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 AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Wednesday, January 15, 2020

1:30 p.m. to 5:05 p.m.

Afternoon Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:30 p.m.)

Call to Order

Introduction of Committee

DR. LITMAN: Good afternoon. My name is Ron Litman, and I'm going to be chairing this afternoon's meeting. I would first like to remind everybody to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd like to also identify the FDA press contact. Nathan Arnold.

Nathan, if you're here, can you stand up and identify yourself? Thank you.

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 introducing ourselves. We'll start with the FDA to my left and go around the table. When you introduce yourself, can you please state your expertise?

DR. STAFFA: Good afternoon. I'm Judy

Staffa. I'm the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology in the Center for Drugs.

DR. ROCA: Hello. My name is Rigo Roca. I'm the acting director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

DR. LOWY: Hi. I'm Naomi Lowy. I'm acting deputy director of the same division.

DR. KILGORE: Good afternoon. My name is Elizabeth Kilgore, medical officer in DAAP.

DR. TOLLIVER: My name is James Tolliver. I'm a pharmacologist within the controlled substance staff within the FDA.

MS. SHAW PHILLIPS: Hi. Marjorie Shaw Phillips, pharmacist and med-use safety; area of expertise, I'm a clinical research pharmacy coordinator at AU Medical Center, Augusta University, and a clinical professor of pharmacy practice, University of Georgia College of Pharmacy.

DR. GARCIA-BUNUEL: Good afternoon. Martin

Garcia-Bunuel. I'm a primary care physician and the deputy chief of staff of the VA Maryland Health Care System.

DR. GREEN: Traci Green. I'm an epidemiologist, and I'm a professor and director at the Opioid Policy Research Collaborative at the Institute for Behavorial Health, at The Heller School for Social Policy and Management, at Brandeis.

DR. HOFFER: Lee Hoffer. I'm an associate professor of medical anthropology and psychiatry at Case Western Reserve University in Cleveland, Ohio.

DR. MICHNA: Ed Michna, anesthesia and pain management, Brigham and Women's Hospital, Boston.

DR. SETOGUCHI: Soko Setoguchi, general internist and pharmacoepidemiologist from Robert Wood Johnson Medical School.

DR. McCANN: Mary Ellen McCann. I'm an associate professor of anesthesiology at Harvard Medical School and a pediatric anesthesiologist at Boston Children's Hospital.

DR. ZACHAROFF: Good afternoon. I'm Kevin

Zacharoff. My expertise is in anesthesiology and pain medicine. I am a faculty and clinical instructor and course director of pain and addiction at the Stony Brook School of Medicine in Stony Brook, New York.

DR. McAULIFFE: I'm Maura McAuliffe. I'm a professor of nursing, director of the Nurse Anesthesia Program at East Carolina University, Greenville, North Carolina.

DR. ZELTZER: Hi. I'm Lonnie Zeltzer, distinguished professor of pediatrics, anesthesiology, and psychiatry, University of California Los Angeles and director of Pediatric Pain and Palliative Care.

DR. GOUDRA: Hi. I'm Basavana Goudra, associate professor of anesthesiology in Penn medicine, Philadelphia.

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

DR. LITMAN: Ron Litman, anesthesiologist at the University of Pennsylvania, Children's Hospital Philadelphia. I'm also the medical director of the

Institute for Safe Medication Practices.

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

DR. SHOBEN: Abby Shoben. I'm a biostatistician at Ohio State.

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

DR. HIGGINS: Jennifer Higgins, consumer representative to AADPAC. My background is in gerontology and clinical trials in neurology.

MS. ROBOTTI: Suzanne Robotti, executive director of MedShadow Foundation and executive director of DES Action USA.

DR. BLOCK: Laura Block. I'm a patient representative, but I'm also a pharmacist and a partner with Usagi Medical Group.

DR. AMIRSHAHI: Maryann Amirshahi. I'm associate professor of emergency medicine at Georgetown University. I practice in the D.C. area at MedStar Health, and my specialties are emergency

medicine, medical toxicology, addiction medicine, and clinical pharmacology.

DR. PISARIK: Paul Pisarik, urgent care physician, Saint Francis Health System, Tulsa, Oklahoma.

DR. SANDBRINK: I'm Friedhelm Sandbrink. I'm a clinical associate professor of neurology at Uniformed Services University in Bethesda. I'm the director of pain management at the Washington, D.C. VA Medical Center, and I'm the national program director for pain management for the Veterans Health Administration.

DR. ZAAFRAN: Sherif Zaafran. I'm an anesthesiologist in Houston, the Acute and Chronic Care Committee for the Memorial Hermann Healthcare System, and vice chair of the Clinical Governance Board for US Anesthesia Partners.

DR. SUAREZ-ALMAZOR: Good afternoon. Maria Suarez-Almazor. I'm a rheumatologist and clinical epidemiologist. I'm a professor at the University of Texas MD Anderson Cancer Center.

DR. SULLIVAN: Patrick Sullivan. I'm an

infectious disease epidemiologist professor of epidemiology at Emory University.

DR. MARSHALL: Brandon Marshall. I'm an epidemiologist and associate professor at the Brown School of Public Health in Providence, Rhode Island.

DR. TYLER: I'm Linda Tyler. I'm the chief pharmacy officer for University of Utah Health and associate dean in the College of Pharmacy. I have a background in drug information practice and medication safety.

DR. MEHTA: Hi. Reema Mehta serving as the industry representative for the Drug Safety and Risk Management Advisory Committee and currently work at Pfizer as the head of Risk Management and Safety Surveillance Research.

DR. HORROW: Good afternoon. I'm Jay Horrow. I'm an anesthesiologist. I'm the industry representative to the AADP Advisory Committee. I'm a clinical trial lead for cardiovascular medicines at Bristol-Myers Squibb.

DR. LITMAN: Thanks, everybody.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the 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.

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

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of 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 interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to discussions of today's afternoon 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 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.

The afternoon session of today's agenda involves discussion of new drug application, NDA 209653, for an extended-release oral tablet formulation of oxycodone, submitted by Intellipharmaceutics Corporation, with the management of moderate-to-severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product. The committees will be asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that will support labeling, as well as to discuss the overall risk-benefit profile of the product.

This is a particular matters meeting during which specific matters of Intellipharmaceutics' NDA will be discussed. Based on the agenda for today's

afternoon 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. Jay Horrow and Reema Mehta are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Drs. Horrow's and Mehta's role at this meeting is to represent industry in general and not any particular company. Dr. Horrow is employed by Bristol-Myers Squibb and Dr. Mehta is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. LITMAN: Thanks, Moon. We will now proceed with the FDA's introductory remarks from Dr. Rigoberto Roca.

FDA Opening Remarks - Rigoberto Roca

DR. ROCA: Good afternoon. Mr. Chairman, members of the committee, invited guests, welcome. My name is Rigo Roca. I'm acting division director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine. As was just mentioned, we're going to be discussing Aximris, which is an extended-release formulation, and the indication was read by Dr. Choi, so I will not repeat it.

As was mentioned in the background package, this application actually came before this

committee back in 2017, and at that time, several deficiencies were identified, primarily in the description of the abuse deterrent formulation properties as well as certain excipients. During today's meeting, the results of the applicant's in vitro physical and chemical manipulation studies from both NDA review cycles will be presented, as well as the newly submitted human abuse potential studies assessing abuse potential by the oral and nasal route.

With respect to the agenda, after the presentation by the company, we'll be having a presentation by the division and several members of the division of epidemiology. There will be four presentations. The first one will be by Dr. Daubresse from the Division of Epidemiology, who will speak to the use, misuse, abuse, and deaths involving oxycodone and other opiates in the United States; followed by a presentation by Dr. D'Agostino, who is a pharmacotoxicology reviewer within my division, who will speak to the nonclinical safety assessments of Aximris' XR

excipients.

After that, Dr. Tolliver from the controlled substance staff will speak to the agency's interpretation of in vitro and human abuse potential studies; and lastly Dr. Kilgore, a medical officer in my division, will be speaking with respect to the clinical summary of Aximris' application.

As has been done before, as you listen to the presentation and you ask your clarification questions, there are a couple of things that we would like you to keep in mind, and perhaps we can pull up the first slide, which is discussion point 1. I will not read it, but just basically, from a very high level, one of the things that we would like you to consider is whether the applicant has demonstrated that their product has properties to be expected to deter abuse by the following routes that are noted: intravenous, intranasal, and oral. By the way, there will be four discussion points and one voting.

The second point will be for you to discuss

the implications of approval of the product that can be expected to deter abuse by a single route, and particularly to discuss whether this product is expected to deter abuse by the intravenous route.

The third point is to take into consideration the potential effect of abuse of this product, as well as potential consequences from the administration of this product by unintended routes. Then as we've been doing previously, when you consider all these points, to discuss whether the benefits outweigh the risks for the proposed indication, and similarly discuss any additional data that you feel are needed for the application to be approved.

That will be culminated with a voting question, which is at the end, and as you have done previously, whether you recommend approval for this particular product for the indication that's listed on the next slide. Thank you, and we look forward to a very productive meeting.

DR. LITMAN: Thanks, Dr. Roca.

Both the Food and Drug Administration and

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

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

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

We will now proceed with

Intellipharmaceutics Corporations' presentation.

Applicant Presentation - Isa Odidi

DR. ODIDI: Good afternoon. My name is Dr. Isa Odidi, and I'm the CEO and co-chief scientific officer of Intellipharmaceutics. I'd like to thank the FDA and the committee for allowing us to present our data today. We're here to discuss our NDA for oxycodone extended-release tablets that uses physical and chemical barriers and [indiscernible] technologies to discourage abuse. For this presentation, we will refer to our product as Aximris XR. Aximris XR is an opioid agonist indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Why do we need more abuse-deterrent formulation options? 1) the current products have not eliminated intravenous abuse of extended-release oxycodone; 2) intravenous drug abuse or drug use pose additional risks for serious health consequences; 3) improved ADF options are

needed to address vulnerabilities in easily abusable products; 4) a development of products with incremental improvement in opioid-abuse deterrence was anticipated in the FDA guidance.

Aximris XR, which you are about to hear of today, is an example of such development efforts. I shall now share with you data from respected sources showing that injection-used opioid abuse remains a problem.

Records from poison centers indicate that injection was involved in 15 to 20 percent of the fetal opioid abuse cases, so we can say that injection remains a substantial problem among the prescription opioid. We see the same result in epidemiology data from various poison center programs.

The proportion of respondents indicate the injected OxyContin decreased, but about 15 to 20 percent of the cases continue to involve injection. An improved ADF that can potentially address these vulnerabilities and improve upon these statistics is a good thing.

Aximris XR was developed to address the gaps in IV abused deterrence. Aximris XR represents over a decade of didactic research and development work involving comprehensive in vitro and clinical studies. We have filed an NDA for Aximris XR under the 505(b)(2) drug approval pathway using OxyContin as the listed drug and comparator. The proposed dose strengths range from 10 milligrams to 80 milligrams and are the same as OxyContin.

The development program for Aximris XR followed FDA guidance with the FDA providing significant input. We carried out extensive in vitro physical and chemical manipulation studies to evaluate abuse potential of Aximris XR compared to OxyContin with respect to IV abuse.

