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

Thursday, August 4, 2016

9:30 a.m. to 4:05 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Stephanie L. 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

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

Jeffrey L. Galinkin, MD, FAAP

Professor of Anesthesiology and Pediatrics

University of Colorado, AMC

Director of Pain Research

CPC Clinical Research

University of Colorado

Aurora, Colorado

Anita Gupta, DO, PharmD

Vice Chair and Associate Professor

Division of Pain Medicine & Regional

Anesthesiology

Department of Anesthesiology

Drexel University College of Medicine

Philadelphia, Pennsylvania

Jennifer G. Higgins, PhD

(Consumer Representative)

Director of Strategic Planning and Business

Development

Center for Human Development

Springfield, Massachusetts

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

W. Joseph Herring, MD, PhD

(Industry Representative)

Neurologist

Executive Director and Section Head

Neurology, Clinical Neurosciences

Merck Research Laboratories, Merck & Co.

North Wales, Pennsylvania

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBER (Voting)

Tobias Gerhard, PhD, RPh

Associate Professor

Rutgers University

Department of Pharmacy Practice and Administration

Ernest Mario School of Pharmacy

New Brunswick, New Jersey

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)

Cynthia Arfken, PhD

Professor

Department of Psychiatry and Behavioral

Neurosciences

Wayne State University

Detroit, Michigan

Patrick Beardsley, PhD

Professor

Department of Pharmacology & Toxicology,

Institute for Drug and Alcohol Studies, & Center for

Biomarker Research and Personalized Medicine

Virginia Commonwealth University

Richmond, Virginia

Warren Bilker, PhD

Professor of Biostatistics

Department of Biostatistics and Epidemiology

Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Harriet de Wit, PhD

Professor of Psychology

Department of Psychiatry and Behavioral

Neurosciences

Pritzker School of Medicine

University of Chicago

Chicago, Illinois

John Farrar, MD, MSCE, PhD

Associate Professor of Epidemiology in Biostatistics and Epidemiology

Co-Director, Biostatistics Analysis Center

Biostatistical and Epidemiology Consulting Center

Center for Clinical Epidemiology and Biostatistics

University of Pennsylvania

Philadelphia, Pennsylvania

Randall P. Flick, MD, MPH

Medical Director

Mayo Clinic Children's Center

Associate Professor of Anesthesiology and Pediatrics

Mayo Clinic College of Medicine

Rochester, Minnesota

James Floyd, MD, MS

Assistant Professor, Department of Medicine

Adjunct Assistant Professor

Department of Epidemiology

University of Washington

Seattle, Washington

Scott Novak, PhD

Senior Research Analyst

Behavioral Health Epidemiology Program

RTI International

Research Triangle Park, North Carolina

Joseph O'Brien, MBA

(Patient Representative)

President and CEO

National Scoliosis Foundation

Stoughton, Massachusetts

Sharon Walsh, PhD

Professor of Behavioral Science, Psychiatry,
Pharmacology and Pharmaceutical Sciences
Director, Center on Drug and Alcohol Research
University of Kentucky
Lexington, Kentucky

Ursula Wesselmann, MD, PhD

Professor of Anesthesiology and Neurology
Department of Anesthesiology
Division of Pain Medicine
University of Alabama at Birmingham
Birmingham, Alabama

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

Acting 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

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

(9:30 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'd also like to identify the FDA press contact, Michael Felberbaum, who is at the other end of the room.

My name is Rae Brown. I'm the chairperson for today's meeting. I'll now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We'll start by going around the table and introduce ourselves, and we're going to start with the FDA to my left and go around the table.

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

DR. HERTZ: Sharon Hertz, director for the Division of Anesthesia, Analgesia, and Addiction Products.

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

DR. BILKER: Warren Bilker, professor of biostatistics at the University of Pennsylvania.

DR. FLICK: Randall Flick, pediatric anesthesiologist, Mayo Clinic.

DR. WESSELMANN: Ursula Wesselmann, professor of anesthesiology and neurology at the University of Alabama at Birmingham.

DR. BATEMAN: Brian Bateman, associate professor of anesthesia, Harvard Medical School.

DR. CRAIG: David Craig. I'm a clinical pharmacist in Moffitt Cancer Center, Tampa, Florida.

DR. GALINKIN: Jeff Galinkin, professor of anesthesiology and pediatrics at University of Colorado.

DR. GUPTA: Dr. Anita Gupta, vice chair and associate professor in Department of Anesthesiology

and Pain Medicine at Drexel University College of Medicine.

DR. EMALA: Charles Emala. I'm an anesthesiologist and vice chair for research at Columbia University.

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

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

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

DR. FARRAR: John Farrar, neurologist, epidemiologist, at the University of Pennsylvania.

DR. NOVAK: Scott Novak, pharmacoepidemiology, pharmacovigilance at RTI International.

DR. FLOYD: James Floyd, general internist at the University of Washington.

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

DR. HIGGINS: Jennifer Higgins, consumer representative.

DR. WALSH: I'm Sharon Walsh. I'm a professor of behavioral science, psychiatry, pharmacology, and pharmaceutical sciences at the University of Kentucky.

DR. ARFKEN: Cynthia Arfken, professor at Wayne State University.

DR. DE WIT: Harriet de Wit. I'm professor in the Department of Psychiatry and Behavioral Sciences at the University of Chicago.

DR. BEARDSLEY: Patrick Beardsley, professor of pharmacology and toxicology at the Virginia Commonwealth University.

DR. SCARAZZINI: Good morning. Linda Scarazzini. I'm the vice president at AbbVie for pharmacovigilance and patient safety. I'm the industry rep for DSaRM.

DR. HERRING: Hi. I'm Joe Herring, a neurologist employed at Merck in the clinical neuroscience group, and the industry representative to the Anesthetic and Analgesia Drug Products

Advisory Committee.

DR. BROWN: Welcome to this open session. 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, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings.

However, FDA will refrain from discussing the details of this meeting with the media until

its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Now I'll pass it over to Lieutenant Commander Stephanie Begansky who will read the conflict of interest statement.

Conflict of Interest Statement

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

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

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

limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interests 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 208603, morphine sulfate extended-release tablets, submitted by Egalet U.S. Incorporated, with the proposed indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It has been reformulated with the intent to provide abuse-deterrent properties.

The committees will be asked to discuss whether the data submitted by the applicant are sufficient to support labeling of the product with the properties expected to deter abuse.

This is a particular matters meeting during which specific matters related to Egalet'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. W. 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 and Company, 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 they may have with the firm at issue. Thank you.

DR. BROWN: We'll now proceed with the FDA's introductory remarks from Dr. Ellen Fields.

FDA Introductory Remarks - Ellen Fields

DR. FIELDS: Good morning. Dr. Brown, members of Anesthesia and Analgesia Drugs Advisory Committee, members of the Drug Safety and Risk Management Advisory Committee, and invited guests, thank you for joining us this morning.

Today we will be discussing an application from Egalet for a new extended-release tablet formulation of morphine sulfate with the proposed trade name Arymo ER. If approved, Arymo ER will have the same indication as the already approved extended-release long-acting opioid analgesics,

that is the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Arymo ER has been formulated with the intention to deter abuse, based on physical and chemical properties that resist manipulation for the purposes of abuse. During this meeting, you will hear presentations from Egalet on the development of Arymo ER and the results of the in vitro physical and chemical manipulation studies and human abuse potential studies they conducted to demonstrate abuse-deterrent properties.

FDA will present drug utilization data for morphine sulfate and other extended-release opioids, as well as the agency's interpretation of the oral human abuse potential study.

We are aware of the immense public health problem that exists in the United States today from the abuse of prescription opioids. As part of a larger effort across HHS, we at FDA have encouraged drug companies to develop novel interventions to

reduce this abuse.

To this end, we have supported the development of novel formulations through multiple interactions with both the pharmaceutical industry and the academic community. And in April 2015, we issued the guidance for industry abuse-deterrent opioids, which explains the agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. It makes recommendations about how these studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

As discussed in the guidance, the development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products. The evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect

that deterring abuse by one route may have on shifting abuse to other possibly riskier routes.

Abuse-deterrent properties can generally be established only through comparison to another product. The fact that a product has abuse-deterrent properties does not mean there is no risk of abuse. It means rather that the risk of abuse is lower than it would be without such properties.

Because opioid products must in the end be able to deliver the opioid to the patient, there will always be some risk of abuse of these products, and as long as the product can deliver the opioid, the risk for addiction will remain.

In response to the growing epidemic of opioid abuse, dependence, and overdose in the United States, the commissioner announced an opioid action plan in February of this year to take steps towards reducing the impact of opioid abuse on the public health.

As part of this plan, the agency has committed to work more closely with its advisory

committees before making critical product and labeling decisions. As you know, we are calling on all of you more often to fulfill this goal.

As we work to make opioid analgesics less desirable targets for abuse, we cannot forget that the underlying purpose of these products is the management of pain in patients for which other alternatives are inadequate, and opioid analgesics remain an important component of pain management.

With every new product we weigh the risks and benefits. With new abuse-deterrent formulations, we are also watchful for any evidence that the product results in a new or increased safety risk for patients who take the product as directed, and for any evidence that by deterring abuse by one route of administration, the new product may shift abuse to a riskier route of administration; for example, deterring oral abuse but inadvertently making nasal or intravenous abuse more attractive.

There are currently six approved extended-release opioid products, including two

extended-release morphine products with abuse-deterrent properties, and we are watching the postmarketing data closely for any signs of unintended problems associated with these products.

Today, you will be asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, the routes of abuse for which abuse-deterrent properties have been demonstrated, and whether Arymo ER should be approved.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience, and your best insights, in order to help us find a reasonable and responsible path forward.

Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us and look forward to this important discussion.

DR. BROWN: Thank you, Dr. Fields.

Both the Food and Drug Administration and

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and other 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're now going to proceed with Egalet's

presentations.

Applicant Presentation - Robert Radie

DR. RADIE: Good morning. My name is Bob Radie, and I'm the president and CEO of Egalet Corporation. Egalet is a specialty pharmaceutical company focused on developing, manufacturing, and commercializing innovative treatments for pain and other conditions.

We'd like to thank the FDA and the advisory committee members for your time today to discuss our NDA for Arymo ER, morphine sulfate extended-release tablets for the treatment of chronic pain.

Arymo is designed to deter many of the most common forms of opioid misuse and abuse. The need for an abuse-deterrent formulation is particularly urgent in the case of morphine, since morphine is the most commonly prescribed extended-release opioid.

In the first four months of this year, more than 98 percent of the extended-release morphine products dispensed had no abuse-deterrent

properties. That means these morphine medications can be easily abused by chewing, crushing, snorting, or injecting.

We want to be very clear. We're not here advocating for just another morphine pain medication to add to the 98 percent. Rather, we believe that Arymo can be an important part of the effort to replace these products with effective abuse-deterrent formulations.

Arymo provides a broad abuse-deterrent profile. It has physical and chemical barriers to all common routes of abuse, including chewing and other types of manipulated oral abuse, snorting, and intravenous injection.

It's important to define exactly what we mean by oral abuse. We do not mean someone taking too many intact pills. Unfortunately, no abuse-deterrent product can prevent that type of abuse since the intact pills must release opioid to provide pain relief.

By deterring oral abuse, we mean that Arymo is extremely hard and would be difficult or

impossible to chew.

In addition, it cannot be turned into an immediate-release product through physical manipulation, and it resists chemical extraction in solution. We'll also show data demonstrating that Arymo cannot be reduced to particle sizes amenable to snorting, and subjects who tried to snort it, did not like the experience. Finally, the data show that Arymo cannot be extracted and prepared for IV injection, the most common non-oral form of morphine abuse.

I'll describe how our manufacturing technology imparts physical and chemical abuse-deterrent features to Arymo.

Arymo is manufactured with Egalet's proprietary Guardian technology, which combines a polymer matrix formulation with the established well-characterized manufacturing process of injection molding.

Morphine sulfate and polyethylene oxide are blended together and melted in the injection-molding machine using heat and high pressure to

force the blend into a very hard dense tablet. The tablet's matrix composition with polyethylene oxide imparts Arymo's extended-release profile and hardness.

It also results in resistance to particle size reduction, chemical extraction, and syringeability by forming a gel on contact with liquid. Overall, Guardian technology results in an extended-release product with robust physical, chemical barriers against abuse.

The Arymo development program was conducted in accordance with FDA guidance and frequent interaction with the agency. Arymo was shown to be bioequivalent to the reference listed morphine drug, MS Contin, across the proposed dosages of 15, 30, and 60 milligrams.

These data create the scientific bridge that supports the approvability of Arymo through an accepted FDA pathway. In addition, a fed/fasted PK study with Arymo 60 milligrams, the highest proposed dose, demonstrated no evidence of a clinically significant food effect. In fact, Arymo

60 milligrams is bioequivalent in the fed versus fasted state.

While we won't elaborate on these data today, they are included in your briefing book. We also conducted an in vitro alcohol interaction study, which showed no evidence of dose dumping in the presence of alcohol.

Egalet conducted the full battery of abuse-deterrent Category 1 through three studies in accordance with the FDA guidance on abuse-deterrent opioid development and in consultation with experts, several of whom are here today. These studies are designed to reflect as closely as possible what abusers do in the real world.

Category 1 in vitro studies assess how easily products can be manipulated physically and chemically to facilitate various routes of abuse. Category 2 pharmacokinetic studies evaluate whether a product can be converted into an immediate-release product by manipulation. And finally, Category 3 studies assess the human abuse potential by measuring how much recreational opioid

users like the manipulated product versus the comparator. The results demonstrate that Arymo can be expected to deter abuse by the manipulated oral, nasal, and IV routes.

If Arymo is approved, Egalet is committed to fulfilling the post-approval requirements for an extended-release opioid. These include participation in the ER/LA REMS program and conducting our own Category 4 study to assess the real world impact of Arymo on abuse of extended-release morphine products.

Prescription drug abuse is a very complex problem and needs a multifaceted solution. Education, prescription monitoring, proper prescribing, and proper disposal can all help reduce misuse and abuse.

We believe that abuse-deterrent opioids like Arymo can be another important piece of this puzzle. With this background in mind, I'll review our agenda and presenters for this morning.

Dr. Richard Dart will discuss the public health need for abuse-deterrent, extended-release

morphine formulations to help address the opioid abuse epidemic. Dr. Jeffrey Dayno will review the results of our abuse-deterrent studies. And lastly, Dr. Nathaniel Katz will conclude the presentation with his perspective on the clinical relevance of the data for Arymo.

We are also joined by additional experts who are available to respond to your questions. All of our external experts or their institutions have been compensated for their time and travel expenses, and none have an equity interest in today's outcome.

I'll now invite Dr. Dart to the 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 and a professor at the University of Colorado. I'm also the executive director of the RADARS System, which provides surveillance of prescription drug abuse and diversion throughout the United States.

Today, I will provide a perspective on

morphine and abuse-deterrent formulations that I hope you'll find useful. Arymo is an extended-release morphine formulation with abuse-deterrent properties, and morphine is a highly abused drug. And I'll discuss how it is abused, how abuse-deterrent formulations work, and why an extended-release morphine with physical, chemical barriers is needed.

Now some opioid abusers swallow intact pills, but many chew or manipulate in other ways, the tablet first in order to speed up and intensify their high. For a pharmacologist it's real-world proof that increasing the surface area of a drug in the gut dramatically increases the rate of release. We call this particle size reduction. You'll hear that term a lot today.

As the particle size decreases, the surface area for the drug increases. This produces the fastest and highest blood levels. It's a crucial concept, because the goal of all abusers who manipulate their drug is to reduce the particle size and increase the intensity of their high.

Unfortunately, all of these routes have increased risks of overdose, and for intravenous abuse, the long-term consequences of HIV and hepatitis C. So if we can reduce chewing, snorting, and injection, we have made progress.

The appeal of an opioid analgesic for manipulated abuse is the sum of several factors that really boil down to a simple equation. How much effort is needed to get the drug into an abusable form with enough yield to produce the desired high?

Effort is very important to abusers. Given a choice, abusers will choose the tablet that can be crushed into a powder in seconds, like almost any non-abuse-deterrent analgesic. In contrast, if an abuser has to work hard and long to get the drug out, they're not going to choose that drug.

Category 1 studies assess in the laboratory how hard it is to do that manipulation of the drug, while Category 2 and 3 studies assess how much abusers like the drug. Together, the results from all three categories are meant to provide an

indication of whether or not a formulation can be expected to lead to a reduction in abuse.

As you know, there is more than one way to make a product abuse deterrent. The most common approach is physical chemical where the product is difficult to crush and resists extraction of the active ingredient.

The first product with physical chemical abuse-deterrent formulations was OxyContin, which was designed to resist manipulation and chemical extraction, and to form a thick goo when mixed with water. Arymo also uses the physical chemical strategy to deter abuse, but is manufactured using a different technology.

The main alternative approach is the use of an antagonist. In these products, the tablet is easy to crush, but manipulation releases an antagonist like naltrexone that prevents the euphoric effects and may induce withdrawal in some patients. Whatever the formulation employed, an abuse-deterrent formulation can intervene at several points in the progression of substance

abuse.

This process begins when an individual is first exposed to an opioid. Whether a pain patient or a recreational drug abuser, they may like the euphoria and desire to intensify their experience. They often start by swallowing extra tablets and then go on to chew the tablet and to crush the tablet to release the opioid faster and faster. Each of these manipulations increases the speed of onset. Some abusers proceed to snorting or injecting to further intensify their high.

Now, many people think, and unfortunately it's often portrayed this way in the press, that the main purpose of an abuse-deterrent formulation is to stop the experienced abuser from injecting the drug. An abuse-deterrent drug can help with that problem, but it's important to realize that wherever a person is on this pathway, abuse-deterrent products have the potential to deter progression down the pathway to more dangerous forms of abuse.

Now this is the theory, so let's look at

data that demonstrate the effectiveness of these abuse-deterrent barriers. Of the six approved extended-release, abuse-deterrent formulations, only one has sufficient data to allow analysis. The data indicate that the introduction of reformulated extended-release oxycodone, which has the brand name OxyContin, has been followed by a considerable reduction in misuse, abuse, overdose, and aversion.

This forest plot shows the change in these endpoints across several databases since the drug's reformulation in 2010. These analyses are remarkably diverse coming from poison centers, treatment centers, law enforcement agencies, IMS prescription data, and a specific cohort of abusers from Kentucky.

Similar trends have also been seen from outside the United States. This slide shows the number of cases of intravenous oxycodone in Australia from 2009 to 2014. After oxycodone extended-release reformulation, represented by the dotted line, cases of intravenous oxycodone abuse

dropped from about 3500 per month to about 100, and the reformulated abuse-deterrent oxycodone, shown by the blue line in the right-hand lower corner, had very few cases of IV abuse in the first few months after introduction.

This raises another question that should be addressed, whether the introduction of an abuse-deterrent opioid might lead to an overall increase in opioid prescribing. But on the contrary, even though six extended-release abuse-deterrent opioids have been approved between 2011 and 2015, the number of prescriptions for extended-release opioid has actually decreased by 1.6 million prescriptions annually by the end of 2015.

However, morphine has not followed this overall downward trend. In fact, the number of prescriptions has slightly increased over the last several years. Morphine remains the most commonly prescribed extended-release opioid in the United States.

As you heard earlier, 98.5 percent of these

morphine analgesics are not abuse deterrent, creating more opportunities for abuse and diversion.

Surveillance data show that extended-release morphine is abused by all routes. As one would expect, the most common route of abuse, as shown by RADARS Poison Center program data, is oral. In addition to simply swallowing intact pills, poison center data include chewing and swallowing, as well as crushing and swallowing in the category of oral.

Chewing is an important transition because it's the easiest way for a novice abuser to experience more rapid onset of euphoria. With the more experienced abuser population, like individuals entering substance abuse treatment centers, we see an increase in injection and snorting. In terms of the different forms of manipulated oral abuse, chewing was the most common.

In summary, abuse-deterrent products with physical chemical barriers can prevent chewing, hinder particle size reduction, and resist being

turned into an immediate-release formulation. Epidemiologic data suggests that the widespread adoption of abuse-deterrent opioid, like OxyContin, will reduce misuse, abuse, and aversion. And importantly, the introduction of abuse-deterrent formulation has been associated with a reduction, not an increase, in prescribing of opioid analgesics.

Morphine is the most commonly prescribed extended-release opioid, is abused through all routes, and nearly all extended-release morphine products prescribed in the U.S. today can be easily chewed, crushed, and snorted or injected. For these reasons, an effective abuse-deterrent, extended-release morphine pain medication would be an important addition to the public health landscape.

Thank you. I'll turn the presentation over to Dr. Dayno.

Applicant Presentation - Jeffrey Dayno

DR. DAYNO: Thank you, Dr. Dart.

My name is Jeffrey Dayno, and I am the chief

medical officer at Egalet. I will present the results of our abuse-deterrent studies for Arymo.

The abuse-deterrent program for Arymo was developed in accordance with FDA guidance, which recommends that sponsors conduct studies in three categories during the postmarketing/premarketing phase. The extended-release morphine product MS Contin was used as the non-abuse-deterrent comparator throughout the program.

I'll begin with Category 1, laboratory-based in vitro studies. This slide shows an overview of the Category 1 studies. The check marks indicate the relevant routes of abuse for each study. We agree with the FDA assessment in their briefing document that these Category 1 data demonstrate that Arymo is hard and resistant to particle size reduction, which would make all routes of abuse more difficult to access.

As Dr. Dart mentioned, particle size reduction is the first step to get the product into an abusable form for manipulated oral, intranasal, and IV abuse. I'll start with the results from our

single-tool studies.

The degree of particle size reduction was considerably lower for Arymo than MS Contin across the 10 mechanical and electrical tools evaluated. After assessing multiple tools, we narrowed it down to these 10 tools, based on two things: one, they represented different methods of manipulation such as cutting, crushing, grating, and grinding; and second, these 10 tools proved most effective at particle size reduction of both Arymo and MS Contin.

This figure shows that most of the tools reduced more than half of the MS Contin particles to less than 500 microns. In contrast, manipulation of Arymo produced a very small output of particles less than 500 microns.

It is also important to quantify the amount of effort needed to produce this very limited output. We did this using an instrument called ALERRT. ALERRT captures the combination of time, effort, and resources needed to physically manipulate a tablet on a visual analog scale from

zero to 100. A score of zero indicates that a tablet was very easy to tamper with, like an uncoated aspirin. A score of 100 indicates a tablet was extremely difficult to manipulate, like a metal nut.

Using ALERRT, we evaluated household tools commonly used by abusers that were representative of instruments used for cutting, crushing, grating, and grinding. Four trained laboratory technicians independently applied each tool to Arymo, MS Contin, and a generic immediate-release morphine sulfate tablet. A score for each tool and product was measured.

This graph shows the results using the ALERRT instrument applied to tools representative of different methods of manipulation. Higher scores represent greater difficulty in manipulation. Arymo is shown in blue, MS Contin in orange, and immediate-release morphine sulfate tablets are in red.

The amount of work needed to manipulate Arymo ranged from 70 to 99 on the 100-point scale,

illustrating the extreme difficulty involved in trying to manipulate Arymo.

