective on the questions under discussion by the expert committees today.

The first question is whether RoxyBond should be approved for the proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate.

The second set of questions is whether there are sufficient data to support a finding that

RoxyBond has properties that can be expected to deter abuse by the intranasal and intravenous routes. I'll begin with the first question.

RoxyBond demonstrated that when taken as intended, it has comparable bioavailability to Roxicodone. Therefore, RoxyBond's efficacy and safety should be equivalent. This means a clinician who is prescribing Roxicodone can switch a patient to RoxyBond at the same dose with the same schedule and expect the same level of analgesia.

Furthermore, the fact that food does not have a clinically significant impact on bioavailability means that patients won't need special instructions relating to meals.

Overall, these data suggest that RoxyBond would be effective and poses no additional risks beyond those of existing immediate-release, single-entity oxycodone products. Therefore, I believe RoxyBond should be approved for its intended use.

Turning now to the questions of abuse

deterrence, we must ensure that the abuse we're trying to deter is relevant to what is happening in the real world. Earlier, Dr. Dart clearly laid out the challenges we face, how to balance the needs of the pain patient while also protecting public health.

As a pain management and addiction specialist, I have a unique view on that problem. I see the need for opioid medications for analgesia, but I also recognize the frequency with which these medications are diverted and abused.

We know where most abusers get their drugs. SAMSHA reports that 69 percent of nonmedical opioid users obtain their drugs from a friend or family member either for free or by stealing or buying them, which is shown here in red and blue. Of those who obtain their opioid for free, 82 percent of those prescriptions were from a single licensed prescriber.

Now, in my practice, 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 to the patient, and especially cannot control the risk of diversion.

It is important to remember that the public health benefit of abuse-deterrent formulations are not only for patients but for anyone with access to their medicine cabinet.

There are several important real-world considerations to keep in mind for abuse deterrence. One is that most abusers start with immediate-release opioids, so an abuse-deterrent IR therapy like RoxyBond presents an opportunity to intervene at an earlier stage in the cycle of abuse and can be expected to deter some individuals from progressing to more dangerous routes.

Another consideration is that abuse-deterrent products are just that, deterrent. None are abuse-proof. All can be defeated with enough time, knowledge, and effort. Therefore, in my opinion, the clinically relevant questions to ask today about an abuse-deterrent formulation are: does the product make abuse more difficult, and

does it make the experience less rewarding? From my perspective, as I'll discuss in a moment, RoxyBond meets these criteria.

Based on the category 1, 2, and 3 data shown today, RoxyBond can be expected to deter intranasal and intravenous abuse, an important accomplishment for public health, as IR oxycodone is commonly abused by these risky routes.

Overall, RoxyBond slows release and resists extraction of oxycodone when manipulated compared to intact oral administration. As you've heard, this will be counterintuitive for abusers who usually associate manipulation for non-oral routes with a faster and greater high. RoxyBond is not expected to deter oral overconsumption. No product is yet to have that profile.

For the intranasal route, RoxyBond was not only difficult to get into an abusable form for snorting, it was also more difficult to snort than Roxicodone. The human abuse potential study also showed that manipulated intranasal RoxyBond led to lower and slower oxycodone absorption,

significantly lower drug liking and less willingness to take drug again compared to crushed and snorted Roxicodone.

In short, RoxyBond achieved two goals of intranasal abuse deterrence. The formulation made it more difficult to manipulate, and importantly, reduced the reward associated with snorting. In terms of IV abuse deterrence, RoxyBond was resistant to particle-size reduction and was difficult to extract.

When RoxyBond was manipulated and prepared for injection, it formed a viscous material that resisted being syringed. Further, even the worst case scenario for extracting oxycodone from RoxyBond for IV abuse required the kind of time, tools, knowledge, and materials that are generally beyond what I've seen substance abusers are willing to do.

When considering its ability to deter the dangerous intranasal and intravenous routes of abuse, it's my opinion that RoxyBond is a significant improvement over non-abuse-deterrent

products and should be approved with a label that reflects these properties.

I would like to close by placing abuse-deterrent formulations in perspective. Certainly, there's not a single simple solution to the prescription drug crisis. Doctors need to do their part by following prescribing guidelines and implementing risk management strategies.

Abuse-deterrent products are also an important component of the larger public health initiative. A joint effort of sponsors, the FDA, and these committees have led to the approval of nine abuse-deterrent opioid formulations for extended-release products. However, as you heard previously, there are no approved immediate-release, abuse-deterrent formulations.

It's time to start providing the same public health advantages to immediate-release products. The full impact of abuse-deterrent technologies on the prescription opioid epidemic cannot be realized until all prescribed opioids are abuse-deterrent. And in fact, the FDA's stated goal is to eventually

have abuse-deterrent formulations for all major opioids.

As a clinician treating both pain patients as well as those struggling with substance abuse, I look forward to the day when we have analgesics without rewarding properties. But until then, if an immediate-release opioid needs to be in the medicine cabinet, it should be one with abuse-deterrent properties.

Thank you for the opportunity to share my perspective. I'll now turn the lectern back to Dr. Aigner.

DR. AIGNER: Thank you, Dr. Gudin.

We would like to open this session up to questions, and we would appreciate if you could use the codes, which are included in the last page of the briefing document to keep the conditions blinded.

Clarifying Questions

DR. BROWN: Please remember, members of the committee, when you are asking clarifying questions for Inspirion to state your name for the record,

and if you can, please direct your questions to a specific presenter.

Dr. Kibbe?

DR. KIBBE: Just so you know where I'm coming from, I'm a formulator, okay? So I don't deal with abuse potential in patients; I deal with pharmaceutical formulations.

So earlier I asked about dissolution standards because the USP has a dissolution standard for an immediate-release oxycodone, and then I look at your CO-33, and even at 30 minutes, very little is coming out. And yet, your dissolution standard has to be over 75 percent.

Where am I going wrong? How am I not connecting these two correctly?

DR. AIGNER: You are correct that we are at 80 percent at 30 minutes in a special dissolution medium. It would not be solvent A or any of the solvents listed here.

DR. KIBBE: If I go to the USP, are you using the medium that the USP recommends for immediate-release oxycodone tablets?

DR. AIGNER: No. It would be -- no. It's different because the tablet is formulated to release in the GI environment, so the dissolution spec, 80 percent is tied to a dissolution method which mimics the GI environment.

DR. KIBBE: Right. So the USP requires 70 percent in 45 minutes in a hydrochloric acid solution, 500 mLs. Okay.

The next question is because of the mechanism of your tablet, what would be the impact on a patient who is achlorhydric?

DR. AIGNER: We did give some thought to if patient's achlorhydric, PPI treatment, and we have a slide. Here it is.

As to the searches of what PPIs do to the pH, we found two references. One is for esomeprazole, Nexium, the other one for tenatoprazole. And there for the median, you get an increase to 4.8 and 5, and you see the ranges as well. As you compare that now to what food does to the pH, we did some searching there, and fasted would be at 1.7, fed at 5.0.

Now, if we look at the results of our fed versus fasted -- results I think is a page behind this page -- you see that for RoxyBond fed versus fasted, very similar changes in pH. The AC increased for RoxyBond again, RoxyBond fed compared to RoxyBond fasted, 23 percent and an 18 percent increase in Cmax. And as you go to the last bullet point, Inspirion does agree with the FDA in the conclusion that a food restriction should not be recommended for RoxyBond.

So although the pH is important, it's not the only parameter driving the dissolution of oxycodone out of RoxyBond.

Would that answer your question?

DR. KIBBE: I think so. I have I think a question on CO-59, which goes to the same issue, so that basically -- let me see if I can find 59.

Your outer film is then pH independent?

DR. AIGNER: If we could stick to the code, it would be -- the outer film would be pH dependent.

DR. KIBBE: pH dependent?

DR. AIGNER: Dependent.

DR. KIBBE: Okay. Therefore, changes in pH that you just discussed should have an effect on that film.

DR. AIGNER: We studied it in our PK studies, and both at fasted as in fed, we did not see big differences in absorption.

DR. KIBBE: So that the pH-dependent outer film didn't act like it was pH dependent?

DR. AIGNER: It certainly would. We put a lot of resources into creating that barrier, and we had to pick exactly the right balance allowing it for effective release in the GI, being comparable bioavailable to Roxicodone, both fed and fasted. So there was some significant engineering going on to hit the right balance.

DR. KIBBE: But it also then prevents it from being dissolved conveniently in non-GI tract solutions --

DR. AIGNER: Outside the human GI system, as the data was shown in vitro, it significantly reduces the release and creates a significant

hurdle for extraction.

DR. KIBBE: Thank you.

DR. BROWN: Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. I apologize in advance. I have a few questions.

Dr. Dart, the slide CO-16, you talk about the different types of patients that are going to use opioids, and that makes complete sense. But the slides that you showed afterwards on the research on the preference and abuse, which population do those studies pertain to?

It would seem that it would only be the advanced abusers, which are the group that you said won't be affected really much by ADFs.

DR. DART: So the data that were shown are from the NAVIPPRO system, which are individuals entering treatment for substance abuse are used for illustration. I completely agree that they're going to be more likely advanced abusers who manipulate products more, and snorting and intravenous are higher there.

The point was just to say that these routes

are important because in previous advisory committees, sometimes that was a question that came up repeatedly. If you look at the poison center data, for example, you'd find that the oral goes up some, and those go down by roughly half.

DR. LITMAN: So the follow-up question then to that is I'm trying to get an idea, as I'm sure you have also, when you look at that initial slide, is who is being helped by ADF formulations across the board. Is there any kind of data that shows us what proportion of those beginning, those novice pain patients, or their friends, who are just starting to experiment?

DR. DART: The data are weak there. We don't have great evidence. The best we have, I think, are students in recovery high schools who have been questioned in detail about their progression from non-use to abuse of an opioid. And they do feel -- in those, it does seem like they start oral. They do progress along this pathway. The concept of manipulation, they on a survey will say that would have slowed me down or

stopped me from progressing.

Now, I want to emphasize that these are surveys of high school students, and so I'm not saying that's fact. But it gives me some support, intellectual support, to say that that mechanism is possible.

DR. LITMAN: Yes, I think we're probably thinking the same thing. I'm trying to get my head around how many people is this really going to help versus the cost to society, of turning all these drugs into ADFs. Thank you.

I have a follow-up question for Mr. Bianchi, please, or someone else. In slide CO-30, tool G was effective in rapidly getting a powder. I think I just wanted to confirm because I think the question was answered by one of the later speakers.

If you then take that powder using tool G, that's not injectable? Will that form that solid mass there that you showed in that nice picture?

DR. AIGNER: Yes. In small-volume extractions of the tool G, that creates that viscous solid mass.

DR. LITMAN: Even if you used tool G and you got it down to this fine powder easily, if you tried to inject it, it will be too difficult.

DR. AIGNER: Correct.

DR. LITMAN: Thank you. I apologize again. I think I had one more question for Dr. Webster.

The studies that you showed us, were those separate patients that were taking the different types of preparations, or is it the same patient that's comparing the likeability to each preparation? I'm trying to get an idea of whether it's relative.

DR. WEBSTER: You're talking about the human abuse studies?

DR. LITMAN: Yes.

DR. WEBSTER: Yes. They're the same patients -- same subjects rather get all arms of a study. So it's a comparison to themselves.

DR. LITMAN: So it's very possible that if someone snorted the manipulated Roxicodone and then next snorted the RoxyBond, it would make sense that it wouldn't be as good, right, as opposed to the

other way around or separate people?

DR. WEBSTER: Yes. It's randomized, so some are going to get RoxyBond first and some are going to get Roxicodone, some are going to get placebo, but that's correct. They're comparing each of the arms themselves.

DR. LITMAN: Thanks very much.

DR. BROWN: Dr. Emala?

DR. EMALA: Charles Emala. My question is slide 38 but probably also applies to 39 and 40. These are small-volume extractions where the percent of Roxicodone recovered was measured. And I'm curious. I assume that that's the amount that's measured in a small liquid volume that's left over mixed in with this gelatinous mix. I'm curious, in that liquid component whether any of the excipient concentrations were measured.

DR. AIGNER: We did not measure the excipient concentrations.

DR. BROWN: Dr. Choudhry?

DR. CHOUDHRY: Niteesh Choudhry. I've got two questions, both relate to public health impact,

probably picking up on what Dr. Litman was talking about.

The first is for Dr. Dart, and it's CO-21. What I'm trying to figure out -- we've talked a little bit, I think, about the cohort from whom this might be drawn already.

What I'm trying to figure out even further is to reconcile these numbers with the numbers that I understand to be related in the briefing book, which give slightly -- they come from the RADARS Treatment Center, so perhaps a different context, but rates of IV and intranasal abuse are somewhat lower than what's presented here.

If you could, Dr. Dart, kindly just clarify some of the discrepancy.

DR. DART: The main difference that always generates confusion on this issue is that these are the single-entity oxycodone products, which are openly preferred by abusers, like if you look at web postings and stuff, whereas a lot of the data includes the combination immediate-release and acetaminophen, for example, which do have lower

rates of snorting and intravenous abuse.

DR. CHOUDHRY: Great. Okay. Second question is for Dr. Webster, and it's about CO-54. I'm sure the same would apply for 55. Hard to find this paper online briefly, but tried to. And it seems as though the data on drug liking comes from abuse studies, and the other data on nonmedical use comes from population-based surveys, so different patients, and in fact, different potential outcomes.

Can you just give us -- do you have more detail that you can provide about these studies and what we should make -- I appreciate that the science is very nascent.

DR. WEBSTER: Well, I don't have much more. That's why I wanted to be clear in my presentation that this is embryonic research, I think. We are at the beginning of trying to understand real-world impact, a difference of 10 millimeters, or 20 millimeters, or even drug liking versus take drug again means.

But it is a start, and these are the only

two studies that I'm aware of that gives us some reference, and as I said, kind of an anchor from which now we go forward. And I think since we have now nine ER products out there with abuse deterrence, and hopefully today's, we will be able then in another year or two to maybe go back and take a look at a larger amount of data.

But this is taking a look at a surrogate for the real world, and we're trying to apply that to the real public health problem, but there's not much real good data.

DR. STAFFA: This is Judy Staffa. Could I add some clarity to that? Because we have looked at that paper actually, and I agree, it's very new science. But since we're very, very interested in trying to understand how the premarket data actually translate to postmarket, we took a careful look at this.

It is very crude. It's a very crude measure because the predictors are basically a meta-analysis of a whole bunch of heterogenous house studies, so they're all very different. So

the measures there are pretty crude, and then they're used to predict nonmedical use in the National Survey on Drug Use and Health, which, again, what we've learned about is that nonmedical use is also a very broad category.

The majority of it seems to be misuse, which is using someone else's medication to treat pain, which is very, very different than altering the product and snorting it and injecting it to get high.

So these are two very crude measures being connected, and the 10 percent reduction is really akin to more like 2.21 percent to 1.96 percent, so it's very, very small. So we applaud the effort to try to do this, but the actuality of it, I think, as Dr. Webster said, is going to be quite a long time before we get there.

DR. BROWN: Judy, can we use this data? Does it make sense for us to think of this as something that is useful for us to use against other products, or do we need to --

DR. STAFFA: In my opinion, no, because I

think, again, this is just too crude. And remember, none of the nine products that were approved actually have, to FDA's satisfaction, postmarketing data that actually demonstrates that they have reduced abuse in the real world and that that reduction is due to the product.

We're not there yet. I think we're diligently trying to learn more, and the companies are diligently working on that through their postmarketing required studies. So I think we don't know at all yet what these products are actually doing in the marketplace, but we are all trying to figure that out.

I think once we have that piece and we have a product where we believe the results of the postmarket study suggest that that product in the reformulation has changed abuse, then that could be the anchor which we then go back and look at the premarket work to see what were the dimensions in the premarket work for that product, and then we could use that to inform other product development.

DR. BROWN: Thank you.

Dr. Warholak?

DR. WARHOLAK: Terri Warholak. I have several questions. I'm going to ask them one at a time, if you're okay with that. Okay.