Next, clinical pharmacokinetic studies to demonstrate bioequivalence of Aximris to OxyContin and establish a bridge to OxyContin safety and efficacy data were conducted. We also carried out pharmacokinetic and pharmacodynamic studies to assess the human abuse potential of Aximris XR compared to OxyContin via the oral and intranasal

routes of abuse. Finally, we evaluated the potential safety risk of IV injection of syringeable material from ground Aximris XR.

Aximris XR and OxyContin have some similar characteristics, but Aximris XR has additional features intended to provide incremental improvement in the abuse deterrence of OxyContin. Both products offer resistance to physical manipulation and chemical extraction, and both form a viscous material on contact liquid to resist the preparation using standard methods, volumes abusers commonly used for IV injection. However, Aximris XR also displays greater hyperviscosity and hypercoagulability features, which makes it more resistant even to internet and advanced recipes used by drug abusers to defeat ADFs. Aximris XR also has local irritating effects and was rated difficult to snort in HAP studies.

Intellipharmaceutics is aware of a public health risk opioid medications can create, especially when they are diverted, misused, and/or abused. We understand that multifaceted and

multidisciplinary approaches to solving the opioid crisis is required and that the formulation of improved ADFs is only part of the solution. That is why if Aximris XR is approved, we believe we have a responsibility and are committed to the safe and responsible use of Aximris XR through various programs such as opioid analgesic REMS.

Here is the agenda for the rest of our presentation. First, Dr. Aloba will discuss the detailed results of the comprehensive set of Category 1 abuse deterrence studies as well as studies to assess excipient safety of Aximris XR. Dr. Ruth Stevens will then discuss the detailed results of the clinical pharmacology and Category 2 and 3 abuse-deterrent studies. Finally, I will round up this presentation by summarizing Aximris' benefit-risk profile and Intellipharmaceutics' risk mitigation management and postmarket surveillance plans.

We also have additional experts here with us today. First we have Dr. Richard C. Dart for REMS and postmarketing surveillance and Stephanie

Stanworth for human abuse potential. All our speakers' organizations are being paid for their time and expenses. None has a financial interest in the outcome of this meeting. I would now like to call Dr. Aloba to the lectern.

Applicant Presentation - Olu Aloba

DR. ALOBA: Good afternoon. My name is Olu Aloba. I'm senior director of CMC Services for Camargo Pharmaceutical Services and a consultant to Intellipharmaceutics. I am a registered pharmacist and pharmaceutical scientist, and I have experience in developing opioid alternatives and abuse-deterrent opioids. I will be presenting information this afternoon demonstrating that Aximris XR is a deterrent to the most common forms of abuse and is in some cases superior to OxyContin.

Aximris XR was designed to make injections by people with severe opioid-abuse disorder more difficult and also to impede drug abuse in legitimate pain patients or novice recreational abusers who may want to transition to the most

dangerous route of abuse.

With this in mind, a design approach was centered around following the extensive FDA guidance for developing abuse-deterrent products and also following the feedback received through the development program; targeting established and anticipated manipulation practices of routes of abuse; focusing on known or expected behavioral tendencies; using OxyContin, the most widely prescribed extended-release oxycodone product as the comparator; and finally, making incremental improvements to deter abuse. Aximris XR succeeded in these goals and in some measures achieved superiority to OxyContin.

The Category 1 studies looked at extractability, syringeability, and injectability following the physical and chemical manipulation of Aximris XR. These studies were route-specific with a focus on the IV and smoking or inhalation routes. First, we evaluated physical manipulation of particle size reduction and measured particle size distribution to select the most efficient tool and

method for grinding tablets.

The common methods and tools used to grind and defeat extended-release properties of abuse-deterrent formulations were obtained from online sites and from FDA guidance documents. Ten household tools were selected, representing the different methods an abuser might use to cut, crush, grate, and grind tablets. An optimized particle size reduction method using an advanced kitchen appliance was chosen as the most effective tool for grinding.

Here's the particle size distribution chart for Aximris XR and OxyContin after being ground using the selected optimized tool. While Aximris XR had a higher percentage of finer particles, both products had 99 percent of their particles reduced to less than 600 microns, a particle size range that's suitable for snorting. Although Aximris XR yielded finer particles than OxyContin, we'll show you later in the presentation that the smaller particles actually result in higher viscosity and more rapid coagulation than OxyContin.

I will now review syringeability, injectability, and small-volume extraction data. We conducted syringeability and injectability studies of both Aximris XR and OxyContin to evaluate resistance to IV abuse. In the most common scenario, abusers first grind or crush the tablet. They then use 1 to 2 mL of water in a spoon to extract the drug. They may heat the spoon with a lighter to accelerate drug release.

Most abusers will then syringe the material through a piece of cotton or a cigarette filter to avoid clogging the needle or injecting particulates. Most abusers use a 27- to 29-gauge needle, although sometimes lighter syringes and needles may be used. Most abuse-deterrent formulations are designed to resist these common methods for IV abuse.

We simulated these common abusive practices using the conditions listed on the slide here. None of the conditions yielded a suitable amount of injectable oxycodone even with the largest needle gauge. Both Aximris XR and OxyContin resist

extraction for IV abuse using common abuser practices.

This slide shows a representative example of the abuse deterrence of both drugs using these standard methods. You can see that both products become viscous on mixing with aqueous liquid, making it essentially impossible to inject. As mentioned earlier, this viscosity is more pronounced for Aximris XR than it is for OxyContin.

The pictures on the right of the slide show that ground Aximris XR coagulates more than does OxyContin in aqueous solution. The blue circles and the orange circles show they coagulate. This is supported by higher viscosity for Aximris XR in comparison to OxyContin at zero shear rare as shown graphically on the left of the slide by the red circles. The viscous semi-solid is virtually impossible to syringe and inject. In this slide, we're showing the observation for 2 mL of solvent, but the same observation was true for 5 and 10 mL of solvent.

I will now provide information on advanced

methods of abuse. These advanced methods include some of the techniques shown on this slide here. The FDA specially requested using convection heat pretreatment method, so we tested Aximris XR and OxyContin by applying convection heat pretreatment to intact or ground tablets under a variety of conditions, and here are the results.

On this slide, we see that a manipulated Aximris XR is not syringeable in 2 mL of an alcoholic solution at room temperature and elevated temperature in contrast to OxyContin, where a solution suitable for IV injection was obtained, and the oxycodone recovery was between 53 percent and 69 percent. In 5 mL alcoholic solution, Aximris XR, as shown by the blue bars in the graph, have markedly lower recovery compared to OxyContin, which is shown in orange in different solutions and different volumes. A similar trend is observed in 10 mL of alcoholic solution.

Now I will present information for other solvents. We see the same trend in 2 mL of neutral solution between OxyContin and Aximris, and also

here for 5 mL of neutral solution and 10 mL of neutral solution; also for 2 mL of isotonic solution, 5 mL isotonic solution, and 10 mL of isotonic solution.

Another study requested by FDA was performed to see the highest number of tablets that will yield in non-syringeable mixture. In this study, we started with a single tablet and 30 mL of solvent, then increased the number of tablets until the solution was no longer syringeable after 30 minutes of incubation.

In neutral solution, less drug was extracted from Aximris XR compared to OxyContin, and as more tablets were added, no drug was extractable from Aximris XR as compared to OxyContin. A similar trend is seen with hypertonic solution. A less or simulate drug was extracted from ground tablets for Aximris XR compared to OxyContin, whereas for intact tablets, drug recoveries remained lower for both products.

Now I'll talk about extraction using internet recipes. One of the most common methods

cited on drug abuse websites is to perform radiant heat pretreatment prior to drug extraction. Radiant heat pretreatment was applied to ground Aximris XR and ground OxyContin tablets before extraction using the listed conditions on the slide.

Using 2 mL of neutral solution and a large needle gauge, 15 to 44 percent of drug was extracted across both temperature conditions for Aximris XR compared to 57 to 73 percent for OxyContin. With 5 mL of neutral solution, less or similar drug was extracted from Aximris XR compared to OxyContin, and for 10 mL neutral solution, similar amounts of drug was extracted for both products. In summary, Aximris XR displayed greater resistance to extraction compared to OxyContin.

Next, we conducted large-volume extraction studies. The rate of drug released from Aximris XR and OxyContin intact or ground was evaluated at different temperatures and agitation conditions in large volumes, meaning 100 and 200 mL of solvent, using a variety of household and advanced solvents,

some ingestible and some not ingestible.

For intact tablets, Aximris XR had similar or low extraction efficiency than OxyContin, except for one of the solvents, while for ground tablets, when analytical variations are considered, there are no apparent differences in drug extraction between the two products.

Next, we assessed the potential for Aximris XR to dose dump in alcohol. It is well known that some extended-release opioids may rapidly release drug when co-ingested with alcohol. In this graph, the dissolution study results are shown, and they demonstrate that Aximris XR actually released less drug as the concentration of alcohol released, therefore, Aximris XR does not dose dump in alcohol.

To speed the release of drug for purpose of oral abuse from extended-release opioid formulations, abusers sometimes heat, crush, cut, or grind tablets prior to ingestion, therefore, dissolution studies were designed to evaluate the impact of different types of manipulation to defeat

abuse-deterrent properties.

In this slide, we see the dissolution profiles of split Aximris XR and OxyContin tablets, and the data demonstrate that Aximris XR and OxyContin maintain extended-release properties even when split or cut. By contrast, after radiant heat pretreatment, Aximris XR retains its extended-release properties, whereas OxyContin doesn't. As earlier stated, the most common method for defeating abuse-deterrent properties is heat pretreatment, and the data we presented shows that Aximris XR is much more resistant to this method than OxyContin.

Finally, abusers may try to vaporize the product so they can smoke it, and the common procedure for smoking opioids involve crushing or cutting the tablets, spreading the material on foil, and heating the underside. The heat melts or chars the ground material and some drug may be vaporized.

We developed two standardized procedures to simulate this form of abuse. We simulated smoking

using a block heater and a Bunsen burner, and then analyzed the vapor for recovery of drug. As you see on this slide, because of low recoveries, neither method will be considered an efficient route of administration for either product, however, the results showed that Aximris XR is less efficient to vaporize.

In summary, there are five takeaways from the Category 1 studies: 1) grinding Aximris XR to smaller particles intensifies the viscosity and coagulation features of Aximris XR more than seen in OxyContin; 2) Aximris XR resists common methods of IV abuse; in fact, it's practically impossible to syringe Aximris XR using these common methods; 3) Aximris XR provides strong resistance to IV injection using internet advanced recipes while OxyContin is easily defeated; 4) Aximris XR does not dose dump in alcohol; and 5) smoking is not an efficient route of administration for Aximris XR.

I will next discuss the nonclinical excipient safety studies performed at FDA's request. First, I'll say that excipients used in

Aximris XR are safe for oral use if used as labeled. However, due to the potential for abuse of Aximris XR, FDA requested that we perform toxicological risk assessment on the components of Aximris XR following manipulation for abuse. These risk assessments evaluated the safety of Aximris XR excipients or their degradation products if abused by the oral, intranasal, vaping, or intravenous routes.

Excipient exposure risks were assessed based on comparison to maximum levels listed in FDA's active ingredient database or information from published literature. Exposure to excipients in Aximris XR by the oral route at the maximum tolerated daily dose, or MTDD, of oxycodone is anticipated to have low risk of toxicity.