In comparison, for MS Contin and IR morphine sulfate tablets, no tool achieved a score greater than 20, which indicates that these non-abuse-deterrent products are very easy to manipulate. The significantly greater level of effort required to get Arymo into an abusable form is an important abuse-deterrent property, because as we heard from Dr. Dart, abusers want a quick, easy high.

Due to the hardness of Arymo tablets, many tools actually broke during attempts at particle size reduction. The upper left photo shows a mechanical crushing tool that broke during manipulation. The middle picture depicts an electric grinding tool with a blade that was broken by Arymo. And in the upper right, another electric grinding tool whose plastic housing broke during the attempt at manipulation.

Because single tool manipulation was ineffective in producing small particles of Arymo,

we had to go even further to try and defeat the physical barriers of Arymo with sequential multi-tool procedures.

Tool F, followed by Tool B, achieved no additional particle size reduction beyond either of the tools alone. Tool F, followed by Tool J, achieved a minimal increase in small particles. We then applied Tool F followed by Tool J, and then Tool B, but that was no more effective in producing small particles than the two-step procedure with Tool F and Tool J.

So Tool F was identified as the optimal single tool particle size reduction method, and Tool F, followed by Tool J, was found to be the optimal multi-tool particle size reduction method for Arymo. Tool B alone was sufficient to crush MS Contin to a fine powder.

Now we'll look at the drug yield using these respective methods. This slide shows the distribution of particle sizes for the optimized methods of particle size reduction for Arymo. The optimal single tool procedure with Tool F is shown

in light blue, and the optimal multi-tool procedure with Tool F followed by Tool J is shown in dark blue.

These findings demonstrate what is concluded in the FDA briefing materials, that multiple manipulations used in sequence did not yield any significant changes in particle size reduction compared to single tool manipulation.

In contrast, MS Contin was reduced to a fine powder by a single tool, and this resulted in a high yield of small particles. The highlighted area shows particles smaller than 500 microns, a size recognized by the FDA as amenable to snorting.

Comparing Arymo and MS Contin, only 1 to 5 percent of Arymo particles were amenable for snorting, as compared to more than 75 percent of MS Contin particles.

We then tried pretreating Arymo tablets with different temperatures before applying the maximal particle size reduction method. In this experiment, before pretreatment, nearly three-quarters of MS Contin particles were reduced

to smaller than 500 microns with a single tool. Therefore, we did not further evaluate MS Contin in this study.

We pretreated Arymo with three different temperatures followed by the optimal multi-tool method. None of the pretreatments resulted in a meaningful increase in the yield of small particles.

Next, I'll move to the study that assessed the tablet hardness of Arymo to determine the feasibility of chewing, which is the most common form of manipulated oral abuse.

We evaluated the hardness of Arymo and MS Contin tablets using a conventional hardness tester. We determined that the hardness of Arymo exceeded 400 newtons, which was the limit of the tester. This compares to the hardness of MS Contin, which was 63 newtons.

While the force generated with routine mastication is in the range of 70 to 150 newtons, the average maximum human bite force is 300 to 350 newtons. Therefore, we concluded that

Arymo would be very difficult or impossible to chew, and chewing would not be an effective method of manipulation in the oral human abuse potential study.

Next, in vitro experiments for IV injection assessed the feasibility of small-volume extraction and syringeability. This is important because IV injection is the most common non-oral route of abuse for morphine and is also the most dangerous. These pictures show what happens to Arymo and MS Contin when exposed to small volumes of liquid after particle size reduction. Arymo deters IV injection by forming a viscous hydrogel, while MS Contin can be easily prepared for injection.

The first IV experiment evaluated how much morphine could be extracted in small volumes of injectable solvents after optimal particle size reduction. Even with modifications to temperature, less than 10 percent of morphine could be extracted from Arymo, but this was in volumes of solvent not typically used by IV abusers. In contrast, 52 to 66 percent of morphine was extracted from

MS Contin under the same conditions.

The Gel Blob syringeability study was conducted to evaluate whether the gelling effect of Arymo could be overcome with longer extraction times. Twelve different extraction conditions were evaluated including long extraction times out to 4 and 24 hours, using two different solvents, and testing Arymo under three conditions: intact; manipulated with the optimal single-tool method with Tool F; or manipulated using the optimal multi-tool method with Tool F followed by Tool J.

In 9 of the 12 conditions, less than 10 percent of morphine could be drawn up into a syringe of any size. In the remaining 3 conditions, between 16 and 18 percent of morphine could be syringed from the Gel Glob. However, this required the largest needle evaluated, needle gauge D. This represents an extreme case because this needle size is much larger than the needles commonly used for IV abuse.

Because of the IV findings, and based on the Category 1 results, we determined that subjecting

human beings to an IV abuse potential study with Arymo would be neither feasible nor ethical.

Next, I'll cover large-volume extraction, which is relevant primarily to the manipulated oral route of abuse, but could also be used for the IV and nasal routes. The full battery of solvents was shown in your briefing book. I will review the results of two model solvents. These were representative of different pH and polarity and were highlighted in the FDA briefing book.

We assessed extraction with Arymo tablets at all to-be-marketed dosage strengths. Tablets were manipulated using the optimal multi-tool method. As a reference, the red line shows the recent recommendation from the FDA draft guidance for generic abuse-deterrent opioid development that identifies 80 percent extraction within 30 minutes as a threshold for failure of abuse deterrents against extraction. This threshold is what characterizes immediate-release products. Eighty percent extraction at 30 minutes was not achieved in these two model solvents.

Finally, the in vitro alcohol dissolution study tested the potential for alcohol dose dumping with intact Arymo. We measured the amount of morphine released from an intact Arymo tablet in simulated gastric fluid in various alcohol concentrations ranging from zero to 40 percent. We found that alcohol did not accelerate morphine release. In fact, higher concentrations actually slowed morphine release.

Despite no evidence of alcohol dose dumping, if approved, the label for Arymo would state that it should not be taken with alcohol.

I will now review the Category 2/3 studies for the manipulated intranasal and oral routes. Category 2 pharmacokinetic studies evaluated whether Arymo could be converted into an immediate-release profile after tampering. Category 3 pharmacodynamic studies evaluated important subjective endpoints, including drug liking and take drug again.

I will begin with our intranasal human abuse potential study, a randomized, double-blind, active

and placebo-controlled 5-period crossover study. It was conducted in adult subjects who were non-dependent, recreational opioid users experienced with snorting prescription opioids. Forty-six subjects completed the study.

There were five treatment arms. All treatments were prepared by the site pharmacy and then administered to subjects in a blinded manner. MS Contin was crushed with Tool B, while Arymo was prepared with Tool F followed by Tool J.

Since Arymo cannot be crushed into a fine powder, we included two different manipulated Arymo treatment arms. In one arm, subjects snorted all the manipulated product. In the other arm, the manipulated Arymo tablet was sieved to remove large particles that would be difficult to snort. An intact Arymo treatment arm and placebo arm were also included.

The primary endpoint was maximum drug liking or Emax measured real-time out to 24 hours post-dose. Key secondary endpoints included overall drug liking and take drug again assessed at

12 and 24 hours post-dose. The drug effects questionnaire evaluates important aspects of the drug taking experience, such as feeling high. This was administered real-time out to 24 hours post-dose. Pharmacokinetic parameters including Cmax, Tmax, and area under the curve were measured out to 24 hours.

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. As you can see, both manipulated Arymo treatment arms demonstrated statistically significant reductions in Emax compared to crushed and snorted MS Contin, so the co-primary endpoints were met.

Moving to the key secondary endpoints. For both manipulated and snorted Arymo treatment arms, subjects reported significantly lower willingness to take the drug again and overall drug liking, compared to crushed and snorted MS Contin. Scores

on these endpoints for manipulated and snorted Arymo were similar to or lower than both intact oral Arymo and snorted placebo powder. These data corroborate and support the results of the primary endpoint.

These graphs show two key parameters from the drug effects questionnaire, which are measured using a unipolar scale. As you can see, both Arymo treatment arms were associated with significantly lower ratings than crushed and snorted MS Contin on visual analog scales for drug high and good effects. This provides further support for the reduced abuse potential of intranasal Arymo.

Turning now to the pharmacokinetic results. These are the morphine plasma concentration curves over the first 6 hours after intranasal administration. Crushed and snorted MS Contin produced a considerably higher Cmax and earlier Tmax, compared to either of the manipulated Arymo arms after snorting.

The dotted light blue line is the PK curve for manipulated and sieved Arymo. The low morphine

plasma concentration demonstrates that sieving Arymo to remove large particles results in a loss of a substantial amount of morphine.

So overall, the PK results from the intranasal HAP study are consistent with and supportive of the primary and secondary pharmacodynamic outcomes. Based on these results, we conclude that Arymo has a reduced potential for intranasal abuse compared to MS Contin.

Next, I will discuss the results from our oral human abuse potential study, a randomized, double-blind, triple-dummy, 4-period crossover study of non-dependent recreational opioid users. Thirty-eight subjects completed the study.

The most common method of manipulation for oral abuse potential studies has been chewing. However, because of the hardness of Arymo, chewing would not be an effective method to achieve particle size reduction and would also pose a potential safety risk to subjects. Therefore, Arymo had to be manipulated with a tool by the clinical pharmacist and then given to subjects for

oral consumption in this study.

There were four treatment arms. To ensure consistency of dosing, the clinical pharmacist conducted the manipulation for all products in advance. Each manipulated product was administered to subjects in a blinded fashion.

MS Contin was crushed into a fine powder with Tool B. Arymo was manipulated with the optimal single-tool procedure, Tool F. This took more time and effort than needed to crush MS Contin, but provided a very low yield of small particles.

This study also included an intact Arymo arm and a placebo arm. The endpoints in the oral study were the same as those in the intranasal study without the scale specific to snorting.

This graph shows the results of the primary endpoint, Emax drug liking. Again, this is a 100-point bipolar scale where 100 is strong liking, 50 is neutral, and zero is strong disliking. Manipulated Arymo showed a statistically significant reduction in maximum drug liking

compared to crushed MS Contin, so the primary endpoint was met.

This graph shows the time course of mean drug liking for the different treatment arms. As you can see, drug liking was higher during the first few hours for crushed MS Contin, represented by the dotted orange line, compared to manipulated Arymo, shown by the dotted blue line.

Of note, the area under the drug-liking curve through 4 hours after dosing was significantly lower for manipulated Arymo compared to crushed MS Contin.

The secondary endpoints, take drug again, and overall drug liking were assessed only at 12 and 24 hours after dosing; also on a bipolar visual analog scale. The scores for manipulated Arymo were lower than those for crushed MS Contin, but the differences did not reach statistical significance.

As we interpret these results, it is important to remember that subjects did not have to manipulate MS Contin or Arymo themselves to get the

drugs into abusable forms. It was done for them. When subjects were asked about their overall drug liking and if they would take the drug again, they had not experienced the greater difficulty and greater challenge of physically manipulating Arymo.

Significant differences were observed on the drug effects questionnaire endpoints: drug high and good effects. These particular domains are relevant as another way of assessing positive drug effects that could lead to abuse.

Turning to the pharmacokinetic results. This figure shows the PK curves for each of the treatments over the first 6 hours after dosing. The PK profile of crushed MS Contin again showed a high Cmax and an early Tmax. We know from the literature that this PK profile begins to approach that of immediate-release morphine, but not to the point of losing the extended-release properties. Compared to crushed MS Contin, Arymo shows a lower Cmax and longer Tmax, maintaining more of its extended-release properties.

The fact that MS Contin does not completely

turn into an immediate-release product when crushed is relevant because clinical HAP studies of other abuse-deterrent formulations have often used an immediate-release form of the opioid as the comparator. Overall, the PK data are consistent with and supportive of the PD outcomes.

The totality of the Category 1, 2, and 3 data support that Arymo has a reduced potential for manipulated oral abuse compared to MS Contin.

To conclude, the Category 1, 2, and 3 studies demonstrate that Arymo would be expected to deter abuse by all common routes. This effect is primarily driven by Arymo's robust physical characteristics and resistance to particle size reduction.

Looking first at IV abuse deterrents. Since Arymo gels in solution, it is difficult to extract and draw into a syringe. In regard to deterring intranasal abuse, Arymo is difficult to reduce to a snortable powder. The Category 2/3 study was statistically significant for all primary and secondary endpoints. Importantly, pharmacokinetic

results were consistent with pharmacodynamic results.

Finally, in regard to the oral route, Arymo tablets would be very difficult or impossible to chew, which prevented chewing as a method of manipulation for the oral HAP study. Even with rigorous manipulation in the clinical pharmacy, Arymo met its primary endpoint and demonstrated a statistically significant reduction in Emax drug liking, compared to MS Contin. These results were supported by the secondary outcomes, and again, the PK results were consistent with the PD results.

Thank you very much for your attention. I will now turn the presentation over to Dr. Nathaniel Katz to provide his clinical interpretation of the data.

Applicant Presentation - Nathaniel Katz

DR. KATZ: Good morning. My name is Nathaniel Katz, and I'm the CEO of Analgesic Solutions, and associate professor of anesthesia at Tufts University School of Medicine in Boston. I'm a neurologist and pain specialist, and have spent a

good bit of the last 25 years trying to better understand both the benefits, as well as the harms, of opioids in the treatment of pain. Much of that work has been focused on better understanding the abuse potential of opioids.

You have been asked to provide guidance to the FDA on whether Arymo should be approved for the treatment of chronic pain and whether it should be labeled as abuse-deterrent for the IV, nasal, and oral routes of abuse. I will now offer you a perspective on both of these questions.

First, Arymo has met the regulatory standard for approval because it is bioequivalent to MS Contin. This rationale is based on the fact that for extended-release opioids, pharmacokinetic equivalence leads to therapeutic equivalence.

Furthermore, food has no clinically significant effect on the absorption of Arymo, and the release of morphine does not accelerate in the presence of alcohol, which are both additional beneficial features.

Moving on to whether Arymo should receive

abuse-deterrent labeling, the key question is always the clinical relevance of the findings from the premarketing studies. In other words, how do you know whether premarketing studies of abuse-deterrents predict real-world reductions in abuse?

There are essentially two ways to try to figure this out. The first is to compare results from premarketing studies of abuse-deterrent products to real-world observations of whether those same products actually deter abuse.

The second approach involves using established psychometric methods to determine the clinically important difference of an endpoint in a human abuse potential study that is associated with a change in a real-world drug taking behavior.

Let's start with the first approach and look at the IV route of abuse, which is the most dangerous. The label for reformulated abuse-deterrent OxyContin states that it forms a viscous hydrogel when subjected to an aqueous environment resisting passage through a needle.

As Dr. Dart showed us earlier, a number of studies have shown that the real-world intravenous abuse of OxyContin drops substantially after its reformulation. In other words, the in vitro finding of non-syringeability predicted a reduction in the intravenous abuse of OxyContin in the real-world. Since Arymo also demonstrates this property in vitro, it seems reasonable to provide this label expecting similar deterrents against IV abuse in the real-world.

Similarly, one can look at the intranasal human abuse potential study of OxyContin, which showed that the maximum drug liking was about 14 millimeters lower for the abuse-deterrent formulation, compared to the original formulation. This difference in drug liking also appeared predictive of real-world abuse.

Several studies have indicated that the nasal abuse of OxyContin declined substantially after the new formulation was introduced. In the human abuse potential study for Arymo, the differences in maximum drug liking between Arymo

and MS Contin were similar to the difference between the original and reformulated OxyContin. Therefore, it's reasonable to expect that Arymo will also deter nasal abuse.

While no drugs labeled as abuse-deterrent by the oral route have been prescribed enough to generate data on real-world reductions in abuse by those routes, we can still make some reasonable predictions about Arymo.

As you heard earlier, chewing is the most common form of manipulation for oral abuse of extended-release opioids. The hardness of Arymo, which is greater than 400 newtons, is higher than the average maximum biting forces reporting in the literature, which, as you heard, range from about 300 to 350 newtons. Therefore, it's reasonable to conclude that it would be very difficult or impossible to chew Arymo.

Turning to the other way to assess clinical relevance, as far as I know there are only two studies that have attempted to define the clinically important difference for endpoints in

human abuse potential studies. I was involved with the first one where we estimated the clinically important difference for Emax drug high as a predictor of real-world abuse.

We used a variety of different methods and found that a difference in Emax drug high of 8 to 10 millimeters on a unipolar scale was associated with the clinically important changes in a real-world drug-taking behavior. We did not look at the drug liking endpoint in that study since it was not available to us across the clinical trials that we had access to at that time.

The second study on this issue of clinical important differences took a meta-analytic approach. Data form a number of human abuse potential studies were compared to real-world abuse rates from two large national surveys of prescription drug abuse. These investigators determined that a 5-point reduction in Emax drug liking, that's the endpoint that I didn't look at, which was measured on a bipolar scale, would predict a 20 percent reduction in lifetime non-

medical use of an abuse-deterrent extended-release morphine product, which I think is clinically significant.

While these studies have a number of limitations, they provide us the best guidance that we currently have to determine the clinical importance of endpoints in human abuse potential studies.

Now let's consider the Arymo data in light of these benchmarks.

Shown here are the results for Emax drug high, and Emax drug liking, for the nasal human abuse potential study. The differences between manipulated Arymo versus MS Contin for Emax drug high ranged between 33 and 45 millimeters, which exceeded the 8 to 10 millimeter clinically important difference threshold I showed you for that measure. For Emax drug liking, differences of 12 to 18 millimeters also exceeded the clinically important difference threshold I showed you, of 5 millimeters. Those are the nasal studies.

In the oral study, after the drug had been

optimally manipulated by the study pharmacy and then administered to the subjects orally, there was a 13-millimeter difference for Emax drug high, and a 5-millimeter difference for Emax drug liking. The FDA briefing package raises the question of whether a 5-millimeter difference in Emax drug liking is clinically meaningful. This is a reasonable question since the differences in the oral study are smaller than the differences shown in the nasal study.

To address this concern, the differences between Arymo and MS Contin are at, or a bit beyond, the clinically important difference threshold established in the two studies I presented. At a minimum, these results indicate that Arymo is likely to be an incremental improvement over non-abuse-deterrent extended-release morphine products by this route of abuse.

It is important to remember that the subjects in this oral abuse study did not experience the primary abuse-deterrent attribute of

Arymo, which is that it's difficult to manipulate Arymo to get it into a more abusable form in the first place.

In this experiment, the manipulation had to be conducted by a pharmacist to keep the study blinded and also keep dosing consistent. In the real-world, the difficulty in manipulating Arymo might impact an abuser's assessment of a drug liking and their interest in taking the drug again.

In summary, the totality of the data support that Arymo has features that can be expected to deter abuse by the three routes under discussion today. For the IV route, Arymo resists extraction through 24 hours and its gelling properties make it difficult to inject through a needle.

For the nasal route, because of Arymo's resistance to particle size reduction, there was a low yield of small particles and recreational abusers liked snorting Arymo significantly less than crushed MS Contin.

For the oral route, the primary way that people tamper with extended-release morphine

products is by chewing. Because of the hardness of the tablet, chewing Arymo would be difficult or impossible.

Manipulations for oral abuse with tools are less common. Nonetheless, substantially more effort was required to prepare Arymo for oral administration compared to MS Contin. Despite this additional effort, Arymo's liking scores were still lower.

In summary, the data on the abuse potential of Arymo suggests that Arymo can be expected to deter abuse through all common routes. This information will be important for prescribers to consider when choosing an extended-release opioid to treat their patients with chronic pain.

The progressive replacement of non-abuse-deterrent formulations with abuse-deterrent formulations can be expected to reduce the harm associated with tampering and abuse of extended-release opioids in the United States.

Thank you. This concludes our presentation. I'll now turn the lectern back to Dr. Dayno to

answer your questions.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for Egalet at this time? Please remember if you're asking a question to state your name for the record before you speak, and if you can, please direct questions to a specific presenter.

Dr. Emala?

DR. EMALA: I have two questions I think both for Dr. Dayno. First one, slide 43. Both my questions have to do with large-volume extraction data. I note that this is the amount extracted at 30 minutes in two different solvents, and I just wanted to confirm that the 30-minute time point is based on -- and the 80 percent cutoff based on FDA recommendations, because I'm a little surprised that one would stop at 30 minutes in the sense that putting this into a simple solvent and letting it sit overnight seems to me to be a potential direction.

But are the 30 minutes and the 80 percent based on FDA recommendations?

DR. DAYNO: So the large-volume extraction studies were carried out to 24 hours. The 80 percent criteria are based on the draft guidance for generic abuse-deterrent opioid developments as a potential threshold at 30 minutes. But there's data that I can share with you on this slide, looking at the 1-hour time point and the large-volume extraction across the panel of 18 solvents.

We also have an extraction-over-time curves that we can show you. It would take it out to longer periods of time, beyond 30 minutes.

If we can bring up the large-volume extraction over time?

DR. BROWN: Dr. Hertz, do you have a comment?

DR. HERTZ: Yes. We do not recommend sponsors refer to the draft generic guidance for developing novel products. That guidance is intended to assist sponsors who are trying to compare a generic with an innovator that already has been labeled with abuse-deterrent properties.

It's not relevant for criteria for a new product.

DR. DAYNO: In terms of the extraction over time, we will get that data for you after the break to show you carried out over time.

DR. EMALA: Yes, as a follow-up to that, in your briefing document in figure 20 where solvent 18 is looked at again at 30 minutes, there's a text comment in the briefing document that the extraction actually decreased at subsequent time points. So it would be particularly interesting to see solvent 18 over time.

DR. DAYNO: Okay. I can bring up Dr. Cone to provide the explanation of why it decreased over time.

DR. CONE: Solvent 18 -- well first let me say this is a range of different solvents across a broad range as recommended by the FDA guidance. And most of these are not practiced in the real-world very much. Solvent 18 is a particularly toxic solvent, and if you extract the product after manipulation, eventually you can get a substantial

portion of the drug out.

Does that address your question?

DR. EMALA: Yes. Thank you.

DR. BROWN: Dr. Novak?

DR. NOVAK: I think from the real-world abuse studies, we know that abusers are very creative. And I was a little curious in terms of smoking and using foil to inhale product, while rare, it still is common. And I notice that none of the laboratory studies addressed any of that. So can you speak to a little bit about that?

DR. DAYNO: Yes. So simulated smoking studies were conducted as a part of the Category 1 panel and some of the challenges in producing vaporized morphine, and Dr. Cone, as being involved in some of those experiments, can give you that rationale.

DR. CONE: We tried to simulate how people smoke. It's pretty rare, but some people attempt to smoke any opioid there is. So in the laboratory, we set up a simulated vaporization process that is as close as we could get to the way

it's practiced in the real world.

DR. DAYNO: And just to add to that, the part of the briefing materials, less than 3 percent of the morphine was produced in those simulated smoking studies.

DR. NOVAK: And does that differ than to the comparison products?

DR. DAYNO: So Dr. Cone, so compared to --

DR. NOVAK: MS Contin.

DR. DAYNO: Compared to morphine comparator.

DR. CONE: I want to understand your question a little better. Could you repeat it again?