The first one, I believe, is probably for Mr. Bianchi. I was looking at the briefing booklet, and there's a page that indicates at 60 minutes intact, there's a significant more percentage of the active drug extracted. Then it was indicated on the next page that 60 minutes was not used because of a study about how much time abusers are willing to spend.

I looked at some internet chatrooms really quick, and at least from what I could find, that doesn't seem to be the case. It seems like they're willing to spend quite a bit of time. Could you tell us a little bit more about that study?

DR. AIGNER: Dr. Webster, would you be -- the study which indicated the 10 and the 16 minutes, is the study?

DR. WARHOLAK: Yes, it's the supporting study that abusers tend not to spend more than 10

to 16 minutes trying to manipulate a product for abuse.

DR. AIGNER: You have the Weisberg study?

DR. WEBSTER: Well, I don't know about the chatrooms that you're look at, but of the published data, we're looking at a meantime of about 15 minutes for most people that are willing spend time to manipulate something.

Obviously, there are people who will spend a lot more time. If they have the expertise and the interest, there are people who will spend a large amount of time. But the average amount of time or the median amount of time, I believe, is about 10 to 15 minutes.

DR. AIGNER: Also, if I just may add to Dr. Webster's comment, as we think about what abuse-deterrent products are supposed to do, put an incremental hurdle in to make it more difficult, less rewarding. If you're nothing but 30 minutes, taking that to 60 minutes, we would believe -- and we presented the data for Roxicodone, which is widely available -- abusable to date is 1 minute,

100 percent together with in solvent A, temperature A. And all the extractions, at 30 minutes, we showed the worst case. It's really important to study the conditions with pretreatments and extreme solvents, H, extended time periods, agitation, requiring additional steps before injection.

From our perspective, as we said, no product is abuse-proof today, only abuse-deterrent, and is that what an abuser has to do with 30 or 60 minutes together with all these conditions, a significant hurdle?

DR. WARHOLAK: Okay. My next question is, again, utilizing the quick search I just did, it looks like rectal abuse is something that people are talking about. Have you studied that at all? And if so, what have you found?

DR. AIGNER: We have not studied rectal abuse. If we had to guess, based on the data, all of us had to guess on the data, given the pH in the rectal environment and as you use your code sheet to decipher what were promising agents and

solvents, we would not think that RoxyBond would lend itself to rectal abuse. Roxicodone certainly would.

DR. WARHOLAK: Then the last one is I applaud you for making an effort to have abuse-deterrent formulations, but I wanted to think about unintended effects. So the MorphaBond ER uses the SentryBond technology, which is similar or the same to what you're using, right?

DR. AIGNER: Very similar.

DR. WARHOLAK: With MorphaBond ER, what kinds of adverse events have you had for IV abuse?

DR. AIGNER: MorphaBond has not been launched yet. It's just making large quantities for launch later on this year. Hopefully we can provide that data earlier next year.

DR. WARHOLAK: Thank you.

DR. BROWN: Dr. Walsh?

DR. WALSH: Thank you. Sharon Walsh. I have a couple of questions. I think that they're probably all for Dr. Webster. If I understand it correctly in the HAL study, the intranasal RoxyBond

was first manipulated with tool G, and that tool from the in vitro data looks very effective at reducing particle size.

Do you have a picture of the preparation the subjects then insufflated in the study available for us to see?

DR. AIGNER: We actually do not have in the deck right now, but if it would interest you, we would find it over the break and show it to you after the break.

DR. WALSH: Okay. I appreciate that.

I'm curious, given the in vitro data that show the very small particle size, the fact that the subjects uniformly rated the snortability of the product as being very low compared to the comparator, can you comment on what was it about the drug that made it difficult to snort?

I don't see -- you haven't discussed any addition of an aversive agent or anything like that, so I'm wondering what it was about the subjective experience.

DR. WEBSTER: Even though it was in a small

powder like, it wasn't really a powder. I think that the subjects sometimes do a comparison because they get everything, and obviously, the Roxicodone is very fine, and it's easy to insufflate. But there were granules within the RoxyBond, so it was more difficult for them to insufflate, and it was more irritating.

We have a slide actually, if I could have you pull up on the irritation slide, which can reflect why. It's kind of an indirect answer, if you can give that to me, and show you the score here.

You can see here the difference between RoxyBond and Roxicodone on these indices, on irritation, burning, runny nose, nasal discharge, facial pain, pressure, and nasal congestion. That doesn't directly go to the ease of snorting, but it does probably have an impact on their perception of ease of snorting.

DR. WALSH: Thank you. I have a follow-up question about this. If you look at CO-46, which are the pharmacokinetic data, the curve for the two

intranasal formulations really look identical in shape, and the exception, the difference is simply that the concentrations are lower for RoxyBond that's manipulated.

Given that the subjects are saying that they're having difficulty snorting it, I'm wondering if this difference is really just that they are not snorting all of the drug that's available to them.

DR. WEBSTER: No, they snorted it all unless they swallowed it and we didn't detect that. But we don't think that that was a factor. They could insufflate the Roxicodone in a minute and in a minute and a half or 2. They were very similar in the length of time formed to insufflate, but not more than 2 or 3 minutes for both of them.

I think that it all was insufflated, and I think it was just a slower release because it was manipulated. That's the understanding I have from I think the compound itself.

DR. AIGNER: If helpful, so RoxyBond as we thought about for the snorting route what we'd like

to do, and we indicated earlier RoxyBond, either intact or manipulated, relating to the pH of the nose is not releasing as fast.

So to be honest, we're not surprised that the curve was lower. We believe that the RoxyBond itself just releases a lot less in the nasal cavity than Roxicodone does, and there's plenty of in vitro data.

DR. WALSH: Right. I think that the thing that you point to in the briefing book is that there's a difference in the Tmax, which we think is relevant to the abuse experience. I think the Tmax -- I don't remember what table it was in, but it was 1 hour compared to 1.8 hours. When you look at the range of scores, actually the ranges look virtually identical for the two products.

So I guess the final question then for Dr. Webster, since you think that they're snorting all of it, but you also said that some of it is more granular, do you think that there's an appreciable amount that is being swallowed because of the particle size?

DR. WEBSTER: I'd have to guess on that, but I do think that some of it's probably being swallowed because it's large enough. That's about the only other explanation I have, other than the slow release that may be something that's about the formulation because of the pH.

DR. WALSH: Thank you.

DR. BROWN: Dr. Schmid?

DR. SCHMID: Chris Schmid. This is I think more for Dr. Webster. The same set of slides, 46 to 51, let's say. My question is really about the oral formulation. It looks to me as if the Roxicodone manipulated is liked about as much as the RoxyBond oral, and if you look at the Cmax and the mean drug liking curves, the peaks are fairly close to each other.

I'm assuming that the manipulated taken intranasally would be liked or you'd get the effect quicker than you would in an oral form. So since you didn't do a Roxicodone oral form in the crossover, I'm just wondering what we should think about the fact that the RoxyBond intact is getting

results very close to the Roxicodone manipulated.

DR. WEBSTER: I'm not sure I understand your question, but I think that if you saw an oral Roxicodone and an oral RoxyBond, they'd probably be very similar. I think we have that data, but I'll show you here something. Slide up.

This is the liking, and you can see this is the liking of -- the light blue is RoxyBond intact, and the Roxicodone manipulated with the red, and then you see the RoxyBond manipulated. So there's a delay, a significant delay, or I should say an earlier Tmax for Roxicodone when it's manipulated. But the oral RoxyBond and the manipulated are similar up to about a half an hour.

DR. SCHMID: So if I look at slide 47, then, for example, which shows an 83 percent mean drug liking for the manipulated Roxicodone and 81 for the RoxyBond oral, those are pretty much the same. But you're saying here that it would take an extra half hour for them to reach the peak.

DR. WEBSTER: Yes.

DR. SCHMID: That doesn't seem to bother

them, or how do I interpret that?

DR. WEBSTER: This is an intranasal abuse-deterrent formulation. If you take it orally, they're going to have the same Cmax. The difference here is the timing, and that is important to the subjects. So they want to get it as soon as they can, and any delay would be a problem.

Did I answer your question?

DR. SCHMID: I guess. I'm just wondering why their -- slide 47 is their maximum drug liking, so that seems to be fairly similar between the two, and yet I would think that if it took them longer to get the high, that they'd like it less. That's what I'm wondering.

DR. WEBSTER: Yes. That's just the data.

DR. AIGNER: But would it make sense to go back to the time curve of liking and really explain why abusers do snort oxycodone?

DR. WEBSTER: This is the drug liking that we have. I'm not sure what your point was, Stefan. Go ahead.

DR. AIGNER: Roxicodone IR is widely snorted, and I believe this graph explains why people really appreciate snorting Roxicodone today, and RoxyBond does not allow them to get that benefit.

DR. WEBSTER: Yes. That's what I was saying. So it's the earlier Tmax. Same Cmax, but earlier, and it's that ratio. That's what important. It's always the Cmax over Tmax. You can get to the same Cmax, but if you get there faster, it's going to be liked more.

DR. AIGNER: Dr. Dart?

DR. DART: Just for clarification, this is specifically at-the-moment liking. And so I think that's what's being missed here, is that each of those points is at right now, what do you think, not what has been your experience over the previous 30 minutes or half hour -- 30 minutes or whatever the time period is.

You can see where the blue line eventually gets there, and that gets back to Dr. Aigner's point, that that's the whole point, is it takes

them a long point to get there.

DR. AIGNER: And abusers do appreciate that very fast ramp up in the red line, and at the earliest time points, they've got a significant euphoria versus for the other lines, they do not. The same for injection, that follows that rush immediately, is what they seek.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. I have a couple of questions. My first question is for Dr. Bianchi with respect to slide CO-33. It seems to me that for solvent H, the large-volume extraction, that more oxycodone was released in the intact RoxyBond as compared to the manipulated RoxyBond at 30 minutes. I just wanted to make sure that I'm interpreting that correctly.

MR. BIANCHI: Yes, you are.

DR. ZACHAROFF: Is there any data that you have along different time points, as was mentioned earlier, to see whether that continued with time beyond 30 minutes?

MR. BIANCHI: No, we don't have any

additional time points.

DR. ZACHAROFF: Any thinking as to why more was released from the intact formulation as opposed to the manipulated one?

MR. BIANCHI: Well, the design of the RoxyBond is to slow the release, and that's exactly what it did, slow the release when it was manipulated.

DR. ZACHAROFF: So when it's intact form in a solvent, does it not necessarily act as an abuse-deterrent formulation?

DR. AIGNER: If I could answer that question, too.

DR. ZACHAROFF: Sure.

DR. AIGNER: On the left-hand side, you see Roxicodone -- and it's always very easy to miss that -- Roxicodone at 1 minute in solvent A, manipulated gives you 100 percent. I think it really was 100 percent.

DR. ZACHAROFF: Right.

DR. AIGNER: Now, the blue numbers in graphs of 30 minutes, so if you now take the most

releasing agent, solvent H at 30 minutes, you get to a little more than 22 percent, which that's how RoxyBond is formulated, a very significant reduction in release if not exposed to the GI environment versus Roxicodone, very easily, quickly abusable, and available to be abused in any route of administration.

DR. ZACHAROFF: Right, but in its intact form compared to its self-manipulated, it seemed to release more oxycodone in solvent H?

DR. AIGNER: You're correct. I would turn it around. We formulated it so if you manipulate it, you do not get an increase, and that's what you see.

DR. ZACHAROFF: Okay. Thank you.

Second question is for Dr. Gudin with respect to the clinical utility of abuse-deterrent single-entity formulation of oxycodone. I guess my question would be who do you think would be an appropriate candidate for an abuse-deterrent formulation of this medication?

Would you consider it to be all patients for

whom immediate-release oxycodone is considered, or would it be a situation where maybe the indications would not only be for whom patients have moderate to severe pain where an opioid analgesic is required, but maybe who are at an increased risk of aberrant drug-related behavior?

DR. GUDIN: Thank you, Dr. Zacharoff, for your question. I think currently that's a question that the whole medical community of prescribers is considering right now, where do abuse-deterrent formulations best fit into the treatment landscape of opioids?

Currently, I have some colleagues who are selecting them in the extended-release formulations only for the patients at risk or with high-risk factors for substance abuse.

Looking at the larger public health picture, as you heard a little bit this morning, knowing that the end user is often not the patient sitting in front of us, I think the greater public health initiative and where I think our community is moving is to having all products with some

abuse-deterrent technology.

So the way that I look at ADFs is that they should be prescribed to any patient who gets an opioid if you want to consider the larger public health benefit of avoiding misuse and abuse outside of the patient sitting in front of you.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: Jeff Galinkin. So my first question is a follow-up to Dr. Emala's question, and are all the excipients in this generally regarded as safe in that category?

DR. AIGNER: They qualify through the inactive ingredient database, or they're in a currently approved product.

DR. GALINKIN: My second question really is a follow-up to that last question. It seems to me that the effectiveness of these drugs will eventually be based on market penetration, and how will both the FDA and your company look at this in postmarketing surveillance in terms of the effectiveness of ADF products?

Do you guys have any plans on how to look at

that and how it's affecting abuse, since it's not naive enough to think that suddenly we're going to replace all of the oxycodone out there with an abuse-deterrent formulation?

DR. AIGNER: We're definitely thinking about phase 4 right now. It's an evolving field, and certainly, gathering all the information from the existing surveillance data by age group, by geography, by route of administration, to design going forward formal studies, we're looking forward to interact with FDA and other experts to design those.

But you're correct. Highlighting some of the issues, how much utilization do you have? Are you looking at OxyContin being switched over? That's certainly something we have to figure out over time and how to design those phase 4 studies.

DR. BROWN: Dr. Staffa?

DR. STAFFA: Judy Staffa. As you saw in one of the sponsor's slides, all of the products that are approved with abuse-deterrent properties in the label have postmarketing required studies. What we

started to do and what was reflected in that slide is more of a two-phase approach, recognizing the challenges with market penetration, that if a drug is not being picked up and prescribed, it's going to be very difficult to have the statistical power to actually look at it.

So we have a two-phase where we asked sponsors to begin looking and monitoring the utilization, monitoring the anecdotal data with regard to abuse, and then we make a mutual decision when we get to the part where we believe there's enough penetration to actually support a formal study, and then we move into that phase.

So I would assume that would be what would be planned with this product as well.

DR. BROWN: We will now take a 15-minute break, and panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume our discussions at 11:15. We will get to the remainder of our questions after the FDA presentation.

(Whereupon, at 11:01 a.m., a recess was taken.)

DR. BROWN: If we can take our seats and continue. We'll now proceed with the FDA presentations.

FDA Presentation - Tracy Minh Pham

DR. PHAM: Good morning. My name is Tracy Pham. I'm a drug utilization analyst from the Division of Epidemiology, Office of Surveillance and Epidemiology. I will present the outpatient retail utilization of oxycodone-containing analgesics to provide context for today's discussion.

The outline of my presentation is as follows. I will present the outpatient retail utilization patterns of oxycodone-containing analgesics followed by the data limitations and a summary of my presentation.

Our analyses include all oxycodone-containing IR and ER products to put into context of the use trends of single-ingredient oxycodone IR products compared to other

oxycodone-containing products.

For the purposes of today's presentation, we focused on the outpatient retail setting, which is the primary setting of care where oxycodone-containing analgesics were used. To conduct these analyses, we used multiple databases with different features. I will briefly describe each database before presenting the results of each analysis.

We first start with the prescription utilization data. We obtain the prescription utilization data from the Quintiles IMS National Prescription Audit database, which measures the dispensing of prescriptions from outpatient retail pharmacies to patients. The prescription data are protected to provide national estimates of drug utilization.

Throughout the study time period, combination- and single-ingredient oxycodone-containing IR products accounted for the majority of total prescriptions. As shown by the red line, prescriptions dispensed for single-ingredient

oxycodone IR products more than doubled from 7.1 million prescriptions in 2009 to 17.8 million prescriptions in 2016.