For the intranasal and smoking or vaping routes, based on the limited information available for the excipients, the potential for irritation and respiratory tract toxicity were identified, although a quantitative prediction of the risk was not possible. With respect to the intravenous

route, excipient exposure risk assessments of syringeable material consisted of characterizing the volatile and semi-volatile organic components, in vitro hemocompatibility study, and repeat dose IV toxicity study in rabbits.

The conclusion from the assessment of the volatile and semi-volatile organic components of syringeable material is that lifetime exposure would not pose significant toxicity or cancer risk. However, this does not mean that injecting abused Aximris XR will not result in serious adverse effects. Cases of thrombotic microangiopathy due to injection abuse have been reported for other extended-release oxycodone products.

Now, looking at the hemolytic potential of Aximris XR if abused, we studied hemocompatibility of syringeable solution of pretreated Aximris XR tablets extracted as shown on this slide. They were designated as test items 1 and 2. We also tested tap water, normal saline, and 2 percent saponin in water as the vehicle, the negative control, and positive control, respectively. The

tests were performed with human plasma serum and whole blood. From the study results shown on the table, it can be concluded that syringeable material extracted from Aximris XR using normal saline or tap water and non-hemolytic, they do not cause flocculation, and they are therefore hemocompatible.

I will now review the in vivo repeat dose IV toxicity study. In this study, rabbits were randomized into three groups as shown on the slide. Each animal received once daily bolus injections, 1 mL per kilogram for three 3 days. Note that this level represents a much higher exposure level than is typical for intravenous abuse situation in humans.

The rabbits were evaluated for local effects, hematological effects, thrombotic microangiopathy, overt toxicity, and tissue damage. Overall, this study found no evidence of overt toxicity or tissue damage that would be associated with thrombotic microangiopathy, retina damage, or acute kidney injury. No local or systemic adverse

effects were seen in any organ or system.

Therefore, the overall conclusion for the nonclinical excipient safety studies are as follows: the safety of the excipients for intranasal and intravenous use is indeterminate. The excipients were shown to be hemocompatible. The excipients have a low potential for thrombotic microangiopathy and other blood vessel adverse effects.

I will now invite Dr. Ruth Stevens to present information on the clinical pharmacology.

Applicant Presentation - Ruth Stevens

DR. STEVENS: Thank you.

Good afternoon. I'd like to thank the FDA and the panel for the opportunity to present today. My name is Ruth Stevens, and I'm the chief scientific officer at Camargo Pharmaceutical Services, serving as a consultant to Intellipharmaceutics. My regulatory experience with abuse-deterrent products spans 11 years. Today, I'll review briefly the clinical pharmacokinetics of Aximris XR, including its

bioequivalence to the comparator OxyContin, and then end with the human abuse potential or HAP studies.

The Aximris XR clinical pharmacokinetic program followed FDA guidance with FDA providing significant input. All the studies listed on this slide were conducted under naltrexone cover in a total of 190 healthy subjects, and all fed states were administered as the standard high fat/high calorie meals. I will cover the assessment of bioequivalence, food effect, multiple dose out to steady state, and dose proportionality studies.

The clinical pharmacology studies were designed to demonstrate the bioequivalence of Aximris XR to OxyContin to establish a scientific bridge so that the FDA can rely upon OxyContin safety and efficacy data. The next slides will demonstrate that all these clinical PK studies met their objectives.

FDA's criteria for bioequivalent specifies that the PK parameters maximum concentration, Cmax, and the area under the curve, AUC, the ratios and

the 90 percent confidence intervals should fall within the range of 80 to 125, which is shown by the gray shading. This criteria serves as a basis for drug approval.

The two single-dose bioequivalence studies shown in the plot demonstrate that Aximris XR 80 milligram is bioequivalent and has comparable bioavailability to OxyContin, thus supporting the scientific bridge to prior findings of efficacy and safety of OxyContin. Likewise, Aximris XR fast and fed study demonstrates that there was no clinically significant effect of food on the bioavailability of oxycodone with Aximris XR, so Aximris XR may be taken without regard to meals.

Moving now to the multiple dose steady-state bioequivalent study, this slide shows the study results of the multiple-dose, steady-state study between Aximris XR versus OxyContin. The multiple dose steady state looked at 80 milligrams of Aximris XR versus 80 milligrams of OxyContin every 12 hours. The three primary PK parameters were examined at steady state. As demonstrated, the 90

percent confidence intervals and their ratios for Cmin, Cmax, and AUC were contained within the 80 to 125 range. This demonstrates that Aximris XR was bioequivalent to OxyContin at steady state.

The dose proportionality study was conducted with Aximris XR 7 dosage strengths. A power analysis model was applied and showed that the slope estimates and 90 percent confidence intervals for Cmax and AUC were contained within the 0.8 to 1.2 criteria. Aximris XR demonstrated dose proportionality among all 7 dosage strengths.

In summary, Aximris XR was shown to be bioequivalent to OxyContin under fasted and fed conditions. A clinical food effects study demonstrated that there is no clinically statistically significant effect of food on the bioavailability of oxycodone with Aximris XR, so Aximris XR may be taken without regard to meals. Multiple dose, steady-state pharmacokinetic parameters, as listed in the slide, were comparable between Aximris XR and OxyContin tablets.

Aximris XR demonstrated dose proportionality

of all seven proposed dosage strengths, which provides support for approval for all seven dosage strengths. Overall, the clinical pharmacokinetic program supports the approval of the 505(b)(2) application for Aximris XR and forms the scientific bridge to a well-established safety and efficacy profile.

I'll now discuss Category 2 and 3 studies conducted by in Intellipharmaceutics. The Category 2 PK studies were combined within the Category 3 human abuse potential studies. These studies were designed in consultation with the FDA. OxyContin and oxycodone immediate release were used as the comparators.

I will now present the results of the intranasal HAP study. Thirty subjects completed the treatment phase and they each received 5 treatments in a crossover design. The intranasal HAP study manipulated Aximris XR and OxyContin by grinding them and comparing them to a crushed oxycodone IR product.

The table presented here contains PK

parameters for each manipulated treatment. As shown in the red box, the comparator PK of Aximris XR and OxyContin reached mean peak concentrations rapidly following intranasal administration compared to oxycodone IR. The green box shows that compared to oxycodone IR, Aximris XR had a higher peak and early exposure as seen in the orange box and is represented here by the partial area under the curve, 0 to 1 hour.

OxyContin has similar peak and early exposure compared to oxycodone IR. Although Cmax and partial AUCs were higher for Aximris XR in the blue box, the overall exposure represented by AUC was similar for all the active treatments.

In order to understand these PK observations and whether they are clinically meaningful, they need to be contrasted with the PD or pharmacodynamic endpoints obtained in this study. This is discussed in the next slide.

The pharmacodynamic endpoint drug liking scored by the VAS analog scale, or VAS, maximum effect, or Emax endpoint, shows that Aximris XR and

OxyContin have similar drug liking VAS-Emax scores. The VAS scoring ranged from 0 to 100 with 50 being neutral, and scores higher than 50 described increased liking. As seen in the red box, Aximris XR and OxyContin were not statistically significantly different with respect to the drug liking VAS-Emax scores. Likewise, as observed in the green box, take drug again VAS-Emax scores for Aximris XR and OxyContin were not statistically significantly different. From these results, Aximris XR and OxyContin appear to have similar human abuse potential.

Next, I would like to compare the PK observations with the PD endpoints. This slide shows Aximris XR, OxyContin, and oxycodone IR concentration profile versus pharmacodynamic profiles over 24 hours. There appears to be no correlation among the PK parameters Cmax and partial AUCs versus some of the mean drug liking VAS scores. Even though Aximris XR displayed higher Cmax and partial AUCs compared to OxyContin and oxycodone IR, the PD files were not

statistically significantly different and appeared to be the same.

Moving next to how subjects rate the ease of snorting, subjects rated ease of snorting 5 minutes post-dose on a VAS scale where 0 indicated the drug was very difficult to snort and 100 very easy. This bar graph shows the mean ease of snorting VAS scores. Aximris XR was rated to be statistically significantly more difficult to snort compared to treatment shown.

Moving next to look at how subjects rated local irritation effects and the reporting of treatment-emergent adverse events collected during this study, the subject rated assessment of intranasal local irritation effects used a scale of 0 to 5; 0 indicating no effect and 5 the most severe.

As illustrated by the blue boxes, Aximris XR had a higher rate and more severe scores of nasal congestion and facial pain and/or pressure with significant differences from oxycodone IR. In addition, the highest incidence of

treatment-emergent adverse events were observed with Aximris XR.

Following administration of Aximris XR, one subject was discontinued due to vomiting, however, no subject experienced serious adverse events. The difficulty to snort increased local irritating effects and higher treatment-emergent adverse events from snorting. Aximris XR make the intranasal abuse route unattractive.

I will now present the results of the oral human abuse potential study. Forty subjects completed the treatment phase with each subject completing all five treatments in a crossover design. The table presents the oral PK from the manipulated treatments in a comparison to the intact Aximris XR 40-milligram strength. As shown in the green boxes, Cmax AUC last and AUC infinity, as well as AUC 0 to 4 hours, were all similar for both Aximris XR and OxyContin compared to oxycodone IR.

As shown in the orange box, while early exposure AUC 0 to 1 hour and AUC 0 to 2 hours were

significantly lower for Aximris XR as compared to oxycodone IR, the overall rate and extent of exposure to oxycodone was similar for Aximris XR compared with OxyContin as represented by AUC infinity seen in the blue box.

Turning now from the PK results to the PD endpoints, here the PD endpoints drug-liking VAS-Emax and take drug again VAS-Emax were not statistically different between Aximris XR and OxyContin in the manipulated state. Both Aximris XR and OxyContin did not have statistically significantly lower abuse potential compared with oxycodone IR.

In summary, the findings from the intranasal PK study, Category 2 data showed that Aximris XR has higher Cmax and partial AUCs, but similar overall exposure to the active treatments. The intranasal PD study Category 3 showed that Aximris XR drug liking VAS-Emax and drug take again VAS-Emax are not statistically significantly different from that of OxyContin. Aximris XR was rated more difficult to snort compared with

OxyContin and also displayed local irritating effects.

In the oral HAP study, Aximris XR and OxyContin PK findings were similar. Aximris XR and OxyContin co-primary PD endpoints, drug liking VAS-Emax, and take drug again VAS-Emax were not statistically significantly different from oxycodone IR. There is no statistically significant difference between Aximris XR and OxyContin in terms of abuse potential.

I will now turn the podium back to Dr. Isa Odidi.

Applicant Presentation - Isa Odidi

DR. ODIDI: Thank you, Dr. Stevens.

As presented by Dr. Aloba and Dr. Stevens, Intellipharmaceutics has designed Aximris XR with abuse-deterrent properties to both provide a benefit to patients who need this treatment and minimize the risk of its abuse. Aximris XR is bioequivalent to OxyContin. This supports the approval of the 505(b)(2) application for Aximris XR and forms the scientific bridge to a

well-established safety and efficacy profile.

Aximris XR is proportional among all 7 doses. Patients can take medications without regards to meals. Aximris XR has features expected to discourage intravenous abuse, for example, physical tampering enhances hyperviscosity and hypercoagulability. With respect to intravenous abuse, when tampered with and exposed to aqueous solution, Aximris XR turns into a highly viscous substance that is difficult to syringe and inject in volumes of solution abusers typically use.