DR. NOVAK: That's a simple question. I guess it sounds like you conducted a simulated smoking study. Did you compare it against the comparator and what were the results? Were they favorable, unfavorable, about the same?

DR. CONE: Yes. What we typically do for any product is we start with reference standards of the salt and free base and identify the most optimal condition that is suitable for

vaporization, and then we test the product. For the comparators, we could get very good vaporization for the reference material, but for the product we got -- it just didn't vaporize out of the matrix. So we got very trace amounts, and we took temperatures up to the point of degradation.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. First, a comment briefly to FDA just echoing a comment that we heard earlier in the closed session, just a call to think about standardizing the physical tools that were used for the manipulation. I think that both in the choice of the specific tools within the categories that were used, I think might make real differences. And now having been at several of these meetings looking at abuse-deterrent formulations, I've certainly noticed that there are different tools used in -- of these meetings for different studies.

Here it seems that it was a somewhat smaller set of tools used than we've seen in some of the

earlier studies, so it makes it very difficult to compare.

Now to my question for the sponsor, and I think this is for Dr. Dayno as well, if I follow this correctly, then the method of physical manipulation used for the intranasal studies were different than the ones used for the oral study. One was the multi-tool methods including Tools F and up to J. I'm not sure whether there were two or three tools used there. And then, in the oral study, if I follow this correctly, it was only Tool F that was used?

DR. DAYNO: That's correct.

DR. GERHARD: If so, then do you have data? You show the ALERRT data on slide 28 showing the difficulty of manipulation. Here, Tool F is not shown. So one question would be whether you have any data for this specific tool.

One other question would be, is this relative data? Have the subjects that gave these scores basically performed the manipulation of all three dosage forms here and then scored, so that

it's relative? Or is this somebody that just looks at the new product, tries to manipulate it, and gives it a score that's very easy or extremely difficult?

Just saying, because if you manipulate a product, that basically offers no resistance and then you score that in comparison to that, you might get much bigger differences than if you basically let a subject naively manipulate the new product and then give a score.

My last question would be, while this is useful to give a degree of difficulty of manipulation, do you have -- particularly for the method used, but maybe for some of the other methods as well -- just an estimate of how much time it takes to manipulate the drug?

From the description of the methods in the closed session, this doesn't seem to take a lot of time or effort. While it might not be as simple as manipulating a product that poses no resistance, it doesn't seem that this would take a lot of time.

You kind of alluded to the fact that the

subjects that rated drug liking in the other measures didn't have to do the manipulation themselves. If they had to do that, maybe they would have liked the drug even less. But while that argument obviously has some face validity, it would very much depend on the effort of time and the difficulty of the manipulation.

DR. DAYNO: Yes, I understand. Several questions there. Let me start with the development process and the logic and the flow in terms of how tools were selected, and I'll try to break down the different questions.

In the exploratory phase, we actually started with 25 tools representative of the different methods of manipulation. So we started with a larger panel of tools to see what would be effective. From that larger group, we got to 10 tools, both mechanical and electrical instruments, and that was in a screening phase.

We tested MS Contin to failure and crushed it to a fine powder. The time frame was Arymo was tested up to 5 times longer, or to tool failure, to

compare to MS Contin. We thought that was a reasonable amount of time, because MS Contin could be defeated so easily.

But after that, MS Contin only required a single tool. Beyond that, we then went further, and in discussions with the FDA, looked at sequential multi-tool manipulation, and that's how we got to F to J. At that point, time wasn't as much of a factor as the optimized combination of tools and the optimized method, to arrive at that one.

So at the end of all the testing, we had optimized single-tool manipulation, Tool F, and then the optimized multi-tool manipulation F to J.

If I could then answer the question about why the two different methods in the studies. So the oral HAP study compared intranasal. It begins with -- it's a route specific thought process. For the oral HAP, chewing is the most common form of oral manipulation, and we explained why we felt chewing would be very difficult and pose a safety risk, so we had to go further and select tools. We

had both the optimal single-tool and multi-tool.

If I could have slide OD-6, in terms of the difference in particle size reduction for Tool F versus Tool F to J, you see that in both of these manipulations the vast majority of particles are greater than a thousand microns. As noted in the FDA briefing book, there was no significant different in particle size reduction in the two methods.

I think it's important that in terms of the oral HAP study, it couldn't be conducted with chewing. For the intranasal HAP, since particle size reduction is the key thing, we tried to give it the best effort, even though the yield was still small.

Back to ALERRT. I'm sorry. There was another question. In terms of the ALERRT findings, I will ask Dr. Cone, who was involved in the development of the instrument and how it's tested with laboratory technicians, to respond to your question.

DR. CONE: Yes. We selected tools early in

the program, and we spent thousands of hours trying to find the right tools that would reduce this product. This is the hardest tablet I've ever worked with. So we tried single tools and multiple tools to find whatever the best way would be to get the product reduced down to a snortable size.

In the ALERRT study, we chose the tools as representative across the range. Tool F just didn't happen to get selected in that selection, but we had other tools that represented the same mechanism of particle size reduction.

I think the effort in every regard in the ALERRT was to get a subjective measure of work, and the amount of effort that these technicians reported trying to work on these products was just out of sight. This product is the most difficult, it's just like a rock, so we spent a lot of time looking at it.

DR. GERHARD: Just to clarify, the technicians did all these manipulations and then scored it relative to each other.

DR. CONE: Yes.

DR. GERHARD: Then the other question, do you have an estimate of how long Tool F, the manipulation for the oral study, how long did it take the pharmacist that prepared, or the technician that prepared the drug? How long did that process take?

DR. DAYNO: I can respond to that, Dr. Cone. Preparation Tool F in the HAP study, it was done for 3 minutes, but if I could have the slide showing in these methods of manipulation, there was a plateau effect. So when you tried to manipulate it for more time, it plateaued, and there was no greater yield of small particles.

Let me share that data with you on this slide here. This is Tool F at 3 minutes, and that was the procedure in the oral HAP study, and then out to 5 minutes. Because of the characteristics of the tablet and that method of manipulation and that tool, it plateaus. So there was no greater yield beyond that time point.

DR. GERHARD: Makes perfect sense, but basically we're talking about a 3-minute effort to

put in before the manipulated product is available, yes.

DR. BROWN: Dr. Gupta?

DR. GUPTA: I have a question about slide 43. This represents temperature A and agitation B. Do you have the data for temperature B and agitation B for solvents 9 and 10?

DR. DAYNO: I can see if we can get you those data after the break. I don't have them right now. We'll look for them after the break.

DR. GUPTA: Okay. All right. Regarding the various studies that you did, the oral HAP, intranasal HAP, you demonstrated manipulation with intact oral and the manipulated product. Is there data that you have on this 2-step manipulation with the solvent, and then use some other type of manipulation in these studies; or just the solvent and then administration?

DR. DAYNO: In reference to the large-volume extraction solvents?

DR. GUPTA: Correct. Yes. Particularly

solvent, I think it was 9 and 10. I'm just wondering if those were evaluated in those studies after -- if someone were to use those solvents, extract the medication, and then administer it, do you have results on that?

DR. DAYNO: So the panel of testing that we did to try to be representative of different methods, to try to defeat the product in different tools and extraction methods, did not include looking at extraction in large volume and then manipulation once it was put in. But I'd like Dr. Cone to comment on the question of the two-phase extraction or going further, and what would happen with this form in terms of the output.

DR. CONE: When we did the extractions, we got recovery of morphine, but for most of the common solvents, the two that you mentioned as well, they have characteristics where they dissolve the PEO as well. So if you evaporated the solvent, you would end up with a gooey mess like you have seen in pictures for the injection study.

Another way of approaching it is to try to

take that solvent and do a liquid-liquid extraction, and we did try that as well. When we did a liquid-liquid extraction, we ended up with less than 20 percent of morphine; most of it was left behind.

DR. DAYNO: And I would also add to that, what is unique about this technology and the formulation is that given the injection molding process, the PEO and the morphine are blended together in this matrix.

So even at cut surfaces and with particle size reduction at the surface and surface erosion, there's still the element of the controlled-release aspect because of the way it's manufactured and it comes together.

DR. BROWN: Dr. Farrar?

DR. FARRAR: Thank you. I have a couple of clarifying questions and then a third question, too. With regards to the large solvent, I was wondering what the volumes were approximately.

The second one I think you just answered, but in the sieved particles, if you were to combine

the sieved particles at the lower end of the scale with water, would you again get the gooey mess, as you described it? Implying that if people were to snort it, they would get some of the other agents used in the particles as well.

Then the third is just to be very clear that there has been safety data relative to the propylene product that's used in the manufacturing.

DR. DAYNO: I'm sorry; I didn't hear the last part of your third question.

DR. FARRAR: The issue is whether there is safety data about the process used to create the tablet in the first place; is there any reason to believe that the tablet itself, or if it were manipulated in some way, that the broken particles would do damage in some way or create a problem for the patient.

DR. DAYNO: Okay. The first question in terms of volumes of solvent, in the exploratory phase, you see data with a 100 milligrams. That was done in 50 mLs of solvent in the early phase of the program. When testing the proposed

to-be-marketed dosage strengths, consistent with FDA guidance, it was done in 200 mLs of solvents.

The second question, the tablet is exquisitely sensitive to fluid, so even the small particles, if they would be mixed, would gel. The gelling properties, because of the PEO, it's very sensitive, so those would likely gel as well.

The last question, polyethylene oxide, it's a release-controlling agent that's extensively used in pharmaceutical products across multiple therapeutic areas. It's a compendial-listed excipient and considered to be safe. It's also listed on the FDA's inactive ingredients database.

DR. BROWN: Dr. Bilker?

DR. BILKER: Yes. I have a question about the gelling property. If one of these tablets were softened in some way, say placed in the mouth and softened with even saliva, or softened with prolonged exposure to -- they'd steam it somehow, they'd come up with difficult ways of softening the tablets -- and then chewed, the gel was chewed, does the gelling property prevent circumventing the

ER product, the ER properties if the gel itself is chewed?

DR. DAYNO: The PEO, even in that form, it continues to retain some of the extended-release properties. In terms of the tablet swelling, across the clinical development program, there were no reports of tablets swelling or getting stuck in the throat.

DR. BILKER: My question was, if somebody were to actually chew the gel, I guess like gum, would it release -- would that circumvent the ER property?

DR. DAYNO: I don't know the answer to that. We did not expose any subjects to potentially trying to chew because of the hardness of the tablet and what we shared with you.

DR. BILKER: After it softened as a gel, if they actually chewed the gel, which they would be able to do, right? Would that release the substance?

DR. DAYNO: I mean, eventually it would. As we know, these products are designed to be

abuse-deterrent and not abuse-proof. So the morphine eventually has to release to be an effective analgesic.

DR. BROWN: We're going to stop at that point and take a break until 11:15. There are many other folks that would like to ask clarifying questions to Egalet, and we will get to those after the FDA presentations. So let's adjourn now and return at 11:15.

(Whereupon, at 11:03 a.m., a recess was taken.)

DR. BROWN: It's 16 after 11, and we are going to move ahead with the FDA presentations. But before we do, if I could get you to pull up CO-43, because I want to clarify something that might have gone over the heads of members of this committee. It certainly did mine.

The 80 percent red line there does not represent any guidance by the FDA relevant to anything other than generic products. So for new products, 80 percent is not part of the guidance. So if we could go ahead and begin our FDA comments.

FDA Presentation - James Tolliver

DR. TOLLIVER: Good morning. My name is James Tolliver. I am a pharmacologist for the controlled substance staff within the Office of the Center Director, Center for Drug Evaluation Research at the FDA.

This morning I'd like to briefly discuss oral human abuse potential study 067-EG-008 submitted as a Category 3 study under NDA 208603, in support of EG-001 ER tablets. In referencing this product as part of this presentation, I will use the designation EG-001 instead of Arymo tablets.

The pharmacodynamic measures I will discuss include the visual analog scales, abbreviated VAS, for drug liking high, take drug again, and overall drug liking. The drug liking VAS, the only primary measure is used to assess at-the-moment drug liking.

It is administered at various time points post-dosing starting from 0.5 hours out to 24 hours. Subjects are asked, "Do you like the

effect that you are feeling now?" The response is documented on a zero to 100-millimeter bipolar scale, anchored on the left by zero, strong disliking, in the center by 50, neither like nor dislike, and on the right by 100, strong liking.

High VAS is also an at-the-moment assessment, in this case of high or euphoria, using a zero to 100 millimeter unipolar VAS scale with anchors on the left of zero, not at all, and on the right by 100, extremely. It is also taken at various time points post-dosing from 0.5 hours to 24 hours. Subjects are asked to respond to the question, "How high are you now?"

A third measure is the global assessment of take drug again VAS. In contrast to drug liking VAS and high VAS, this measure is taken only at 12 and 24 hours post-dosing, at a time when most, if not all, the treatment effect has dissipated. In responding to this scale, subjects are required to reflect back on the treatment experience.

The specific question asked is, "Would you want to take the drug you just received, again, if

given the opportunity?" It is rated on a bipolar VAS scale anchored on the left by zero, definitely would not, at 50 by do not care, and on the right by 100, definitely would.

The fourth measure, overall drug liking VAS, is also a global assessment taken only at 12 and 24 hours post-dosing; again, when most, if not all, of the treatment effect is dissipated. In this case, subjects are asked to think back over their treatment experiences.

Subjects are required to respond to the comment, "Overall, my liking for this drug is" is rated on a bipolar VAS anchored on the left by zero, strong disliking, in the center by 50, neither like nor dislike, and on the right by 100, a strong liking.

Pharmacodynamic parameters used in this presentation include maximum effects, designated Emax, and the time to maximum effect, designated TEmax. Primary endpoint is Emax of drug liking. Statistical analysis of pharmacodynamic measures were conducted by the FDA CDER Office of

Biostatistics, utilizing a mixed-effects model with treatment period and sequence as fixed effects, at a random effect for subjects nested in sequence. Tests were one-sided with an alpha set at 0.025.

CDER Office of Biostatistics also conducted responder analysis using a test of binomial proportions with a one-sided test of significance of 0.025. There were two comparisons of interest. For the purposes of this presentation, the first is MS Contin manipulated, which is the positive control versus placebo.

For purposes of validating each of these four measures, I will note now that validation was achieved for each of the four measures, meaning that the positive comparator, MS Contin manipulated produced a maximum response that was statistically significantly higher than that produced by placebo.

The other important comparison in this presentation will be that of MS Contin manipulated versus EG-001 manipulated.

For purposes of examining pharmacokinetic/ pharmacodynamic relationships, I will limit my

discussion to the pharmacokinetics plasma morphine following after treatments and rely on bioavailability analysis conducted by sponsor. Pharmacokinetic parameters, which I'll discuss, include the maximum morphine concentration designated Cmax and the time to Cmax designated Tmax.

In this study 067, EG-008 is a randomized, double-blind, triple dummy, placebo-controlled, crossover study having the primary objective to compare the relative abuse potential of oral intact and oral manipulated EG-001 tablets versus oral manipulated MS Contin.

Thirty-eight subjects comprised the completer population. The oral treatments included MS Contin 60 milligrams manipulated as the positive comparator, as well as EG 60 milligrams manipulated, and EG 160 milligrams intact and placebo.

The methods of manipulation were based on the results of Category 1, physical manipulation studies. I want to digress from my written

statement here for just a minute, and I do want to make clear that the manipulation that was done does not require any special knowledge such as to require someone with certain chemical or whatever ways in order to prepare it.

The manipulation that was used utilizes a very common tool that's available in any household, and I would suspect that abusers would certainly use that tool in that form of manipulation and may possibly be successful at it.

I would also comment that with regard to this kind of study, it's not required that you have to reduce the particle size down to below 1 millimeter or 1000 microns in order to potentially change the release characteristics in the EG-001 formulation. I just want to make that clear to you as we go along.

Provided here is the mean plasma morphine concentration as a function of time following active treatments. Oral MS Contin 60 milligrams manipulated produced a mean Cmax for morphine of 43.34 nanograms per mL, which based upon

bioavailability analysis, was determined to be higher than that produced by EG 160 milligrams manipulated, namely 28.75 nanograms per mL.

Based upon the mean plasma morphine time-course curves, most of the rise in morphine levels occurred within 0.5 hours and 1.5 hours for MS Contin manipulated and EG-001 manipulated, respectively, while median Tmax values were 0.88 and 2.12 hours, respectively.

This slide provides the mean drug liking time course following treatments. I've purposely provided the whole VAS scale. Keep in mind the drug liking is assessed using a bipolar VAS in which 50 millimeters equates to neither like nor dislike, 100 equates to strong liking, and zero equates to strong disliking.

Over the first 4 hours there's little indication of any degree of disliking produced by the treatments. At the same time, the mean drug liking time courses of the treatments are found within a fairly narrow range, ranging from around 50 millimeters to 73 millimeters. This is in that

part of the VAS scale reflecting some limited degree of drug liking. Median TEmax for drug liking is 1.02 hours and 1.99 hours following MS Contin manipulated and EG-001 manipulated, respectively.

This slide provides the mean high as a function of time for each of the treatments. Based upon the time curves, most of the high is achieved within about 0.75 hours and 1.5 hours, following MS Contin manipulated and EG-001 manipulated, respectively.

Due to the plateau for high observed with both of these treatments, the median TEmax is out at 1.5 hours and 3 hours for MS Contin manipulate and EG-001 manipulated, respectively.

This slide provides a table of the means of standard errors for Emax of drug liking, take drug again, and overall drug liking for all treatments. With respect to the primary endpoint of mean Emax of at-the-moment drug liking, oral EG-001 manipulated was associated with a 5-millimeter reduction compared to MS Contin manipulated.

While the 5-millimeter difference was statistically significant at a p-level of 0.019, it is not clear whether it is clinically relevant. We wonder about that.

Oral EG-001 manipulated produced a mean Emax of at-the-moment high that was 13.1 millimeters lower than that produced by MS Contin manipulated. This was statistically significantly different.

EG-001 manipulated compared to MS Contin manipulated showed a reduction in mean Emax of take drug again of 7.2 millimeters and an Emax of overall drug liking of 4.7 millimeters. For both measures, these differences were not statistically significant, as reflected in the p-values.

As noted earlier, these two measures are administered when most or all of the drug effect has dissipated. Subjects are required to think back to their experience under each of these treatments and reflect upon whether or not they would be willing to take the drug, the treatment again if given the opportunity, and also upon the overall drug liking experience.

So whereas EG-001 manipulated compared to MS Contin manipulated was associated with a lower Emax of at-the-moment drug liking and at-the-moment high, when subjects were subsequently allowed to reflect back on their experiences with these two treatments, subjects displayed no preference of one treatment over the other, with respect to a willingness to take the treatments again or in the degree of the drug liking experience.

This slide provides responder analysis with regard to Emax of drug liking. This analysis is described in detail in the 2015 FDA guidance for industry regarding abuse-deterrent opioids. For purposes of this presentation, a responder is a subject having a selected percent reduction in the Emax of drug liking following oral EG-001 manipulated compared to following oral MS Contin manipulated.

So in the first column of the table you can see different levels of percentage reduction in Emax of drug liking. As a percentage reduction in Emax of drug liking increases, there will be a

corresponding decrease in the number of subjects displaying these percentage reductions.

One criteria of interest is in determining whether or not a majority of the subjects demonstrate a given percentage reduction in drug liking. As noted in the FDA guidance document, this is evaluated statistically using the proportion test in which a null hypothesis is if 50 percent or fewer subjects demonstrate a given percentage reduction as examined at a 0.5 percent significance level.

Looking at the first row of the table, you can see that 27 out of 38 total of subjects had at least a zero percent reduction in Emax of drug liking following oral manipulated EG-001 compared to following oral manipulated MS Contin.

Statistical analysis using the proportions test yielded a p-value of 0.0075 indicating that a majority of the subjects had at least a zero percent or greater reduction of Emax of drug liking when taking EG-001 manipulated compared to MS Contin manipulated.

Second line of the table pertains to at least a 5 percent reduction in Emax of drug liking following manipulated EG-001 compared to manipulated MS Contin. Again, using the proportions test, p-value of 0.0258 was achieved, indicating that the majority of subjects, from a statistical standpoint, did not in fact demonstrate a 5 percent or greater reduction in Emax of drug liking.

This also provided the additional, further increases in percent reductions, and you can see that there's obviously not going to be a significance level there either.

So what this table is saying and what this slide is actually showing is that a majority of subjects did not in fact show some reduction in Emax of drug liking following -- let me repeat that.

So what this table actually shows is that a majority of subjects did in fact show some reduction in Emax of drug liking following the oral EG-001 manipulated compared to oral MS Contin

manipulated, but this reduction was less than 5 percent.

In summary, all EG-001 60 milligrams manipulated was associated with a maximum level of at-the-moment drug liking and at the moment high that was statistically significantly lower than that produced by the positive comparator, MS Contin 60 milligrams manipulated.

For both measures, the differences between the two were limited. Particularly in the case of drug liking, the issue of clinical relevance does exist. For the measures of take drug again and overall drug liking, in which subjects reflect back on their treatment experiences, there were no statistically significant differences with respect to maximum response between oral EG-001 manipulated versus MS Contin manipulated.

Subjects expressed a similar willingness to take either treatment again, if given the opportunity to do so. In addition, collectively, subjects did not perceive a difference between the two treatments with regard to their drug liking

experience.

Finally, a majority of subjects did not demonstrate a 5 percent or greater reduction in Emax of drug liking following oral EG-001 manipulated compared to oral MS Contin manipulated. This is not surprising considering the limited Emax of drug liking of the manipulated MS Contin, as well as just simply the tightness of the data.

This raises a question of what is the significance of less than a 5 percent reduction in drug liking with regard to a possible deterrent effect of EG-001 to oral abuse? Thank you.

FDA Presentation - Joann Lee

DR. LEE: Good morning. I'm Joann Lee, drug utilization analyst in the Office of Surveillance and Epidemiology within the FDA. I'll present the drug utilization patterns for morphine extended release and other extended-release, long-acting opioid analgesics from 2011 through 2015 to support today's discussions.

I'll describe the sales distribution of extended-release opioid products followed by

prescription utilization of morphine extended-release and other opioid analgesics focused on the outpatient retail pharmacies. I'll then present our findings on the top prescriber specialties for morphine extended release.

We'll focus on the morphine extended release given that today's discussions involve Arymo, which is a morphine extended-release product. We also examined the other extended-release, long-acting opioid products as shown on this slide. These drugs represent the opioid market into which Arymo extended release will be introduced to if it is approved.

This opioid market includes oxycodone, methadone, oxymorphone, tapentadol, hydromorphone, hydrocodone, and the transdermal patches fentanyl and buprenorphine.

So we used the IMS National Sales Perspectives Database to determine the primary settings of care. This provides the sales distribution data of morphine and other extended-release, long-acting opioid products that

were sold from manufacturers and wholesalers into the various settings of care. Please do note these sales data are nationally projected to all settings of care.

As displayed in this chart, 86 percent of morphine extended-release products were distributed from manufacturers to the retail settings, and the majority of the other extended-release, long-acting opioid products examined were also distributed to the retail settings. So based on these sales data, we focused on the U.S. outpatient retail pharmacies.