Prescriptions dispensed for combination oxycodone-containing IR products, as shown by the green line, remain relatively steady. Prescriptions for single-ingredient oxycodone ER decreased by 45 percent from 7.3 million prescriptions in 2009 to 4 million prescriptions in 2016.

We now move on to the patient data. We used Quintiles IMS Total Patient Tracker database to obtain the national estimates of patients who were dispensed oxycodone prescriptions from U.S. outpatient retail pharmacies.

Overall trends in the patient data were similar to the trends observed in the prescription data. The number of patients who were dispensed single-ingredient oxycodone IR products also doubled from 2.4 million patients in 2009 to 5.9 million patients in 2016.

We now move on to the prescriber specialty

data for single-ingredient oxycodone IR products. Based on dispensed prescription data in 2016, primary care physicians were the top prescribers for single-ingredient oxycodone IR products at 36 percent of dispensed prescriptions, followed by midlevel practitioners at 24 percent, and anesthesiologists at 7 percent.

Now we will transition to the analysis of diagnoses associated with the use of single-ingredient oxycodone IR products. To determine this, we used inVentiv's Health Treatment Answers database, which was derived from monthly surveys of 3200 U.S. office-based physicians who reported all patient activity during one typical workday each month. These data are nationally projected by physician specialty and region and are based on the number of office visits where drugs are mentioned, therefore providing insight into prescriber intent.

In 2016, the top group of diagnoses associated with the mentions of single-ingredient oxycodone IR products were conditions related to

the diseases of the musculoskeletal system and connective tissue such as back pain. The diseases of the nervous system followed with diagnoses such as unspecified chronic pain. Neoplasms accounted for 6 percent of the drug use mentioned during the examined time.

I will now go over the limitations of the databases used to conduct these analyses. There is no linkage between a dispensed prescription and a diagnosis, and no medical charts are available for data validation. The outpatient retail dispensing trends might not apply to mail order, specialty, or nonretail settings such as inpatient and clinic settings.

The diagnosis data are obtained from surveys that capture the number of times a product has been reported during a patient visit to an office-based physician and may underestimate or not capture prescribing patterns of physicians who practice in other settings such as hospice care, pain, or cancer clinics located in the hospitals or oncology clinics.

In summary, the outpatient retail utilization of single-ingredient oxycodone IR products more than doubled from 2.4 million patients in 2009 to 5.9 million patients in 2016. The top prescribers were primary care physicians followed by midlevel practitioners. The top groups of diagnoses were conditions related to the disease of the musculoskeletal system and connective tissue such as back pain. Thank you.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for the FDA or the speaker?

Dr. Zacharoff?

DR. ZACHAROFF: Yes, just one clarifying question on slide 10, the survey by inVentiv of the 3200 office-based physicians. Is there any breakdown of specialty of that group of physicians? Were they primary care or experts as well?

DR. PHAM: Yes, that would include family practice, general practice, doctor of osteopathy, internal medicines.

DR. ZACHAROFF: So basically primary care.

DR. PHAM: Yes.

DR. ZACHAROFF: Okay. Thank you.

DR. BROWN: Dr. Morrato?

DR. MORRATO: Elaine Morrato. So the FDA won't be presenting the drug-liking studies and the in vitro, so are we to assume then that the FDA is okay with the presentation that we received already?

DR. HERTZ: Shaking your head doesn't make it into the record.

(Laughter.)

DR. HERTZ: Sorry. Yes, we do not have any disagreements with the interpretation of the data.

DR. MORRATO: Thank you.

DR. BROWN: Dr. McCann?

DR. McCANN: Thank you. Mary Ellen McCann. On I guess the fourth-to-the-last slide, I don't see a number for it, on the diagnosis data, I just want to make sure.

When you have injury at 7 percent and then you have diseases of the musculoskeletal system and connective tissue at 47 percent, are they exclusive

or not, meaning a lot of times you injure your back. Which group would that be included in?

DR. PHAM: They were grouped separately. They were not --

DR. McCANN: So the injuries were non--musculoskeletal injuries?

DR. PHAM: Yes.

DR. McCANN: Thank you.

DR. BROWN: Dr. Choudhry?

DR. CHOUDHRY: I've got a brief question, which is partly speculative, and I'm wondering if you might offer or someone else at the FDA. So if we look at the trends, there's clearly a trend upwards in IR prescribing, and I think that's quite clear, so, for example, slide 8 in your deck.

I'm wondering if we had to imagine what the impact of more recent guidance, either CDC or state level prescribing restrictions, might have on IR relative to ER use.

DR. HERTZ: Sorry. This is Sharon Hertz. I'm apologizing already because that's a discussion item, and these are clarifying questions. Our

rules say that discussion should not occur until we've heard from everyone, including the open public hearing.

DR. BROWN: Dr. Kibbe?

DR. KIBBE: I had a small clarification. On the end, the previous speaker said that the excipients used in the product were generally regarded as safe, but the generally-regarded-as-safe list, or the FDA list of excipients, lists them with a route of administration. Okay?

The polymers we use in oral preparations -- and I was the editor-in-chief of the Handbook of Pharmaceutical Excipients, so I can speak with some expertise -- come from or derived from in one case from cellulose. And we are not termites. We cannot digest cellulose. So it goes through the GI tract.

The others are the polymethyl methacrylates, which are all artificial, and they cannot be digested either. So they go through the GI tract, and they're never ingested, so they don't have to be excreted because they're egested. But if you

put them in intravenously, they're not going to go anywhere, and they'll probably accumulate in capillary beds.

I have a real feeling that if there is sufficient number of polymers being injected by drug abusers, they're going to have early kidney failures, but we have no definitive toxicity data on -- so I've advocated that there should be a black box in these products that warns the physician to warn the patient that if anybody uses these other than they're intended, that they can do serious harm to their cardiovascular system and their renal system.

DR. HERTZ: Okay. So that's also discussion.

(Laughter.)

DR. HERTZ: I know it's unusual for us not to present separately our interpretation of the results. I don't know if we want to break early or what, but if there's no more actual clarifying questions for the presentation that we just gave or from this morning --

DR. BROWN: We actually do have some clarifying questions from this morning, if we could just move -- Mr. O'Brien, did you have a clarifying question for the FDA?

MR. O'BRIEN: I think it's a clarifying question. Regarding slide 11 and the diagnosis data, we're able to identify the largest population of patients that are using single-entity IR. Do we have any data to suggest of that group what is the potential or the prevalence of abuse within that group?

DR. STAFFA: This is Judy Staffa. I can try to tackle that. These data are simply about -- they're office-based practice, so they focus on prescribing. And they're talking about a mention of a drug during an office-based visit, and then the diagnosis of that patient that the physician was seeing during that visit. So it's not longitudinal; it's a snapshot in time.

The answer is no, but part of what we've asked the manufacturers of extended-release and long-acting opioids to do is to look and assemble

cohorts of patients who are prescribed those drugs, and to follow those patients over time, and to better understand the experience of a patient who is prescribed an opioid and what happens to them with regard to abuse, misuse, addiction, overdose, and death.

So we're hoping to have that data in the future, but right now we don't have any such data.

MR. O'BRIEN: I asked because I am one of those patients, and that's the patient community that I represent. So I'm very interested to see because our experience is we don't snort and we don't do intravenous. So I'm very curious to see what the data is regarding that large population group.

DR. BROWN: We're going to move ahead or move actually back to this morning.

DR. GALINKIN: I have a clarifying question.

DR. BROWN: Okay.

DR. GALINKIN: In terms of the single-use products, one of the reasons that a lot of the single-use products get prescribed -- is in kids

because we've started to divide those things up because of several publications in the AP Journal.

Do you have this broken down into under 18 and over 18?

DR. BROWN: You said single-use, but it's single entity?

DR. GALINKIN: Yes, single entity. I'm sorry. Single-entity.

DR. PHAM: Tracy Pham, FDA. We did not do that analysis, but for the future, we can take a look into that and stratify the data by age.

DR. HERTZ: This is Sharon Hertz. Usually the number of pediatric prescriptions is dwarfed by the number of adult, though, so if that helps.

DR. BROWN: Dr. Morrato, you had a question for the sponsor?

DR. MORRATO: Yes, from this morning, so thank you.

I'm wondering if -- it builds off of what Dr. Choudhry was saying about the papers, and I know Dr. Staffa talked as well. I was thinking of it in another way and thinking of really where it's

a subjective reason we're here or relative, and it's evolving as to what constitutes a dedicated user, what makes it more challenging, what magnitude of reduction in liking is meaningful, et cetera.

I was wondering if the sponsor could maybe explain or share a little bit what goes into the design of these liking studies and how they're powered in terms of what is commonly used as a clinically meaningful difference, not just looking at the p-value, which can be influenced by the number in the sample.

DR. AIGNER: Could I ask Dr. Webster to comment?

DR. WEBSTER: So there's a little history behind these. As you know, or probably know, they were originally designed just for basically scheduling, to schedule a drug, and to look at the abuse potential relative to schedule I, II, III, et cetera.

Over time, we've gotten to where we are, and along that course, the number of subjects who have

been enrolled have increased because we're trying to understand more. And often there are more arms to a study, which obviously means that we are doing a lot more comparisons, and then the statistics require that we have larger populations.

Now, we don't often power necessarily for these studies, although there are sometimes situations when we will be looking at a difference of something that we want to know depending on what that endpoint is. And it may not be the primary endpoint because, as we just talked about, we don't know what difference is clinically meaningful in the real world. We're kind of trying to creep up to acquiring that knowledge.

So the size of these groups used to be in the 20s, sometimes in the teens, some 15, 20 years ago, but now most completers are in the mid-30s to low 40s. Sometimes if we are using two controls, two active controls and we've got 3 or 4 arms, at least three of the test drug, we may have to get into the 60s, and particularly if we want to power.

So if we want to power take drug again, for

example, which is in a totally different ballgame, requiring far more subjects in order for us to -- depending upon what that power is set as.

There isn't an answer to your question. This is a discussion, and it is an evolving discussion where we're trying to get as much information that really does apply to the real world.

Is that helpful or not?

DR. MORRATO: A little. I'll stick with clarifying. So for these particular studies we're looking at, it wasn't a prospective power. It was more of a historical we tend to have this many in an arm.

DR. WEBSTER: Correct.

DR. MORRATO: Is that correct?

DR. WEBSTER: Yes.

DR. MORRATO: And it may be obvious to others, but I'm less familiar. Is the crossover design the way this was done here common as well?

DR. WEBSTER: Yes. I'd say 90 percent of the time. Unless you have a really complicated

study in a large -- there may be some pharmacologic reasons. It may be a population size. We've looked at a couple of modified crossover designs, but otherwise, they're all crossover.

DR. MORRATO: Okay. I think it's nice that in the FDA's briefing materials they're starting to provide that historical, if you start to look across all of these drugs that are going through, some sense of what is the general magnitude. So I just wasn't sure of the variance in study design.

DR. WEBSTER: You could imagine a parallel design would be in the hundreds, and that's cost prohibitive.

DR. MORRATO: Right. Thank you.

DR. BROWN: Dr. Amidon?

DR. AMIDON: Yes, a question from earlier this morning. This is Greg Amidon. In one of your early slides, you mentioned, slide 4 I guess, that RoxyBond uses your SentryBond technology and pointed out that there's an FDA approved, although I understand not on the market yet. MorphaBond ER uses that technology.

I'm wondering if you can provide us any perspective on maybe similarities or differences between these and how they might relate to abuse deterrence by nasal and IV route that might be helpful or insightful.

DR. AIGNER: Since we're in the open session now, if you go back mentally to the closed session, many of the components -- actually, all the components are identical. The major difference is for MorphaBond, we had to match the release profile for a long-acting morphine product, not for an immediate-release oxycodone product.

As we tried to highlight before, for making an abuse-deterrent product for an extended release, you can, A, lock in that maintained release, sustained release, and if you do the particle-size reduction, you grind it up, whatever you do, you don't get a dose dump and get all the opioid available immediately, and of course it can make the tablet harder and hard to manipulate.

For MorphaBond, the application was to maintain the release, a sustained release. For

RoxyBond, we created something novel because it had to be an oxycodone immediate-release product where we actually decreased, made it slower, made it lower, the release if you do not take it as intended.

So it's all about what the rate of release is for the active and what route of administration. Does that make sense?

DR. BROWN: Dr. Shoben?

DR. SHOBEN: I just had a quick question about your clinical PK data showing the bioequivalence, and you said you started with 75 subjects and ended up with 58 completers.

Can you talk about that drop-out rate? That seems fairly high in a should be very short trial.

DR. AIGNER: On that one, I will have to get back to you after the break, if that's okay.

DR. SHOBEN: Yes.

DR. AIGNER: Okay, good.

DR. BROWN: Dr. Kibbe?

DR. KIBBE: I gave my speech already. It would be nice to look at the slide that was in our

background material on the bioequivalency because it wasn't presented.

DR. AIGNER: We can pull that up.

DR. KIBBE: Because I think it shows a relatively tight confidence interval for Cmax and AUC, and all to the left, right? It's a little bit lower than 100 percent in all cases, right?

DR. AIGNER: As you're familiar, you should stay in the 80 to 100 --

DR. KIBBE: Yes, I understand that it's an acceptable bioequivalency test. I'm just saying that's what it looked like, and it looked like your product was a little bit slower but not clinically, significantly slower.

DR. AIGNER: Yes, we agree with FDA that it's not clinically significant.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: This question is for Dr. Webster. It pertains to slide 52. Dr. Walsh brought up this issue earlier. I'm still struggling to understand why the means of snorting scores are so much higher for the RoxyBond.

In the category 1 studies, the manipulation of the medication with tool G resulted in 92 percent of the drug having a particle size of less than 2000 microns, so very fine powder. You think it would be very easy to snort.

I'm just wondering, were the same conditions for physical manipulation used, and was there any quality control to make sure that you attained the same fine powder in the human abuse potential study?

DR. WEBSTER: No. I think we did what we could to make it as comparable as possible, but we used different tools. If you remember, it was -- I get confused on these tools, but they were different tools. You can take a look at your -- one, we had a simple way to crush Roxicodone, and we used a different device to manipulate RoxyBond. But they ended up having visually the same appearance, but they weren't the same. The RoxyBond had little particulates that were unable to be made to the same size that we had with Roxicodone.

Now, under 2000 is not -- I mean, that's still pretty large for snorters. 2000 particle size is a pretty large piece. We know that in order to insufflate, you have to be below 500. You really need to get it down very, very small for it to cross the mucosal membrane. And there may well have been some that's above 500 with the RoxyBond. I don't know.

DR. BATEMAN: But the tool was tool G, which is the same as what was used in category 1, right, for the manipulation of RoxyBond?

DR. WEBSTER: Yes, yes.

DR. BATEMAN: I guess just along the same lines, is the way that the subjects rate ease of snorting related to the effects that they observed? So if they don't get the high that they expect, could that influence the way in which they evaluate ease of snorting. And I guess the way of getting at that would be looking at the ease of snorting associated with the placebo.

DR. WEBSTER: It's not intended, and we do a lot of education for these studies. For all of the

assessments, we routinely put them through an education about what we're assessing and what we're not assessing. So I can't tell you that a subject might not crosstalk with their impression, but that's not the intent, and we do everything we can to separate their impression of what we're asking.

DR. BROWN: Dr. Schmid?

DR. SCHMID: I just want to ask a question about the sample sizes for the intranasal study. They weren't on any of your slides here, but one of the documents that we got, I think table 11, it describes the adverse events. The sample size listed there are 30, 30, 31, and 29 for the 4 crossover groups.

I'm wondering, was 31 the number that were enrolled in the study, and what did you do about any dropouts or missing data? Because there obviously was a little bit here since these aren't exactly equal.

DR. AIGNER: Dr. Webster?

DR. WEBSTER: I did not hear the question. I apologize.

DR. SCHMID: What I'm just trying to find out is was the number 31 that was actually initially enrolled in the study?

DR. WEBSTER: Yes.

DR. SCHMID: Okay. So what we're seeing here is that there's 1 individual in 2 groups and 2 individuals in another group that didn't complete the crossover; is that correct?