Most importantly, compared to OxyContin, Aximris XR was much more difficult to prepare adequate amounts for injection using advanced or typical recipes found on drug abuse websites. This represents an important improvement and does not introduce additional risk to those associated with OxyContin or any other ADFs.

Although Aximris XR displayed higher Cmax and partial AUCs when compared to other treatments, the overall exposure was similar. From the HAP studies, co-primary endpoints such as drug liking

VAS-Emax and take drug again VAS-Emax for both Aximris and OxyContin were not statistically significantly different. Although Aximris XR and OxyContin appear to have similar abuse potential, Aximris XR does display some features which may make it difficult to insufflate. Aximris XR was rated more difficult to snort compared with OxyContin in the HAP study. Aximris XR also displayed local irritating effects.

From the clinical studies conducted, no new safety signals beyond what is already known for oxycodone products were observed. There were no deaths or serious adverse events. Aximris carries similar benefits and risks as OxyContin and other approved extended-release ADFs if used as labeled.

Opioid analgesic products have serious safety risks, which must be taken into account when prescribing opioids such as Aximris XR. Therefore, patients treated with opioids such as Aximris XR require careful monitoring for signs of abuse and addiction. There are risks if any opioid analgesic product is not used as labeled.

Aximris XR is intended for oral use only. Like all other opioids, manipulation and/or abuse can enhance drug release and poses a risk of overdose and death. Excipients in Aximris XR are intended for oral use only, however, their parenteral administration can be expected to result in severe health consequences.

Now let's discuss the benefits and risks of Aximris XR to public health, which is a very important issue. Aximris XR has demonstrated superior intravenous abuse-deterrent properties. The approval and addition of an IV abuse-deterrent formulation such as Aximris XR adds an incremental improvement in abuse deterrence and is expected to add to already available abuse-deterrent products.

We are aware of public concerns regarding approving another opioid and adding a new opioid to the marketplace, however, a recent research study showed that approval of new branded opioid products alone does not appear to be a primary driver of increased opioid prescribing.

Evidence for this is the fact that a number

of opioid analgesic prescriptions dispensed has declined since 2012 despite the increasing number of opioid analgesic approvals. There are no unique features identified that will result in new unintended consequences following the use of Aximris XR; nevertheless, we are committed to closely monitoring Aximris XR for these risks post-approval.

It is recognized that no abuse-deterrent formulation can be considered abuse proof. We acknowledge that misuse and abuse of pain medications can lead to addiction, overdose, and death and are aware of the public health risk these potent medications can create, especially when they are diverted, misused, and/or abused.

That is why if Aximris XR is approved, we believe we have a responsibility and are therefore committed to take measures that will help minimize the risk of its misuse and abuse such as, 1) participation in the opioid analgesic REMS and deploying Aximris safe-use program; 2) putting in place a secure supply chain together with

responsible sales and marketing practices; 3) carrying out pharmacovigilance and risk minimization studies; and 4) deploying a surveillance program made up of prescription drug abuse monitoring or assessment.

We intend to work with the FDA and RADARS using the RADARS system to collect and analyze our data for a comprehensive postmarketing surveillance solution and development of formal epidemiologic studies by FDA guidance.

To summarize, I'd like to remind you of some of the attributes of Aximris XR. We recognize that there's a need for incremental improvement, thus we have developed a superior intravenous abuse-deterrent formulation for what is recognized as the most dangerous route of abuse, the IV or the intravenous route.

Additionally, we developed a product that is bioequivalent to OxyContin and has similar drug liking and take drug again measures to OxyContin. Aximris XR have similar risks and benefits to other approved abuse-deterrent, extended-release opioid

products. Aximris XR can be taken by patients without regards to meals.

Approval of an intravenous abuse-deterrent formulation such as Aximris XR adds an incremental improvement in abuse deterrence and is expected to add to already available abuse-deterrent products. In this manner, we hope to play an important part in addressing opioid abuse and misuse. Thank you.

Clarifying Questions

DR. LITMAN: Thank you, Dr. Odidi.

We'd now like to start the clarifying questions to the applicant. Please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter. Unfortunately, we only have 15 minutes to do this, this afternoon, so I will ask for clarity and terseness, and I may cut somebody off if there isn't a clarifying question.

Dr. McAuliffe?

DR. McAULIFFE: Hi. Thank you for your presentations. I saw a lot of data about different types of solutions and different volumes of

solutions for the small-volume syringeability, and I'm wondering if somebody can just give me a synopsis on what is the largest percent and also the largest amount in terms of milligrams that OxyContin was able to be extracted.

DR. ALOBA: With respect to small volumes, we were using volumes up to 10 mL of the different solutions, solvents, that were used. That's typically the volume that would be used by an abuser for the purpose of intravenous injection. The higher volumes were targeted at -- we used 30 mL for the multiple tablet extractions, and the large-volume extractions, which were like 100 mL and 200 mL, were geared towards oral abuse preparatory to other types of manipulations that would be typical in an abuse situation.

Did that answer your question?

DR. McAULIFFE: Not really. For example, multiple 80-milligram tablets, what would be the maximum amount in terms of milligrams that would be extracted?

DR. ALOBA: Yes. Could you please put up

slide 35?

Experiments were performed in hypertonic solution. If you look at the box in the middle, between the two graphs that I put up there, it shows the amount of drug in terms of milligrams extracted from the multiple tablets. For Aximris, you had 3 to 255 milligrams, and for OxyContin, you have between 0.5 to 374 milligrams.

Can you put up the other slide on room temperature extractions? These are elevated temperature extractions. They require a lot of efforts and knowledge to put this together, but let's look at what typically can happen, the first line of action for a typical addict.

Yes, please. Put that slide on, 34. This is the typical scenario. Obviously, you can't predict what analytics we want to do. They can go extreme, as we know, from literature and from experience or what we're doing. We started at room temperature. In that case, look at the box in the middle again. Aximris, between intact and ground tablets, you had from 8 to 46 milligram only for

Aximris, whereas for OxyContin, you had between 15 and 235 milligram in neutral solution.

I don't know if that answers your question.

DR. McAULIFFE: That does. Thank you.

DR. ALOBA: Thanks.

DR. LITMAN: Dr. Zeltzer?

DR. ZELTZER: Thanks. This is for Dr. Odidi. I must be missing something because if it's harder to inject and harder to snort than OxyContin, why is there similar liking and willingness to take again?

DR. ODIDI: A very interesting question. Could you pull up the PK slides comparing two products, one on top of the other? So your question is why should there be similar drug liking between the two? I can explain that to say --

DR. STEVENS: Yes. I want to double-check that you're talking about this graph, the PK versus PD comparison or are you asking another question?

DR. ZELTZER: Comparing OxyContin to your product, there was no significant difference in

drug liking and willingness to take again even though you demonstrated it was harder to snort and harder to inject.

DR. STEVENS: Well, that is true, in general, in terms of statistical, but we did look at a global scale called overall drug liking, where it's taken later on at 12 and 24 hours, where the subject is not influenced by the euphoria effect, the immediate effect, when drug liking scores are taken. At the post-dose numerically -- can you pull up a slide? It's in the backup slides.

Numerically, there is a trend that, actually, Aximris, they didn't want to really take it again, and they didn't really like it compared to OxyContin. That's after the immediate effects have worn off. And when they looked at the -- yes.

Do you want to put up -- it's a backup slide. It's with the comparison.

DR. LITMAN: Can we move on to another question, and we can get back to it? Just because of limited time.

DR. ODIDI: In addition, you'll notice there

are three possible routes that you can get a label for. OxyContin, for example, doesn't have a label for oral. So it's very possible to do well in intravenous and not do well in intranasal because it's a different route of abuse.

DR. LITMAN: Dr. Sandbrink?

DR. SANDBRINK: Friedhelm Sandbrink. It's actually very similar to what Dr. Zeltzer asked. Slide 74, that's really where you make a comparison in the VAS take drug again and the liking. You compare that. If you go to slide 74, please, you show the difference, on one hand, on Aximris XR being intact, and it's a score of 75. But again, in that graph, the missing question is really what is OxyContin at the same dosage, because you documented that it has a higher Cmax. So that would possibly indicate that at least if you take the medication in an intact form, that there could be a higher likeability. I'm just speculating that here. I just don't know.

DR. ODIDI: Thank you very much. Slide 74 is referring to the oral study. It's not the

intranasal study. Perhaps, as you well know, OxyContin has no claims for the oral label. These products were designed to fail in terms of the oral study. Typically, it's basically difficult to pass an oral study. You actually grind this to smithereens, you dissolve a solution, and you give it. Blood products all have similar drug liking and take drug again. Their Cmax ratios and their AUC ratios, there was no significant difference between OxyContin and our product for the oral route.

DR. SANDBRINK: My question really was about the likability of the intact drug that the majority of patients will likely take. That's what I was asking.

DR. ODIDI: Thank you very much. As you said in your preamble, you're just speculating. There's no experiment done in that respect, looking at intact drug, drug liking for inhalation products; you can't do that. For the oral products, it's done, but because the intact drug is intact, it's not ground, the results show -- can

you put up OR-8, please?

Intact drugs, obviously the drug liking will be much, much less than ground drug, and that's what we find here, and other published studies have found the same.

No, 7-8; you had it earlier, R-8, drug liking oral, overall. Yes, this one.

DR. LITMAN: We can come back to it. Can we go on to another question? Dr. Tyler?

DR. ODIDI: Oh, it's back on. Sorry about that.

So you can see the oral is the green sample, and it's very low in terms of drug liking, whereas OxyContin, Aximris, it's right up there, the same, no difference. So that's what you get when you cross oral, in terms of oral intact tablets, and you'll find the same thing for OxyContin as well.

DR. LITMAN: Dr. Tyler?

DR. ODIDI: Thank you.

DR. TYLER: Thank you. Linda Tyler. I have a question for Dr. Stevens. It's referring to slide CO-67.

DR. STEVENS: Who's speaking? I can't -- thank you.

DR. TYLER: So my question is around the first three columns.

DR. STEVENS: Yes?

DR. TYLER: Looking at the Cmax, it looks like it's almost twice as much higher than the others. The Tmax occurs much more quickly, and the area under the curve in the first hour is, again, almost twice as much. So that looks, to me, like it has higher abuse potential because of its very rapid and higher levels, and I believe this was the intranasal.

DR. STEVENS: That is correct. This is the intranasal pharmacokinetic results. However, the PK did not materialize into any observed differences in PD, pharmacodynamic, responses compared to OxyContin.

If you can look at slide 68, please -- 69, the concentration versus time curve. So what you're pointing out is what is represented in the top graph, the figure where, yes, we acknowledge

that it did have a rapid onset and higher Cmax as you point out, but when we looked at the co-primary endpoints for the pharmacodynamic effects, it didn't materialize into mean drug liking VAS scores; it's all similar between all three treatments of the oxycodone IR, OxyContin, as well as Aximris XR.

So we didn't see any difference due to a difference in the pharmacokinetic effects. There appeared to be no correlation.

DR. TYLER: Just to orient, this is your product ground administered intranasally.

DR. STEVENS: That is correct, and OxyContin is ground and manipulated as well. So the dark blue circles are Aximris XR in the top graph.