Now, for the prescription data analysis that I'll present next, we used the IMS Health National Prescription Audit Database. This measures the dispensing of prescriptions from retail pharmacies into the hands of consumers through prescriptions within the United States. This prescription data can also be stratified by prescriber specialty, which will be shown next.

Let me now draw your attention to the top line of this graph, which shows the nationally

estimated number of prescriptions dispensed for morphine extended-release. The remaining lines represent the other extended-release, long-acting opioid analgesic prescriptions, which were dispensed through the U.S. outpatient retail pharmacies from 2011 through 2015.

As shown, morphine extended release was the most frequently dispensed opioid product among the extended-release, long-acting opioid market. The total number of morphine extended-release prescriptions dispensed remained relatively stable since 2011. And by 2015, there were 6.4 million prescriptions dispensed for morphine extended-release, while utilization of extended-release oxycodone declined.

This table shows the top prescribing specialties for morphine extended release in 2015. Over one-quarter of morphine extended-release prescriptions were written by family practice, general practice, and osteopathy, followed by anesthesiology and nurse practitioner, approximately 13 percent each; then internal

medicine and so on.

Please keep in mind that anesthesiologists may also practice as pain management specialists, in which case pain medicine may actually be the second top prescribers of morphine extended release for the year 2015.

Limitations to mention are that only outpatient use was assessed. That is inpatient and mail order data were not included in this analysis, and top specialties that prescribe morphine extended release were captured based on prescription data.

To summarize, there was a relatively stable utilization of morphine extended release from 2011 through 2015. Of the extended-release long-acting opioid analgesic market, morphine extended release was most frequently dispensed with 6.4 million prescriptions dispensed by 2015. The top prescriber specialties, again, were family practice, general practice, and osteopathy in 2015.

Thank you. This concludes the FDA presentations.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for the FDA at this time? Please remember as you ask questions to state your name for the record before you speak. If you can, please direct questions to a specific presenter. If you're worried that we're not seeing your name, if you just take your card and turn it up on the side, we can make certain that we get everybody on the list.

Dr. Bateman?

DR. BATEMAN: This question is for Dr. Tolliver, and it pertains to slide 11 from his presentation, the responder analysis.

DR. TOLLIVER: Before you start, I would like to mention that I have hearing problems, and so I would urge you to speak up. And if I ask you to repeat it, I -- there's nothing I can do about that.

DR. BATEMAN: Okay. I'm just wondering if you can help us interpret this a bit more. So as I understand it, the table shows the number of

subjects that report reductions in Emax at various thresholds, 5 percent, 10 percent, 20 percent, and so on. If I was looking at this, my interpretation would be 65 percent of patients showed at least a 5 percent reduction, 40 percent of patients showed at least a 20 percent reduction, and a quarter of patients showed at least a 50 percent reduction. But the statistical testing falls off after the 5 percent threshold.

DR. TOLLIVER: At least another way of looking at that is it produced zero percent or greater. You know at least for 5 percent, it was at least 5 percent or greater reductions. So you see a reduction in the number of subjects simply because some of them are falling out. They're producing -- some produce greater than a 5 percent reduction, but they produce less than a 10 percent reduction. So that's why you're seeing that change over time; I mean, the number of subjects.

DR. BATEMAN: The summary sentence at the bottom says the majority of subjects did not demonstrate a 5 percent or greater reduction. But

it looks like 65 percent show at least a 5 percent reduction. Am I misunderstanding the --

DR. TOLLIVER: Yes. The next column over is the number of subjects. And if you do just the division of the number by the total number of subjects, which you have 38 subjects, then you come up with your percentage reduction.

(Pause.)

DR. TOLLIVER: The p-value is based upon a statistical test called the proportions test, and it is because of that -- yes, I agree, I understand where you're coming from, that the numbers suggest that the percentage is higher. But when you do a statistical test of it, it is not significant. And I would have to have Dr. Liu come up and briefly describe the -- if that's what you would like.

DR. BATEMAN: Sure. I mean, I --

DR. TOLLIVER: The patient test is something separate.

DR. BATEMAN: So the statistical test is testing whether 50 percent -- at least half the patients show reduction at a particular threshold.

So at least 50 percent of patients show a reduction of at least 50 percent would be the bottom line. And there, clearly the point estimate is 23 percent, so that's not significant.

DR. TOLLIVER: Yes. According to the statistical test that was done, it was not statistically significant. Here, the specific question that's being asked is, is it more than 50 percent of the subjects, the majority.

DR. BROWN: This is really not clear. Could we get a more specific explanation of the statistical method?

DR. LIU: Yes. The calculation is based on FDA guidance, and for each subject we can calculate what's the percentage reduction that each subject has after taking the positive control and the testing drug.

So for each subject we'll have a number of percent reduction, and then we can see how many subjects have a percentage reduction given percentage reduction level.

Then we perform a statistical analysis, a

proportional test to test at least 50 percent or less subjects has such a percent reduction. Then the p-value tells if this one-sided test for this hypothesis test for a given percent reduction level and either 0.25 to 0.5 percent level.

DR. BATEMAN: So each of these thresholds, you're testing the hypothesis that at least half of the patients had a reduction of that amount. The final line, the bottom line would be testing the hypothesis that at least half of patients had at least a 50 percent reduction in the Emax of drug liking.

DR. LIU: Yes.

DR. BATEMAN: Okay. But I think it's important for us to pay attention to the observed data as well. These data suggest that half of patients have at least a 10 percent reduction, and nearly a quarter of patients have a 50 percent reduction.

DR. LIU: Yes, because there are some variations. So although numerically we can see that 65.8 is larger than 50 percent, but if we

consider the variation, it's not significant at this 2.5 percent level.

DR. BROWN: Dr. Flick?

DR. FLICK: If you look at the table, the key column is the number of subjects. The power to detect a difference in any of these cells is so low that I'm not sure that there's any value in this table at all.

So I guess I would ask my statistical colleagues to comment on the ability to differentiate these things using the statistical proportions test. The raw value of the percentage, yes, it maybe has some value, but again, the numbers are so small, and I would guess the variation in each one of those cells is quite large. And it makes it very difficult to differentiate one from another.

If I go back to slide 51 from the sponsor, there is no difference between MS Contin crushed and the Arymo intact, which makes it hard for me to understand why this information is useful in any way at all. What that says is that the drug liking

for the crushed MS Contin is the same as Arymo extended-release intact. I guess I'm trying to put that into context. Maybe somebody can help me with that.

DR. BROWN: Dr. Hertz?

DR. HERTZ: Yes. I think that's a better focus than the analysis of the responder percentages. It was just one more way to look at the numbers. And I think the points raised, particularly the power and the other, are well taken.

So in terms of this slide, I think it's just one cut of the data. I'm hearing perhaps not the best cut. So rather than -- anyway, point taken.

DR. BROWN: But the statement at the bottom of this slide that the majority of subjects did not demonstrate a 5 percent or greater reduction in Emax is incorrect.

DR. HERTZ: No. What we're trying to say -- and let me just say that, honestly, I don't know that we need to focus on whether it's a 5 percent reduction as clinically meaningful or

not. But I think that the way to correct the statement at the bottom of the slide is, "Using a statistical analysis, the responder definition of reduction of at least 5 percent didn't reach a statistically significant outcome." So the 65 percent would not have been considered statistically significant.

What I'm hearing from the committee that applying a statistical analysis to this might not have been very informative.

Is that what you folks are saying? Heads are nodding, for the transcript.

(Committee members nod affirmatively.)

DR. HERTZ: So that point is taken. And I think we can either use the correction of adding statistically or we could just say, numerically, but not statistically, the 5 percent responder definition -- I don't know. Something.

But perhaps we'll just take note of that for the future as not to be applying the proportion test when we think that in fact the power may be as low as suggested.

DR. BROWN: I want to move on.

Dr. Beardsley?

DR. BEARDSLEY: I'm not quite sure who to address this question to, maybe Dr. Tolliver. But given that there is a borderline difference in drug liking, given the manipulated oral studies, I was curious whether there'd be any difference in the kinetics of this product if the manipulated product was rapidly swallowed, versus kept under the tongue and try to utilize a sublingual route of administration, I guess as a gelatinous gel. That's just maybe a question for Dr. Tolliver's speculation or for the committee members.

DR. HERTZ: This is Sharon Hertz. We haven't explored the transmucosal absorption of this product. I don't think that's a particularly popular route for morphine. I don't recall offhand, in general, if there's much transmucosal absorption. It's certainly not a popular route that we hear about, nor do we have any products that are using that.

I am aware that in some settings of hospice

care, high concentration oral solutions may be used, but I don't know what the relative bioavailability is in that setting.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: This question is for Dr. Tolliver. I just wanted to confirm the matrix effect. In looking at your slide 7, and also their figure 32, it doesn't go on beyond 6 hours. My question is, does the manipulated Arymo have the same AUC as the manipulated MS Contin? And so does the Arymo then have a long, long plateau after 6 hours of concentration where the MS Contin falls off?

DR. NALLANI: About the oral?

DR. GALINKIN: I'm talking about the manipulated and the oral, because my question is whether -- if the matrix stays the same, then the AUC should essentially be the same; is that correct? Between the total AUC between the MS Contin and the Arymo. Did you have that data or is that a company question?

DR. NALLANI: Srikanth Nallani, clinical

pharmacologist. In terms of drug liking, typically we don't go beyond a certain timeline. But to answer your question, what will happen to AUC infinity? Yes. The pharmacokinetics of the drug in terms of AUC infinity, it will end up bioequivalent.

DR. BROWN: Dr. Farrar?

DR. FARRAR: Just a quick comment on Sharon Hertz's point, which is that in palliative care, we've tried sublingual liquid unadulterated morphine, and it's not rapidly absorbed there because of the hydrophilic nature of the agent and other issues.

So one would not presume that any other administration would get you a rapid absorption that way. It's been actually an area of interest, because it would be nice to be able to use it that way, but it hasn't been successful.

The second issue is that the slide that was just shown -- also, the slide that shows the mean liking -- so this slide clearly demonstrates a more rapid plasma level with the manipulated MS Contin

versus the manipulated EG compound. Then if we go to the slide from Dr. Tolliver's talk of the mean drug liking time course profile, again what you see is a mean liking that is earlier with the MS Contin, consistent with a higher level achieved more rapidly.

The fact that they are the same at 4 hours simply means that the drug allows normal release over the course of the time. So the fact that they're both liked as much in terms of a long time frame doesn't surprise me, at least with regards to the fact that they're both morphine. They both have to release over the prescribed period.

I think the issue is with regards to the oral liking, I'm surprised actually at the low level of difference between those two early on, given the pharmacokinetics, but it is what it is.

DR. BROWN: We're going to break now for lunch. We're going to reconvene again in this room in one hour at 1:00 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember that there

should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience.

(Whereupon, at 12:02 p.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 move ahead to the public forum.

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

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

The FDA and this committee place great importance in the open public hearing. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

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

MS. KULKARNI: Good afternoon. My name is

Shruti Kulkarni, and I'm the policy director for the not-for-profit Center for Lawful Access and Abuse Deterrence, CLAAD. 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 extended-release morphine sulfate. CLAAD works to reduce prescription drug fraud, diversion, misuse and abuse, while also 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 industry is responding to our coalition's call to develop safer medications to reduce prescription drug abuse. Medications like the proposed ER morphine sulfate can satisfy patient needs and improve public health and safety.

In assessing the medication and whether it merits an abuse-deterrent labeling, the committee should consider the following facts. According to recent IMS data, morphine is the most commonly prescribed ER opioid analgesic, and 98.5 percent of prescriptions filled for ER morphine were for products with no abuse-deterrent properties.

These products are most susceptible to diversion, misuse, and abuse, via alternative routes of administration. Data presented by the Centers for Disease Control and Prevention at the National Prescription Drug Abuse and Heroin Summit, shows that the most common transition pathway from oral opioid abuse to heroin use is to start with oral ingestion of pills, move to crushing and snorting of pills, continue on to snorting of heroin, and finally, to inject 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.

Sponsor's Category 1 studies support the conclusion that the proposed formulation is an

improvement compared to ER morphine medications currently on the market because it's significantly more difficult to crush and grind the tablet, given its extreme hardness.

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 morphine using alternative routes of administration.

Clinical data also supports a conclusion that the proposed formulation prevents any unintended effects for those who unintentionally misuse opioids, such as the elderly population who might have difficulty swallowing, because chewing, cutting, or crushing does not result in the immediate release of the medications active ingredient.

Additionally, given the difficulty associated with manipulating this product and the inability to gain immediate access to its active pharmaceutical ingredient, the proposed formulation

is less likely to be valuable on the black market.

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 they do not pose additional risks of addiction and overdose.

Thank you again for this opportunity. Please contact CLAAD if we can be of any service to you.

DR. BROWN: Thank you, Ms. Kulkarni. Will the second speaker please step to the podium and identify yourself? Speaker number 2.

(No response.)

DR. BROWN: Will speaker number 3 step up to podium and introduce yourself?

MR. COHEN: Thank you, Mr. Chairman. My name is Dan Cohen. I am the chairman of the Abuse Deterrent Coalition. Attached here are my

disclosures. I have no financial incentives from the sponsor, though they are a member of the coalition.

As of 12:00 noon today, according to the CDC website, we have probably the most significant number that's faced by this community and the committee; 16,882 individuals have overdosed through the use of prescription opioids through this calendar year. During the course of this public session, another three deaths will likely occur based on the CDC numbers. We are here to fight this prescription abuse death rate and try and lower it. That is the message of ADS.

The Abuse Deterrent Coalition was created by abuse-deterrent manufacturers, patient advocacy groups, pharmaceutical manufacturers, and others, to educate the public about abuse deterrents, but abuse deterrents is just one part of a bigger puzzle. It is not about addiction. It is about opioid-naïve individuals and deterring and preventing the progression through the process of prescription drug abuse.

This panel has an important challenge and duty. It is the first advisory commission since the President signed into law the CARE legislation, which has now mandated that if a product has an opioid in it, an advisory panel will be brought together.

The FDA, this division, are going to rely heavily on your judgment, more so than any other advisory commissions that this agency runs through. We charge you with the balance of moving through the subjective measures of measuring abuse deterrents, such as the vast scales that we've talked about today. And you also need to consider and advise the agency on the real-world challenges of abuse, those that affect products, the time it takes to manipulate the product, the increased cost that goes along with it, and the amount of exposure that a product does to the abuser.

Arymo as a product thoroughly demonstrates deterrence by the evidence that's provided for you today. It meets the criteria and exceeds it, for oral manipulation, both by chewing and swallowing,

by intranasal abuse, and intravenous abuse. It is beyond an incremental improvement. It is clinically significant, it is medically relevant, and it provides a significant public health benefit.

As you look through this deck here, you'll see the products that have an ADF that have been approved by this division with a label, and the products that are currently under active consideration; those that have appeared before an adcom either now or will in the next several months. It is a starting point, and it is a very important part of the public health process.

When I ask you to look at ADFs, ADFs do have an impact and they do provide a benefit. Looking at this deck from RADARS, I ask you to look at the left-hand column. The oxycodone ER, oxycodone, shows its abuse prevalence rate up until the time in the first column of when it was a non-abuse-deterrent product. When the abuse-deterrent went in effect, you can see a significant drop off in the amount of abuse of OxyContin.

In the middle chart, oxymorphone ER, and dose Opana, you'll see the same time frames, the level of abuse when oxycodone received its abuse-deterrent indication, the amount of abuse of Opana went up dramatically until Opana itself was also reformulated and its abuse dropped off.

The last chart on the right shows all other opioids and how they performed during the same period of time. Clearly, ADFs do have an impact on this process.

But as we're looking through this, we also need to look to the data. Right now, we are having a significant impact on branded opioid products. As this data through the end of 2015 clearly demonstrates, of the branded products, 8.8 million scripts of branded products were issued in the last year, and a little over 5 million of those now have an abuse-deterrent formulation.

In generic products, we are 240 million scripts, and again, only approximately 5 million with an ADF. We still have 96 percent of the market uncovered.

Looking at this data in another way, you can see that in 2011, products with opioids in them had their maximum number of scripts issued, and since that point the scripts have dropped. This is three years before the combination products were upscaled from C3 to C2. Another way to look at it for all opioid analgesics, and you see the same number, extended-release, immediate-release, this is still a problem that we have to work through.

Massachusetts Department of Public Health published information just last week that is very relevant to your --

DR. BROWN: Mr. Cohen, if you could finish up please, sir.

DR. COHEN: I'm on my last slide, Mr. Chairman. Thank you.

In that information, the Massachusetts Department of Public Health in data that was published last week, and just became available to the public this week, indicated that of all opioid deaths, 8 percent of those individuals that had an opioid-induced death had a script within the last

month. Eighty-three percent of the decedents of an opioid-induced overdose death had a legally obtained or likely legally obtained substances in their systems at the time of death.

This is a very relevant factor in your consideration, because ADFs help to mitigate that event. These are the members of the coalition. We thank you for your consideration.

DR. BROWN: Thank you, Mr. Cohen. Will speaker number 4 step to the podium and introduce yourself?

DR. WOLFE: I'm Sid Wolfe, Public Citizen Health Research Group. I have no conflicts of interest.

You've seen these data before. I just want to focus on the fact that the last 2 of these 5 extended-release morphine sulfate products are quote, "abuse-deterrent." I put it in quotes because the ultimate evidence is not there on any of them, since there aren't epidemiological studies.

I want to point out though that Embeda,

which was approved in 2009, did not get any "abuse-deterrent" labeling. For four and a half years, I was on the Drug Safety Advisory Committee, and we met a couple times about this. One of the meetings, it was made clear that when you do these in vitro manipulation studies and the abuse-deterrent liking studies, it only suggests the possibility of abuse deterrence. You don't actually prove abuse deterrence until you have epi data. Again, we don't have any epi data at all on any of these products.

Despite this, once Pfizer had bought up from King, Embeda, and not long afterwards it got approved with the abuse-deterrent properties. And the language here really is misleading. These data, along with the results from the oral and intranasal human abuse potential studies, indicate that Embeda has properties that are expected to reduce abuse via the oral/intranasal route. That's the labeling then, and it's still the labeling now.

The eagerness of the company to get this drug approved can be seen in an announcement they

made concomitant with their first quarter earnings a few months ago, and they essentially said, which is accurate, that the FDA has accepted our NDA for Arymo ER, an abuse-deterrent extended-release morphine.

It's assumed it's abuse-deterrent, and then it cranks in the marketing thing, which is what you would expect a company, which does have a fiduciary responsibility to stockholders to say, "If approved later this year, we'll be able to begin promoting Arymo ER, leveraging our commercial experience over the past 12 months, having built relationships" and so forth.

Now the remaining two and a half minutes, I'll just deal with some of the evidence. You've heard some of it. This is the FDA's take. It's basically saying that solvent 5, a non-toxic solvent, as they point out, you'll see in the next slide, does a much better job of extracting in 30 minutes a lot of morphine from either the 15-, 30-, or 60-milligram dosage forms.

This is actually from the company's briefing

package. They showed a slide similar to it this morning. I think it was called slide 43, the company slide 43, which several people brought up. I think one of the important things, which remember the panel asked about this morning, is you look at the third group on the right, this is 60 milligrams And what you see is that in 30 minutes, someone using solvent 5 and these breakdown product properties that happened before the solvent extraction, they're able to get out 36 milligrams of morphine sulfate. Not bad.

The ability of anyone who's interested in this kind of thing, and you'll probably hear more about this later in the public hearing, to figure out what solvents they are and match these things up is quite skillful. It will not be hard to defeat this, I believe, even in the in vitro extraction.

These are data from the briefing package again. The only difference, the p-values were half as large in the FDA presentation. I suspect this one-sided analysis, the p-value was .025. The

conclusions are the same. Drug liking, p .0385, the FDA said relevance; as they told you before, the possible abuse-deterrent is not known.

How high now, that was statistically significant. And neither of the other ones were even remotely close to being statistically significant. People would take it again in a statistically not different way than they would MS Contin, and the same is true for the overall drug liking.

In conclusion, the guidance that allowed, or at least comported with labeling that was as strong and I think misleading as we now have in Embeda, really needs to be pulled back and modified or changed better into a regulation as opposed to a guidance. And the current labeling for opioids, it needs to be done in a way that encourages companies not to insert misleading language, which is what it does now.

Finally, Arymo ER should not be approved because of serious concerns about increased risk and abuse, with some residual in vitro

manipulability, 60 percent of a 60-milligram dose being extracted in 30 minutes with a solvent, and unsatisfactory performance in oral human abuse likeability studies. Three of the four were either statistically insignificant or questionable. Thank you.

DR. BROWN: Thank you, Dr. Wolfe. Would the fifth speaker step to the podium and identify yourself?

MR. CICHON: Mr. Chairman and members of the advisory committees, I served during the 70s and 80s in the Baltimore City Police Department. I knew very little about prescription drug abuse and diversion.

After 16 years in law enforcement, I moved over to the state side as an investigator for the Maryland Department of Health and Mental Hygiene, where I eventually investigated and managed compliance investigations for the Maryland Board of Physicians. After my 30 plus career in law enforcement, I went to work for Eli Lilly, where for six years I managed counterfeit drug

investigations in the Americas.

Good afternoon. I'm Charlie Cichon, and I'm here today as the executive director of the National Association of Drug Diversion Investigators.

Relief from pain is important to millions of individuals who suffer from 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 aware, the misuse and abuse of opioids has reached epidemic levels in many of our states.

Prescription drug abuse is the fastest growing drug problem in America, one that does not discriminate by region, socioeconomic status, or age. The Center for Disease Control and Prevention have identified prescription drug abuse as an epidemic, reporting more than 15,000 American deaths each year, from prescription opioids.

An important step in the abuse prevention

process for both new and chronic pain sufferers is the development of abuse-deterrent formulas for opioids. The National Association of Drug Diversion Investigators, NADDI, is a non-profit membership organization that works to develop and implement solutions to the problem of prescription drug abuse and diversion.

NADDI advocates for the responsible use of prescription drugs by people who need them. At the same time, we aggressively work with law enforcement and regulators to pursue those involved in related criminal activity. Our primary focus is training and education, which include law enforcement personnel, regulatory agents, health professionals, healthcare fraud investigators, and the pharma companies.

Continuing progress in the field of pain management involves a juggling act that balances the need and interests of those involved. The development process involves all the stakeholders in the medical treatment of pain -- clinical, legal, regulatory, law enforcement, industry,

commercial, personnel, and societal.

NADDI recognizes that no one approach to maintaining this critical balance will succeed unilaterally. Therefore, NADDI supports ongoing interaction and cooperation among all who can impact the access to and provision of competent healthcare, and who can affect diversion and abuse of medications.

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

In October 2014, hydrocodone combinations were rescheduled as Class II controlled substances. A rescheduling of hydrocodone combinations had a dramatic impact on when they're prescribing. And according to the U.S. Department of Health and Human Services, over 26 million fewer hydrocodone combination prescriptions were written in the first year after rescheduling, amounting to approximately

over 1 billion fewer dosage units.