DR. WEBSTER: That's correct.

DR. SCHMID: And so presumably, that didn't have any effect on the final results.

DR. WEBSTER: That's my understanding. That's correct, yes

DR. AIGNER: I think 2 subjects discontinued early and never completed all forms, and not including those or including them made no difference to the ITT statistical analysis.

DR. BROWN: Are there any other clarifying questions for -- Mr. O'Brien?

MR. O'BRIEN: For Dr. Webster, just a clarifying question. In the cohort, the population that's used, which is recreational, nondependent

users, forgive me if this is a simple question, but how do you screen for that, and how do you determine nondependent recreational users?

DR. WEBSTER: We ask how often they take an opioid. Actually, we ask how often they take any illegal substance or any medication, but they're required to have taken a minimum amount in the last year and within the last 3 months.

Once they're brought in, prior to a discrimination phase where we give them an active drug to determine whether or not they can actually detect liking, we give them naloxone. So naloxone is given to assess whether any of them go through withdrawal. So they won't be physically dependent. If they have any withdrawal, then they're not allowed to proceed.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: This is for Dr. Webster, and this is off of what Dr. Bateman was asking with respect to the 2000 micron size. On slide CO-29, it talks about Roxicodone being easily manipulated with tool E, and it sort of implies the idea that

less than 2000 microns is an easily reduced fine powder that could be snorted and prepared for IV abuse.

I hear what you're saying about the less than 500 micron size, but it seems to me that the reason that no other tools for the Roxicodone were evaluated is because 100 percent of particles were reduced to less than 2000 microns. And that means it's a fine powder that could easily be snorted or prepared for IV abuse.

So it doesn't seem necessarily a direct line then that that wouldn't apply then to slide CO-30 where 92 percent of RoxyBond was reduced to less than 2000. Could you clarify that for me?

DR. AIGNER: Can I take that, Dr. Webster, help you out on this one?

DR. WEBSTER: Sure.

DR. AIGNER: We have our slide here. As we thought about best summarizing it, we just used that cutoff of 2000 microns just to make it -- of course, we want to have the smallest percentage of very large particles, but in reality, we, of

course, studied the particle size across different segments. You see about 425 microns, 150, above 153, below 53.

Here we really studied tool G, consistently had the best provision of small particles, and that description, less than 2000, is actually not perfect. But as you look at particle-size reduction, you see why we picked tool G for a snorting study because it gives you the best distribution for small particles.

DR. BROWN: Any other clarifying questions for the FDA or for the sponsor? Yes?

DR. BATEMAN: So I guess given those data, when we are looking at the drug-liking curves, if only particles that are less than 500 are going to be absorbed nasally, if abusers were able to further manipulate the drug to obtain a finer particle size, the curves may look very different.

I think we've been saying that the lower time to Cmax and all of that is related to the binding, but could it be just that not enough of the drug is manipulated into a powder that can be

nasally absorbed?

DR. AIGNER: Actually, we did use tool G for 2 minutes, but we also studied up to 10 minutes. So we have data that as you increase the time in tool G up to 10 minutes, you really see after 2 minutes, the particles don't get any smaller.

The other interesting piece about RoxyBond -- and we believe that is unique -- particle-size reduction really does not accelerate release, and RoxyBond's particles are designed not to release in the nasal cavity. It is really coming out quickly in the GI environment, and the nasal cavity is very, very different.

So we weren't surprised by the results of a drastic reduction compared to Roxicodone because Roxicodone comes out in any solvent 100 percent in 1 minute. So that is very consistent just with the way RoxyBond is formulated and with all the in vitro experiments we have shown.

DR. BROWN: Dr. Walsh?

DR. WALSH: Thank you. Sharon Walsh. I'm still a little bit perplexed by all of this because

the data that you showed, then, shows that actually the majority is even smaller than the threshold that was described.

The only PK data that we saw were the mean data. I'm wondering whether or not inspection of the individual PK curves showed any evidence of some later delivery.

So if not all of the reduction in exposure is due to the technology and because the particle size, some of it's getting into the GI tract, you would expect then that that would have good release properties because of the way that the deterrent technology is designed.

Was there any evidence of later absorption that would be more correspondent to oral absorption for individual subjects?

DR. AIGNER: This might actually be a great opportunity to revisit something we heard in the break, a quick discussion where they really explained it well, the reason why subjects snort Roxicodone, not just take it orally. Maybe we'll have a go with that again real quick.

Dr. Webster, is that something -- because we want to make sure we create something which is abuse-deterrent for the route the abusers today abuse Roxicodone. And they have a very good reason why they snort Roxicodone over taking it orally. You could always take Roxicodone or RoxyBond intact orally. That's something that we can address, as the oral route.

But they have a very good reason why they snort it, and that is what we want to take away from the abuser in making RoxyBond abuse-deterrent and making that route not viable.

DR. WALSH: Thank you. I agree, and I understand what that is. And I'm happy to have Dr. Webster address that. But what I'm actually trying to understand is how the product is performing.

DR. AIGNER: You want to find the reasons? Let us actually think over the break. I believe I understand what you're saying, and it's a very good question.

DR. WALSH: And, Lynn, if you want to

respond to whatever --

DR. AIGNER: I believe it might be worthwhile clarifying that.

DR. WEBSTER: Yes. I don't know that we have the data, and we can look after the break to see if there is something that would suggest that there is a second phase of absorption, which is I think what you're asking, right?

I don't know, and I think that that is a probable explanation, that some of it is swallowed, and it's probably absorbed. But if so, that's the purpose. If that's what happens, then obviously, that's the intention, so that it's not going across the mucosal membrane and that they have a high from it nasally. But let's see if we can find some of the data for you after the break.

DR. BROWN: We're now going to break for lunch. We will reconvene again this room at 1:00, and please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during

lunch amongst ourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 11:53 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. BROWN: We're going to start with the open public hearing portion of the committee meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, 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 for your travel, lodging, or other expenses in connection with your attendance at this meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and fairness. 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?

MR. MANDALE: Good afternoon. Michael Mandale. By way of disclosure, my travel-related expenses are being paid today.

As I said, good afternoon. My name is Michael Mandale. I'm not in recovery. Rather, I'm here to tell you the story of a few hundred people who are. I encounter these people through my work in the southern portion of New Jersey, just outside of the Philadelphia metro area.

I am the chief executive officer of Solstice Counseling and Wellness Centers, an agency specializing in intensive outpatient substance abuse treatment through two facilities licensed by the State of New Jersey. To that end, we provide addiction treatment services with the understanding that addiction is a disease that affects the entire person, their body, mind, and spirit.

Without discrimination, heroin has spread its death-inducing arms and put a stranglehold on the populations of the Eastern Seaboard. Since December of 2013, I have personally witnessed superstar athletes, promising young engineers,

nurses, retired grandfathers, loving mothers, and adoring sons and daughters lose years of their lives or die because of this drug.

It kills regardless of class, race, age, or gender. It kills in our cities and our suburbs, but the one thing most heroin addictions have in common is that they start in the same place, with the first taste of an opioid prescription pill.

From there, an addict's progression down the road of use is clearly marked. It is an unfortunately short and simple trip. One pill turns into a few on the weekends to daily use of hundreds of milligrams, then a visit to the open-air drug markets of Camden, New Jersey or the Kensington section of Philadelphia for the cheaper alternative, heroin. And all too often, the wrong of addiction ends at the morgue.

The nonmedical use of prescription opioids has skyrocketed in the United States, and so has the number of deaths associated with it. In New Jersey alone in 2015, 1,587 people died from drug overdoses. This is a 21 percent increase from the

year before. Heroin was to blame in nearly 1,000 of those 1,587 deaths, the highest level since accurate records have been kept in the Garden State. We expect the 2016 numbers to be even worse.

Perhaps the most telling number I can give you is from the American Medical Association. In July of 2014, the AMA surveyed addiction treatment seeking patients. Of them, 85 percent responded. 75.2 percent of those who responded said they were introduced to opioids through prescription drugs.

At my agency, I took a formal anonymous poll with two questions. One, was your drug of choice heroin? And two, if yes, do you attribute your use of heroin to use of opioid pharmaceutical drugs? Of the 180 clients who responded, 62 said their drug of choice was heroin. Of the 62 people whose drug of choice was heroin, 96 percent of them said one opioid pill led to their heroin addiction.

Ninety-six percent of our clients who abused heroin attributed their use to opioid prescription drugs, 96 percent. Not marijuana, not alcohol, not

cocaine, not amphetamines, not LSD, not barbiturates, not benzodiazepines; rather 96 percent of our clients who abused heroin attribute their use to one pharmaceutical opioid pill.

I think it's important to recognize, as did President Barack Obama in remarks made in 2015, that today we are seeing more people killed because of opioid overdoses than traffic accidents.

Think about that. A lot of people tragically die in car accidents, and the government spends a lot of time and resources to reduce those fatalities, and they've actually done a good job at that. Traffic fatalities are much lower today than they were 50 years ago because the government systematically looked at the data and looked at the science and developed strategies to reduce such incidents.

The problem with the opioid epidemic is that the trajectory is heading in the opposite direction. Although federal, state, and other vested interests are implementing a variety of

programs aimed at curbing inappropriate prescribing, it is the drugs that are being prescribed in the first place that are the root of the problem.

The marketplace is full of opioids that do not incorporate abuse-deterrent technologies. If a consumer was prescribed an abuse-deterrent opioid at the onset of their introduction to such medication, the likelihood of future abuse of opioids would diminish greatly. As with traffic fatalities, over time, we may be able to slow down the progression of heroin abuse, reverse its course, and eventually stop it altogether. Thank you.

DR. BROWN: Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. COHEN: Thank you, Mr. Chairman. My name is Dan Cohen. I'm the chairman of the Abuse Deterrent Coalition; an officer of KemPharm, a biopharmaceutical company developing prodrug

therapies for CNS, ADHD, and pain; and a former consultant for Grunenthal USA and Purdue Pharma. I have no financial relationship to the sponsor.

The Abuse Deterrent Coalition was formed as a talk forum comprised of ADF innovators, patient and issue advocates, and research groups to educate the public, policymakers, and the FDA on the importance of developing and expanding ADF technologies.

In the primary question before you today, is it reasonable to approve RoxyBond ADF formulation as safe, effective, and as discouraging of intranasal and intravenous abuse? As you prepare to answer this question, it is important that we are using appropriate and similar terms for this discussion. Failing to agree or having unrealistic expectations will yield a faulty decision and not appropriately address the question.

The terms in question are "abuse deterrence" and "who is the customer or the target of ADF?" What is not under consideration today is RoxyBond as an abuse-prevention formulation or APF. There

is no APF. Products with ADF technology do not and are not expected to prevent abuse of scheduled products, only to lower through deterrence the abuse potential of those products.

Innovators in the ADF technology space want to do more, but the question to ask yourself, will we adopt science that is possible today and not wait for what we hope may be a technology tomorrow? Technological feasibility is why intranasal and intravenous abuse deterrence is a consideration, and oral abuse deterrence remains as aspiration.

The development of abuse-deterrent formulations is part of a multifactorial effort to reduce the risk of abuse and diversion. Neither APF nor oral ADF is technically feasible today even as both aspirations remain the goal of us innovators.

Every step we take in approving technologies that are possible today make future development closer to our goals of tomorrow. And no doubt we achieve effective therapies for patients while making abuse, misuse, and diversion of important

medications as difficult as possible within the bounds of known science. ADF is getting more effective, but we can get to future innovation by failing to approve current discovery.

To give full meaning to this, it's also important to agree on that second term. Who is the customer for ADF? Most of the discussion, data, and anecdotal stories that will be reviewed on ADF have focused primarily on the addicted or criminal abusers of drugs but little focus on the misusers.

Abuse-deterrent technology, ADF, is best understood as a technology that reduces the risk of misuse and diversion by focusing primarily on the opiate naive or early stage recreational abusers.

Current ADF is not a technology capable of effectively deterring a professional at manipulation, a desperate addict, or a highly experienced abuser. However, we believe ADF will ultimately reduce the number of addicts and highly experienced abusers by reducing abuse progression at its earliest stages. Abusers that are deterred from progressing or starting to ever more

aggressive and risky forms of abuse is the goal of abuse-deterrent technology.

The population-adjusted rate of abuse for immediate-release products is over 4 times greater than that of the extended-release products. Over 240 million immediate-release opiate scripts were issued in 2015, yet there are no abuse-deterrent IR opiate products approved today.

Do not seek in your review to make the perfect the enemy of the good. IR oxycodone is a common target of abuse with relatively high rates of intranasal and IV routes of abuse. The data presented today demonstrates that RoxyBond offers an abuse-deterrent IR oxycodone product that provides similar safety and efficacy to its comparator but at a reduced risk of abuse and misuse. That is the pure definition of an ADF.

If we recount, overall, RoxyBond can be expected to provide effective analgesia for patients with pain severe enough to require the use of an opioid analgesic and for which alternative treatment options are inadequate.

In vitro experiments demonstrate that RoxyBond's physical and chemical properties provide substantial barrier to particle-size reduction necessary for intranasal or IV abuse and to extract oxycodone. Laboratory evaluations demonstrate that RoxyBond can be expected to make abuse via injection difficult, and clinical human abuse potential studies demonstrate that RoxyBond produces clinically relevant reductions in drug liking that can be expected to reduce abuse, misuse via the intranasal route.

In conclusion, overall, the results of in vitro and clinical studies leave this panel with one remaining question. If you are not convinced, what more do you need to see to vote yes? To close with a relevant quote, "Policymakers pressed the drug makers to come up with these tamper-resistant formulations as one way to combat diversion and abuse. It was rightly hoped that these new formulations could become one tool in combating illicit diversion and abuse, and it has worked."

Those comments were by Dr. Scott Gottlieb,

commissioner designee of the FDA, who is going through his confirmation hearing as we speak. Thank you.

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

MR. CICHON: Thank you, Mr. Chairman, and good afternoon. I'm Charlie Cichon, the executive director of the National Association of Drug Diversion Investigators, NADDI, and I have no financial obligation.

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.

Relief from pain is important to millions of

individuals who suffer with chronic illness, and prescription drugs such as opioids have proven a valuable tool in the relief process. However, the potential for the abuse of prescription drugs, especially opioids, presents a significant risk. And as we are all well aware, the misuse and abuse of opioids has reached epidemic levels in many of our states.

Prescription drug abuse is the fastest growing problem in America, one that does not discriminate by region, socioeconomic status, or age. The Centers for 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 is a nonprofit membership 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 activities.

Our primary focus is training and education for our members, which include law enforcement personnel, state regulatory agents, health professionals, healthcare fraud investigators, and pharmaceutical companies.

Continuing progress in the field of pain management involves the juggling act that balances the needs and interests for 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, NADDI supports ongoing interaction and cooperation among all who impact the access to competent healthcare and who affect diversion and abuse of medications. A scientific

approach was taken to reduce illegal street activity. In speaking with and surveying our NADDI law enforcement members at our training throughout the country, it appears likely that the rates of diversion decreased dramatically after the introduction of reformulated opioids.

I'd like to draw your attention to a 2016 op-ed in a North Carolina newspaper from one of our NADDI members. Julie Billings is Carolina's chapter president and also the assistant special agent in charge of the North Carolina State Bureau of Investigation, diversion and environmental crimes.

I quote, "Over the past decade, dealing with skyrocketing rates of prescription drug abuse has become inevitable for those of us on the frontlines of law enforcement. A 2016 report identified four North Carolina cities among the worst cities for drug abuse in the country.

"Prescription drug abuse relentlessly and indiscriminately targets the intersections of communities we as members of the law enforcement

community try to protect every day. The availability of abuse deterrence will help save more lives and equip law enforcement in order to further protect the communities they serve."

The new drug application under review, oxycodone hydrochloride, immediate-release oral tablets, have been formulated with the intent to provide abuse-deterrent properties. While there are currently nine approved abuse-deterrent, extended-release opioid formulations, there are no approved immediate-release formulations with abuse-deterrent labeling.