DR. TYLER: Right.

DR. STEVENS: The oxycodone IR crushed, the immediate release, is the orange, and OxyContin is the ground black.

DR. LITMAN: I'm sorry. I'm going to just cut you off there. We don't have a lot of time.

DR. TYLER: Thank you.

DR. LITMAN: I want to just get to one more question by Dr. Hoffer, and we'll keep track of the other people that have questions, and we'll circle back after the public presentations.

Lee, please?

DR. HOFFER: Thank you. Lee Hoffer. I was just actually curious about the gel blob. I like the name. Can you do anything with it? What happens to the blob after it's a blob? And can you actually rock up the drug adding baking soda and something like this, and smoke it, or is it just completely inert when it's mixed with liquids?

DR. ODIDI: Thank you. The multiple tablet experiment where you start with one tablet and increase the tablets until you can no longer syringe from the tablet could be referred to as a gel blob. A gel blob, it's a different technique, but that's okay. What you get is what you see on slide C-22. We'll put this up.

Look at the photograph, upper left quadrant. You see how thick it is? That's what you end up getting, and this is just for one tablet. As you

add more tablets, it just becomes even worse. You just get something that is -- we call it a semi-solid. It's like bubble gum. That's what you get. You can't take drug out of that.

DR. HOFFER: You can't take drug. You can't heat that --

DR. ODIDI: No, there's no liquid. It just sucks up all the liquid.

DR. HOFFER: But you can't burn it. You can't smoke that product.

DR. ODIDI: Yes, that's true. You could not burn or smoke. The same thing with OxyContin; you can't burn or smoke it easily, as well.

DR. LITMAN: Thank you.

We will now proceed with the FDA presentations.

FDA Presentation - Matthew Daubresse

DR. DAUBRESSE: Hi, everyone. My name is Matthew Daubresse, and I'm the epidemiology reviewer from the drug abuse team in the Division of Epidemiology. Today I'll be presenting data on the use, misuse, abuse, and deaths involving

oxycodone and other opioids.

FDA recently formalized our assessment of benefits and risks of prescription opioids in a draft guidance published in June 2019. For opioid approvals, FDA considers the broader public health effect of opioid analgesic drugs, which includes risks related to misuse, abuse, opioid-use disorder, accidental exposure, and overdose for both patients and others.

This presentation will provide information that may be helpful to the committee in assessing the public health risks and benefits of Aximris' XR approval. More specifically, our objectives are to first describe the utilization patterns of oxycodone products and other prescription opioid analgesics, and second, present epidemiologic data on misuse, abuse, and deaths involving oxycodone products and other opioids.

For this presentation, I'll focus more on route of oxycodone abuse since that may be more useful when considering the public health risks and benefits of Aximris XR, which is expected to deter

intravenous abuse. More information on misuse and abuse of oxycodone is provided in the backgrounder.

I'll start by depicting trends in oxycodone utilization using data from Symphony Health's PHAST database. This figure shows the estimated number of oxycodone prescriptions dispensed from U.S. retail pharmacies from 2014 through 2018. You can see that total oxycodone prescriptions, shown in the bars, declined from about 54 million to 44 million prescriptions during this time period.

Immediate-release combination and single-entity oxycodone prescriptions, in the dotted lines above, made up the bulk of prescriptions dispensed, whereas extended-release, single-entity and combination oxycodone prescriptions, in the solid lines below, make up a much smaller proportion of total oxycodone prescriptions dispensed.

This figure shows the estimated total number of extended-release opioid analgesic prescriptions dispensed from U.S. retail pharmacies in 2018. During this time period, there were about 3 million

extended-release oxycodone prescriptions dispensed, which represents about 19 percent of all extended-release opioid prescriptions.

This similar figure focuses on abuse-deterrent opioid analgesic prescriptions dispensed also from U.S. retail pharmacies in 2018. We can see that extended-release oxycodone products made up about 90 percent of all abuse-deterrent opioid prescriptions dispensed, and the vast majority of these prescriptions were for OxyContin. In 2018, there were about 2.7 million OxyContin prescriptions dispensed, which represents about 80 percent of all abuse-deterrent opioid analgesic prescriptions dispensed. Currently, all marketed ER oxycodone products have properties to deter abuse.

Now I'll present data on routes of misuse and abuse for oxycodone and other opioid analgesics. This figure shows the route of oxycodone abuse in three different data sets. The three data sets are the NPDS, which consists of calls to poison control centers; NAVIPPRO, which

surveys adults being assessed or seeking treatment for substance-use disorder; and RADARS, which surveys individuals entering public and private opioid-dependence treatment programs.

Despite the differences between these populations, we can see that most people report abusing oxycodone orally in the solid red bars on the left and intranasally in the dotted green bars in the middle. Intravenous abuse, in the checkered blue bars on the right, was the least common route reported in each of the three data sets. Here and in the next slide, oxycodone is comprised of extended-release, immediate-release, and combination products, but later I'll show this stratified by formulation.

This figure shows the percentage of individuals reporting oral, intranasal, and intravenous routes of abuse for a selection of commonly abused opioids among individuals being assessed or seeking treatment for substance-use disorder in the NAVIPPRO database. Again, you can see that oral abuse, shown in solid red, is more

common among opioids to the left of the graph like oxycodone, hydrocodone, and tramadol. Intravenous abuse of oxycodone, in checkered blue, appears less common compared to other opioids to the right of the graph like hydromorphone, morphine, oxymorphone, and fentanyl.

When we look more closely at calls to poison centers in the NPDS from 2012 to 2017, we can see that regardless of formulation, oxycodone products are most commonly abused by the oral route, which is the solid red bar. Compared to combination products, intravenous abuse, in the checkered blue bar, appears more common for extended-release and immediate-release, single-entity oxycodone products. We also see that the proportion of individuals reporting intravenous abuse for extended-release and immediate-release, single-entity oxycodone products is similar, with about 12 to 13 percent of callers reporting this route of abuse.

Now, I'll briefly present data on trends in overdose deaths involving oxycodone and other

opioids. Data from the National Vital Statistics System and death certificates shows that the rate of overdose deaths involving heroin and fentanyl increased substantially from 2011 to 2016. The rate of overdose deaths involving oxycodone decreased from 1.8 per 100,000 people in 2011 to 1.6 in 2013, then increased to 1.9 deaths per 100,000 in 2016. Overall, the rates of overdose deaths involving oxycodone appear to have remained stable during this time period.

The background material provides detailed information on the limitations of the data sources used in this review, but I'll briefly describe some key limitations here as well.

The NPDS likely undercaptures exposures, particularly overdoses resulting in out-of-hospital death. The proportion of cases captured may also vary over time and across drugs. NAVIPPRO and RADARS treatment center data may not be nationally representative, as they come from specialized populations with presumably more advanced opioid and substance-use disorders. Product

misclassification can also occur due to self-report.

In the National Vital Statistics System data, reliance on literal text of death certificates is likely to miss some proportion of opioid-related deaths that do not contain information on specific drugs, and the proportion of deaths missing this information changes over time.

In conclusion, extended-release oxycodone makes up about 90 percent of all abuse-deterrent opioid prescriptions in the U.S. Oxycodone products are most often abused via the oral route. Intravenous oxycodone abuse appears less common compared to other opioids like hydromorphone, morphine, oxymorphone, and fentanyl.

Compared to poison center calls involving combination oxycodone products, intravenous abuse appears more common for extended-release and immediate-release, single-entity oxycodone products. And finally, despite large increases in rates of overdose deaths involving fentanyl and

heroin between 2011 and 2016, rates of overdose deaths involving oxycodone remain stable. Thank you.

FDA Presentation - Jaime D'Agostino

DR. D'AGOSTINO: Good afternoon. My name is Jaime D'Agostino, and I'm a pharmacology/toxicology reviewer in the Division of Pharmacology/Toxicology for Neuroscience. Today I will be discussing the applicant's nonclinical safety assessment of excipients in Aximris XR following unintended exposure.

The following is an overview of this presentation. The agency has no nonclinical safety concerns with the excipients in Aximris XR when the product is used as intended. We agree with the applicant that the toxicological data are limited in terms of informing risk of intranasal or inhalation exposure to excipients.

The agency generally agrees with the applicant's conclusion that, based on the limited data available, the risk of abuse of Aximris XR via the intravenous route is likely similar to that of

the reference product OxyContin. However, the FDA cannot rule out the possibility that adverse effects could occur following IV injection of manipulated Aximris XR.

Before continuing, I want to give a bit of background on how the FDA evaluates the safety of excipients. Currently, there is no formal FDA guidance document for evaluating the safety of oral drug products administered by unintended routes of administration. FDA evaluates the safety of excipients for the intended route of administration in accordance with the FDA guidance to industry: nonclinical studies for the safety evaluation of pharmaceutical excipients.

For context, a reformulation of an oral product for IV administration would require IV toxicology studies evaluating both local and systemic toxicity and blood compatibility studies in accordance with the FDA guidance for industry: nonclinical safety evaluation of reformulated drug products and products intended for administration by an alternative route.

In the past, the agency has not required assessments of the safety of excipients of oral drug products for unintended routes, however, this changed based on postmarking experience with Opana ER, which is a reformulation of oxymorphone to have abuse-deterrent properties.

Following approval, adverse events resulted from the manipulation of the oral product for IV administration, including anemia, thrombocytopenia, and thrombotic microangiopathy. Postmarketing data also supported that a shift from the intranasal route of abuse to the more dangerous intravenous route of abuse was occurring. This led to an increase in outbreaks of HIV and hepatitis C in drug users who are sharing, manipulated Opana ER.

The current agency approach to excipient safety for abuse-deterrent opioids requires a risk assessment of the potential adverse events associated with abuse of the final drug product. These data should be based on the results of Category 1 studies, including in vitro assessments, literature-based assessments, and/or nonclinical

studies.

An adequate assessment of the potential risks associated with non-oral abuse is needed in order to determine the complete benefit-risk profile of the drug product. Any excipient-related adverse events related to abuse are included in Section 9.2 of the prescribing information.

For Opana ER, the adverse effects observed following IV abuse were believed to be associated with the excipient polyethylene oxide or PEO. This was supported by nonclinical studies in guinea pigs conducted by Hunt and colleagues. They injected a mixture of 7 million dalton PEO mixed with a small number of other excipients in an attempt to mimic exposure in humans following intravenous abuse.

The mixture was injected either as a single dose or every 1.5 hours for a total of 5 injections. The plasma levels of PEO measured in the animals were similar to predicted human plasma levels based on the amount of PEO extracted from Opana ER, indicating that the doses used in these studies were human relevant. Animals dosed with

the PEO mixture demonstrated anemia, thrombotic microangiopathy, and acute kidney injury consistent with the adverse events observed in people. Interestingly, these effects did not appear to be due to a direct lack of blood compatibility.

It is important to keep in mind that the risk of PEO in various abuse-deterrent opioid drug products cannot simply be extrapolated across the class based on reformulated Opana ER. Other FDA-approved opioids contain PEO, and some of these do not appear to carry a risk of thrombotic microangiopathy. However, there have been 3 cases of thrombotic microangiopathy following IV abuse of reformulated OxyContin containing PEO reported in Australia.