I'd like to draw your attention to a hot bed article in May of this year in Gaston County, North Carolina, and I quote, "Over the past decade, dealing with skyrocketing rates of prescription drug abuse has become inevitable for those of us on the front lines of law enforcement.

"Just recently, a new report identified four North Carolina cities among the 25 worst cities for drug abuse. Hickory ranked first on that list. Prescription drug abuse relentlessly indiscriminately targets the intersections of the communities we our members of law enforcement try to protect every day.

"North Carolina lawmakers should adopt legislation that will reduce barriers in prescribing abuse-deterrent prescription opioids. The availability of abuse-deterrents will help save more lives and equip law enforcement to further protect communities."

The author of that was Judy Billings. Judy Billings is the president of our Carolina chapter

and an assistant special agent with North Carolina Bureau of Investigation. The new drug application under review today, morphine sulfate extended-release tablets has been reformulated with the intent to provide abuse-deterrent properties.

Due to the ongoing problems with pharmaceutical drug abuse and diversion, NADDI is a strong proponent of new abuse-deterrent medicines that make it more difficult for an abuser to reduce law enforcement involvement in healthcare. Thank you.

DR. BROWN: Thank you very much. Would the next speaker please come to the podium and introduce yourself?

MR. THOMPSON: Good afternoon. My name is Edwin Thompson, and I'm the president of Pharmaceutical Manufacturing Research Services, located in Horsham, Pennsylvania.

In 2014, at least 28,000 persons in the United States died from an opioid overdose. That means that while you are meeting here today, there will be an additional 76 people dying. Time is of

the essence, and identifying the root cause of this and taking action is critical.

You're being asked today to approve an additional extended-release drug for long-term opioid treatment, which would add more fuel to an already out of control fire. Please do not make it worse.

Moreover, there is no scientific, medical, or legal evidence to justify the approval of an extended-release opioid drug. None. You're being asked to approve a drug for the management of pain severe enough to require daily, around-the-clock, critical, long-term treatment for which alternative treatment options are inadequate. However, there is no scientific evidence showing the efficacy of long-term opioid treatment. There's none.

Before you vote, ask the FDA for substantial evidence of efficacy for long-term treatment. Ask them where it is. They owe it to you; you deserve to get; there is none.

The Center for Disease Control and Prevention is the FDA's sister agency, and it has

scientific and medical standing equal to the FDA's. The CDC's guidelines for prescribing opioids for chronic pain were published in April of this year, and they clearly state, "Evidence on long-term opioid therapy for chronic pain outside of the end-of-life care remains limited, with insufficient evidence to determine the long-term benefits versus no opioid therapy, though evidence suggests risk for serious harms that appear to be dose-dependent."

So how did previous extended-release opioid products receive FDA approval, and why are you considering the approval of an additional opioid product? Based on the CDC guidelines, when asked to approve an extended-release opioid drug for long-term opioid treatment, you must say no.

After a U.S. Senate hearing on June 22nd of this year, Senator Angus King and five other U.S. senators sent DEA administrator, Charles Rosenberg, a letter questioning the significant increases in opioids allowed to be produced for sale in the United States.

The senators pointed out between 1993 and 2015, DEA allowed aggregate production quotas for oxycodone to increase 39-fold, hydrocodone to increase 12-fold, hydromorphone to increase 23-fold, and fentanyl to increase 25-fold. The result is 14 billion opioid pills are now dispensed annually in the United States. Of course, we have an opioid epidemic.

The senators conclude, "We remain deeply troubled by the sheer volume of opioids available; volumes that are approved by the DEA." They urged the DEA to lower the manufacturing production quotas saying, "We believe the recent CDC guidelines for prescribing opioids for chronic pain constitute a change in the currently accepted medical use of opioids and should be taking into consideration when setting future years and opioid quotas."

Their quote continues, "The CDC guidelines recommend dramatic changes in how opioids are prescribed for chronic care patients. For instance, the medical experts at the CDC recommend

that patients receive immediate-release opioids instead of extended-release or long-lasting opioids; that patients receive the lowest effective dosage of opioids possible, and that patients receive opioids for the shortest possible effective duration."

Taken together, these CDC recommendations clearly demonstrate that fewer opioids will be medically necessary for the coming years. Nevertheless, you are being asked to approve an additional extended-release, high-dose opioid product for long-term treatment. Something is very wrong here, very wrong.

As a member of this advisory committee, you should vote no on the approval of an extended-release, long-term opioid product. Thank you.

DR. BROWN: Thank you, Mr. Thompson. Could the seventh speaker come to the -- and introduce yourself?

MS. DUENSING: Good afternoon. My name is Katie Duensing, and I'm the assistant director for

legislative and regulatory affairs at the State Pain Policy Advocacy Network, a project of the Academy of Integrative Pain Management. I have no financial conflicts of interest to declare.

Formerly known as the American Academy of Pain Management, AIPM is a multidisciplinary organization of pain care clinicians including members of nearly every healthcare profession you can imagine.

As our name suggests, our organization espouses a model of integrative pain management. While we recognize the important role played by traditional biomedical treatments for pain, such as medications and procedures, we also advocate for access to and affordability of additional treatments that may supplement, complement, or even replace traditional treatments in the service of providing optimal improvement in pain and functional status for people with pain.

The Academy is keenly aware that opioid pain relievers and other controlled substances have become controversial because of their prominence in

prescription drug abuse. We are also acutely aware of the plight of those who live with chronic pain, more than those affected by heart disease, cancer, and diabetes combined, according to the Institute of Medicine, some of whom require the use of opioid analgesics to manage their conditions.

Therefore, we have been extremely active in a variety of policy advocacy efforts related to those two major public health concerns. One subject of these efforts, which is the purpose of today's meeting, is the development and uptake of so-called abuse-deterrent opioid analgesics, also known as ADOs.

When opioid analgesics are prescribed and monitored appropriately, many patients do well, experiencing improvements in pain and function, and quality of life. However, for many people who eventually overdose on licit or illicit opioids, misusing prescription pain relievers by means of crushing, melting, or otherwise altering the medication to get a more powerful effect is common.

Because ADOs significantly reduce the

effectiveness of alteration tactics like these, they are far less desirable to those who divert the medications for unlawful use. Therefore, AIPM views continuously improving ADOs as a vital component of a comprehensive approach to addressing prescription drug abuse and improving patient care.

Our understanding of the documents provided for this meeting is that Arymo ER has demonstrated significant superiority to MS Contin in terms of preventing an abuser from significantly and productively altering the product.

Further, there is no evidence of alcohol dose-dumping with Arymo ER, a problem that has been associated with Embeda, a currently available ADO. Therefore, this drug appears to us to represent an incremental improvement in the extended-release morphine products available on the market.

Given that we should be expecting improvement with respect to abuse deterrents to be primarily, if not exclusively, of the incremental variety, we think this product meets that standard and thus ought to be approved with abuse-deterrent

labeling.

We are grateful to FDA for its efforts to support the ongoing development of abuse-deterrent technology. We also recognize, as I'm sure everyone here does, that this is not a static process with well-defined endpoint.

People who tamper with these products in order to abuse them are very creative, and history has shown that they are adept at overcoming efforts to thwart them. For that reason, we want to take this opportunity to encourage both manufacturers and FDA to continue innovating in the ADO space, developing new approaches that may be even more impervious to, or discouraging of, alteration, even if those approaches only buy us a few years of relative success.

Our policy advocacy efforts related to ADOs have also focused on one of the troubling aspects of this form of innovation; namely, the burden it places on people with pain who have no intent whatsoever to do anything other than to use their medication exactly as prescribed in order to obtain

pain relief.

Unfortunately, the research and development process that produces these valuable new products is expensive, and the cost of that process inevitably is passed along to consumers. The end result is that people with a legitimate medical need for opioid analgesics are forced to foot the bill for protecting others who use the medications illegitimately in dangerous ways that were never intended.

It's patently unfair that this happens, and while many patients can understand why it's a sort of necessary evil that enables them to have access to their medications, we need to find ways to ensure that this unfair burden does not result in patients foregoing pain relief for financial reasons.

We will continue working on this issue in federal and state legislative bodies and regulatory agencies, hoping that more will emulate success as seen today in Massachusetts, Maryland, Maine, and West Virginia, that ensure improved insurance

coverage of ADOs.

While we attempt to overcome opposition derived from the fiduciary interests of the insurance lobby, we hope that FDA will continue to encourage, and that manufacturers will continue to pursue innovations that will bring us a few steps closer to the ultimate goal of being able to provide pain relief while minimizing risks to those who misuse these vital medications.

Thank you very much for the opportunity to speak today.

DR. BROWN: Thank you, Ms. Duensing. Will speaker number 8 step up to the podium and introduce yourself?

MR. BRASON: My name is Fred Brason, and I'm the CEO of Project Lazarus, which is a community-based public health approach to address the issues of opioid and heroin overdoses, and we take the approach of "to prevent," but also to present responsible pain management and to promote substitute treatment and support services. I have no disclosures and no conflicts.

Developing a public health approach meant that we had to work with a lot of different people. My background of 25 years in hospice and home health had me managing the care of thousands of individuals. Personally, as a chaplain and a local pastor, I've been involved with many families in recovery, many individuals and families who have suffered overdoses. I've done way too many memorial services for both end-of-life care, and for those having suffered and not survived an overdose.

So I have personal engagement, but also professional. And as a professional, we began to investigate our overdoses within our community in North Carolina, and as we did that, we found patients who simply misused the right medication for the right reason, and suffered an overdose.

We have in rural communities especially a lot of sharing of medication, not for the purpose of getting high or for selling or diverting, but to self-medicate because they have pain. And mom had pain meds, and Johnny would take mom's pain meds,

and unfortunately that would overdose Johnny.

We have a lot of accidental ingestion because a number of meds that are in the home. We have recreational users who just go out to have a good time. They have no addiction or substance use disorder, and they themselves found that they had suffered an overdose from taking something they've never taken before. And then we also have individuals that do have a substance use disorder taking 10, 25 pills a day.

As you can see from that list, when we look at at least three of those, the family, the recreational user, and the substance use disorder, you can see that those are primarily diversion areas from the opioids, and we could argue that too for the accidental ingestion, not for the patient that misuses.

But as we looked at this from a perspective of trying to make a balance between making sure we have pain care that's accessible and acceptable with no stigma, we also wanted to make sure that the person who shouldn't have the medication, can't

get the medication, and we try to strike that balance through our public health approach, and one of that is prescriber education.

As we've been able to do that, we do bring forth more of the risks and the assessing the benefits of opioids. We use the prescription drug-monitoring program. We are educating to use abuse-deterrent formulations on those situations where there could be diversion, where there could be problems, either because of the patient, patient history, but also because of the environment that that patient lives in. And there could be other family members that have other issues and want to get into their right medication for their right reasons, and then of course, the co-prescribing of naloxone.

In our own community, we have not had to stop prescribing in order to make a change, but we've made changes. And it's here that one of our local narcotics officers made the statement that "I think our local docs are doing a heck of a good job because the diversion is coming from outside of

where our community is."

What we've done now in 92 counties in North Carolina is implement the Project Lazarus model. Ad this shows from the University of North Carolina, The Injury and Prevention Research Center -- and they did a study and have been doing an evaluation of our project statewide for CDC. And they are showing that we have embedded the project.

We've funded the project in those communities. Those with a local health department have a 26 percent lower emergency department visit rate from an opioid-related substance use problem. That translates into four less emergency department visits per 3,000 prescriptions. That equals money and it equals lives from the perspective at the state level.

We have been able to reduce the overdoses; about a 50 percent drop over five years. We've been able to prevent more school incidences with that, and we helped develop Operation Opioid SAFE with the U.S. army at Fort Bragg. And they were

having 15 overdoses per 400 soldiers. We reduced that to one per 400. They had 17 per 1,000 that survived. Now we've reduced that to 1.4.

But a systematic approach to pain management emphasizing risk stratification, risk mitigation, provider education, and alternatives to opioid for pain management has resulted in a reduction of opioid prescribing with decreased healthcare utilization and improvement in patient satisfaction.

One of the things that they've done at Fort Bragg is any refill for an opioid medication is an abuse-deterrent formulation. That is part and one of the strong components of the entire model that can be utilized to ensure that a person does get the medication that they need.

But again, because of rural communities and some of the problems that we have, you can see from this slide the number of arrests for diversion. And being a community that's rural, we're known as the moonshine capital, so we've gone through moonshine, marijuana, meth, and medicine, and it's

become an underground economy. Abuse-deterrent formulations aren't part of that economy because it doesn't serve the purpose that the individuals want.

The study that was mentioned earlier by Dan Cohen from the Massachusetts Department of Public Health, does an abnormally high number of prescribing physicians increase a patient's risk of fatal overdose? Yes, seven times greater for individuals who use three or more prescribers, within three months, concurrent use of opioids and benzodiazepines.

At least two out of every three people who died of an opioid overdose have been prescribed an opioid between 2011 and 2014, but just 8.3 percent of those decedents had an active opioid prescription in the same month.

Eighty-three percent of the opioid overdose deaths had a toxicology report completed. The person who died had illegally obtained or likely obtained that. In the report, the DPH points to the information that illegally obtained substances

as evidence to support an emerging hypothesis that illegally obtained substances are the driving force behind the state's epidemic.

Abuse-deterrent formulations help us, at the ground level address this important issue that we can change lives and save lives and still care for individuals that have pain issues. Thank you very much.

DR. BROWN: Thank you, Mr. Brason. Would speaker number 9 come to the podium and introduce yourself?

MS. STOUCH: Good afternoon. Thank you for allowing me to speak with you today. I have no financial disclosures. I am here as Pamela's mom today. I am a stay-at-home mom for the last 23 years.

In 2008, my daughter, Pamela, was a senior in high school. She saved her money, and she bought her own car when she was 14. And at age 18, she was managing our local Pizza Hut. Pamela paid for her own car insurance, her phone, gas, clothes, her own entertainment.

Pamela writes in her journal, dated October 9, 2009, and I quote, "I met my now ex-boyfriend and began smoking weed every day. In a couple of weeks I was snorting OxyContin."

I said Pamela, at 18 she was managing our local Pizza Hut. Pamela paid for her own bills, and she was an average student in school. Pamela got accepted into two colleges and began at Albright after graduation.

I knew something was very wrong, but I thought when I dropped her off at school and got her away from this boy that things would get back to normal, but I was very wrong. I didn't know when I dropped her off that she was detoxing from opioid medication.

After her first semester, Pamela transferred home, to a college closer to home and moved, and that's when things got really bad. I didn't know about prescription medication abuse. I got her into treatment thinking that she would come out and be herself and move on with life, but I was very wrong.

I began to educate myself, and I attended meetings and I read and I learned when Pamela went into rehab at 19 years old, on her birthday, August 9th in 2009; August 9th, next week, her 26th birthday, another birthday I won't get to celebrate.

Pamela lost everything, school, her job, her car. She was ashamed and embarrassed, but she stayed in treatment and attended meetings and outpatient. Pamela tried to get her life back together. She was to begin a new job and register for community college.

On March 27, 2010, six months after treatment, Pamela slipped. She used heroin, and she overdosed. In two years, I lost my daughter to opioid medication abuse.

Recently on the news I saw a clip on the Egalet Pharmaceutical Company. I saw how this medication could not be crushed, and if snorted, would leave a very unpleasant feeling. I immediately shared this news with my friends and family. I thought to myself, if only this had been

developed years ago, my Pamela may never have become a substance abuser. Her brain would not have become diseased, and we would have gotten treatment for her marijuana use. The marijuana became her gateway drug.

I feel this medication must be approved. We are losing a person every 20 minutes in this country. If there is a way to stop and deter people from chopping these pills up and snorting them and abusing them, then we must move forward and we must save lives. Thank you.

DR. BROWN: Ms. Stouch, we appreciate your comments. And I want you to know that everyone in this room is working hard to stop the things that took your daughter from you.

MS. STOUCH: Thank you very much.

DR. BROWN: Could speaker number 10 step to the podium and introduce yourself?

MR. PETERSEN: Yes. I'm Adam Petersen. I'd like to thank the advisory committee for hearing from me today, and my only disclosure is that my travel was paid for.

I was raised in a wonderful home with parents that taught me well and showed me an exceptional example. I've always had a strong entrepreneurial drive and high ambitions. In fact, I envisioned long ago that I would one day come to D.C. with my business empire. However, this is obviously not why I'm here today.

Instead, I stand before you, not as the head of the next tech giant, but as a man who is emotionally battered and beaten, in large part due to my history of prescription drug abuse and addiction.

Growing up, I was a pretty straight-laced kid. I never experimented with alcohol nor drugs my whole time in high school or college. So how did I end up becoming someone who would intentionally abuse prescription medications?

Just before my son was born, I found myself in the middle of some very painful business failures. I was feeling the worthlessness, knowing that I couldn't take care of my wife and son financially.

As a result, I experienced crippling depression. My wife begged me to go to the psychiatrist to get help, which made me feel even more inadequate. Before long, doctors were prescribing me meds for depression, sleep, and anxiety.

Around the same time, I had multiple surgeries and was prescribed pain medication. The combination of severe pain and severe depression were a disastrous combination for me. I got to the point where rather than living in a constant physical and emotional hell, I'd rather not feel anything at all, even if that meant just for a moment.

I began abusing the prescriptions that had been legitimately prescribed to me, and eventually I began taking them from friends and family. Ultimately, this and other addictive behaviors cost me my family.

Much is said about the annual costs associated with chronic pain and prescription abuse, largely measured in hours and dollars and

cents, but for a moment, I'd like to talk about the human cost. How does one accurately assign a value to an hour missed in a child's life because Daddy was emotionally and mentally checked out while abusing opiate prescription medication? How do we attach the cost of broken trust or shattered dreams?

I've had ample time to reflect on the damage that I've experienced, but ever so more heartbreaking, the damage that I've caused others. I wonder, will my son ever be able to respect me, since we are now all living with the harsh consequences of the choices of mine long in the past.

I have an angel little girl that was a year old at the time of our divorce. The day will come when she will find a young man that will want to sweep her off her feet. On that special day, there is always a daddy/daughter dance. I can't help but agonize over the question, on that day, will she want to dance with me? Or will she choose her stepdad who she's lived with her whole life?

Just last week -- here's an example of the ongoing human cost associated with prescription drug abuse -- I got a letter from my little girl, and it said, "Dear Dad, I love you. I am sad. I want my dad back. I am miserable."

It haunts me to know that some of the very first words my little girl ever wrote by herself, were words describing deep, emotional pain, which are a direct result of my prescription drug abuse. Try to put a price tag on that.

The truth is the prescription pain medications are a blessing and a curse. They're miracle is they give temporary leave to those who are in debilitating pain. The nightmare side is they are so easily manipulated and abused. The ease of manipulation most certainly aids and accelerates the downward escalation of abuse. I would know; I've experienced it firsthand.

Each of you are very familiar with the challenges we face in regards to opioid drugs as they stand now. I do believe if I couldn't have abused prescription medications, my path would have

been less destructive. I don't want others to go down the road that I went down.

Each of you on this committee are in a very special situation in that your decisions will impact millions of people. I humbly implore you, please do everything in your power to clear the way and foster an environment for the drug companies that are willing and committed to developing safer, more responsible pain medications. Thank you.

DR. BROWN: Thank you, sir, very much. We appreciate your comments, Mr. Petersen.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee now is going to hear some information from the sponsor of this compound that we asked for this morning, after which we will go back to clarifying questions, which we were not able to manage this morning. So if I could ask the sponsor to give us --

DR. DAYNO: Yes. Thank you, Dr. Brown.

First, I'd like to thank the panel for the

opportunity to respond after the break and clarify some questions. There were three questions that came up that we'd like to clarify for you.

First, Dr. Emala asked about large-volume extraction over time and if we could provide that data. So if I could have slide AA-1, please?

Starting with the model solvents, solvent 5 and 11, this is extraction over time, out to 8 hours. This is with 60 milligram and 200 mLs, and showing the plateauing effect over time in these two model solvents.

Also, to remind the panel that in these large-volume extraction experiments, the opioid eventually has to come out, so it has to come out to be an effective analgesic, but we're seeing the plateau here over time.

Slide AA-2. This was solvent 18 that was asked in particular. Now, this is in 200 mLs of solvent, with solvent 18, temperature A, agitation B in triplicate, showing a similar pattern and plateauing at about 60 percent.

Let me have slide AA-3. This was the

pattern that I think, Dr. Emala, you referred to about decreasing over time. This was in the exploratory phase of the program in 50 mLs of solvent 18; so because of the decreased volume of solvent and difference in solubility contributing to the different pattern from the pattern that you saw with solvent 18.

The next question, Dr. Gupta had asked also in terms of large-volume extraction. Slide AA-4. So the request was solvents 9 and 10, looking at temperature B, agitation B, with 60 milligrams the highest dose of Arymo in 200 mL of solvent. This is at the 30-minute time point.

A similar pattern in terms of extraction at this time point and also carried out over time would be a similar pattern of plateauing out over 8 to 12 hours.

The third question, importantly, actually was about the time that was used in manipulation of the product for the oral HAP study and was it enough. I think that we demonstrated with that method of manipulation that more time to use that

tool resulted in a plateau effect in terms of there was no further reduction in particle sizes.

But I'd like to invite Dr. Webster up, because I think it's important -- Dr. Webster was a principal investigator for the oral HAP study, and his observations in the clinic and how much time and effort it took and the impact on the study.

DR. WEBSTER: Thank you. First, I have to say thank you to all of the public speakers. I think I can probably say for most of you, but certainly for me, that that is why we're here today. And I hope we continue to make advances so we can safer and more effective medications. So I want to thank you.

This is an important question because it's not collected in our data, that is the work effort. The tool that was used for the oral HAP is, is a tool that's available -- as you know, because you're all aware of what that tool is, but it's not easily used to manipulate the product. In fact, one of our pharmacists could not manipulate the product. This pharmacist had to defer to the other

pharmacist in our clinic to manipulate it in a way that it then could be fed to the subjects.

So it is impossible to collect the difficulty of manipulating in the Category 3 studies where you have a liking and then most importantly, take the drug again, because if they're given something that's already been manipulated, they're only assessing that element of it at that time. It's like giving a baby applesauce rather than giving them the apple. In this case, it's even much worse, because it is a very hard substance.

If a pharmacist, who knows how to best manipulate this, based upon all the preclinical work, can't manipulate it, I believe very few recreational drug users, or even those who are more advanced, are going to be able to manipulate it to maximum the oral liking effect. And clearly, when there are so many other options out there, it's not going to have an overall take-drug-again effect that you've seen here; that plus the inability to chew it because of its hardness.

So we can manipulate it by the way in which it's been instructed, and then we can reduce it into some size, but we can't ask our subjects to chew it. Our whole staff agreed that we could not do that because we were afraid they would fracture teeth.

So we really have almost a false setup here when we're asking some of these questions, particularly take drug again or overall drug liking. It is a very hard substance, and it is very difficult to manipulate, and that data is not collected in the results that we've shown you.

DR. DAYNO: Thank you.

DR. BROWN: Could I ask a couple of questions just to clarify the comments that you just made. Number one, how did you choose the model solvents that were presented during the original presentation?