While the first generation of abuse-deterrent formulations have reduced abuse and diversion, many advances to this technology that would further erode the street value of opioids and maintain access to the individuals who benefit from the relief would be welcomed.

NADDI is a strong proponent of new abuse-deterrent medicines that make it more difficult for an abuser and reduce law enforcement involvement in healthcare. Thank you very much.

DR. BROWN: Will speaker number 4 step to the podium and introduce yourself?

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I'm a licensed clinical psychologist in Washington, D.C. and a senior fellow at the National Center for Health Research. I previously trained at Johns Hopkins University School of Medicine.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device industry, and I have no conflicts of interest.

The development of opioids formulated to prevent abuse is a public health priority, and we support the FDA's efforts to encourage the creation of opioid analgesics that deter abuse.

The FDA states that a product that has abuse-deterrent properties means that the risk of abuse is lower than it would be without such properties. According to the FDA materials

provided, it appears that RoxyBond is more abuse-deterrent compared with Roxicodone. However, there is still abuse potential for the intranasal and intravenous use of RoxyBond.

The studies about RoxyBond's abuse are limited. In the laboratory setting, it appears to meet the FDA's current standards for abuse deterrence. Whether its abuse-deterrent properties are effective in the real world and whether RoxyBond is a better drug are much more difficult questions that will require postmarketing data.

We know from previous experience with opioids that the FDA has designated as abuse-deterrent, that once this drug is on the market, it may be abused more widely than current laboratory studies suggest. That is exactly what happened with reformulated Opana ER, as several members of this panel are aware.

Compared with the FDA approved extended-release, long-acting, abuse-deterrent opioids, RoxyBond's characteristics are similar regarding drug liking and taking the drug again. Thus, it

does not appear more likely to be abused than extended-release long-acting opioids.

Unfortunately, this comparison is rudimentary and less than ideal for several reasons. First, a direct comparison is impossible, given a lack of sufficient information. Second, we are utilizing extended-release, long-acting opioids currently on the market as a comparison, which does not set a high standard.

The FDA's guidelines state that a drug's label should reflect and describe a product's specific abuse-deterrent properties such as an abuser's ability to crush a tablet and extract the opioid. Thus RoxyBond's label should include its specific abuse-deterrent properties and clearly specify the potential risks of intranasal and intravenous abuse.

Most important, the FDA should require opioids to have a black box warning indicating that although the drug may be more difficult to crush or inject, it is still highly addictive.

Opioid addiction is an epidemic in the U.S.,

and labeling a drug as abuse-deterrent influences doctors, patients, and family members. Unfortunately, many doctors think abuse-deterrent means an opioid is less addictive.

To be part of the solution rather than part of the problem, the FDA should be diligent in analyzing whether this drug's abuse-deterrent properties result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes compared with Roxicodone once it is marketed to consumers.

Although current data suggests that this drug will be less likely to be abused, abusers of the drug can be more creative or implement unique techniques to overcome these deterrents. Thus, sufficient follow-up is critical in order to determine is this is actually the case.

If approved with abuse-deterrent labeling, this will be the first immediate-release, abuse-deterrent opioid, and it will likely be favored for prescriptions and will set a standard for future drugs to meet. Thus, it is important

for this panel and the FDA to make approval decisions based on good science and strong data.

To reduce the opioid epidemic, the FDA must hold pharmaceutical companies to a high and truthful standard. We urge this advisory committee to advocate for patient safety by demanding that the FDA include labeling regarding RoxyBond's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter.

We also urge this committee to recommend that if RoxyBond is approved, postmarket studies should be required immediately to evaluate its use and abuse once it is on the market. Thank you.

DR. BROWN: Speaker number 5, if you will step up to the podium and introduce yourself.

MR. BRASON: Good afternoon. Thank you, Mr. Chairman, and the opportunity. My name is Fred Brason, president and CEO of Project Lazarus out of the great state of North Carolina, currently known as NCB&B. That would be North Carolina, basketball and bathrooms, unfortunately.

I appreciate the science that you need to look at today, but I want to talk to you about the public health approach and the issues that we deal with at the street community level.

These are individuals that you see on your screen, patient misuse through substance use disorder. All of these individuals, we've had in our communities that unfortunately have suffered adverse events and overdoses from prescription medications. Therefore, we have to strike the balance of preventing, intervening, and treating both the person that has pain and both the person that has substance use disorder, and strike an even balance across that.

We've done a lot of prescriber education throughout North Carolina and other states, the military, and tribal groups, and part of our CMEs and so forth that we bring forth definitely stress the abuse-deterrent formulations when it's available, when it's covered, when there's no preauthorization for that, so that the prescriber can look at the entire patient, looking at their

substance use possibly, their history, and mental health capacity.

Some of the changes that we've made is shown here by the officer from Wilkes County saying, "Our doctors are doing a heck of a good job. Most of the supply unfortunately is coming outside of the county from other sources." And we know that abuse-deterrent formulations on our street, at least the quote is, "You can't give them away." It's too much of a problem to be able to use it, thankfully so.

But the communities that we have in the Appalachian region where I live, we have a sordid history, and it started with moonshine. We do and have moved into marijuana, we do and have moved into meth, and we do and have moved into medicine.

Medicine is our new moonshine. It has created an underground economy for individuals because we are in the Appalachian region. We have high poverty, we have high levels of depression, unemployment, and so forth. And those are areas that we have to address ongoing because it's the

social determinants that drive, unfortunately, substance use.

You can see here, just from these roundups that our law enforcement has had to do just in our county alone, multiple individuals who are selling prescription medications that they have been able to obtain at somewhere, again, mostly outside of the county and other places, to supplement what income they do or they don't have. And it just shows you how it's driven economically for those individuals.

For a county like ours, the number two in the nation from 2000 to 2014 for income loss, just shows you the level of need that we have from the economic perspective, and abuse deterrents kind of remove themselves from that marketplace.

Some of the results that we've had in our community in North Carolina is a drop in mortality, is a drop in adverse events, is a drop in emergency department utilization for substance-use events throughout the entire state by those who developed a Project Lazarus type model for public health with

a coalition within that county.

One success we've had at Fort Bragg with the Department of Defense was introducing much of the chronic pain initiative that we introduced. Overdoses are down, adverse events are down, and any refill within the Department of Defense at Fort Bragg is an abuse-deterrent formulation because it just stops that progression that could be possible with individuals.

A study that is continuing on in Massachusetts, that those individuals that unfortunately had died from an overdose and looked at from 2011 to 2014, did have a prescription at one time. But at the time of their death, it was only 8.3 that had an actual active prescription at the time of their death, which indicates the conclusion that diversion is what is the source driving, unfortunately, the epidemic that we're in. And any way that we can deter, stop, or change that diversion is going to have a positive effect on the public that we're dealing with of all ages and all communities.

You can't really see this. I just wanted this in the record, but these are every county in North Carolina, and the graphs shown are those that have increases in injection use of substance use. And these are testaments from those previous three months before they entered into treatment, and over 50 percent of the counties in North Carolina show an increase in injection from prescription medications.

This is the graph that shows you that progression overall that has continued from 2008 through 2014 and into '15, that it is an issue, it is a problem. And any way that we can deter from that and still maintain pain care for the individual that needs it, being it safe and responsible, helps us within the community to do that.

When the music changes, so does the dance. The climate is not where it used to be. We have to make progressive steps in order to ensure there's proper care and treatment for everybody from pain to substance-use disorder, and the circle of family

and friends surrounding them. Thank you very much for your time today.

DR. BROWN: Could the next speaker step up to the podium and introduce yourself? Speaker number 6?

(No response.)

DR. BROWN: Could speaker number 7 step to the podium and introduce yourself?

MR. THOMPSON: Hello and good afternoon. I am Edwin Thompson. I am the president of Pharmaceutical Manufacturing Research Services.

Today marks a milestone in the opioid epidemic. Seven years ago today, OxyContin, reformulated for abuse deterrence, was approved by the FDA. It is almost three years to the day that OxyContin was given abuse-deterrent labeling.

Since 2009, FDA has held 22 advisory committee meetings regarding opioids. The FDA has approved nine opioids with abuse-deterrent labeling. These advisory committees have also recommended extended-release opioid REMS education programs, which the sponsors have participated in

for the last five years.

What are the results of all of this time, this money, and these resources? The opioid epidemic continues to rage out of control.

In 2015, 91 Americans died of an opioid overdose each day. More than 33,000 opioid overdose deaths were recorded that year, and morbidity and mortality continue to accelerate at the same breakneck pace.

Unquestionably, the attempted strategies are wrong and ineffective. This is a failed system. Advisory committee decisions have not reduced the rate or the number of opioid overdose deaths.

Speciously, these decisions have licensed pharmaceutical companies to promote abuse-deterrent properties of opioids to physicians. In effect, these committees have provided or extended patent protection to opioid products, resulting in nothing but increased cost passed on to patients. We are all familiar with the consequences. The opioid epidemic rages out of control.

But what's really wrong with these

practices? Neither the sponsors nor the FDA follow the FDA guidance for abuse-deterrent evaluation and labeling. Abuse deterrence is like the distraction in a magic trick. Things don't seem to be what they are, do they?

The guidance stipulates, quote, "The potentially abuse-deterrent product and comparator should be manipulated to cause the highest release of the opioid and the highest plasma levels." As well as, quote, "For a product with potential for abuse by the nasal route, the methods to provide the smallest particle size should be used in subsequent studies."

Only manipulation through extraction provides material able to meet these criteria. In the background information for today's meeting, the in vitro study results demonstrate that approximately 85 percent of oxycodone can be extracted from a RoxyBond tablet within 15 minutes.

Let me be very clear. Grinding tablets is not comparable to extracting API. Why then would the HAP study be performed with ground material?

The extracted material can readily be made into powder -- powder, not particles -- and in this form, the manipulated product is unable to be differentiated from Roxicodone.

As such, the studies are unnecessary and should have never been conducted. The only reason the approved drugs have been able to differentiate from the comparator in human abuse potential studies is by deliberately avoiding the use of extracted material.

These advisory committees have wrongly evaluated human abuse potential studies and recommended abuse-deterrent labeling without considering whether the studies are being performed as intended. This committee must ensure that the extracted material with the lowest particle size and highest release was used to study the abuse-deterrent properties of the drug before you can properly evaluate these human abuse potential studies.

If these studies did not use extracted material, they were not conducted according to the

guidance, and there is insufficient data to support abuse-deterrent properties. Thank you.

DR. BROWN: Could speaker number 8 please step to the podium?

MS. FOSTER: Good afternoon. My name is Wendy Foster, and I'm the senior state advocate for U.S. Pain Foundation, an organization founded by people with pain for people with pain to help support, empower, educate, and advocate for the chronic pain patient. Neither U.S. Pain nor I have received any compensation for appearing here today.

I have been living with chronic pain for over 24 years, not take an aspirin and wait a while pain, but chronic unrelenting pain. I have bilateral restrictive lung disease secondary to a proximal myopathy, severe migraines, spinal stenosis, and degenerative disks, Parkinson's disease, and effects from a stroke.

While opioids are contraindicated for migraines, they can be used successfully for my other conditions. However, not all medications can ease the pain for all types of chronic pain, and

the medications that help my chronic pain may not help the next person.

The Institute of Medicine estimates there are 100 million Americans living with chronic pain. That's 100 million chronic pain patients with varying conditions. No two people are the same. No two chronic pain issues are the same or react the same way.

As a person with chronic pain and as an organization, we realize that pain and addiction are serious diseases and both need to be addressed. Having safer medication with abuse-deterrent properties is one of the tools we need to both fight addiction as well as pain. In addition, we also need more education and other tools to combat chronic pain and addiction.

I'm not blind to the epidemic of opioid abuse in our country. I have a child who has OD'ed on at least two occasions. There is nothing that can prepare you for that call. He was lucky, though, and is currently doing well in his recovery.

But that doesn't change the number of people living with chronic pain. In fact, when their medications are stopped or given in limited supply, the chronic pain patient will cut back on their prescriptions to make sure they have them when absolutely needed or stop them altogether.

This can further complicate matters as the chronic pain patient will withdraw from society and begin to feel there is no hope. This feeling can lead to despair and in some cases, suicide. It is vital to have as many options for the chronic pain patient available so that along with their doctor, they can find the medications that help with their pain.

We say it is necessary to have all pain medications new and existing, which have abuse-deterrent formulas be available for the chronic pain patient. Thank you.

DR. BROWN: Will speaker number 9 step up to the podium and introduce yourself?

MS. KULKARNI: Thank you, Chairman.

My name is Shruti Kulkarni, and I'm counsel

to the not-for-profit Center for Lawful Access and Abuse Deterrence. CLAAD's funders include treatment centers, laboratories, and pharmaceutical companies, and are disclosed on our website at claad.org.

Thank you for the opportunity to provide CLAAD's input on the abuse-deterrent properties of the proposed immediate-release oxycodone. CLAAD works to reduce prescription drug fraud, diversion, misuse, and abuse while ensuring that individuals with legitimate needs have lawful access to medications that safely and effectively treat their health conditions.

Our organization has taken an active role in encouraging a market transition of all commonly abused medications to abuse-deterrent forms. We're pleased that the industry to responding to our coalition's call to develop safer medications to reduce prescription drug abuse.

Medications like the proposed IR oxycodone can satisfy patient needs and improve public health and safety. In assessing whether this medication

merits an abuse-deterrent labeling, the committee should consider the following facts.

As the FDA noted, in 2016, approximately 19 million patients were dispensed prescriptions for oxycodone IR products with no abuse-deterrent properties. As noted in the RADARS study last year, these products are the most susceptible to misuse and abuse via alternative routes of administration. In fact, IR opioids are abused over five and a half times the rate of ER products.

Research presented by the New England Journal of Medicine and by the CDC at the National Prescription Drug Abuse and Heroin Summit last year showed that the most common transition pathway from oral abuse to heroin use is to start with oral ingestion of pills, move to the crushing and snorting of pills, continue to the snorting of heroin, and finally injecting prescription opioids and heroin.

In order to prevent this transition, it is important to make the abuse of manipulated opioids more difficult and less rewarding. Therefore, any

newly proposed IR oxycodone product should address these concerns prior to FDA approval.

Sponsor studies support the following conclusions. First, the proposed formulation is significantly more different to crush, cut, or grind with common household tools. As a result, those who seek to abuse it are less likely to gain immediate access to its active pharmaceutical ingredient. Therefore, this product will be less desirable to inexperienced individuals who seek to abuse oxycodone using alternative routes of administration.

Second, even if an individual crushes, cuts, or grinds the product for intranasal abuse, less of the manipulated product is absorbed and at a lower rate than if the product is taken orally or even compared to the manipulated intranasal administration of IR oxycodone without abuse-deterrent features.

Third, if the product is manipulated and introduced to a liquid environment, it creates a viscous matter that it is difficult to syringe,

creating a barrier to IV abuse.

Finally, every time an abuse-deterrent medication enters the market, it increases the likelihood that we can improve the quality of healthcare, spur competition, and fund additional research and development. Our ultimate goal is to ensure patients have access to effective treatment for conditions like pain, anxiety, ADHD, and addiction that do not pose the risks of addiction and overdose.

Thank you for the opportunity.

DR. BROWN: Speaker number 6? If speaker number 6 is available, could you step to the forum?

(No response.)

DR. BROWN: If not, the open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. Dr. Sharon Hertz will now provide us with the charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: Thanks. You have heard today data from the in vitro and in vivo evaluation of the abuse-deterrent properties of RoxyBond along with general information about the use of IR oxycodone analgesic products.

We generally reserve FDA presentations to information not presented by the applicant or areas where we may have a different perspective. While we don't have questions about the methods or results of the applicant's studies, we may have noted from the background package, there is some concern about how the drug-liking results from intranasal manipulated RoxyBond and oral intact Roxicodone relate to the significance of abuse-deterrent effects by the intranasal route.

We heard some questions and a little bit of clarification on this during the earlier clarification period, but as you discuss question 1, I'd like to ask you to please consider describing your opinion of these data, particularly in light of the different pharmacodynamic outcomes

that were evaluated. So we had the drug liking, as well as take drug again, and overall drug liking.