It is not clear at this time why all PEO-containing formulations do not carry the same risk for thrombotic microangiopathy. Current hypothesis include differences in the manufacturing processes used, differences in the molecular weight of the PEO used, differences in the methods of manipulation of the products prior to IV abuse, or

differential patterns of abuse. Let's look at the molecular weight hypothesis in a little more detail.

PEO polymers are complex molecules of different molecular weights depending on the number of repeating units. Low molecular weight PEO polymers under approximately 100,000 daltons are often referred to as polyethylene glycols. Polyethylene glycols of about 600 daltons or less are liquids and are used in FDA-approved products for IV administration. PEO polymers of 100,000 daltons or higher are often referred to as polyethylene oxides.

The data to date suggests that polyethylene oxide polymers of a molecular weight of 2 million daltons or higher have the potential to cause TMA if extracted and injected, as indicated by the red circle. Currently, there are inadequate data to evaluate the risk of thrombotic microangiopathy for PEOs below 2 million daltons.

Aximris XR contains PEO with a molecular weight of 4 million daltons, so it falls in the

range of the red circle. Therefore, when looking at the applicant's data to address the risk of excipients, it is important to keep in mind the following question. Does Aximris XR have the same risk for thrombotic microangiopathy as Opana ER?

Now let's look at the applicant's data. As indicated in their earlier presentation, the applicant attempted to identify the chemical composition of the Category 1 syringeable material and compared the profile of compounds to OxyContin manipulated under similar conditions. They then performed a literature-based risk assessment on the identified compounds. They also conducted an in vitro human compatibility test with human blood in the Category 1 syringeable material and a 3-day IV toxicity study in rabbits using the Category 1 syringeable material.

The applicant identified over 60 different chemicals above 5 micrograms from both Aximris XR and OxyContin. Many of the compounds found in Aximris were also found in OxyContin, however, it is important to note that there were also

7 compounds that were unique Aximris XR and 10 unique to OxyContin. Permissible daily exposures were estimated from existing literature toxicology data and compared to the levels detected in the syringeable material. The analysis suggested a relatively low risk for any given compound.

There are some limitations to the applicant's analysis which must be kept in mind. The safety of the combination of 50-plus chemicals in Aximris XR could not be evaluated by the literature review. No data were provided for compounds above 600 daltons, therefore, it is unknown if any large molecular weight PEO may be present in the syringeable material. The analysis was also limited in that it only looked at volatile and semi-volatile components. Finally, the methods were not validated, which reduces the confidence in the identification and quantification of the compounds reported.

For the in vitro hemocompatibility testing, the results indicated that the Category 1 syringeable material did not result in hemolysis or

flocculation. However, it is also important to keep in mind that the Hunt study suggests that the risk of thrombotic microangiopathy cannot be predicted by in vitro hemocompatibility testing. The proposed mechanism by Hunt et al. involved an indirect effect due to increase shear stress on the microvasculature and deposition of free hemoglobin in tissues.

The IV toxicity study was conducted in female rabbits who received a bolus injection of the syringeable material in an ear vein once daily for 3 days. Expected opioid-related effects were observed following dosing. In addition, there were some effects on organ weights and increased incidence in severity of histopathological findings in the lung, liver, and kidney.

The presence of toxicological findings after only 3 injections suggest that there could be a potential risk for increased toxicity with more frequent or repeated abuse. There was no evidence of anemia or thrombotic microangiopathy under the conditions tested.

There are also some limitations to this study. Histopathological evaluation was limited with some organs not undergoing analysis, including those with organ weight changes. The duration of the study was relatively short and only single doses per day were used. Therefore, the study does not inform risk following repeated or prolonged abuse and it may not mimic clinical abuse patterns. The study also did not employ a recovery group.

Here is the FDA's overall assessment of the risk following IV exposure for Aximris XR. Injecting any manipulated oral drug can result in significant toxicity. Based on the limited data available, Aximris XR is likely to have a similar risk profile for unintended IV exposure as OxyContin. If the high molecular weight PEO in Aximris XR is able to be extracted into a syringe and injected, we would expect similar results as with Opana ER, such as thrombotic microangiopathy, and it would be expected that these effects would occur in a dose- and duration-dependent manner.

FDA cannot rule out the possibility that

adverse events, including thrombotic microangiopathy, could occur with IV administration of manipulated Aximris XR. If approved, Aximris XR would likely have similar warnings in labeling regarding the risk of IV injection as other abuse-deterrent opioids. Thank you.

FDA Presentation - James Tolliver

DR. TOLLIVER: Good afternoon. My name is James Tolliver. I'm a pharmacologist in the controlled substance staff with the Office of Center Director at FDA for CDER. As part of the premarket abuse-deterrent assessment, sponsor submitted under NDA 209653 one oral human abuse potential study, one intranasal human abuse potential study, and Category 1 in vitro intravenous studies.

With respect to these studies, I wish to make some comments regarding the following topics: physical manipulations used; primary comparison used to assess abuse-deterrent properties; use of OxyContin in these studies; and general findings of the in vitro intravenous studies.

In the oral and intranasal HAP studies, manipulated Aximris XR tablets at doses of 30 milligrams and 40 milligrams, respectively, were compared to similar doses of manipulated oxycodone IR and manipulated OxyContin. The OxyContin served as an exploratory arm in the HAP studies.

In Category 1 intravenous studies, whole and manipulated 80-milligram Aximris XR tablets were compared to whole and manipulated 80-milligram OxyContin tablets. For both HAP studies, as well as for the in vitro intravenous studies, the physical manipulation method used on both Aximris XR and OxyContin tablets represented a worst-case scenario in order to produce substantial particle size reduction.

OxyContin is a hard tablet that resists physical manipulation. Advanced tools and work are required to reduce the OxyContin tablet to a small particle size. By contrast, Aximris XR tablets are much less resistant to physical manipulation. Simple tools can be used to reduce Aximris XR

tablets to a small particle size. The manipulation method used in the studies was necessary for OxyContin but not for Aximris XR tablets for which simple tools could have resulted in reduced particle size.

Both HAP studies were standard in design and involved collection of pharmacokinetic and pharmacodynamic data from non-dependent recreational opioid users. Primary subjective measures included visual analog scales for drug like and take drug again. Among the various secondary measures were high VAS and overall drug liking VAS.

For evaluating abuse deterrence in both HAP studies, the primary comparison was that of manipulated Aximris XR tablets to manipulated oxycodone IR tablets, the latter of which has no abuse-deterrent properties. In essence, we are looking at the ability of manipulation to a small particle size to compromise the controlled release properties for oxycodone inherent within the Aximris XR formulation.

No statistically significant differences were observed for maximum effect, Emax, of drug liking, take drug again, high, or overall drug liking. Manipulated Aximris XR tablets resulted in maximum oxycodone plasma levels equal or higher than that observed following oxycodone IR administration. For both HAP studies, collectively these results suggest that under the manipulation conditions used, the extended-release properties for oxycodone and Aximris XR was defeated.

As already noted, OxyContin used an exploratory arm in the two HAP studies. For both studies, manipulated OxyContin demonstrated similar effects to manipulated oxycodone IR with respect to Emax or drug liking, take drug again, high, and overall drug liking VAS, thereby suggesting no evidence of potential abuse-deterrent effects by oral or intranasal administration.

The two treatments were similar with regard to plasma pharmacokinetics of oxycodone. Collectively, these results demonstrated compromise of the controlled-release properties of oxycodone

and OxyContin, suggesting no evidence of a possible abuse-deterrent effect. OxyContin has in fact an intranasal but not an oral abuse-deterrent claim. Failure of OxyContin to demonstrate an intranasal abuse deterrent effect may be due to the substantial physical manipulation utilized in the study.

Now I want to turn to the intravenous studies. In vitro intravenous studies were conducted under the first and second review cycles for NDA 209653. Their intent to assess the use of Aximris XR tablets to produce solutions suitable for intravenous abuse.

Under cycle 1, most studies were conducted on non-heat pretreated whole or manipulated tablets of Aximris XR and OxyContin using a common solvent. Under various conditions regarding solvent volume, solvent temperature, and extraction duration, non-heat pretreated whole and manipulated Aximris XR tablets and OxyContin tablets did not result in suitable solutions for intravenous injection due to limited fluid recovery and limited oxycodone

recovery.

Under cycle 2, the focus was on heat pretreated 80-milligram Aximris XR and 80-milligrams OxyContin tablets, whole and manipulated. This was at the request of FDA, so keep in mind what the difference is now. We're talking about heat pretreated tablets, whereas in the previous slide, I was talking about non-heat pretreated; no pretreatment. A common solvent was examined at starting volumes of 2, 5, and 10 milliliters.

In the next slide, I will show you some solutions resulting from the use of both products. To provide some backdrop to understanding the relevance of these solutions for possible intravenous abuse, I note the findings of Colucci et al. 2014.

In this study, intravenous infusion over a 1-minute time period of a solution containing 4.9 milligrams of oxycodone into non-dependent recreational opioid users resulted in maximum scores of 96.4 and 94.4 for drug liking and high

VAS, respectively, as well as a score of 82 on the bipolar take drug again VAS. This was a single dose. Other doses were not examined.

Now, with this in mind, look at the table in the next slide. This slide provides results obtained utilizing a commonly used solvent to prepare solutions for intravenous abuse. We're talking about the use of single tablets here, not multiple tablets. Both Aximris XR and OxyContin tablets are 80 milligrams, the highest dosage strength, that have undergone heat pretreatment. Extraction times for manipulated and whole tablets are 30 seconds and 30 minutes, respectively. Starting volume, which is in the third column, is either 2, 5, or 10 milliliters of a commonly used solvent.

To understand the table, focus on manipulated Aximris XR at the starting solvent volume of 5 milliliters. Manipulated 80 milligrams preheated tablet is placed in 5 milliliters of a commonly used solvent for 30 seconds. Next, a syringe with a small bore needle is used to recover

1.3 milliliters of solvent, which, upon analysis, contains 16.3 milligrams of recovered oxycodone for a concentration of 12.5 milligrams per milliliter. Based upon the results of Colucci et al., such a solution could very likely be used for intravenous abuse in non-dependent recreational opioid users.

For both extraction times of 30 seconds for manipulated products versus 30 minutes for the whole products, that is non-manipulated heat pretreated tablets, much more rapid release of oxycodone from manipulated versus non-manipulated products testifies to the importance of physical manipulation to compromising the controlled-release properties for oxycodone from both of these products.

Finally, fluid recovery in this table was achieved using a fine bore needle, which would typically be used by intravenous injectors. With respect to the use of manipulated products, you can see that fluid recovery was less with use of Aximris XR tablets compared to OxyContin tablets, suggesting a greater gelling effect with Aximris

compared to OxyContin.

This slide provides some general comments to come out of the table just shown. For heat pretreated manipulated tablets, the volume and milligrams of oxycodone recovered were less for 80 milligrams Aximris XR compared to 80 milligrams OxyContin. For heat pretreated whole tablets, the volume recovered and the milligrams of oxycodone recovered were more similar between 80 milligrams Aximris XR and 80 milligrams OxyContin with use of a longer extraction time.

With the exception of manipulated Aximris XR in 2 milliliters of solvent, resulting solutions from either product, manipulated or whole, could likely support intravenous abuse, particularly in non-dependent users. OxyContin would be more likely to support multiple injections either by one or multiple users. Studies used 80 milligrams in terms of tablet strength. It is not known and it is questionable to what extent lower dosage strengths may be used for intravenous abuse. We do not have data on these lower strengths for the most

part.