DR. DAYNO: The model solvents were chosen based on the original 18 solvents in the overall panel, and we looked at the pattern of results and saw that extraction was greater in the solvents

that were digestible, and the aqueous solvents. So solvents 5 and 11 represented a range of pH and polarity across those solvents, and then we repeated the studies in the proposed to-be-marketed dosages with those model solvents.

DR. BROWN: But there was a remarkable difference in some of the solvents that were not model solvents. So were they chosen as a mean of the results that you had?

DR. DAYNO: The main difference for that was when we did the initial exploratory work at 100 milligrams in the early phase of the program, it was in 50 mLs of solvent. When we repeated the study with 60-milligram dose, it was in 200 mLs of solvent. So the different rates of extraction representing different solubilities in the different volumes of solvent.

DR. BROWN: The last question that I want -- and then we need to get on to the questions that the committee has. But you just showed us about a 60 percent extraction rate with solvent 18 for your medication. And I'm wondering if we put

MS Contin in solvent 18, what would that show?

DR. DAYNO: We didn't compare it to MS Contin, solvent 18. Solvent 18 is toxic and non-ingestible. We did, however -- in the two model solvents, we did look at MS Contin 60 milligrams compared to Arymo 60 milligrams.

DR. BROWN: Can you show that to us? I think that will help us --

DR. DAYNO: Okay. So first let me check with Dr. Hertz. That data was not submitted as part of the NDA. It's a comparison to MS Contin 60 milligrams, the comparator, in the two model solvents compared to Arymo, the extraction.

DR. HERTZ: You can share it, but just the committee should recognize that it's not been reviewed.

DR. DAYNO: Okay. Thank you. So I'll show you those data on this slide and what it shows. So this is solvents 5 and 11 in 200 mLs of solvent, and this is the manipulated Arymo with the optimal multi-tool manipulation F to J, crushed MS Contin. You see that with MS Contin, when you crush it to a

fine powder, it releases almost immediately over the first couple minutes with 100 percent extraction of the morphine.

Clarifying Questions (continued)

DR. BROWN: Thank you very much. We have several more questions from our group. Dr. Walsh?

DR. WALSH: Thank you. I need to find my question because it was from earlier this morning. So it's related to the intranasal study, slide number CO-53. I'm just curious about the choice of conditions that you decided to show here, and just looking maybe for a little bit of guidance about this.

In the Arymo manipulated and sieved, I gather that you have taken out all the large chunks and left mostly the very small powder that's more suitable for snorting, correct?

DR. DAYNO: That's correct.

DR. WALSH: So can you just tell us by weight, what portion of the overall tablet is represented in the amount that's powdered?

DR. DAYNO: So that was about 15 to

20 percent of what is represented in the manipulated, sieved arm. If we take a step back, the logic, the rationale behind this design -- and actually, this was in discussions with the agency. Because of the challenge in particle size reduction, we knew that it would be very difficult to snort in terms of the full output, using the optimal multi-tool method.

So we included that arm and had subjects snort that. And then sieving to try to at least improve the ability to snort, and that's represented in the manipulated, sieved arm and with a low yield.

I'd also like to call up Dr. Webster again as the PI on this study with some observations of the difficulty in that experience in the intranasal HAP study.

DR. WALSH: Can I ask a couple of questions first, and then maybe Dr. Webster --

DR. DAYNO: Sure. Absolutely.

DR. WALSH: Yes. The second question related to this is that clearly a lot more of the

drug got in when you gave the whole crushed formulation, although it might not appear to be optimal. Perhaps what we're looking at here is a lot of oral absorption of the chunks that would have gone down into the GI tract with a larger set.

Then the other part of it is probably -- well, I guess would you agree with that, just based on the shape of the curve? I know that we can't really differentiate that.

DR. DAYNO: Yes. We would agree with that. I think we came to the same conclusion because material -- although the majority of the subjects were able to snort most of it, we think that a fair amount may have been swallowed and absorbed in the GI tract, reflective in that PK curve.

DR. WALSH: Okay. Then can I just clarify, for this manipulation, am I correct that this was manipulated for a period of 3 minutes?

DR. DAYNO: This was manipulated using the optimal multi-tool method, Tool F, followed by Tool J.

DR. WALSH: Right.

DR. DAYNO: Yes. There wasn't a time factor to that multi-tool tool procedure.

DR. WALSH: Okay.

DR. DAYNO: It was optimized based on many combinations of testing of how to get to the best particle size reduction.

DR. WALSH: Okay.

DR. DAYNO: What we were trying to accomplish here was cover the full range of experiences that abusers may try, the full output of the product manipulated that would be hard to snort, and then seeing the chunks, what would be more amenable to snorting in the other manipulated sieved arm.

DR. WALSH: Right. Then I guess my last question about this would be a good question for Dr. Webster, and that is what the qualitative experience was, and are the chunks sharp, are they -- what's --

DR. DAYNO: I will let Dr. Webster respond to that.

DR. WEBSTER: That's exactly correct. In

fact, a number of the subjects said things like, "This feels like ground glass that we're snorting. Do we really want to do this?" I mean, they did it because they're almost professionals. This is what they do. But they did not like it. And the reason we saw take-drug-again difference here so significant is because they're not going to take drug again. They will not repeat this. And they said that to me, as they were doing it, saying, "Oh my God. If you're trying to develop an abuse-deterrent, you've got one here" for this route. Yes.

Obviously, because of those hunks and the glass-like stuff that they were insufflating, that's not going to be absorbed, so basically it's swallowed. That's the only way they could get it in basically to evaluate it.

DR. DAYNO: Let me just add to that supported by the data, what I'll show you here is from the ease of snorting scale on this slide coming up. This is a unipolar 100-point scale reflecting the subjects' experience, which is asked

a couple minutes after, 5 or 10 minutes after snorting, from very difficult to very easy.

So it reflects the pattern of crushed MS Contin with a very high ease of snorting rating, and then the manipulated Arymo with all the particles very low, and the manipulated, sieved, achieved the ease of snorting outcome compared to placebo. You see that represented by the data here.

DR. WALSH: Okay. Thank you very much.

DR. BROWN: Dr. Flick?

DR. FLICK: Thank you. Randall Flick. This question is for Mr. Radie.

Mr. Radie, the crux of the decision that the committee faces is based on the abuse deterrence of Arymo. I think some of us are a little bit dismayed or surprised that there isn't a more standardized approach to determining abuse deterrence.

Earlier, one of your folks talked about thousands of hours that were spent trying to determine what the right methods or tools were in

determining the abuse deterrents. And I think it's important for me and for the committee to know that at the end of those thousand hours, that the tools and methods chosen were the ones that were most appropriate to determine the abuse deterrence value of this formulation.

I think it's important for us to hear a definitive statement from you that says that is indeed the case. Otherwise, we're left to look at only a small portion of work that may have been done by your people.

MR. RADIE: Sure. I'll start by saying that I understand the dilemma of standardization because each of the technologies are different. So I think it requires the flexibility to look at different tools and mechanisms and solvents, because each of these technologies are quite different. So I do understand the FDA's challenge in trying to standardize those tests.

I feel extremely confident and I can assure you that everything was done to figure out how best to particle-size reduce this product, to dissolve

it, to figure out the best way forward in the work that has been done.

DR. FLICK: So that no more effective means of defeating the abuse-deterrents were left in the laboratory, so to speak.

MR. RADIE: We do not believe so.

DR. FLICK: You don't believe so or you know so?

MR. RADIE: I mean, you know everything --

DR. DAYNO: Dr. Flick, if I may add to that, because I was sort of charged with that. I think that the tests that were done were very iterative in terms of trying to get to optimal manipulation, and a lot of it is based on characteristics of a product.

I think the challenge of standardization in Category 1, it was actually the topic of a meeting on Category 1, a focus group meeting, about a year ago. Members of FDA were there. I sat on one of the panels. A lot of it depends also on the characteristics of a given product and in an iterative fashion, and working with the FDA to make

sure you test it to fail, you have taken it as far as you could go.

The example of that with Arymo is with single tools, which is often the endpoint for particle size reduction, we realized the yield was low and then went and did multi-tool manipulation to try to test it further.

DR. FLICK: I appreciate that. I think it's just part of the committee's due diligence, right? We have to know that you did your best, that there was nothing left in the laboratory, and that you're willing to say that definitively. Because if you can't say that definitively, there isn't a person on this committee that's going to vote for approval, at least not me. If you can say that definitively, then we can move on.

DR. DAYNO: Yes, I can say that definitively.

DR. FLICK: Good.

DR. BROWN: Dr. Floyd?

DR. FLOYD: This is James Floyd, University of Washington. I think this question might be for

Dr. Katz. I think during your presentation, attempts were made to link differences in drug liking and the high scales to basically clinical endpoints of differences in abuse. I didn't really understand the link there or what the data were to establish that linkage. Maybe if you could explain that a little bit.

DR. DAYNO: Dr. Katz?

DR. KATZ: Yes. In the study that we did, we worked with Sandy Comer from Columbia who's a substance abuse researcher, and we got a hold of a number of datasets of clinical trials that she had done in heroin users where they were using depo naltrexone, and we were able to get VAS drug-high measures within patient across multiple ones of those studies. Those were meta-analyzed and combined.

Then as the outcome measure, we had drug-taking behavior of those very same heroin users when they had gone out into the community. So we were able to look to what extent was the subjective perception on the clinical drug high predictive of

their actual drug use in the community. In doing so, we were able to establish that link between the 8 to 10 millimeter range of VAS drug high and their heroin use in the community.

DR. FLOYD: So these were measured within the same study, and what was the measure of the use of the opiate? Was it episodes of overdose? Was it frequency of use? What was the measure?

DR. KATZ: We did two different ways. The first way was actually treatment or retention. So when the heroin user either fails to show up or shows up with signs of heroin use in their urine, they're counted as a failure. We looked at the degrees of drug high that separated the group of patients who were retained from the ones that were not retained. That was one approach.

A second approach, we used what's called a breakpoint approach where Sandy in her lab has a way of assessing at what point patients would prefer money over heroin. We looked at that breakpoint as another endpoint against which to compare the drug high scores from the subjective

endpoint studies.

DR. FLOYD: I'm sorry. I'm still a little bit confused. I understand the clinical endpoint being relapse into heroin use or failure to adhere or show up for study visits. What was the surrogate measure? Was it -- I don't understand what the intervention was.

DR. KATZ: The surrogate endpoint that we used in the second example was what's called a breakpoint analysis. Actually, probably Dr. Walsh knows more about it than I do. But it's a method of giving patients increasing doses of heroin and determining at what point would they prefer to accept money rather than heroin. Depending on how much naltrexone they had on board, we're able to compare the degree of drug liking they experienced when given heroin to their value of that same dose of heroin as expressed in that money versus heroin breakpoint.

DR. FLOYD: Okay. That's helpful. So there are no studies linking liking or high for abuse-deterrent formulations of opiates and risks

of adverse effects. These are a different type of intervention.

DR. KATZ: Well, the closest that's been done to that is the second study that I showed early, which I didn't do. It was done by Allen White and colleagues in Boston. What they did is they collected up about 21 different human abuse liability studies in which drug high, Emax drug liking, and other endpoints were ascertained. And then they went into the National Survey of Drug Use and Health, which is run by the gentleman sitting to your left, as well as DAWN, which is another database, and attempted to compare the degree of liking in the abuse liability studies with the lifetime non-medical use of those very same molecules. And these are very large survey studies, so they were also able to establish a linkage that way, between the human abuse liability studies and those drug-liking scores, and real events in the community, across a variety of drugs.

So two different ways at actually both triangulating and more or less the same result.

DR. FLOYD: Thank you.

DR. BROWN: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien, patient representative. My question actually was from early this morning, and it's really a discussion of the real-world and get clarification and to specifically address Dr. Dart with slide 15, relative to the pathway of progression to substance abuse.

DR. DAYNO: Dr. Dart. We can show slide 15.

MR. O'BRIEN: So in my world of patients, which includes those patients that have pain severe to require daily, around-the-clock, long-term opioid treatment for which alternative treatments are inadequate, that group is there.

I'm not sure of that group. I don't know any data that shows me how many of those are crossovers to the endpoint of poison centers. However, we do know, both in communication with them and personally actually, that there is tendency towards addiction and down this scale. But most often, for that community, and what I was

looking for Dr. Dart is some granular view between the susceptible to addiction and a chew, crush, swallow, through that first manipulation. Because in our experience, it seemed that the real first level is obviously taking multiple pills. And we discussed about that, you can't be proof versus that.

However, our experience, anecdotally, we see a trend that with the changes in regulatory and policy, that in effect is helping with that because it's harder to get a prescription, so therefore you don't want to use it up by just taking multiple pills, because now you have to go explain yourself in seven days, depending on what state you're in.

However, the easiest one and it seems to be that the -- in our experience, and I have to clarify for my understanding of this, is that it's the path of least resistance. So the first thing is to take multiple drinks. It's easy to get alcohol to include with it. More and more, as we say, another gateway drug, which we heard from one of the speakers, is smoking dope. And smoking weed

is becoming more and more easily acceptable. So the combination of those are helping to elevate that Emax even though most patients don't know what an Emax is, but they're going for that.

So relative to that, how much does that play, Dr. Dart? And is there more granular between here, from a preventive basis that perhaps doesn't address the endpoint and the crisis? Which I readily understand we have to address. But that crisis begins with a very broad novice person who starts to get introduced to these drugs and then becomes addicted and eventually gets down there.

DR. DAYNO: Yes. Dr. Dart?

DR. DART: Yes. I mean, I basically agree with your progression that you're describing. And I think part of the problem may be the necessity to kind of crunch these things together to get them on one slide. I have more expanded versions of this, that I agree that what happens in the pain patient, they don't necessarily start out to be addicted, but if they want their pain relief faster, most people figure out that they can chew it and get

their pain relief faster. But then they realize that they actually liked that feeling as well.

For a small proportion of patients, they will go and develop other -- in fact, I've had people in my own division at Denver Health, who we've had to get through treatment, who started exactly that way.

I think you were mentioning the proportion of those patients compared to others, I can't put a good number on that. I would like to, and I've looked. But how many people start as a legitimate pain patient and end up going down the spiral, and how many were experimenters who really came for recreational purposes and ended up going down the spiral, I don't know. Maybe other people have a better idea, and I'd love to know that information if they have it.

MR. O'BRIEN: Well, again, the concern here is we have a study and we have a drug and it's looking at 38 intentional users as a study, but from my perspective, we have thousands of patients that are being introduced to this that could end up

down there. And that's the ones that I'm particularly concerned with in there.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: Brian Bateman. This is a question for Dr. Katz and relates to slide 72. You talked a bit about the study that you did, but I'm wondering in this meta-analysis, did they look at other measures that are commonly used in human abuse potential studies like take drug again, or drug high, and attempt to correlate those and define clinically meaningful differences in association with rates of non-medical use.

DR. DAYNO: Dr. Katz?

DR. KATZ: Yes, they did look at other endpoints, subjective endpoints from abuse liability studies. They looked at drug high. And I can't remember. They looked at one more that I can't remember offhand. They used regression models to try to attempt to discern what the relationship was between the degree of liking seen in the human abuse liability study, and then these real-world events. They did find that there was a

relationship between each one of those subjective endpoints in the real-world events.

I just put on the slide the one final bottom line with respect to an abuse-deterrent ADF, which is that this degree of production and drug liking, they modeled that that would be expected to correlate with that degree of reduction of lifetime non-medical use.

They had similar numbers for some of the other subjective endpoints, but I just don't have them in my head. I do have the paper though, so I'd be happy to show it to you later if you'd like.

DR. BATEMAN: Thank you.

DR. BROWN: Dr. Wesselmann?

DR. WESSELMANN: I wanted to come back to the solvents, solvent 18 that we discussed. It was mentioned that although it resulted in a high release of this preparation of opioids, that the substance was toxic. But my question is what was actually the toxicity?

So if an applicant would have taken this preparation, was it life threatening? And what was

the toxicity of the other solvents? It was unclear to me why a solvent was even tested if it was toxic, or was it just mildly toxic, if you can explain.

DR. DAYNO: I'll invite Dr. Cone up to respond in terms of the range of solvents. But first we'd like to say that a broad range is tested to include extreme conditions, so both ingestible and non-ingestible. Consistent with trying to challenge the formulation, it represents a broad range, some of them being extreme conditions.

Dr. Cone?

DR. CONE: Yes. The range of solvents is really identified -- not the specific solvents, but the types of solvents are identified in the FDA guidance for Category 1 studies. So we typically pick out a range of solvents that are non-toxic and toxic. And all of the organic-type solvents are toxic in different ways.

The solvent 18 happens to be one of those that's particularly toxic; probably would be life-threatening if they drank it. But we covered

the range because there's always more things that people could do if they wanted to spend hours evaporating solvents and doing things.

It's another way to isolate morphine. In this case, it would be morphine in combination, morphine and PEO. But we really just follow the FDA guidance to look at a broad range of solvents; not that people really use these solvents very frequently, but they could be done.

DR. WESSELMANN: I still want to ask more questions about it because it seems there was something very particular about this solvent that made it very different from all the other ones. Is there a non-toxic version? What made it so toxic, and is there another solvent available? Because it concerned me to see that this really was sticking out on the slide that was provided with the material that we received prior to the meeting.

DR. CONE: Well, again, the selection of solvents are also based on availability, real-world availability. These solvents can be obtained, and people could try to use them.

Solvent 18 is just one of those quirky organic, toxic solvents that has a little bit better way of extracting out morphine. So it's a quirky-type solvent in a laboratory. I doubt many people would use it, but it did what it did.

DR. BROWN: Dr. de Wit?

DR. DE WIT: Yes. I'm struggling a little bit with the results of the oral abuse liability study, that's EG-08, and I'm looking at slide 58, and there are other ones.

It seems like we're getting conflicting messages from this study. One is that the kinetic profile and the ratings of liking over time look terrific. So it's exactly what we would want to see from abuse-deterrent point of view; that is a slow onset, that's the most important thing, and a slightly lower peak. I think it's the combination of those incidentally that's a critical variable to look at, the rate of onset and the peak. So neither one of those alone is going to be informative.

But then we were told that on the secondary

measure, which is sometime later the people are asked would they like to take it again, and there we don't see the differentiation. So there are these post-abuse liability studies, apparently, that may be able to tell us which of those two indicators is the more accurate for predicting whether people will go back to use; that is whether people say at the end of the study that they would like to take it again, or how they actually experience the drug effect during the study.

So to some extent, it's an empirical question. But for us, it's a little bit of a struggle because based on those secondary measures, the critical comparisons didn't look very different on the self-report measures, whereas they did look different in the laboratory session.

So I don't know whether you could extract from the post-abuse liability studies which are those indices we should be paying more attention to.

DR. DAYNO: I'll call up Dr. Katz to comment on the clinical relevance of the endpoints. Let me

start by saying that first, subjects couldn't chew the tablets. So the method of manipulation was different than some of the other oral HAP studies.

We had to go even further and use tools to manipulate the product in the clinical pharmacy, and then it was given to the subjects. So some of that experience was not part of the overall HAP study. And with that, I'll ask Dr. Katz to comment on the clinical relevance of the secondary endpoints.

DR. KATZ: Well, your observation is correct that the primary endpoint was statistically and I also think clinically meaningfully different between the two main groups. One of the key secondary endpoints was positive. I think you're focused on the take-drug-again endpoint, and people do wonder, well, which is actually the best predictor of real-world abuse? Is it the Emax drug liking? Is it the take drug again? Is it something else?

I haven't seen any studies looking specifically at take drug again, as to whether that

predicts real-world behavior, better or not as well as some of the other endpoints. Right now, that's just a matter of conjecture as to whether that might be more or less predictive.

In terms of the actual results of take drug again though, I went back to the study report and wrote down the p-values. I'm not sure if they're all in the briefing package, but it was assessed at 12 hours, at 24 hours, and then the maximum effect that each patient reported was also looked at separately as endpoint.

The p-values for those were at 12 hours or .033, at 24 hours was 0.048, and the Emax version of it was 0.054. So they were either just under or just over the statistical significance threshold, so maybe not as bad as it might have looked.

DR. BROWN: Dr. Hertz?

DR. HERTZ: This is Dr. Hertz. I just to want to address that point as well from our perspective. As we've been embarking on these studies, we've borrowed methodology from the abuse liability world to evaluate abuse deterrents. And

as you've heard, this is a growing new, evolving field.

We are dealing with subjective endpoints, and we don't really have objective measures, at least not yet. This is what we encounter throughout the work in analgesics as well. So our approach is to basically ask the patient, in this case ask the subject, what they're experiencing. And when we look at trying to determine whether a difference between two products is meaningful, we're trying to understand what some of these different outcomes mean and create context.

So if somebody finds one drug results in a greater high, which is often associated with a greater liking, what does that mean in terms of whether the product, the comparator, is abuse-deterrent or not? So if there's a difference in drug liking, is the difference big enough for the individual to care?

So we use the willingness to take the drug again as a way to provide context for these other measures because if one drug provides a drug high

of 78 and the other of 84, they apparently are high, and if the drug liking scores are a few points apart, they apparently like them both.

So liking one drug more than another is interesting, but it doesn't clearly indicate whether the reason for the difference represents a deterrent effect.

So in the absence of better data, we had to make a decision on what the endpoints that we think are really the relevant ones. Take drug again seems to have some value in terms of when we ask subjects because we have seen it differentiate across products.

When we don't see a difference, we know it's certainly possible to get a difference. We, in this case, have bigger differences in take drug again for the nasal route that we think may provide context for the other outcomes for the nasal study. But for the maximum effect in the oral, there wasn't much of a difference, and it didn't meet statistical significance.

Remember, the statistical significance in

the difference in drug liking means it's not a difference by chance. It doesn't mean it's a difference that has clinical value. That's why we struggle with understanding the intersect between the numbers, the statistical evaluations, and the meaning for the product as it's expected to behave once it's out in the community.

So we don't emphasize the statistical significance in the drug liking or the drug high. Once subjects are getting high, once they like the drug, the question just for abuse deterrents -- I'm not minimizing the importance of this in other spheres. But the importance of trying to understand a potential deterrent effect is the challenge.

Right now, we think the take-drug-again score is important to helping us understand it in the context of these all being subjective measures, so we basically ask the subject.

DR. KATZ: Just to add yet another complexity to the conversation, I was interested in this issue also of the sensitivity of the different

endpoints, so I did a review of all the oral abuse-deterrent studies that I could find. And it turns out that the take drug again endpoint gives you about 0.7, 0.75 of the effect size that you would see in the Emax drug liking, which means that the studies are underpowered for the secondary endpoint of take drug again. If we wanted to know whether those were statistically significant, we'd have to power our studies adequately to show that.

DR. BROWN: Dr. Hertz will now provide us with the charge to the committee.

Charge to the Committee

DR. HERTZ: So that's all nice and clear to everyone, right?

(Laughter.)

DR. HERTZ: In the past when we reviewed NDAs for these products, even in a few cases during development, we came to the advisory committee to seek advice. We prospectively sought advice for ideas about how to study these products in the postmarketing period.