I look forward to hearing the discussion. We take a lot of notes because we really value the discussion, not just the outcome of votes or final comments. Thank you again for your time.

DR. BROWN: Thank you, Dr. Hertz.

We're now going to proceed to the questions to the committee and the panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Our first question is a discussion question, but subsequently, we will use our electronic voting system for this meeting, and I will speak about that in a few minutes.

If we could go on to the first discussion question, please discuss whether there are sufficient data to support a finding that RoxyBond oxycodone hydrochloride immediate-release tablets has properties that can be expected to deter abuse,

commenting on support for abuse-deterrent effects for each of the following routes of abuse: nasal, intravenous.

Is that question clear to all the members of the panel, and does everyone think that we can make assertions based on the question such as it is? Does anybody have any questions or comments about question number 1?

DR. AIGNER: Mr. Chairman, could I ask whether I could be recognized just for a minute, answering some of the questions we said we would find answers for, or is that no longer relevant?

Clarifying Questions (continued)

DR. BROWN: I think that will be fine. Go ahead.

DR. AIGNER: Dr. Webster, I believe the first question was to just show a physical image of manipulated RoxyBond.

DR. WEBSTER: Yes. This is the visual of the material that the subjects would snort, and I think, as I mentioned to Dr. Walsh before the break or before lunch, is that there were some larger

particles, and you can see that those are the larger particles. And I think that this is probably what contributes to part of the difference because they probably swallowed that, swallowed some of those particles.

I'd like to address then the other question that was related to that, which is the ease of snorting. I think that that contributes. Those larger particles will contribute to the ease of snorting. And then there was another question about how does that PD effect assessment relate to the ease of snorting.

Actually, we take the assessment about the ease of snorting within 5 minutes after snorting, so there is not really the liking assessments yet.

DR. AIGNER: I believe there was a second question about the PK dropouts, Dr. Webster.

DR. WEBSTER: Oh, yes. Obviously, this was my study, too, and I'll bring the data up for your question about the dropouts on the PK. I don't have the slide for that, but I do have some information.

There were 75 subjects that entered and 17 total dropouts. Ten of them were for AEs, and 8 of those 10 dropped out because of naltrexone, side effects to the naltrexone. One was to loss to follow up, and then a few had withdrawn their consent.

Now, we followed the protocol, which said that if they -- prior to the drug exposure, and this was a part of the FDA guidance as well, so they were removed before there was any data, really, on the drug.

DR. BROWN: Dr. Walsh, do you have a clarifying question?

DR. WALSH: I do. I just want to understand fully what was done in the study. I guess the question goes back to Dr. Webster.

The picture that you're showing, is that of product that was prepared for the human abuse liability study?

DR. WEBSTER: Yes.

DR. WALSH: Where was the preparation for that done? Was that done in advance and then

shipped to you --

DR. WEBSTER: No, no.

DR. WALSH: -- or was that something that was done on-site?

DR. WEBSTER: Yes. We prepare all of these. In fact, this is placed in an amber bottle, and the subjects are in a dark room. Usually, we have a black light as the only light that we have, so they can't visually see this. And a straw is placed in the amber bottle, so that they're blinded. The subjects cannot see, smell, look in any way to differentiate the Roxicodone from this.

DR. WALSH: So the manipulation that you use with tool G, I think if I interpreted what you said earlier, you suggested that it wasn't the same protocol that was used in the in vitro testing. Is that correct, or it wasn't the same --

DR. WEBSTER: Yes, it was the same. If I said different, then I made a mistake, but it was the same.

DR. WALSH: Okay. I don't know what the scale is on that figure, but those look like really

big chunks in that way that they're presented. It might just be a magnification problem.

DR. WEBSTER: It is a little magnified, but there were chunks. There were chunks, but yet they could insufflate them through a straw.

DR. WALSH: I don't know whether or not you know this or if it's a formulations person. Clearly, some of it is very powder fine, as you would expect for the comparator product. Other parts are not.

Is it the core that is chunky? Is it the crust that's chunky? Is it both?

DR. WEBSTER: You're right. That's not my question.

(Laughter.)

DR. WALSH: Right.

DR. AIGNER: We would expect that tablet form B is what creates the larger particles. Just to calibrate a tiny bit, most of these particles are less than 2000 microns.

DR. WALSH: Right. Right. I guess it's all tied in together, the interpretation of the PK and

PD findings for the intranasal study. One thing I had asked for clarification earlier, that maybe you're going to still show, is given that the drug has excellent absorption profiles orally, if all of it from the vial is going into the person's nose and some of it's not being absorbed by the mucosal membrane, then it's going into the gut, and you would expect to see absorption then.

So we see differences in the area under the curve between the two comparisons. I don't know what that means. Does that mean that the rest of it's being excreted unchanged? Did you consider, or did you do any studies to look at unchanged excretion of the product?

How do you account for that? I know that you think it's bound to your secret formula, but eventually, it's got to come out.

DR. AIGNER: You're correct. The RoxyBond is formulated to release in the GI, not the nose. And of course, the nasal cavity is connected to the GI. So if your thinking is correct, which is part of what our physiochemical abuse barrier

is -- because you don't get what you get for Roxicodone. When you snort it, it ramps up much faster. You might remember that red graph we had. That's what abusers are really wanting, very high liking and very fast, versus what this is.

Even if snorted, they have to wait till it slowly goes into the GI, and actually, it's less than taking RoxyBond intact orally. So there's no reason for an abuser to snort RoxyBond. And compared to Roxicodone, it's a very significant improvement.

We do have some PK graphs, but they're a little messy, spaghetti graphs, if they would be helpful to you.

DR. WALSH: You can show them, and we can see.

DR. AIGNER: Real quick. It is hard to digest, but we did want to bring the information we had.

On the left-hand side, you see crushed RoxyBond compared to intact RoxyBond on the right-hand side. I believe it is consistent with

what you have been thinking about.

DR. BROWN: Can you go back to the picture that we were just looking at? Because I've got some questions.

Is this one tablet, 2 tablets, 9 tablets, 3 tablets?

DR. AIGNER: It's one tablet.

DR. BROWN: This is for Dr. Webster. In doing these studies, Lynn, did the subjects inhale one tablet, half of that, all of it? What was the percentage?

DR. WEBSTER: They inhaled all of it. It took just a little bit longer than the Roxicodone, but still, everybody within 5 minutes, most of them inhaled all of it within 2 minutes.

DR. BROWN: Okay. I don't know what the scale of that is either, but I doubt seriously that there's much chance that those larger particles are going to go directly across the nasal mucosa. Would you say that's reasonable?

DR. WEBSTER: I think those larger particles, yes. Now, let's keep in mind that

that's about 8 percent or larger than 2000 microns.

DR. BROWN: That's not what it appears. Pictures being what they are, worth some number of words, it appears that 25 percent or more of those are large particles.

I guess the only thing that I'm suggesting is that -- and this is pursuant to what Dr. Walsh, I think, was getting at -- that if you're not inhaling those and they're not crossing the nasal mucosa, then they're most likely to go into the GI tract, so that we're not really measuring the amount of uptake from intranasal inhalation, but a combination of that with the amount that gets into the gut.

DR. WEBSTER: I think you're right, and that's the purpose of having a good abuse-deterrent for intranasal route. If it can't be rapidly absorbed across the mucosal membrane, then it's an abuse-deterrent. It's being swallowed. Some of it's being swallowed. Some of it goes across the mucosa, but not all of it.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: Can I just ask, how long was the pill manipulated by tool G for that experiment?

DR. AIGNER: Two minutes.

DR. BATEMAN: And with longer manipulation, will the particle size become smaller, you said, or not?

DR. AIGNER: Actually, because that is such a key question, we actually manipulated with the same tool up to 10 minutes. And as you see on this graph, after 1 minute, it really doesn't change the particle-size distribution any more.

DR. BATEMAN: Then just one other question. There was a claim made in the presentation that particle-size reduction does not overcome the abuse-deterrent properties by nasal inhalation. Is that based on the PK/PD data from this experiment?

DR. AIGNER: On the in vitro results, if you look at the in vitro results, particle-size reduction does not really significantly increase the release across any of the experiments.

DR. BROWN: Who was next? Dr. Morrato, I believe was next.

DR. MORRATO: Elaine Morrato. Getting back to the standards in terms of the subsequent testing is driven by using the smallest particle size should be used moving forward -- and I can understand how the chemistry may not make a difference, but the idea is that the subsequent experiments should be using the finest, right?

I find it curious that -- it sounds like you used tool G. You've met a threshold of a certain percentage below 2000 microns, and then stopped and moved on. Was there any consideration to really try to more torture test and really try -- in light of pictures like that, really try and get more uniformity, as opposed to just saying you met a threshold and we carry that forward?

So that's one. That's more of the design. But then also, is there any validation that was done with the site practice where they were doing the test to make sure that they are manipulating it equivalently to how you did in the in vitro? So not just the method, but you do some standardization to make sure how they're doing it

is equivalent.

DR. AIGNER: Yes, we did send out our team. They did train the pharmacy, same equipment like a transfer of method --

DR. MORRATO: Okay. Good.

DR. AIGNER: -- that's what it's called.

DR. MORRATO: Yes.

DR. AIGNER: Again, maybe -- I should say it one more time -- in terms of particle-size reduction -- and we had a whole lot in the briefing book, FDA did as well -- particle-size reduction does not help you to get more oxycodone out of RoxyBond. So even if we found small particles, it does not release faster.

DR. MORRATO: But it is impacting this question around the nasal ability to snort and so forth, right?

DR. AIGNER: And I would marry that, but the second aspect, that the nasal cavity and the pH, the nasal cavity is probably the worst place you want to think about oxycodone being extracted.

DR. MORRATO: Right. It's the principle of

following the letter of the law in terms of --

DR. AIGNER: Yes, yes.

DR. MORRATO: -- testing versus I'm really going to try and torture it and see what worst case scenario looks like as you carry through.

DR. BROWN: Dr. Kibbe?

DR. KIBBE: I'm going to do a little bit of a tutorial on micromeritics. Micromeritics is the study of small particles and what they do and how they behave. When you have a polymer that is easily hydrated and will swell, by making it a small particle, it will uptake moisture more rapidly, swell quicker, and reestablish a gel barrier that you wouldn't get if it wasn't as small.

So what our presenter is talking about is that making it a small particle doesn't help because all the ingredients in the core are swellable and gellable. And when you grind it up, you allow those core materials to get wet quicker, and then it makes a jelly mass faster. And the reason it works as a tablet in the gut is because

those things don't get a chance to get hydrated until after the drug's out.

So we're going down a rathole with this particle-size stuff. My concern is not that there is less drug being absorbed, but where is the drug residing if it's not being absorbed. And it's my opinion that because they have such good strong gelling polymers, they're trapping it on the surface of the nose, and the next time that subject sneezes or blows their nose, they get rid of it. And there's a percentage that's not getting in.

There's an interesting fact that we haven't talked about, and that is, what's the total weight of the tablet and what percent of that is the active ingredient? Because all of the stuff we're talking about is the excipients. We're talking about 15 milligrams of active ingredient in an 150-milligram tablet. I don't know the size, but what is it?

DR. AIGNER: The weight of the tablet is 600, and the dosage used for the liking study, 30 milligrams of active.

DR. KIBBE: Okay. We're talking about less than 5 percent of that ground up stuff actually is the drug itself, and it's surrounded by a bunch of polymers. We saw the list this morning. I guarantee you that 90 percent of those polymers will absorb moisture, and they'll swell, and that's the dynamics of the nasal uptake.

DR. AIGNER: Since we're talking about that, if you think about Roxicodone as a tablet, it's a fraction of that, and the vast majority is actually oxycodone. That explains why there's such a dramatic reduction in liking if an abuser uses Roxicodone versus RoxyBond.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Just a comment that regardless of how the photograph of the ground substance by tool G looks, I have to assume that the table that we saw, where the mean percentage of particles that were less than 2000 microns in size, when exposed to tool G was 92 percent.

So I think it was an extremely high level of magnification, but I have to go by the fact that

regardless of what it looks like to me magnified, that 92 percent of it was 2000 microns or less in size.

DR. AIGNER: That is correct, yes.

DR. BROWN: I'm going to give the last question to Dr. Amidon, so that we can move on to our discussion question. Dr. Amidon?

DR. AMIDON: Yes. Thanks. Greg Amidon. I was wondering if you know in that milled sample, a picture that you have, where the drug is. Is it in the fines that we saw, or is it in the big chunks? In other words, are the fines perhaps enriched in drug? Could you give some insight in that?

DR. AIGNER: We don't have any data on that. We never measured where the drug was.

DR. AMIDON: My concern would be, well, if it's the fines, that could be preferentially taken.

Questions to the Committee and Discussion

DR. BROWN: We're going to move back to the question for discussion, and again, we're asking the question about whether there was sufficient data to -- excuse me.

DR. HERTZ: Sorry. The projection was a little off, but it's fine now.

DR. BROWN: All right. The question before us relates to whether there's sufficient data to support a finding that RoxyBond has properties that can be expected to deter abuse, and specifically, we are going to be commenting on abuse-deterrent effects relating to intranasal use and intravenous use.

Comments from the group? Dr. Emala?

DR. EMALA: As I reviewed the drug liking and Emax high and such from the intranasal route, at first glance, I had concerns about what a change of 11 or 12 means on a 100-fold scale, but I was reassured by the publications presented that something as small as 5 millimeters may have a clinical significance. Because I'm worried that looking at these tiny p-values for statistical significance tells us little about the relative clinical significance. I think that translates well.

I also did the exercise of looking through

the briefing documents for the extended-release products that currently carry nasal abuse-deterrent labeling to see what kind of ratio scales differ. The values that are with this product fall well within the range of the extended-release products for drug liking, Emax high, take-drug-again scores.

I think comparing apples to apples at least from interpreting these intranasal scores, there are the extended-release products that are currently carrying that labeling with similar scores.

If I could just finish with a comment about the intravenous, more of a recommendation to both sponsor and FDA that we not continue to ignore what may happen with the various excipients when they are injected. We learned that lesson I think with PEO, and I think it's incumbent upon both the sponsors and the FDA to not ignore the unintended consequences of what these excipients might be doing.

I'm somewhat reassured that this gelatinous mess that occurs with hydration likely incorporates

a lot of those things that you wouldn't want to inject, but my question this morning about whether the liquid portion of that was ever analyzed for excipients I think is an important thing to keep in mind.

DR. BROWN: Other comments from the group?

Dr. Walsh, are you satisfied with the human abuse studies demonstrating lower drug liking and desire to use the drug again? Does it seem reasonable based on your knowledge of this?

DR. WALSH: Well, I think, like Dr. Emala said, in comparison to others that are already approved with this language and with what I understand to be the FDA's expectation, even though it's not nearly a perfect science about how much of a change on a visual analog scale is actually meaningful, I think that they have met the letter of the law with regard to that.

I still do have some reservations just about interpretation of the nasal data, and part of it I think would have been solved by knowing where the rest of the drug has gone. It's fine to say that

somebody is blowing out in a tissue, but nobody presented data about that. It's going into the body, and it hasn't been accounted for. So that just makes me wonder a little bit.

I guess the last comment that the sponsor made, which I had been thinking about, is just the difference in volumes for insufflation because there's a limit to how much surface area you have when you insufflate something, and you've reached that maximum. And it sounds like we're reaching that far earlier with the volume of material that's being insufflated with the RoxyBond compared to the comparator.

I don't know what the difference is. Maybe the sponsor can say. The difference in the volume that people are being asked to insufflate, is it like tenfold? Is that close?

DR. AIGNER: There would be a sixfold difference, 100 milligrams compared to 600. Although as Dr. Webster said, all the material actually was snorted by the subject.

DR. WALSH: Okay.

DR. BROWN: Dr. McCann?

DR. McCANN: I'm actually fairly convinced that it is a nasal deterrent with the data that's been presented. The intravenous route, however, when you look at slide 40, which talks about complex multistep process required to prepare RoxyBond solution for IV abuse, the extreme solvents and the neutralizing solvents are in my kitchen pantry right now. When I get an urge for chocolate, it takes me 5 or 6 steps before I get my brownie.