Conclusions; note the following conclusions. The oral and intranasal HAP studies, as well as the Category 1 intravenous studies, utilized a worst-case scenario for physical manipulation of Aximris XR and OxyContin tablets. Such manipulation was necessary for OxyContin but not for Aximris XR, which of the two is more susceptible to physical manipulation.

Oral and intranasal HAP studies demonstrated that physical manipulation of Aximris XR results in the loss of extended-release properties for oxycodone. This does not support potential deterrent effects of Aximris to oral or intranasal abuse. The failure of OxyContin, as shown in the exploratory arm, to display an intranasal abuse-deterrent claim may be related to the extent of manipulation conducted. OxyContin is, as I've stated before, a hard tablet and requires more advanced tools and additional work to undergo particle size reduction suitable for insufflation.

Category 1 intravenous studies, as conducted

in support of NDA 209653, demonstrate manipulated non-heat pretreated -- I repeat, non-heat pretreated -- Aximris tablets and OxyContin tablets cannot be used but for preparing solutions for intravenous abuse, thereby supporting a deterrent effect for both of these products under the manipulation used as determined in the first cycle of the NDA review.

The results under the second cycle show that manipulated heat pretreated 80-milligram Aximris tablets and 80-milligram OxyContin tablets can be used to prepare solutions for intravenous abuse in non-dependent subjects.

Generally, fluid in oxycodone recovered was lower following use of 80-milligram manipulated Aximris XR tablets compared to following 80-milligram manipulated OxyContin tablets. This may suggest an incremental improvement of heat pretreated Aximris XR tablets over heat pretreated OxyContin tablets in deterring intravenous abuse. However, again, it should be kept in mind that OxyContin is a more difficult product to manipulate

than is Aximris XR. Thank you.

FDA Presentation - Elizabeth Kilgore

DR. KILGORE: Good afternoon. My name is Elizabeth Kilgore. I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine. This afternoon, I will provide a summary of the FDA's clinical findings related to Aximris XR. The topics in this presentation include a discussion of the key safety findings from the human abuse potential studies, benefit-risk assessment, and considerations of abuse-deterrent opioid formulations to the public health.

In the intranasal human abuse potential study, overall, the highest incidence of adverse events occurred in the Aximris XR ground treatment group. Specifically, nasal congestion incidence was highest in placebo Aximris XR treatment group followed by Aximris XR ground treatment group. However, the agency does not consider the slightly higher incidence of nasal congestion in the Aximris XR ground treatment group to have a

clinically meaningful deterrent effect since there was no correlation between this finding and the clinical endpoints in the HAP study.

Safety findings in the oral HAP study reveal Aximris XR milled in solution and OxyContin milled in solution had an overall incidence of adverse events at approximately 95 percent each. In general, subjects in the Aximris XR intact treatment group experienced a lower incidence of adverse events compared to other treatment groups, except placebo.

The primary potential benefits of Aximris XR, if approved, are that if labeled with abuse-deterrent properties, Aximris XR would be an additional product with the potential to increase barriers for misuse and abuse. It would provide additional treatment options for the intended patient population.

The risk of use of opioids, even when taken as labeled, have been well documented. All opioids carry serious risks for numerous safety concerns, including abuse, misuse, addiction, and intentional

or accidental overdose, which may result in respiratory depression and death. Patients treated with opioids require careful monitoring for signs of abuse and addiction.

Aximris XR is for oral use only. Potential risks of using Aximris XR when taken intravenously include the following: inactive ingredients may result in tissue necrosis, pulmonary and cardiac injury, and death. Cases of thrombotic microangiopathy have been reported in another oxycodone extended-release formulation, and parenteral drug abuse is associated with local and systemic infections. Risks associated with intranasal use include nasal necrosis, nasal septum perforation, olfactory nerve damage, other localized tissue damage, and overdose.

Lastly, I will discuss the agency's considerations to the public health of abuse-deterrent opioid formulations in general. While this list is not all inclusive, we want to emphasize the following points.

Abuse-deterrent opioid formulations are

developed to increase barriers for misuse and abuse, not for addictive properties. The public health impact of abuse-deterrent formulation opioids in a real-world, postmarketing setting is unclear, and the agency is cognizant of the public health concern of potentially approving another opioid and adding new opioids into the marketplace. We cite the article cited by the applicant here to support that.

When reviewing abuse-deterrent formulations, the agency also takes into consideration the potential unintended adverse consequences such as a shift to more dangerous routes of abuse, use of tampering methods that could result in harmful effects, and potential safety concerns related to the abuse-deterrent formulation. In addition, we must consider the unknown safety of excipients if used by unintended routes of administration. This concludes my presentation. Thank you.

DR. LITMAN: Thank you.

We will now proceed to clarifying questions for the FDA. To remind everybody, we only have 15

minutes for this portion. We will try and circle back after the public session, but we need to stay on time here, especially because of constraints in the afternoon.

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

(No response.)

DR. LITMAN: That was easy. No questions clarifying questions for the FDA?

(No response.)

DR. LITMAN: Okay. We have only one public speaker for today. Is that public speaker here and want to go ahead? Do you want to go ahead?

(No audible response.)

Open Public Hearing

DR. LITMAN: Alright. We will start the public session.

Before we do, both the Food and Drug administration and the public believe in a transparent process for information gathering and

decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise a 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 such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights

and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair.

Will the speaker please step up to the podium and introduce yourself? State your name and organization you are representing for the record.

MS. ZELDES: Good afternoon. Thank you for the opportunity to speak here today. My name is Nina Zeldes, and I'm here speaking on behalf of the National Center for Health Research where I am a senior fellow. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from drug and medical device companies, so I have no

conflicts of interest.

While opioids can help patients suffering from pain, as we all know too well, they can also cause tremendous harm. The opioid epidemic stems from inappropriate prescriptions, false and misleading marketing, insufficient oversight and regulatory control, inadequate risk mitigation, and insufficient public health and social services infrastructures.

Our center strongly supports research and programs to improve the safety and appropriate use of opioids. All drugs that the FDA evaluates should be held to a high standard for approval, but the standard for opioids needs to be even higher because the known risks of addiction are so high, even when the drugs are taken as directed.

Unfortunately, the term "abuse deterrent" has contributed to the opioid epidemic. Research shows that doctors, patients, and family members have misunderstood the term, thinking it meant less addictive. Instead, abuse deterrent has various meanings such as crush resistant, difficult to

inject, or something else that made the drug harder but definitely not impossible to abuse. In some cases, the drug was difficult to abuse in some ways but easier in other ways.

Most important, the research that the FDA presented at the advisory committee meeting on Tuesday and today shows that the misuse and abuse of opioids is often from patients taking more pills than they're supposed to take. Snorting, injecting, and other means of abuse of opioids are not the most common way that they are abused.

With that knowledge, the FDA needs to rethink its use of the term "abuse deterrent" and it certainly should not apply it to this drug since there is no evidence that it would be significantly less likely to be abused than other opioids. This drug may deter abuse by the IV route to some degree. Unfortunately, individuals who are addicted are highly motivated to overcome those deterrents. At the same time, this new formulation does not deter nasal and oral abuse. In fact, the intranasal abuse potential appears to be higher

compared to oxycodone IR tablets.

We know from previous experience that so-called abuse-deterrent opioids are sometimes abused more widely than current laboratory studies suggest. As FDA pointed out, Opana is one example. Therefore, FDA should require sufficient evidence that this drug's abuse-deterrent properties will result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes. If so, it should be labeled as crush resistant or whatever term is an accurate description of its properties, but not abuse deterrent since that term is widely misunderstood.

This formulation should not be approved, and if FDA in the future labels drugs as difficult to inject, FDA should also require a black box warning indicating that although the drug may have properties that make it more difficult to inject or snort, it is still highly addictive in whatever way it is consumed.

Thank you for the opportunity to share our perspective, which is based on analyzing data from

the FDA's own reports, as well as published sources in interviews with patients and physicians.

DR. LITMAN: Thank you.

We will now take a 10-minute break -- do you want 15 -- a 15-minute break. So it's 3:35. We'd like to reconvene at 3:50. Just a reminder, panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 3:50.

(Whereupon, at 3:35 p.m., a recess was taken.)

DR. LITMAN: We're going to get started with the next session. Dr. Roca of the FDA will now provide us with a charge to the committee.

We want to do clarifying? Thank you. Sure.

There were a couple of panelists that didn't get in there clarifying questions to the company, the sponsor, this morning. I have Dr. Horrow and Dr. Amirshahi.

Do you still have clarifying questions? Jay, you do?

DR. HORROW: Very quickly.

Clarifying Questions (continued)

DR. LITMAN: Dr. Odidi, is that okay?

DR. HORROW: Slide 23 of the presentation shows some data that were not covered. And I was wondering if Dr. Odidi would be kind enough to help us understand what they mean on slide 23.

You pointed out the red circles on the left. I'm curious, what are all these other data points and what do they mean, starting from 50 to 300 along the horizontal axis?

DR. ODIDI: What we're trying to show here is the effects of the physical properties of Aximris and OxyContin on viscosity. We're particularly looking at viscosity measured at the point where shear rate is zero. In order to syringe a material, you have to draw it in; that means you're applying shear. To push it, you need to apply shear as well.

So at a point where there's zero shear rate, what is the viscosity? The higher it is, the more resistant it is to syringing and injecting, and at

the same time, obviously, in this case, the more difficult it is to extract drug from the product, as shown in the results that we put up.

So here you have the value of 600,000 for Aximris. When you extrapolate, it is a zero shear rate versus less than 300,000, between 250,000 and 300,000 for OxyContin. We didn't put up results for 5 and 10 mL. We had for 50; I think it's in the briefing document. The more liquid you use to try and extract the product, the more viscous the product is compared to OxyContin. So that's what this was trying to show.

DR. HORROW: So based on the fact that the two curves are nearly the same for the other shear rates, does that mean that the problem is getting the stuff started, and then once you get it, they almost are the same? Is that what that means?

DR. ODIDI: No. You can't get it moving. You need enough force to get it moving, and that force is higher for our product. When you look at the picture visually, you'll see that it's like bubble gum. You just can't move that. So that's

what that means.

DR. HORROW: Thank you very much.

DR. ODIDI: You're welcome.

Oh, you want to add?

DR. ALOBA: Yes. The data in the graph is also an artifact of the measurement of viscosity because to measure viscosity of the material, you have to apply shear to it. But in order to extract liquid from that material, it's actually sitting in a situation of zero shear. That's why you can see that the data points don't go to zero, but we extrapolate it to zero to see what is the status of the material when no shear is being applied.

At even situations of low shear, you can see that the Aximris XR is much more viscous, based on the shear rate measurement, than OxyContin. The more shear, the more liquid both of them become, and the difference in actual viscosity becomes very minor, but the fact of the matter is that the material that is being syringed is actually in a situation of zero shear, where no mixing or shear is being applied to the material.

DR. HORROW: Thank you.

DR. LITMAN: Dr. Amirshahi?