We prospectively -- well, this wasn't

prospective. But we brought early applications to the committee to hear about the methods that were being used, were they robust, what else should be done. And boy, we heard lot, and we've tried over the years to take all that into consideration. And it went a long way with our experience in reviewing these products to the formation of the guidance that we have for the development of these products, the document that's been finalized.

But we continue to learn, it's not static. We took a little break for a while in coming to AC when we thought that the issues in these applications were not novel, based on the earlier experiences, and we thought we could apply the advice beyond each individual setting.

But it is getting more complex. There are a lot of unanswered questions about the impact of additional products as they come to market. Do they increase the prescribing practices? Do they change prescribing practices? We have seen some data to suggest no. We have seen some data to suggest yes, about different aspects of it.

Then what do we do with these outcomes? We've borrowed a methodology. We don't yet have postmarketing data that we have had the opportunity to make a formal FDA review and comment.

I believe Dr. Staffa will have a comment about some of the studies that have been published, but we have not -- the way you can tell when we're in agreement with sponsors is whether we implement labeling to reflect sponsors opinions about their product. And if there are publications, but no labeling, it suggests quite clearly that either the sponsor hasn't come to us, which one would wonder why if they think they have a finding, or that we've disagreed.

So we do not yet feel that there are data from postmarketing work that support additional labeling for products. So as you think about publications, just know that we have not weighed in, in agreement. So we are not yet ready to say there are correlations with postmarketing data. That makes it harder.

When we have study results that we think our

analyses are in concordance with the applicants, that's pretty straightforward; we try to let the data speak for itself, and then we try to bring up areas, where we have disagreement, to get some input in.

It's extremely important because we have been swayed by committees where we've had disagreements. You folks clearly let us know when you disagree with us, and that's incredibly important. And we actually listen, and we can be swayed.

Today you've heard a lot about this particular product, the analysis, the evaluations that have been conducted, and we're going to now ask you to consider what you've heard. As you go into the questions, they'll be formally read, but we're basically going to be asking about your conclusions about abuse-deterrent properties for this product for three routes of administration, for the oral, nasal, and intravenous, based on the data that you've heard.

If you think that there are potential -- and

again, this is premarketing, so it's potential effects, does it warrant labeling? And then taking everything into consideration, would you support approval of the product or not?

Then what's as important as specific answers is your reason for your answers. You may notice we take quite a bit of notes. I mean we will get a transcript as well, but we look at these notes -- I'm still referring to my notes from advisory committees from years past, because the deliberations are as important as the final votes or the final answers.

So I just want to thank you again for your time, and I really look forward to the discussion of the questions. Thank you.

Questions to the Committee and Discussion

DR. BROWN: Thank you, Dr. Hertz.

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

participate, except at the specific request of the panel.

The first thing to discuss is that we're going to be using, in our voting, 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 if 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, and the DFO will read the vote from the screen into the record.

Next, we'll go around the room, and each individual who voted will state their name and vote into the record. You can state the reason why you voted as you did, if you want to. You're not under pressure to do that. We will continue in the same manner until all the questions have been answered

or discussed.

Question number 1 for discussion; please discuss whether there are sufficient data to support a finding that Arymo ER, morphine sulfate extended-release tablets, has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse: oral, nasal, and intravenous.

Now having read this question, are there any issues among the members of the panel concerning the wording of the question? Is it clear to everybody, and is it a question that we can hope to answer?

(No response.)

DR. BROWN: So we're going to move on to questions and comments about this particular question, and we're going now to Dr. Floyd.

DR. FLOYD: Would you like us to simply vote and just share our comments when we vote? I don't actually have questions about the questions.

DR. BROWN: No. Do you have questions about

this particular question?

DR. FLOYD: I guess what I meant is do you want us to discuss the issues broadly before we vote?

DR. BROWN: Yes.

DR. FLOYD: Okay.

DR. BROWN: We want you to discuss first whether or not you agree that this is a reasonable question to ask and that it can be understood as being a reasonable question.

DR. FLOYD: Okay.

DR. BROWN: And then we would like for you to -- we will discuss among ourselves the issues pursuant to the question itself.

DR. FLOYD: Thank you, Dr. Brown.

This is James Floyd, University of Washington. I have a comment that relates to whether this is a fair question, and I'm glad I have the chance to say something before voting because I think that based on the information we've heard, I can accept that there are properties of these drugs that make them hard to manipulate.

I think that other panel members have identified a lot of limitations of these studies. But I'm very uncomfortable with the language in the question and in the labels for previous abuse-deterrent drugs. Specifically that -- and let me read off the question here -- a given drug has properties that can be expected to deter abuse.

There are two reasons for this. One is that measures like drug liking, like how high you are on some numerical scale, even the PK characteristics, are biomarkers. We really don't know how the effects on these biomarkers relate to effects on abuse for any valid clinical endpoint whatsoever.

The language in this question "expected to deter abuse" suggests to me that we actually have some information or evidence that these biomarkers are validated surrogate endpoints. So the language in the question troubles me.

Secondly, most of these drugs are prescribed by generalists, by general internists like me, by family docs, by mid-level providers, and I think for the most part they're not familiar with the

nuances of the evidence that go into the labeling or what some of the language might mean. And if I see something about "expected to deter abuse" I might think that there's some evidence that actually these drugs result in less abuse compared to other drugs.

I think there's enough ambiguity here that there's a concern about an unintended effect that the language and the labeling could result in potentially more inappropriate prescribing.

So I guess, yes, my concern is with the language. With this language, I might vote a certain way, but with other language in the label, I might vote a different way about what could be included in the label.

DR. BROWN: Not that this will change anything, but do you have a specific suggestion about ways to change the question relevant to --

DR. FLOYD: I do. Thank you for asking. Maybe something more direct, that these drugs have properties that make them difficult to manipulate, or make it more difficult to chew, snort, or

inject; actually, statements that reflect the evidence that we do have. And there's been a lot of evidence presented, but none of it relates to whether these effects on biomarkers are expected to prevent abuse.

So language that directly represents the evidence that we've seen; that's what I would suggest. Obviously, not for just this drug, but for all of the abuse-deterrent drugs. I don't think there's any reason to single out this particular drug.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. First of all, I want to second the comments we just heard. I think they are very relevant. I just want to -- although this is not the topic of discussion -- make a brief statement that there really are concerns about the effectiveness of opiates for chronic pain. And that's something we shouldn't neglect when we make a decision like this, although it's not the topic of the meeting, and I recognize this.

The other issue that I want to briefly comment on, it's going back to slide 15, because this slide that shows the initial exposure to the opiates, susceptibility to addiction, and then this path down towards chewing, crushing, swallowing, snorting, injection, this suggests that this is the only way to get addicted to opiates when opiates are prescribed.

I'm not an addiction researcher, but I certainly don't think that that's the case. There are many patients that may get addicted to opiates without ever doing something along those lines. Maybe even without ever taking additional pills, which is something that we're not even addressing.

That relates a little bit to this very justifiable opening statement by the sponsor, and all sponsors, of abuse-deterrent formulations that say when we talk about oral deterrents, we're not talking about taking two pills. We're talking about manipulating the drug. Again, that's not the only way to become addicted with these drugs. Obviously, it's not something that the sponsor here

is claiming, but it's just important for context.

So I think in many ways, the oral deterrence labeling is particularly problematic because it could have easily the unintended consequence that it basically lowers the bar to opiate prescribing, that the opiate is now considered to be safe, and safe from developing addiction through the oral route. That is one comment I have.

Then just specifically to the question, I think here the data that the sponsor shows for the nasal and intravenous routes is very strong, I think. Although it's not backed up by epidemiologic data, as we just discussed, I think there we really see these big differences that line up between the biomarker-type measures and the take-drug-again question that to me seems just incredibly irrelevant because it pretty much directly asked the question that matters. In terms of addiction, would you take that again?

The oral formulation where it's much more difficult, where you see some differences in the biomarkers, but when you look at the question of do

you want to take the drug again or would you take this drug again, there really isn't much of a difference. And in this particular situation, the manipulation that was implemented are certainly not time-consuming or difficult to achieve.

I think it's one thing if there is basically a small chemistry lab needed and a couple of days to do something, but here it's a pretty straightforward, quick physical manipulation, that might not be pleasant if you're a lab tech and you have to do it for 50 patients, but it's certainly something that you're willing to do as an addict.

So I think, from my perspective I feel that this product probably would deserve a claim for the intravenous route, the nasal route, but I would not give it for the oral route, both because of the comparative weakness of the data with the take-again measure, and the more general problem of the other routes of oral abuse that I wouldn't want to put a claim on there that lowers potentially the bar for prescribing, potentially exposing more patients to the risk of addiction when they don't

have to be.

DR. BROWN: Recognizing that this particular language is the standardized language, I believe, that is placed in the patient and physician record that comes with the drug, "has properties that can be expected to deter abuse," that's what's coming out with these drugs now, just for point of clarification. Dr. Higgins?

DR. HIGGINS: In taking account of everything I've heard today, I'm really kind of conflicted. I find that there are some significant challenges with the data presented. In addition to the subjectivity of the liking endpoints, I find the small samples for the oral and nasal routes to be a challenge. I was swayed by the clinical significance of drug liking being nominal and questionable.

But overall, whether I agree with the endpoints or not, I feel the primary and/or secondary were met, and I would support approval of language about these being abuse-deterrent in the oral, nasal, and intravenous routes.

DR. BROWN: Dr. Emala?

DR. EMALA: I'd like to first comment on the oral discussion, and I think from both Category 1 and Category 3 levels, I'm not comfortable that there is sufficient data to support that type of labeling.

I think in the Category 1 studies, we talked a lot about the toxicity of solvent 18, but I think it should be pointed out that in a lot of totally ingestible solvents, greater than 50 percent of the drug can be eluted in 30 minutes in a volume that is then easily taken orally. So I think the Category 1 data is totally unconvincing as far as an oral deterrent.

In the Category 3 studies, this committee has spent a lot of time discussing what a 10-point difference is in a visual analog scale in various meetings. I remain quite skeptical that a 5 or 10-point change in a visual analog scale means much clinically, but I decided to think about this in comparison to the other six drugs that the FDA provided us in our briefing document with the

labeling language of the other six drugs.

If you look at those that received oral labeling and those that did not receive oral labeling, the one that you can look at is drug liking mean across all the six drugs. And a drug that received a similar score -- so the visual analog that we're talking about for today's drug is between 5 and 10, depending on whether it's manipulated or not.

If you look at other drugs in the category that had values of 9 to 13, they did not receive clearance for the oral labeling. The closest comparator, I guess, is Embeda extended release that had a value of 21 on its mean liking score that did get the labeling that it had perhaps had oral abuse-deterrent. So in both Category 1 and Category 3, I'm very unconvinced that there's sufficient data to support that.

Conversely, for both nasal and intravenous routes, I do think there is sufficient data to suggest that there is potentially abuse-deterrent properties.

DR. BROWN: Dr. Hertz?

DR. HERTZ: I just prepared two very quick slides of what the labeling language looks like, just to project so everyone can see. I mean, feel free to continue the critique because we're listening, but this is what it currently looks like.

(Slide displayed for reading.)

DR. HERTZ: Then the next slide. We always include in that section immediately following, reminding people that no matter what, these are Schedule -- well, in the case of this example, Schedule II, just to remind people that abuse deterrence is not replacing the scheduling determination or the abuse liability.

If we go back to the other slide, if you have recommendations for changing that other language, you can let us know now. You can send it in by email. We're always trying to learn how to improve this.

DR. BROWN: But this is the current language?

DR. HERTZ: This is the style of the language that we've been using, the previous slide.

Steph, the prior slide. That's how we've been trying to put the language in.

DR. BROWN: Dr. Novak?

DR. NOVAK: Actually, just two quick interrelated questions. One is I assume it's possible for the committee to recommend against some labeling claim, and then the sponsor to get approval, look at the real-world postmarketing data, then decide and kind of couple that they might want to go back into, or is this really the only opportunity that's available for the sponsor to seek the label claim?

The second question I have is more of a comment is, the last sentence on the first paragraph, sort of the however, the abuse of trade name blah, blah, blah, as well as by the oral route is still possible, that "still possible" seems to me like it's sort of this binary yes or no. And it seems to me like it's almost leading somebody to believe like, well, they may not be able to abuse

using these other properties, but they can still do it via orally.

So it almost seems like this isn't possible, and in fact, it kind of is. There's always some small possibility. So I guess in changing in more probabilistic language rather than more like -- the possibility reflects uncertainty, but it does have this sort of binary --

DR. BROWN: Dr. Hertz?

DR. HERTZ: So to address the questions, labels can be changed at any point during a product's existence once it's been approved. What a sponsor needs to do is request a labeling supplement or an efficacy supplement. We have different types of supplements, depending on what they contain, to support labeling changes.

In terms of what it takes to get the postmarketing data, I'll turn that to Dr. Staffa.

DR. STAFFA: Right. Judy Staffa. In the guidance that describes what data are required, at least the state of what we know at this point, for the different categories of abuse-deterrent

labeling, Category 4 is the one that deals with postmarketing data.

We've laid out, to our best ability at the time we wrote the guidance -- and of course, we'll continue to update it -- what we'd like to see, but understanding this is an evolving science.

So with that in mind, I'll follow-up on what Dr. Hertz had said before, that none of the six products that are currently on the market with abuse-deterrent properties based on Categories 1, 2, or 3, none of them have Category 4 labeling at this time.

I wanted to just clarify, since we're on that topic, the data that were presented by the sponsor from a publication, earlier, I think it was Dr. Dart's slide 16 that referenced a publication, I wanted to just provide a little context for the record just to make sure that everybody on the committee is clear on FDA's view.

The product, OxyContin, that was discussed in the publication, is a different product than the product we're discussing today, so we did not plan

or arrange or have any presentations on that topic for this meeting.

We don't have any evidence at this point to understand whether different formulations containing different products, even if the strategy is similar, we have no clue whether they would behave the same in a postmarketing environment.

Last year, in 2015, we had announced through Federal Register notice, a meeting of this joint committee on July 7th and 8th, to discuss, actually, a supplement that was submitted by Purdue, to talk about postmarketing studies to evaluate the misuse and abuse of the OxyContin reformulated version.

This was based on a supplement that was submitted, as Dr. Hertz just described, by Purdue, for a labeling change. We subsequently announced on June 30th, that that meeting was cancelled because Purdue had chosen to withdraw the supplement to be able to complete additional analyses.

If you look at the publication on which

slide 16, the footnote, the publication by Dr. Coplan, et al, if you look at that publication, it states in that publication that the data were submitted to FDA.

While Purdue notes -- and these are, again, Purdue authors on the publication -- they note that they did submit the data to FDA, they also publicly noted that they withdrew a supplement that contained data that addressed the same issues as that publication. So that meeting was cancelled.

At the current time, we can't comment on the data because we don't have the submission in front of us. However, on the article, we are not commenting today because that's not really the focus of this meeting. As I've mentioned, I don't think it's directly relevant to this particular drug that we're discussing today.

However, we have publicly noted, and I know the committee has heard as recently as early May when we had the ER/LA REMS discussion, the use of existing data, the challenges in measuring and validating outcomes to be looking at any

intervention to try to change patterns of abuse.

There are many challenges, and you heard some of them in that meeting in May, and we've talked about them publicly in other settings as well. At this point, we do not have any labeling at this time. And we respectfully disagree with the conclusions of the authors of that publication that was cited today, in terms of how to best interpret those data, and we look forward to opportunities to continue to review and discuss those publicly in the future.

DR. BROWN: Thanks, Judy. Dr. Flick?

DR. FLICK: Could we put that statement back, Stephanie? So as I read this statement, it seems to me that we have to be a little bit cautious about expecting perfection and that being the enemy of good.

So the statement, it says reduce on the -- expected to reduce abuse via whatever route, which implies a comparison to something else. Obviously, in this case it's a comparison to existing products.

I think the sponsor has clearly demonstrated that this formulation is likely to reduce abuse via all three routes. I find that in the data that we spent the most time on is the Emax likability as Dr. Floyd pointed out, I think those data are difficult, at best, to interpret, and may not really inform the discussion very much.

If one stands back and takes a 30,000-foot level of this product, I think we can be relatively assured that it's going to reduce abuse via all three routes, at least in my view. Is it perfect? No. Is it close to perfect? That remains to be seen over time.

I do think that our discussions here point out the difficulty and the lack of -- or maybe I should say the need to standardize the approach, define what abuse deterrence is, define how one demonstrates abuse deterrence, and it may be something that the agency and industry can come together to do.

(The chairman temporarily leaves room.)

DR. BEGANSKY: Dr. Walsh?

DR. WALSH: Thank you. Sharon Walsh. I think that the data that were shown for the intranasal and intravenous routes are both strong datasets, and I feel pretty comfortable with that. I think the oral data are a little bit more challenging because while the sponsor met the predetermined endpoint for the primary outcome measure, the difference is small. And then the secondary endpoints weren't met, and then other ones worried about what does this endpoint mean, what is liking in the laboratory and what does that translate to?

For me, personally, it's a little bit of a mixed bag because one of the nice things in the oral data that's clear is that we get the delayed onset that Dr. de Wit talked about, and we know that that's also important.

I think as someone who does these types of studies and uses these types of measures in the laboratory, there is another way that we can think about it. When you do a study and you -- I'm going to go on a limb here -- when you do a study and you

look at different doses, you see that these subjective report measures really perform very well. So they're dose-related, they're time-related, they really capture the time-action curve with opiates. They perfectly map on usually to pupillary response that's an objective measure, things like that.

In this case, the sponsor designed the study the proper way, but what we don't have is we don't have other doses or anything to compare it to, and we don't have, for instance, another full opioid. Morphine tends to be less liked, to be honest with you, than a lot of the full mu opioid agonists by drug users.

But one other way that we can think this, points for those of you that aren't used to that is that at least in this dataset, within the same set of subjects, for a 60-milligram dose of morphine, they basically gave an increase in 23 points, and we can figure out what that is per milligram. These effects do produce dose-related, beautiful dose responses.

So that's about 2.6 points per milligram. And if you use that as a rough proxy, then what that means is that the product performed equivalently to something about 47 milligrams. So it reduced it by about 13 milligrams from the comparison dose.

Then, maybe that's something that, since most of you are physicians, can think, okay, so is there a meaningful difference between 60 milligrams and 47 milligrams roughly, and when we think about abuse on the street, is that going to be clinically meaningful?

DR. BROWN: Dr. de Wit?

DR. DE WIT: We have general comments and specific. In general, I agree with Dr. Flick that I feel we've gotten quite convincing evidence from the sponsor that by all of their various measures they've demonstrated a decreased abuse deterrence with this drug.

I think we're struggling with some of the specifics of the measures, but the measures of drug liking and subjective rating, those are the gold

standard for assessing abuse liability. That's how we determine abuse liability of any new substances, is exactly these measures and the time course of these measures.

So they're not just picked out of nowhere. That's our main measure of determining whether something's going to be abused. And they've done a good job demonstrating it with their time course data, and I think that the one thing I got hung up with was these retrospective reports of an overall rating of or whether they liked the drug or not.

But in general, I think they've put together quite a convincing story that their formulation will produce less likelihood of abuse than the primary drug.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: Since I deal primarily with adolescents and children, I just wanted to make a couple comments about this drug and that. A very high percentage of abuse, especially of prescription opioids, starts in adolescents. And even though this drug initially won't be labeled in

this population, these kids will still probably get it. And if this moves forward, I urge the company to move very quickly, and the FDA to move very quickly, in getting these abuse-deterrent formulations approved for adolescent patients.

I agree with the comments before that I think that this will decrease abuse in an adolescent population. Primarily, one on the alcohol-dumping thing I think is a big deal in adolescents. I think they figure out very quickly what drugs go well with other drugs, and I think that this drug will be less likely to be used as that.

Adolescents like very easy fixes to break the abuse-deterrent features. OxyContin used to be chewed and swallowed, and I think this would help prevent that. And I think crossing the line between crushing and snorting a drug really does increase future likelihood of abuse.

In fact, if somebody snorted or abused a drug, I think about 70 percent of those patients at any time in their life are likely to have abused an

opioid over the course of their lifetime. That feature and making it very difficult to crush and snort I think is a very important thing. So I think it really meets criteria on all three. Thanks.

DR. BROWN: Mr. O'Brien?

MR. O'BRIEN: From my perspective when I looked at it -- you know, we've said over and over again, we've got 76 people a day that are dying. We have a crisis with opioids. As I looked at this though, for those 76 per day, if we look at that funnel that was on slide 5, as we talked about the 76 to the nth power, that is falling down that slide as we go through it. So I look at it from that perspective.

It seems to me, I was very impressed actually. In terms of looking, the question said sufficient data. It appeared to me as a non-expert, but from a patient perspective as I looked it and being very concerned about the patient community that takes these, I said, yes, there is sufficient data to say that this will help

the problem.

Research is also about innovation, and innovation is does it move the pebble forward? This, to me, seemed to be moving the pebble forward. I don't see it as moving the bar down. I see it just the opposite. I think this is moving the bar up from where are right now because we are in a crisis imperfect world at the moment, and I think that's the situation to which we have to make the decisions about this.

Sufficient seems to be fine for me. I think when I get to wording that says expected, expected is a little bit more definitive. It's reasonably expected is what it seems to me. If I looked at that as the criteria, is it reasonably expected that we'll help the problem both in terms of the death level, at the 76, I believe, yes, it will, for a number of reasons here, with the nasal, and with the others.

Even in the oral as I look at it, I think that specifically will help in the top of that funnel. I think it will help to deter some of

those novices that are getting it, and following it down at the adolescent level that was just mentioned, and in the adult level, I think it will begin to stop them from progressing to that level, so they won't be the problems of the future.

So from my perspective, I walk away and say, yes, I think all three levels have been met.

DR. BROWN: Dr. Beardsley?

DR. BEARDSLEY: In regards to the oral route, I had a bit of a conflict. On one hand, I didn't think that there was a meaningful difference when you looked at the comparison between Arymo and MS Contin crushed; that is, I should say, Arymo manipulated versus MS Contin crushed. I wasn't convinced that there was a meaningful difference there.

But one comparison that really wasn't discussed too much and that was between Arymo intact versus MS Contin crushed, because functionally, I think that is a meaningful comparison. If you think about a patient, if he's unable to crush the drug, that's one vector leading

to more dangerous forms of abuse if he's unable to chew the drug.

If you compare Arymo intact versus MS Contin crushed, again, I think that's a meaningful comparison. There the differences are more dramatic. So that softened my initial negative feeling about the meaningful deterrents that this product offered regarding the MS Contin.

Then in regards to the nasal and intravenous studies, I was convinced on the data presented that the product would provide deterrence. I was unconvinced that the methods of pulverizing the drug was the most effective.

I spent probably no more than 30 minutes in preparation for this meeting, surfing the drug user websites, trying to find out what tools they use. One tool that came up was these handheld Dremel rotary tools with a grinding bit. In fact it was linked out to a YouTube video in which someone was using just a common electric drill with a grinding bit, grinding down OxyContin OP to what appeared to be a very fine powder.