I don't know that -- I wouldn't consider it a really complex thing to get sufficient amount of oxycodone using this particular method. I'm not convinced on IV.

DR. BROWN: I need to push back on it because I want to understand what it is that you're trying to say. I believe I agree with you, but it's apparent that the required steps for abuse in slide 40 indicate that there's about a 5- or 6-step process to prepare an opioid for intravenous infusion.

DR. McCANN: And when you're done, you just get two-thirds of the amount. You don't get the full amount. You lose one-third.

DR. BROWN: So my response to that would be that by increasing the number of steps that are actually required, you would in fact improve the likelihood that abusers would not use the drug.

DR. McCANN: I'm pushing back on your pushing back --.

(Laughter.)

DR. McCANN: -- and saying that I don't think it's that difficult. You go online, you find what the six steps are, and 45 minutes later, you have your medication.

DR. BROWN: But if you had a medication that took one step, would you use this drug?

DR. McCANN: In that context, comparing it with the unadulterated oxycodone, I agree with you. I guess what I was trying to get at is I actually don't think it's that difficult to get an injectable form of this drug. That's what I'd like to say.

DR. BROWN: Dr. Kibbe?

DR. KIBBE: First, I want to agree with my colleague. We have to address what's going to happen to people who are determined abusers and start injecting this stuff, and some of those polymers will go into the clear liquid. So there will always be that presentation.

The one issue that came up earlier in the day that we didn't really get around to in terms of nasal is that it's possible to take the product, cut it in half, and peel off the coating, which contains all the drug, and then perhaps grind that up and make it a much smaller insufflation. And they didn't do that, so that's fine.

When I get one of these cases, I sit around the office figuring out how to defeat their product because that's intellectually fun, okay? I've come up with things that I would try because it would be fun, and if it took 4 or 5 steps and I got solution of pure oxycodone that I could do something else with, that would be the challenge. Of course, I don't use this stuff myself, but there has to be a

few people out there who are abusers who think the way I do. And there's always a way to defeat this stuff.

So the question from my mind is not is it possible that it could be defeated -- I think given six months on the market, there would be a website with instructions on how to get the most oxycodone out of it -- but does it do what it says it does, which is deter that, make it more difficult, and it does.

When we look at the three additional things that we need to vote on, I would add to number 3 the saying about possible and deadly use because of the potential for real toxicity. But at some point, you have to say, okay, they're better than the current product in terms of making it more difficult. And if the target is really the casual and first-time user, they probably have won.

If I'm a distributor of oxycodone in Philadelphia, and I can get my hands on 5 bottles of this stuff, I can make solutions of oxycodone that I could sell.

So that's not what we're determining, I don't think. We're hoping for this to be a deterrent and it not to be subsequently diverted. And what they've done with the polymers make it really difficult for you to get a full dose intranasally and make it really difficult to directly get an injectable. So I would vote yes on those things.

My reservation for this whole product is I'm not sure it's a true immediate-release.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: I was just going to make the point, as we thought about the nasal abuse-deterrent properties, we talked a lot about the human abuse studies. But certainly something that should inform this question is just how hard it is to get it into a fine powder.

If you look at the manipulation with most of the tools, it's hard to generate a large volume of fine powder, certainly compared to Roxicodone. We're looking at manipulation with G, which yielded a fairly high percentage of small particles, but

most of the tools had quite low yields of fine particles.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: While I agree that this will help deter nasal use, I do want to point out that the first primary use of these drugs in an adulterated fashion is usually between the ages of 16 and 18, which we don't look at at all because nobody will study -- I'm sure they didn't study any kids under 18.

I think that, as Dr. Emala points out, is that these excipients intravenously injected could be toxic. And will they be more toxic in that age group, we don't know. And I think it's incumbent on the agency, if this gets approved, to make sure that we look closely at kids to see if there's increased problems with using this in an adulterated fashion because kids are persistent, if anything, and will adulterate these drugs.

DR. BROWN: Any other comments?

Dr. Choudhry?

DR. CHOUDHRY: Niteesh Choudhry. For me,

one of the big issues here is what's the counterfactual. What are we trying to compare these manipulations to?

When you look at some of this stuff like, for example, the slide 40 that we were talking about before, which is also figure 15 in the sponsor's briefing document, these are what happen when you manipulate either intact, or grind up, or do whatever you're going to do to these medications and try and extract them. But the real counterfactual is oral use, like regular oral use, in which we know that the PK is similar to Roxicodone.

As I look at this, I say okay, look, if you took it an intact tablet and tried to manipulate it, you get less than the counterfactual as in swallowing. And then if you made the mistake of trying to break up the particles and then trying to extract it, you get even less. In that context, the amount of oxycodone that's recovered to me is compellingly smaller.

So I would argue that at least on the nasal

route, in addition to the idea of the PK studies that we saw and the liking studies that we saw, it's fairly convincing to me, both in terms of direction, effect, and consistency. And the intravenous stuff is perhaps even more convincing on the arguments only that it's not possible to really syringe it in any meaningful way.

That doesn't mean we don't need to understand what the excipients are and their toxic effects, and there might well be hazardous things that we need to know about. But there's other data that was presented, which shows syringeabilities in the 2 to 5 to 6 percentage point range out of a possible 100, which again argues for me that this meets the standard of abuse-deterrent.

DR. BROWN: Dr. Staffa, did you have comments?

DR. STAFFA: This is Judy Staffa. I just wanted to follow-up on Dr. Galinkin's comment about kids because that question came up this morning. And we've gone back and looked at some of the utilization data by age, and I can tell you that in

2015, that calendar year, less than 1 percent of the single-entity oxycodone IR products were dispensed to children. So it's a very small percentage of that particular market.

DR. GALINKIN: The comment that I'm making particularly, abused by children, that's a different category.

DR. STAFFA: Right. Exactly. I'm talking about just what's prescribed to them, knowing fully well they can access what's not prescribed to them as well. Right.

DR. BROWN: Dr. Kaye?

DR. KAYE: Just to the numerous points that were made, I think that it's very important to have labeling for the potential injury to the kidneys and other organs for people who choose to inject this if it comes to market.

DR. BROWN: Dr. Amidon?

DR. AMIDON: My background is really in oral dosage form development, design, and those things related to formulation development. I think this is a challenging task, in my opinion, that the

company has taken on.

I think with respect to the nasal delivery, I would have liked to have known more about the powder and where the drug is and maybe how it might be used to get faster and higher Cmax. But I think it does offer some deterrence as I've seen the data and looked at it.

I think with respect to the IV, I think it would have been helpful, as we've said, to understand what is in the liquid that might be injected. I think would be good to understand that. But again, to me, the swelling technology offers some level of deterrence.

Finally, I'd just comment on labeling. I think we need to get that right. Thank you.

DR. BROWN: Any other comments?

(No response.)

DR. BROWN: This is what I've heard from the panel. RoxyBond is a unique formulation of IR oxycodone that's been created with abuse-deterrent physicochemical properties. It's meant to deter but not eliminate abuse. The properties are

designed to deter inhalation and/or intravenous abuse, and because of the requirement for rapid availability, this formulation would not be expected to deter oral abuse.

I think the company, from what I can determine, as we've listened to discussion, lack of easy syringeability was demonstrated by the sponsor, the human abuse studies, the drug liking, the high associated with the drug, and desire to use the drug again mitigate for this being a reasonably effective ADF formulation. All of these findings were statistically significant.

I also agree with Dr. Kaye's comments about the injury -- and other people have spoken about this, too -- injury from IV excipients. Certainly when somebody is injecting this, it's not used as directed, but I think folks need to know that some of the excipients may be quite toxic.

Is that a reasonable --

DR. AIGNER: Mr. Chairman, could I ask for one more minute? We found some data of interest because we had some interesting questions, but

if -- around the particle size for the nasal and what it means for absorption.

DR. BROWN: I don't really think it's necessary now. I appreciate it, but I think we're fine.

Let's go on to question number 2, which is a voting question. If approved, should RoxyBond be labeled as an abuse-deterrent product by the nasal route of abuse?

Is that question clear to all the members of the panel, and can we move forward to vote on this after some discussion?

Having said that, are there any further points to discuss? We've already discussed this to some extent, but is there any more discussion that anyone would care to have about this particular question?

(No response.)

DR. BROWN: If not, let me say that we'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you

have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record.

Next, we're going to go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all the questions have been answered or discussed.

The question before us, if approved, should RoxyBond be labeled as an abuse-deterrent product by the nasal route of abuse?

(Vote taken.)

LTC BEGANSKY: The vote was 19 yes, 1 no, zero abstain.

DR. BROWN: We're going to start with Dr. Amidon. If you could tell us how you voted and give some discussion, if you care to.

DR. AMIDON: Yes. This is Greg Amidon, and I voted yes. As I mentioned before, I think via the nasal route, it's been demonstrated that there is some abuse deterrence in the system right now.

DR. WALSH: Sharon Walsh, and I voted yes after asking a lot of questions about it. But I think that in whole, the data that were provided to us show that this product demonstrates basically a flipped response compared to what we would expect where an oral formulation given IN would produce higher Cmax and a much faster speed of onset, and here we're seeing a lower exposure. That's it.

DR. MORRATO: Elaine Morrato. I also voted yes. I think the design characteristics in terms of the physicochemical properties set up the theoretical basis, and then I was most persuaded by the drug-liking abuse potential studies, and particularly that the direction and magnitude of the effects were comparable to drugs that have been

approved with similar indication or claim.

DR. CHOUDHRY: Niteesh Choudhry. I voted yes for the reasons already stated.

MR. O'BRIEN: Joe O'Brien, and I voted yes.

DR. HIGGINS: Jennifer Higgins. I was persuaded by the data to vote yes.

DR. GALINKIN: Jeff Galinkin. I voted yes based on PK data and the likeability data. I thought those were very persuasive.

DR. McCANN: Mary Ellen McCann. I voted yes.

DR. ZACHAROFF: Kevin Zacharoff. I voted yes, and that was based on the data that was presented as well as my review of the final guidance provided by the FDA to the sponsor. I thought they did what was requested of them as per the guidance.

DR. SHOBEN: Abby Shoben. I voted yes.

DR. BATEMAN: Brian Bateman. I voted yes for the reasons stated.

DR. BROWN: Rae Brown. I voted yes.

DR. CRAIG: Dave Craig. I voted yes for

some of the same reasons that everybody has already mentioned, primarily because of the similarities with the other currently approved products. Dr. Emala mentioned it quite eloquently. Comparatively, I think it's very, very similar to what we currently have on the market, and it's better than what the other alternative is.

DR. WARHOLAK: Terri Warholak, and I voted yes.

DR. GUPTA: Anita Gupta. I voted yes.

DR. LITMAN: Ron Litman. I voted no. Let me explain. I do agree with a lot of what everybody said here about how much more difficult it is to snort it. There's no question that data is real.

But the reason I voted no is because I'm not convinced what deterrence means. And I do not -- as we talked about, as I asked Dr. Dart before, I'm not convinced that abuse-deterrent formulations are effective. I don't think -- if it's going to affect a very small population of opioid users, I just can't see that making a big

difference in the overall spectrum of use.

I know that it's a very difficult thing to try and project into the future. The FDA has said that they consider ADFs as one possible prong in the fight against opioid abuse.

I just think that there's so much money at stake here. If you look at some of the state legislatures now that have either passed or are considering laws that physicians have to prescribe an ADF when it's available, it's no surprise that so many different companies and people are jumping on this bandwagon.

The horse may be out of the barn. Is that the saying? I'm from New York. I don't know.

(Laughter.)

DR. LITMAN: That may be true, but I'm just not convinced that we could label something as abuse-deterrent when we don't really know if it is or not. I certainly haven't seen the evidence. All the organizations that came up to speak publicly today, I'm looking them up as they're speaking, and they're all supported by the drug

companies. I don't remember which gentleman, but said that he did not receive any compensation for being here, displays Inspirion's logo on their website as a supporter.

So I think ADFs are a red herring, a distraction, from the real problems that underlie the opioid crisis, and I had to vote no on a philosophical basis there.

DR. EMALA: Charles Emala. I voted yes for reasons already stated.

DR. SCHMID: Chris Schmid. I voted yes.

DR. KAYE: Alan Kaye. I voted yes for reasons previously stated.

DR. KIBBE: I voted yes because I think the product actually will make it more difficult for some people to use it, but I agree with Dr. Litman. This is not the answer to the opioid abuse problem. It's going to take -- Dr. Kibbe. It's going to take a very large change in the way we approach how we handle individuals who are addicted to abusable drugs, and this is just perhaps temporary but not the final answer.

DR. BROWN: We have question number 2. If approved, should RoxyBond be labeled as an abuse-deterrent product by the intravenous route of abuse?

Is the question before us clear to the members of the panel? Can we move forward with the vote on this?

(No response.)

DR. BROWN: If so, are there any discussion points that anyone would like to make prior to the time that we go to a vote?

(No response.)

DR. BROWN: Hearing none, we're going to once again use our electronic voting system. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote.

(Vote taken.)

LTC BEGANSKY: The vote was 16 yes, 4 no, zero abstain.

DR. BROWN: So at this time, we're going to start again with Dr. Amidon down on my right and go

around the table.

DR. AMIDON: Yes. This is Greg Amidon, and based on the discussion today and the data presented, I voted yes. I believe that the technology does offer some abuse deterrence.

DR. WALSH: Sharon Walsh, and I voted yes, mostly because of the in vitro data that looked at dissolution of the drug in solutions and in the gelling properties of the product.

DR. MORRATO: This is Elaine Morrato. I voted yes for the same reasons. I do understand, though, it's rather subjective to say how much is more challenging or not for a dedicated user versus a naive user. So I think that is difficult, but if I think about the standards, as Dr. Kibbe and others are talking about, I think it for me met that threshold of deterrence.

DR. CHOUDHRY: Niteesh Choudhry. I also voted yes. I think it's important to acknowledge, as many have, that there's a lot we don't know, and I suspect that the no voters were concerned about some of those things. I think many of us, myself

included, are as well.

That said, there is a standard to be met. There are certain issues that they presented or rather data that has been presented in terms of recoverability in solution and the gelling formulations that make it compelling for me. So that's why I voted yes.

MR. O'BRIEN: Joe O'Brien. I voted yes. Based on what's being asked, and from what I can see and listen to, it appeared to me that that was the appropriate response for that.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. GALINKIN: Jeff Galinkin. I voted yes based on the fact that the syringeability was much more difficult and the fact that much larger volumes were required in order to get this into a form which you could actually syringe. I thought those were important features.

DR. McCANN: Mary Ellen McCann. I voted no for reasons I stated before, I don't think it's very difficult to get two-thirds of this drug

available. Easy way to compensate for that is to use two tablets. I think that if you really wanted to abuse this drug, it's relatively easy to do it in an IV fashion. Thank you.

DR. ZACHAROFF: Kevin Zacharoff. I voted yes, but I would agree with earlier comments about strongly warning about at least the lack of knowing what the possible negative outcomes could be related to intravenous administration of this medication and particularly the excipients.

I did my own research. There's not a lot of data that I could find regarding intravenous administration of methyl methacrylate, and I'm quite concerned about possible negative outcomes relating to that. So I would want that to be in the label.

DR. SHOBEN: Abby Shoben. I voted yes.

DR. BATEMAN: Brian Bateman. I voted yes. I think while highly motivated, sophisticated abusers can overcome the abuse-deterrent features of the drug, I think it's reasonable to think that the properties of the drug, particularly the

difficulties in syringeability, will deter at least some individuals considering abusing this by the IV route.

DR. BROWN: Rae Brown, and I voted yes because I think that, especially for early users of drugs like this, that a multistep process will prevent many of them from going on to this mechanism of abuse, and that is something that I think is important.

DR. CRAIG: Dave Craig. I voted yes primarily because of the inability to syringe the product that you could create by grinding. It was pretty convincing to me.