I think that just emphasizes that there has to be some -- what has been said repeatedly, it has to be some kind of standardization for tool manipulation of these products.

So my take of the data presented, I was convinced that there would be deterrence regarding nasal and intravenous routes of administration. I still am a little bit of in conflict with oral. I think it will provide some deterrence, but not given the major contrast that is presented between Arymo manipulated versus MS Contin crushed.

DR. DAYNO: Dr. Brown, if I may just clarify.

DR. BROWN: Yes.

DR. DAYNO: Thank you. In terms of the tool that you mentioned, that was tried in the original battery of 25 tools on Arymo, and the tool was not effective, and there was actually tool failure with that when attempted to reduce the particle size of Arymo. That, along with the difficulty of chewing, led us to the optimal manipulation that we used in the study, but that tool was part of the original

screen that you identified.

DR. BEARDSLEY: A Dremel grinding tool was? That's very surprising, because we use these to grind steel.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: I wanted to comment on the discussion about oral abuse, and I think the oral abuse is a really heterogeneous category, and it probably doesn't make sense to talk about it or think about it as one thing. It's really three parts. It's taking too much of the intact drug, which this formulation and really no formulation will be able to address.

There's second, chewing, and we saw data from the RADARS system suggesting this is the most common form of manipulation that patients engage in when abusing the drug orally. Here, I think the drug really does make significant advancements over MS Contin by its hardness and is likely to be difficult or impossible to chew.

Then there's the third category, where we've been spending most of our time, oral ingestion

following physical manipulation, and I think here the data are less clear. But the heterogeneity of the category may be something that the FDA wants to reflect in the label. I'd be very comfortable saying this is likely to deter chewing; perhaps less comfortable with reducing oral ingestion following physical manipulation.

DR. BROWN: Dr. Farrar?

DR. FARRAR: As I listen to the very interesting discussion today, I'm reminded of the fact that no single issue is ever going to fix the problem that we have. The piece that we're trying to deal with today is actually a relatively small one; not unimportant, but small.

Certainly in terms of the early experience that young people have with these drugs, they're very often drugs given in prescription for a tooth extraction or other reasons, a small amount of the immediate-release drug that stimulates a latent genetically predisposition to addiction or to addiction personality.

There are obviously experiments or places

where people can get access to these, and the need to reduce the amount of available opioid in grandma's closet or in your mother's closet or your friend's closet is going to be paramount to fixing that problem.

It seems to me that what we're really trying to address here is whether this drug will improve the overall safety if it is obtained by people for whom it's not prescribed, and it builds a little bit on what Dr. Bateman was just saying and what others have said as well.

In that category, though, I think there are two important parts. One of them is the one that we were just discussing. Could somebody who really is an abuser and wants to go online and figure out how to get the biggest bang for their buck, come up with a way to improve the availability of the drug?

I would argue that that's going to occur with every potentially abusable drug. If they haven't figured it out yet, they probably will in the future.

But the argument that was just made by

Dr. Bateman, which is that not being able to chew it, does get at a subset of the population, and these terrible deaths where a relatively opiate-naïve person gets given an OxyContin or an MS Contin pill and said, here, take this. And then they chew it and get that very rapid pharmacokinetic release of the medication, and then suffer a substantial morbidity and often mortality.

My own view of it is that if we can prevent even a few of those kinds of deaths, that we're doing something reasonable. Does it mean that the person wouldn't put it into a bottle of something that might be a solvent that will, over the course of an hour, extract all of that and then drink it down? No, it probably can't prevent that in all cases, but that's an act that takes time and effort and intent.

My view of this is that the evidence presented is that this is a drug that is substantially safer than the standard MS Contin or OxyContin in all of these categories, including oral, with the understanding that perhaps the

language of the approval, or the language in the label, might need to reflect some of those differences.

DR. BROWN: Dr. Flick, and then I'd like to summarize our discussions.

DR. FLICK: Well I was going to make almost exactly the same comments as Dr. Farrar. I think that we spent a lot of time talking about the 76 deaths that will occur today. Many of those deaths are in a relatively opiate-naïve patient, often young people, as Dr. Galinkin pointed out.

Those are the folks that we are most likely to benefit with these kinds of formulations. The determined abuser is determined, and we are not likely to be able to deter them with this formulation or any other. But it's those other abusers, casual abusers, or first-time abusers, who are likely to be sufficiently deterred by this to the point that they may move to something that is less likely to end their lives.

I completely agree with Dr. Farrar that the sponsor has done, I think, a good job, and

Dr. de Wit has said the same thing, that the sponsor I think has done a more than adequate job of demonstrating that this formulation is likely to achieve the desired outcome, and that's deterring abuse, not in all, but in some or even most.

DR. BROWN: So as the former chair, Dr. Flick just did almost most half of my work for me, relating to coming together with a statement about what I believe that the committee has said.

First, the committee I think agrees that the drug was tested well in a collaboration with the FDA. With that being said, some of the definitions of success were based on incorrect analysis or analysis against generic medications and not for new drugs. I'm not certain that that was all-important.

The implications for the use with alcohol are important with this drug, as Dr. Galinkin said, and the lack of this drug being interactive with a patient that is taking alcohol is quite important.

Perhaps the most important part of the analysis of this drug was the phase 1 studies

indicating the true hardness and the difficulty in reducing particle size. The hardness was created through the manufacturing process, and really the sponsor gave us good information that seemed to indicate that the particle size could not be small enough for inhalation, that is smoking or snorting.

The small-volume extraction showed limited removal of morphine for injection. Large-volume extraction studies, however, are a little bit less clear. They did reveal the possibility of removal of relatively large amounts of morphine from the manufactured entity.

The drug liking studies and the reduction in likelihood of using the drug by the oral route was quite unclear to many members of the group, and I think people were all over the board about that. I'm not certain that I can determine right now, in my own mind, whether there was a difference in these studies.

I also cannot determine whether the difference in the laboratory analysis of this drug and the phase 3 studies is clinically important.

My guess is that we will only know that after epidemiologic studies if this drug is marketed.

So it appears that there's some thought that the intranasal and intravenous abuse would be substantially reduced. It's a little less clear for oral use, although the use of the drug for chewing seems almost impossible, according to the data that the folks from Egalet presented to us. The users can take more pills. There are again problems with the phase 3 testing, which were more specific to oral use of this drug.

To just follow-up and say once again, those phase 3 studies were at some odds with certain of the laboratory analysis.

Is there general agreement that that's what has been discussed?

(No response.)

DR. BROWN: All right. Why don't we take about a 10-minute break and come back at about 20 minutes until 4:00 and get on with our voting.

(Whereupon, at 3:27 p.m., a recess was taken.)

DR. BROWN: The voting questions that we have, if we could put the first question up. We have discussed many of these already. The question number 2 for vote of the committee, if approved should Arymo ER be labeled as an abuse-deterrent product by the oral route of abuse?

Are there any issues with the wording of the question?

(No response.)

DR. BROWN: And are there any -- we're open for questions and discussion.

(No response.)

DR. BROWN: If there are not any questions or discussion, we're going to be voting electronically. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash.

If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote was 16 yes, 3 no, zero abstain.

DR. BROWN: Everyone has voted. The vote is now complete. Now that the vote is complete, we'll go around the table and everyone who voted state their name, vote, and if you want to you can state the reason why you voted as you did into the record.

I'm going to start with Warren, Dr. Bilker.

DR. BILKER: I voted yes. I thought that there was sufficient evidence that Arymo is reasonably expected to reduce the abuse rate via the oral route.

DR. FLICK: Randall Flick. I voted yes.

DR. WESSELMANN: Ursula Wesselmann. I voted yes for the same reason that Dr. Bilker stated.

DR. BATEMAN: Brian Bateman. I voted yes because I think there's clear -- data suggests that it will at least deter one of the most common forms of oral abuse, that of chewing.

DR. CRAIG: Dave Craig. I voted yes. Just

looking at the data, it's not perfect, but I think in a real world situation I think it would have some impact. I think the evidence is enough for me to say yes.

DR. GALINKIN: This is Jeff Galinkin. I voted yes. I think it would decrease the incidence based on chewing not causing an increased concentration, and then also the oral dumping phenomenon.

DR. GUPTA: Anita Gupta. I voted yes.

DR. EMALA: Charles Emala. I voted no for the reasons I stated earlier. I think the drug's rapidly extractable in an ingestible volume solvent making it easy to abuse by the oral route. And I think the Category 3 studies were unconvincing.

DR. BROWN: Rae Brown. I voted yes.

DR. GERHARD: Tobias Gerhard. I voted no. This was a close decision for me. I see the advantages of the product. I believe it should be approved and will vote for that. I think the benefit that it's not chewable is significant. However, I think putting that claim of oral abuse

deterrents on the label might do a disservice because I think there's significant potential that it might lower the bar to prescribe a long-acting opiate. And I think we have some issues with the effectiveness of long-acting chronic opiate use.

Generally, the best way to reduce the number of problems with opiate addiction is probably to reduce the number of opiate prescriptions in the first place, although recognizing obviously that there's a great need for opiates and pain treatment. Nonetheless, I think that the public health might be better served if that claim isn't on the label.

DR. FARRAR: John Farrar. I voted yes for the reasons stated earlier, that the prevention of chewing is an important contribution.

DR. NOVAK: This is Scott Novak. I voted yes. I think that the sponsor did a really exemplary job of presenting some very well thought out studies. And I also think that the opiate crisis is largely driven not by oral abuse, at least by the crisis. I mean, the consequences,

overdoses, and deaths, I think they're directly attributable to injection and tampering. I think the product will go a long way toward that.

DR. FLOYD: James Floyd. I voted yes, but it's a very qualified yes for the same reasons that Dr. Gerhard voted a qualified no. I think the language in the proposed label is too strong.

I think "expected to deter oral abuse" should be replaced with, "has properties that may reduce misuse or abuse from chewing." I think "oral" also is too broad. I think it needs to -- the label needs to represent actually the evidence that we were presented today.

MR. O'BRIEN: Joe O'Brien, and I voted yes. I believe both the chewing and the alcohol reduction are very important, significant items for future abuses, as well as current abuses. And I do think that there has to be better definition in a label clearly spelling out what the reasonable expectation is.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. WALSH: Sharon Walsh. I voted yes, although I was somewhat on the fence, and I wouldn't use a 5-point reduction in the future as the gold standard that we want to meet. But I think that the totality of the evidence and the delay in time to reach maximum effect, and the point that Dr. Beardsley brought up earlier about the comparison with chewing for the currently available one, is pretty convincing.

DR. ARFKEN: I'm Cynthia Arfken. I voted no, and it's because the category of oral abuse is too broad for me. If it had been for chewing, I would have voted yes.

DR. DE WIT: Harriet de Wit. I voted yes.

DR. BEARDSLEY: Patrick Beardsley. I voted yes. I thought one vector of oral abuse would be blunted by this compound.

DR. BROWN: We're going to move ahead to question number 3, which will be a question for a vote. If approved, should Arymo ER be labeled as an abuse-deterrent product by the nasal route of abuse? Are there any questions from the committee

about issues relating to the wording of the question?

(No response.)

DR. BROWN: If there are not, are there questions or comments concerning the substance of the question?

(No response.)

DR. BROWN: If not, we will move ahead to voting on this question. If approved, should Arymo ER be labeled as an abuse-deterrent product by the nasal route of abuse? Please press the button on your microphone that corresponds to your vote.

(Vote taken.)

DR. BEGANSKY: The vote was 18 yes, 1 no, zero abstain.

DR. BROWN: The vote is complete. We're going to go around the table and have everyone who voted state their name, vote, and if you want to you can state the reason why you voted as you did into the record again.

DR. BILKER: This is Warren Bilker. I voted yes. I felt that there was strong evidence shown

that Arymo is expected to reduce the abuse rate via the nasal route.

DR. FLICK: Randall Flick. I voted yes.

DR. WESSELMANN: Ursula Wesselmann. I voted yes.

DR. BATEMAN: Brian Bateman. I voted yes on the basis of the challenges of physically manipulating the drug to create a form that's able to be ingested nasally, as well as the human abuse potential studies.

DR. CRAIG: Dave Craig. I voted yes.

DR. GALINKIN: Jeff Galinkin. I voted yes.

DR. GUPTA: Anita Gupta. I voted no, primarily because of the large-volume studies. I mean essentially a solution was created in large volume that was greater than 60 percent in some household solvents, at least from the data that I saw. So I just wasn't comfortable stating that it was okay for nasal use based on that.

DR. EMALA: Charles Emala. I voted yes.

DR. BROWN: Rae Brown. I voted yes.

DR. GERHARD: Tobias Gerhard. I voted yes.

DR. FARRAR: John Farrar. I voted yes.

DR. NOVAK: Scott Novak. Yes.

DR. FLOYD: James Floyd. Yes, but again with suggested labeling change from "expected to deter abuse" to has properties that may reduce misuse and abuse intra-nasally or something like that.

MR. O'BRIEN: Joe O'Brien. I voted yes.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. WALSH: Sharon Walsh. I voted yes.

DR. ARFKEN: Cynthia Arfken. I voted yes.

DR. DE WIT: Harriet de Wit. I voted yes.

DR. BEARDSLEY: Patrick Beardsley. I voted yes.

DR. BROWN: We're going to move ahead to question number 4, which is a voting question. If approved, should Arymo ER be labeled as an abuse-deterrent product by the intravenous route of abuse?

First, are there any issues or questions about the wording of this particular question?

(No response.)

DR. BROWN: If not, are there any questions or comments concerning the substance of the question?

(No response.)

DR. BROWN: If there are not, we'll move ahead to a vote on this question. If approved, should Arymo ER be labeled as an abuse-deterrent product by the intravenous route of abuse?

Please press the button on your microphone that corresponds to your vote.

(Vote taken.)

DR. BEGANSKY: The vote was 18 yes, 1 no, zero abstain.

DR. BROWN: Maybe we can start at the other end of the table this time.

DR. BEARDSLEY: Patrick Beardsley. I voted yes.

DR. DE WIT: Harriet de Wit. I voted yes.

DR. ARFKEN: Cynthia Arfken. I voted yes.

DR. WALSH: Sharon Walsh. I voted yes.

DR. HIGGINS: Jennifer Higgins. I voted

yes.

MR. O'BRIEN: Joe O'Brien. I voted yes.

DR. FLOYD: James Floyd. I voted yes, again with a suggested label change. Suggested remove expected to deter intravenous abuse and replace that with has properties that may reduce misuse and abuse from intravenous use.

DR. NOVAK: Scott Novak. Voted yes.

DR. FARRAR: John Farrar. Voted yes.

DR. GERHARD: Tobias Gerhard. I voted yes.

DR. BROWN: Rae Brown. I voted yes.

DR. EMALA: Charles Emala. I voted yes.

DR. GUPTA: Anita Gupta. I voted no for the same reasons as stated before.

DR. GALINKIN: Jeff Galinkin. I voted yes.

DR. CRAIG: Dave Craig. I voted yes.

DR. BATEMAN: Brian Bateman. I voted yes.

DR. WESSELMANN: Ursula Wesselmann. I voted yes.

DR. FLICK: Randall Flick. I voted yes. And I think Dr. Floyd's suggestions are good ones.

DR. BILKER: Warren Bilker. I voted yes.

DR. BROWN: Let's move ahead to question number 5, and this is a voting question. Should Arymo ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate?

Are there any issues or questions about the wording of this question?

(No response.)

DR. BROWN: Are there any questions or comments concerning the substance of this question? Yes?

DR. DE WIT: I have one question. We haven't spoken at all about postmarketing surveillance. Is that part of the approval process or is that something separate?

DR. HERTZ: Yes, and thank you for that question. We will be asking for postmarketing studies. There are 11. The first 10 are a variety of studies, epidemiologic work. Wait, wait.

(Dr. Staffa nods in the affirmative.)

DR. HERTZ: Sorry. That's true, but not relevant. There's another set of - there are going to be several sets of postmarketing requirements. There will be postmarketing requirements to study the abuse-deterrent effects, and that's four, three or four studies.

Then this product would also be part of the extended release long-acting opioid analgesic REMS. That group has 11 postmarketing requirements to study a variety of safety issues associated with opioids. So sorry. That was where the 11 came from.

DR. DE WIT: So if we're voting for approval for the proposed indication, that's taking into account some postmarketing data that they're going to collect and some vigilance by the FDA, and we don't need to review that?

DR. HERTZ: We have done a fair bit of work on that, so we're not asking to reopen it again. After the meeting, we can certainly share them with you if you want to comment on them, send any of your thoughts to us. They're in the backgrounder.

Okay. So if you want to provide any additional comments on that, you're welcome to.

DR. BROWN: But being subject to the opioid REMS includes postmarketing -- very robust postmarketing studies for each of these drugs, is my understanding. Is that true?

DR. STAFFA: Right. This is Judy Staffa. As Sharon mentioned, there is product-specific postmarketing required studies, which are specific to evaluating during this postmarketing phase of the abuse-deterrent formulation evaluation. So we have guidance that we provide the companies, and then they send in their protocols, and they don't proceed with the studies until we approve them. So there's negotiations and iteration that goes on with that.

In addition, there are class-wide studies to answer broader questions about the safety in general that are not specific to any product, but they're about ER/LA opioids in general, and they will be also subject to those. And the companies have come together in a consortium to work on those

studies as a group, and it's the same group that also then administers the ER/LA REMS, which is the prescriber education programs.

DR. BROWN: Are there any other comments or questions concerning this particular voting question? Yes, Sir?

DR. BEARDSLEY: I just want confirmation. This is the exact language that MS Contin would be approved for?

DR. HERTZ: Do you mean the indication?

DR. BEARDSLEY: Yes.

DR. HERTZ: Yes, the same indication. It's a standard indication across the ER/LA opioids, including MS Contin.

DR. BEARDSLEY: So basically the same language.

DR. BROWN: Any other questions or comments?

(No response.)

DR. BROWN: If not, we're going to move ahead with a vote on question 5. Should Arymo ER be approved for the proposed indication, management of pain severe enough to require daily,

around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate?

Please press the button on your microphone that corresponds to your vote.

DR. BEGANSKY: The vote was 18 yes, 1 no, zero abstain.

DR. BROWN: The vote is complete. We're now going to start with Dr. Bilker again and go around the table.

DR. BILKER: Warren Bilker. I voted yes.

DR. FLICK: Randall Flick. I voted yes, although somewhat reluctantly. At some point the agency and the committee is going to have to address the question of whether these drugs have an indication at all. And unfortunately, we're probably in a position that the lesser of two evils is to approve this drug.

DR. WESSELMANN: Ursula Wesselmann. I voted yes.

DR. BRIAN BATEMAN: Brian Bateman. I voted yes.

DR. CRAIG: Dave Craig. I voted yes.

DR. GALINKIN: Jeff Galinkin. I voted yes.

DR. GUPTA: Dr. Anita Gupta. I voted no. I was on the fence. The question about long-term opioid efficacy remains to be answered, and so it was a little bit difficult for me to answer that question. But in addition, I do see that there is a definite need for innovation and advances, and I am happy to see the advances that the sponsor put forward.

But I did feel that there was more information that was necessary on the large solvents specifically. I wasn't comfortable with the greater than 60 percent release of the drug, and potential for abuse there. But again, I was on the fence for the decision.

DR. EMALA: Charles Emala. I voted yes.

DR. BROWN: Rae Brown. I voted yes. Since all the voting is over, I'm going to take this opportunity to make a statement about my thoughts relating to this drug.

There are six million scripts a year for

long-acting morphine, and right now we're not doing a very good job of reducing that number. There are a limited number of ways to intervene in the current crisis of which it appears that long-acting morphine is playing quite a role.

I think that the replacement of long-acting morphine with this drug, or other drugs like it, will be a step forward. I agree with Dr. Flick that we can't ask for perfection when we're just trying to drive for good.

I'd also like to say that the group from Egalet has done an excellent job in presenting their product, and I really appreciate their doing that.

DR. GERHARD: Tobias Gerhard. I voted yes. I wholeheartedly second Dr. Flick's comments, which were exactly what I wanted to say but probably wouldn't have been able to say as eloquently anyway. So thank you very much, and I completely agree.

One comment that I want to make also since we've commented a little bit on language in the

label. I think particularly in the context of abuse-deterrent labeling, it's important I think to have some language in the label that points out that there is a risk of addiction to opioids without active abuse, that that doesn't get kind of lost or becomes unclear to patients.

DR. HERTZ: We have that in the box.

DR. GERHARD: Great.

DR. HERTZ: So we'll look for it if you want to see it, but we do have it.

DR. FARRAR: This is John Farrar. I voted yes. I wanted to take the opportunity, as somebody who practices primarily palliative care, that there's absolutely no question about the benefit of long-term use of opioids in certain populations, and the need for them in those populations.

That being said, I cannot agree more with the concept of the need for studies in non-chronic -- in non-palliative opioid use longer term where the potential for side effects and other things can be substantially worse.

DR. NOVAK: This is Scott Novak, and I voted

yes. I'd also like to remind the sponsor that their fiduciary responsibility to public health doesn't necessarily end here but it rather begins. I hope that they will remain vigilant and continue to seek the wisdom of outside counsel and experts who know a lot about the area to sort of guide you along the way in your product release.

DR. FLOYD: James Floyd. I voted yes, reluctantly. I strongly agree with Dr. Flick's comment. And I voted yes only because this is a bioequivalent and the other drug has an indication already.

MR. O'BRIEN: Joe O'Brien. I voted yes. I certainly agree with Dr. Flick and others' comments about no indication. But on the other hand, being a patient myself who has required, and who represents and knows many patients who need it at the time, that's all we have at the moment. It's the best what we have. We welcome other options that are equivalent to that. But when you need it, you need it.

From my perspective, the yes is saying that

this is a product that's not -- and being sensitive to what was said in one of the public speakers, that I don't see this as adding to. I think it's replacing what we currently have and making something better than what we currently have, and I think that's a good thing.

DR. HIGGINS: Jennifer Higgins. I voted yes. I have to say that I was really swayed a lot by what the FDA had presented regarding the most frequently prescribed ER/LA being morphine. I really feel like we need increased patient access to safer medications, and I am hopeful that this is one method of doing that.

DR. WALSH: I'm Sharon Walsh, and I voted yes.

DR. ARFKEN: Cynthia Arfken, and I voted yes.

DR. DE WIT: Harriet de Wit. I voted yes.

DR. BEARDSLEY: Patrick Beardsley, and I voted yes.

DR. BROWN: Before we adjourn, can we just take a 15-minute break? That was a joke, okay?

(Laughter.)

DR. BROWN: Before we adjourn, are there any last comments from the FDA?

DR. HERTZ: I know I've been thanking you a lot today, but I feel like we need to because of the frequency that we're calling upon you and the often surprising help and advice that you've delivered. It's nice not to be able to predict an outcome. It just shows how helpful in fact these meetings can be, and safe travels home for you.

Adjournment

DR. BROWN: Panel members, please take all your personal belongings with you as the room is cleaned at the end of the day. All materials left on the table will be disposed of. Please also remember to drop off your name badge.

We will now adjourn the meeting. Thank you very much.

(Whereupon, at 4:05 p.m., the meeting was adjourned.)