I agree with Dr. Zacharoff's comments regarding a special warning or some way to identify the excipients injectable. We were here just recently two days talking about TTP with PEO. I think that that's a real concern for products like this, especially when they're intended not to be used that way. I know it's hard to control for all of those potential problems, but I would support a black box warning or some special warning regarding

the potential for harm with injectable.

DR. WARHOLAK: Terri Warholak, and I voted no. Mostly, I'm conflicted. I'm worried about several things. One of the issues is that I was able to find product-specific information online on how to step through the process for IV drug abuse right now, and it's not even on the market yet. It doesn't seem that difficult, so I'm really worried about that.

I'm also really worried about the excipients when injected and the possible consequences of that. I really support what Dr. Zacharoff said about the labeling. That has got to be watched very closely and very clear to prescribers and patients, that if abused in the IV route, there is perhaps a potential.

DR. GUPTA: Anita Gupta. I voted no. I have to really say that I think the FDA and the industry partnered in an excellent presentation in presenting compelling evidence that it is abuse deterrent for intravenous use. But I really think that the product had compelling questions in my

mind about, one, the excipients, as you've heard.

There is a fear of unknown that I could not come to a decision on regarding the various excipients, and there were a lot of unanswered questions on what the risks were that I just was not comfortable with voting yes for.

Second, I think that the syringeability issue, although compelling evidence was presented that it could become a viscous product, the volume of that could easily be changed, as we heard from Dr. McCann. If you had several tablets, it could easily be manipulated. So those are the reasons why I voted for no.

DR. LITMAN: Ron Litman. I voted no again for essentially the same philosophical reasons as before, but even more so with IV. The way I look at these types of users, if you're going to become addicted to opioids based on starting pills, and at some point, you're going to jump over to intravenous, I think it's just too late. And I don't think this formulation will make a difference.

DR. EMALA: Charles Emala. I voted yes because of the difficulty in syringeability. Regarding some of the comments made about the multistep process, I'm somewhat reassured that that data is done in volumes that are not really appropriate or at least easy for IV administration.

DR. SCHMID: Chris Schmid. I voted yes. There is no IR formulation on the market right now with any abuse deterrence whatsoever. This may not be perfect, but it's a start, and it's a step in the right direction. And it does deter to some extent.

DR. KAYE: Alan Kaye. I voted yes for reasons mentioned. Just a strong comment about a black box warning would be a great idea. Thanks.

DR. KIBBE: Art Kibbe. I voted yes. There's no doubt in my mind that if someone finds a way of defeating this product and tries to make an injectable out of it, they will take in a significant amount of excipients, which are not compatible with the body, and they will suffer serious side effects.

I think one of the best deterrents of abusing this product IV is to let the opioid-using community know that they're not just getting a high, they're getting kidney damage and liver damage and lung embolisms, and they'll go some other way.

DR. BROWN: So we're going to move on to our last question. This is a question for vote again. The question is, should RoxyBond be approved for the management of pain severe enough to require an opioid analgesic for which alternative treatments are inadequate?

Is that question clear to the members of the panel? Dr. Galinkin?

DR. GALINKIN: I believe -- correct me if I'm wrong. Roxicodone is actually labeled in children as well, and I understand only 1 percent of the drug is given. But in the postoperative population, which my colleagues can confirm, single-entity oxycodone is the primary drug that is prescribed for postoperative pain.

Since this is essentially a bioequivalence

formulation study, are we also talking this approval for kids as well?

DR. FIELDS: Hi. It's Ellen Fields, FDA. Although Roxicodone is used a lot in children, it's not labeled for children. The current label doesn't include pediatrics.

DR. BROWN: Dr. Choudhry?

DR. CHOUDHRY: A clarifying question for the FDA, I think. This is a question about whether or not we are recommending that this product be approved. We talked a lot today about safety and abuse-deterrence approval presumably has other characteristics beyond that.

Can you just help us understand whether or not the data we've received today and reviewed today in the briefing documents is the totality of what we would need to answer this question?

DR. HERTZ: We thought so when we put it all together. When a product comes in and wants to demonstrate safety and efficacy for the proposed indication, there's a number of different ways to do that. One is through a comparison with an

approved product that has the same planned labeling to show that you're bioequivalent.

In that setting, if we have a particular reason to get safety data that we think might be formulation specific, we'll sometimes ask for that. But if it's otherwise bioequivalent for the active drug, we don't generally require efficacy data or safety data in the context of the active ingredient.

DR. BROWN: This question is far removed from considerations of abuse potential and lack thereof, so we're looking at whether or not this formulation meets the criteria of being an analgesic, not whether we're approving it for being an abuse-deterrent formulation.

Yes, ma'am?

DR. MORRATO: Elaine Morrato. We can assume then that this labeled wording for the indication is what's the approved indication right now for Roxicodone, and are we bioequivalent to it is the question, really.

DR. HERTZ: Yes. We recently in the last

few months -- I think it was; time is flying -- underwent a very major labeling revision for the immediate-release opioids, and that included Roxicodone. The indications were changed, and there's, I believe, a limitation of use statement as well.

So this would get the same labeling. It would get all of the existing boxed warnings and other warnings, and any additional information we decided based on your input and the data that were presented.

DR. BROWN: Are there any other comments? Dr. Gupta?

DR. GUPTA: Clarify what formulation we're talking about. Are we talking about nasal, all, or PO? What are we approving for? Are we just approving it for pain, or what formulation are we talking about?

DR. HERTZ: Just the pill that was presented. So the approval would be for taking the pill according to the label directions for the indication proposed.

DR. BROWN: Any other comments? Dr. Kibbe?

DR. KIBBE: Dr. Kibbe. I'll get on one of my pet peeves. This is not a pill. This is a tablet. Pills are made a very specific way, and this is not the way they're made. Okay. That's one.

The second is I'm not convinced that this is a pure immediate release. The immediate release by definition is that the dosage form itself does not interfere with the release of the drug, and this dosage form does, in very specific situations, but it still does. And I think it probably slows the release compared to the reference product, but not sufficiently to get it out of a bioequivalency relationship.

The dissolution requirements in the USP are very specific, and I assume that the agency will look at those requirements and compare it to the data that they get from the sponsor and determine whether it's truly an immediate release or is acceptable as an immediate release even though it's not technically an immediate release.

Other than that, I don't have any problem with the wording, and I think we should move forward and all of us go home early.

DR. HERTZ: So for the record, I'd like to correct my earlier statement, and this tablet --

(Laughter.)

DR. HERTZ: -- is the formulation under consideration. Thank you. We should be accurate. We do this for a living.

Regarding as you think about this question about whether it should be approved for that indication, given your comments, yes, we will look at all of the dissolution criteria. And in terms of determining whether or not the formulation is IR or ER, immediate release or extended release, or some other type of modified release, yes, our chemists will look at all that.

Regardless of what that final determination is, perhaps you can weigh in on whether or not you think it should be approved.

DR. KIBBE: Oh, I do. It's not specifically an immediate release the way we define it.

DR. HERTZ: I understood your point.

DR. KIBBE: And I don't know whether that's worth including in the overall labeling or not.

DR. HERTZ: We'll ask for folks to address that in their reviews and whether or not it should be included in the labeling. Thanks.

DR. BROWN: If there's no further discussion on this question, we'll now begin the voting process. Please press the button on your microphone that corresponds to your vote. Again, the question is, should RoxyBond be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate?

Please press the button firmly. After you have made your selection, the light may continue to flash. If you're unsure of your vote, if you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

LTC BEGANSKY: The vote is 19 yes, zero no, 1 abstain.

DR. BROWN: Now that the vote is complete, we're going to go around the table and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted as you did in the record. And just for grins, I'm going to start with Dr. Kibbe.

DR. KIBBE: Well, I'm glad I can make you grin.

I voted yes because I think that's the standard use of the active ingredient in the product, and most of my concerns were about the dosage form and not the active ingredient. The active ingredient is for pain, and that's what we're approving it for. I'm sure the agency will look into whether it should be labeled as immediate release, modified release, or partially modified release. Thank you.

DR. KAYE: Alan Kaye. I voted yes, and for all the reasons we've discussed throughout the day. I'll leave it at that.

DR. SCHMID: Chris Schmid. I voted yes for all the reasons we've discussed and what I

mentioned before.

DR. EMALA: Charles Emala. I voted yes. I'll just add as a broken record that I think the agency and the industry should be very careful to learn more about what's being extracted and potentially injected.

The agency did some elegant studies with PEO in animal models, and that would be my only hesitation in voting yes, is that I think this should be looked at before this is actually formally on the market.

DR. LITMAN: Ron Litman. I abstained because I just couldn't decide which one. I agree with those who voted yes because it clearly, according to the pharmacological studies, will work just fine as an opioid to treat severe pain. But on the other hand, I just couldn't find it philosophically to vote yes because I just think that having another approved ADF on the market will just detract. Even if it's not labeled as an ADF, it's still formulated as one, and that's the message that gets out.

DR. GUPTA: Anita Gupta. I voted yes. I was impressed by the presentations. I thought there was enough evidence to state that this may be an innovative progression of opioid products that may offer an incremental advantage, an option for patients who have pain.

I think there are certainly unanswered questions, as I've already mentioned, regarding the excipients. There certainly is still a risk of abuse, and this certainly is not entirely without that risk. But I am excited to know that there is some innovation occurring, that there is some type of promise with this technology, and that's why I voted yes.

DR. WARHOLAK: Terri Warholak. I voted yes.

DR. CRAIG: Dave Craig. I voted yes.

DR. BROWN: Rae Brown, and I voted yes, and I have a couple of comments. Actually, they're both the same.

I think this is an important formulation, and despite the fact that your data show very few uses for this in children for oxycodone products,

my guess is that this will become the go-to product for treatment of pain in children.

Because of that, I think that it's incumbent on the agency to place a special pressure within the agency to look at the excipients in this drug in the same way that we looked at the excipients in Opana, because if it's used in children and somebody has the crazy idea to inject it, then that could be a significant problem.

DR. BATEMAN: Brian Bateman. I voted yes. I would just say I think this medication represents a really important advance as the first immediate-release opioid with properties intended to deter abuse. While it's not perfect, it does provide at least some barrier to abuse by intravenous and intranasal routes, and therefore, really meets an important public health need.

DR. SHOBEN: Abby Shoben. I voted yes, and I was about to say all the same things Dr. Bateman just said. He just said it better than I would have.

DR. ZACHAROFF: Kevin Zacharoff. I voted

yes, and just a couple of quick comments with respect to that yes. And that would be that if this drug ends up being labeled as an abuse-deterrent product, that there be something that is given in the label to help prescribers decide which patients are appropriate candidates for an abuse-deterrent formulation versus a non-abuse-deterrent formulation, assuming that that non-abuse-deterrent formulation is still available on the market.

I think there's a lot of lack of clarity at the general prescriber level who are prescribing these medications as to what that actually means.

The other thing I think that will come into play didn't come up at this meeting, nor should it have, is the idea of what the cost incentive and formulary acceptance will be for this medication in an abuse-deterrent formulation versus one that's available in a non-abuse-deterrent formulation. All things being equal with respect to cost, that may be an opposing factor, but if they're not, that end up being opposing factor as well.

DR. McCANN: Mary Ellen McCann. I voted yes

for the reasons previously stated.

DR. GALINKIN: Jeff Galinkin. I voted yes, and I would like to say that I would really urge the agency to make sure that they take this opportunity to look at this drug for children. It has become the primary drug for postoperative pain at most of the major children's hospitals in part because the American Academy of Pediatrics has really specified that combination tablets are something to be avoided to avoid the use of Tylenol because parents tend to give Tylenol plus the Tylenol and Percocet. Primary oxycodone has become one of our big postoperative drug that we do use, and we'd like to see it studied.

DR. HIGGINS: Jennifer Higgins. It's a qualified yes. I have a few comments. I say that if it is labeled abuse deterrent, there really needs to be, and I believe there will be, postmarketing data collected and participation in the REMS.

I think also there should be some age stratification analysis completed as we had

mentioned earlier today, and I'd like to see a review of the public health effects of the AD products in general.

MR. O'BRIEN: Joe O'Brien. I voted yes. My response actually went from the simple to the complex in my mind. The simple was from a technical perspective, it seemed to me that it certainly equaled what was out in the market right now.

As we got more complex, I think philosophically I agree with Dr. Litman that I don't think this is the answer, and it has not shown to be the answer to the epidemic that we do have. I think the reality in getting to the more complex and real world and practical world as a patient and representing the patient community, what's that going to mean from a practical perspective in terms of now being forced into another area that will cost more money in the end. But philosophically, it helps those that -- if it can help one, then I guess it's worth doing, but I do have concerns from both safety and a cost

perspective.

DR. CHOUDHRY: Niteesh Choudhry. I voted yes as well, and just to build on what Dr. Higgins was saying, I think this is a real opportunity for the agency to think about the postmarketing space. And there are fundamental questions about whether IR abuse deterrents actually do anything or not just holistically, and then the underlying basic science of the relationship between drug liking PK and then ultimate abuse. This sort of formulation allows for that opportunity to figure out that science, and so I'd urge that those things be high on the agenda.

DR. MORRATO: Elaine Morrato. I voted yes for many of the comments that have already been shared. I'll just focus on thoughts that I have as it might move forward as well. I want to underscore everything that Dr. Choudhry has said about the postmarketing space and knowledge with that.

That's part of the reason why I was comfortable voting yes is because I know there's a

lot of effort that's going on in the FDA in terms of approaching this as a public health initiative evaluation and so forth.

I am also reassured with the labeling in what we saw in our briefing document of excerpts from labeling of others so that there's transparency. It's not just a claim of abuse deterrent, but the evidence that is there that supports it is transparent so people can understand what that's based on and maybe make their own judgement.

The piece I did want to raise -- because these things that we heard today will likely be translated into promotional claims, and the agency also plays a role in oversight in promotional claims. So I would want to be careful in not expecting to see difficulty scores that aren't validated being part of promotional activity because that implies greater level of abuse deterrence than I think the data warranted with that score.

I'm also a little hesitant or skeptical

about the GI tract claim. It seemed to me that this was a product that's formulation was pH dependent. That's not the entire GI tract, so I think that would need to be more specific, too.

I say this because when someone hears abuse deterrent, that can mean many things and much larger, and I think we need to be -- because this is just one piece of a larger, incremental mosaic of activity, being very clear as to what this is and what it isn't.

Then I would underscore also what others are saying about the excipients, and I would leave it to the FDA whether or not it's a premarket requirement or postmarket requirement. I think it's a unique problem in that this safety problem arises from misuse and adulteration or misuse of the products. So I know that's a difficult space on how to regulate approval, but I think because there's prior evidence with other drugs, there is some precedent to be concerned about this.

DR. WALSH: I'm Sharon Walsh, and I voted yes because I think the criteria for the 505(b)

pathway were met with the bioequivalence data.

DR. AMIDON: Greg Amidon. I voted yes based on the pharmacokinetic data and the discussion we had. Perhaps this is a bit out of scope, but I was intrigued by the idea that perhaps guidance could be given as to which patient population this might be most appropriate for. And I'm thinking about that in the context of diversion. This is not a question just of safety for the patient, but for families, for all the possibilities for diversion and perhaps something to consider.

DR. BROWN: Do we have any comments before we adjourn from our industry representatives?

(No response.)

DR. BROWN: Panel members, before we adjourn, are there any last comments from the FDA?

DR. HERTZ: I know every chance I get to speak, I thank you all for being here, but I really mean it because I do understand how disruptive coming back and forth to these meetings can be for the important work that you're doing, be it practice, research, what have you. The time spent

here, the time spent traveling, we understand that that it's not inconsequential. These discussions continually bring up important thoughts and ideas for us to take back and incorporate. So for the last time today, thank you again.

Adjournment

DR. BROWN: Thanks, Dr. Hertz.

Panel members, please take all of your personal belongings with you as the room is cleaned at the end of the day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out.

We'll now adjourn the meeting. Thank you for coming.

(Whereupon, at 3:02 p.m., the open session was adjourned.)