DR. AMIRSHAHI: Yes. My question relates again to slide 67 and 68, which we did touch on briefly. One of the things that's very concerning to me is the fact that the intranasal Cmax was almost double for your product. You present your pharmacodynamic data as likeability and willingness to take the drug again, which is important to me, as we don't want to reinforce abuse, but my concern is do you collect any data about other adverse effects?

When I'm thinking about somebody snorting this in an alley, does that higher peak plasma concentration equate to more CNS or respiratory depression? Because clinically, that's what's going to kill a patient if they're abusing this. I think that information would be helpful to have, particularly because the intranasal route of abuse is more prominent than the intravenous route of abuse. Thank you.

DR. STEVENS: Yes. In this study, it's

highly monitored for the safety and respiratory depression. There were no respiratory adverse events reported, and it was every 3 days that they were monitored for this. There was just nothing reported other than nasal congestion; maybe throat dryness, or worse.

DR. LITMAN: I think the thing that we all worry about is there's this bizarre event here where they have very high blood levels, but yet the PDs don't seem to matter. So it would be nice to know -- and I can't imagine that data's available here today -- some PD/PK curves as to what, really, the effects of this drug are, or oxycodone, on the pharmacodynamic effects, like euphoria or respiratory depression correlated with blood level. I personally don't know that, and I wonder if anybody here can come up with that.

DR. AMIRSHAHI: May I?

DR. LITMAN: Absolutely, of course.

DR. AMIRSHAHI: The other concern is that this is one 30-milligram tablet. In the real world, I have patients that come into me in the

emergency department, and they say I snorted 5 or 6. I know that we can't do those studies, but I think that should also give us a little bit more pause because we can't do those studies, and these aren't really real-world conditions.

DR. LITMAN: I think we're good with clarifying questions to the sponsor, so I'll ask Dr. Roca to come up and provide us with the charge to the committee.

Charge to the Committee - Rigoberto Roca

DR. ROCA: During your discussion this portion of the afternoon, the things that we would like you to consider as you discuss -- and we'll put the first point up, and I'm not going to read them; I'm just going to hit upon the high points since you will be reading them individually -- would be to discuss whether the applicant has demonstrated that the product can be expected to deter abuse by the three routes that are listed there; with the second point, to discuss the implication if the product has proved that it can be expected to deter abuse by a single route.

The third point would be to discuss any concerns you have with respect to the impact on public health, particularly with respect to the potential consequences if the product is administered by unintended routes. The synthesis of those three discussion points actually will end up providing the points for your fourth discussion point, which is to try to discuss the benefits versus the risks of the proposed indication; and as always, any additional data that you feel are needed in order to recommend approval for this product.

The last point is a voting question where we once again will ask you to vote whether you recommend approval of the product for the indication that's listed on this slide. So I'll stop there and allow you to continue with your discussion.

Questions to the Committee and Discussion

DR. LITMAN: Thank you.

We will now proceed with the questions to the committee and the panel discussions. I would

like to remind public observers that while this meeting is open for public observation, public attendees may not participate except that at the specific request of the panel.

Moon, can you please put up the first question? I won't read it again -- Dr. Roca just did -- but if there are any panel members that would like to give their opinions or discuss the question before us -- and that's the individual routes, are they abuse deterrent?

Sorry. We have to read it into the record. Question 1. Please discuss whether the applicant has demonstrated that Aximris XR, oxycodone extended-release tablets, has properties that can be expected to deter abuse by the following routes: number 1, intravenous; number 2, intranasal; and number 3, oral.

So I'll start the discussion since, to me, it's pretty obvious that they have demonstrated intravenous abuse deterrence, but they have not demonstrated intranasal or oral. And in fact, there is some concern from the committee here that

it actually favors intranasal abuse.

There is an apparent disconnect between the very high blood levels that were achieved with intranasal use and its pharmacodynamic effects. I don't know whether or not there's a ceiling on oxycodone levels as far as euphoria or so-called high. Maybe perhaps one of our experts here knows or has some literature. I would certainly, after the meeting, be concerned about finding some kind of PK/PD correlation studies with this drug, especially to determine what Dr. Amirshahi's point was, and that's if a recreational abuser or user will take more than just the dose was used here.

Dr. Meisel?

DR. MEISEL: Steve Meisel. I'm going to take the liberty of actually combining all four questions into one answer because I think they're all the same basic theme. I think part of the problem -- I've been at a number of these meetings over the last few years with applications for abuse-deterrent formulations, and some have been approved and most of them have not been.

I think the problem that we have is that we don't really have a clear definition of what we mean by abuse deterrence. It's hard to establish a threshold by which we say, yep, this is abuse deterrence, and we can approve it or, no, it doesn't reach a threshold because we haven't defined that. It's all subjective, and it's been changing over the course of time.

I would suspect that if this was -- I don't know what year that revised OxyContin was approved, but if it were today, the standards of approving OxyContin would be different enough, based on our informed conversations over the years, that it may have trouble getting approved as an abuse-deterrent formulation. I think it's incumbent upon the agency to provide more objective guidelines in a field that is, by its nature, sort of qualitative and subjective, and I know the ambiguity with that.

I scratch my head, and it's an unanswerable question here in terms of whether any of this stuff makes any difference, because we saw some data from FDA in one of the earlier presentations that people

aren't overdosing on parenteral use of OxyContin or those kinds of things, but I don't know if it's a chicken or an egg. I don't know if they're preferring the rapid release because it's easier, and more widely available, and it's more widely prescribed, or if there is something about the abuse deterrence that's causing that number to be low. I don't think there's an answer to that. But unless we have an answer to that, we don't know whether any of this stuff is doing any good.

So we could approve these meds, we could disapprove these meds, we can nuance the Iv versus the intranasal, versus the oral, but at the end of the day, I don't know that any of this stuff makes any difference in terms of public health.

DR. LITMAN: Thank you. Any other discussion points? Dr. Z?

DR. ZACHAROFF: Hi. Kevin Zacharoff. I guess along the lines of what we just heard from Steve Meisel, I'm sort of mentally rewording this question a little bit, and it probably has to do with the public commentary we heard. I'm rewording

it to properties that could be expected to deter manipulation and not necessarily abuse.

I think with intravenous, I would agree with Dr. Litman. With respect to intranasal, I would agree. I'm not 100 percent sure that anything was proven to me about deterring manipulation for intranasal use. When I look at oral here, I naturally think about things like chewing and manipulating and not swallowing.

I think there was some data that led me to believe that it would determine manipulation for use by intravenous route and possibly by chewing and not by intranasal administration. Thank you.

DR. LITMAN: I'm not sure it belongs in this section, but I will just make a comment. Getting back to what Dr. Meisel said, this abuse-deterrent labeling, to me, abuse deterrence is a tough term because it implies, I think on the surface, that it's abuse deterrent in all the different forms, but that's not true. If we look at the five I guess that are on the market now -- I don't remember -- FDA has approved them for different

routes. So when you look at the label, it says this particular drug deters nasal but not oral, and so forth.

So if this drug were to be approved today, or approved subsequently, it would be approved for intravenous but not intranasal and oral. I don't have a right answer. I think it's a perception, and I don't even know if it matters at this point if that term can imply that it's only deterrent by one route and not the others.

Dr. Staffa?

DR. STAFFA: Judy Staffa. I'm wondering if I can just put this in a bit of context for the folks who've been on the committee for a long time and have talked about a lot of these formulations and those who may have not.

What we do is these formulations are labeled based on what's expected, based on the premarket data, and as you've pointed out, we don't really know how that translates into what happens once these things get on the market. Every company that has abuse-deterrent properties in their label is

required to do postmarketing studies to look at the impact postmarketing, and it's targeted at whatever abuse it is they're supposed to be deterring, as well as overall, and the other routes because, remember, we've seen shifts and we want to make sure we would see those.

Those studies are ongoing and they are incredibly challenging, as I know we've talked with this committee about many times before. They are challenging from a scientific perspective. They are also challenging logistically because, as you saw in some of the utilization data, there's not been a lot of uptake of these products for a variety of reasons.

I can share with you that one product, OxyContin, which is the lion's share of this market in the oxycodone ER space, has submitted all of their postmarketing required studies on this topic, and they are under review. We have said many times that once we review these studies, we will be having a public discussion. At that point in time, once we have a better understanding of the

postmarketing performance, then we can begin to think about relating that postmarket performance back to what we see premarket, and begin to understand what are the characteristics of the premarket performance that are predictive of postmarket characteristics.

I guess that doesn't help you today, but I just wanted to let you know that this is a space that we're all very actively working in.

DR. LITMAN: It does help. To me at least, it clarifies that this is not a concrete concept that we're dealing with; it's something that's evolving with the times.

Let's go on. Dr. Suarez?

DR. SUAREZ-ALMAZOR: One of the concerns I would have is that although it might be a deterrent from an intravenous perspective, the intranasal route, there was a higher Cmax. The liking was similar, though, when compared to OxyContin. However, if I understand correctly, this is a drug that's more easily destructed or made into powder than what OxyContin would be.

If I understood what was said is that it was felt that OxyContin had lost the nasal advantage that it had because it had been manipulated in a way that it really was stronger than what someone would normally do with a number of tools, I don't know, electric kitchen appliances or something like that.

So my concern would be that given the higher Cmax and I guess the nasal irritation, and some of the adverse events that didn't really influence the people that were tested with this, the ease of destruction of the pill or the tablet would make it more likely to be misused in an intranasal route.

DR. LITMAN: Thank you. Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. All of the abuse-deterrent drugs are required to do postmarketing studies, but to my knowledge, we haven't seen them, and it's been years. I don't know when we're going to see them, and it makes it more difficult to draw conclusions when these drugs are out in the marketplace but we don't have the studies. I recognize they're difficult to do, and

I don't know that there's any way to make them faster. But knowing that it's going to be a decade or more, or a significant number of years, that this drug, if approved, would be on the market before we get feedback on whether we've made a massive mistake or made the right decision, makes me very reluctant to take a risk.

DR. LITMAN: Dr. Shoben?

DR. SHOBEN: This is Abby Shoben. I just wanted to, for the record, state the obvious answer to this question, which is to say that the properties that can be expected to deter abuse by the intravenous route I think have been pretty well documented, and they in fact are superior to even the OxyContin that has abuse-deterrent properties for the intravenous route.

If you look at the amount of drug extracted in almost all settings, it was lower for this product compared to the abuse-deterrent OxyContin. I just want that stated for the record before we lose sight of that with the rest of the discussion.

DR. LITMAN: Thank you. Dr. Hoffer?

DR. HOFFER: I just wanted to go back a little bit to elements of the discussion about these ADF formulations. I think we need to remember some history as well, as to how did we come to this position. It was by the oral ingestion of opiate medications primarily. It was of course a high rate of medication use, but I think that we need to be careful about just saying, well, you know, if they can inject it, it's of course going to allow them to abuse it more. I think we still need to be careful about high potency opiates like this one being ingested orally as well. There is a history of this being a problem in the United States.

DR. LITMAN: While your mic is on, are you seeing in your drug abuser individual population -- what's going on with abuse deterrence? What we've been hearing through different publications is that they're just going right to either bootlegs or heroin.

DR. HOFFER: I think now there are enough people that are injecting heroin and heroin mixed

with fentanyl that it makes it much easier for people who want to use opiates to go directly to those medications -- or excuse me, to those drugs. Back in 2008, we would see a lot of people who would start out in pain, being treated for pain or what they thought was pain, and going into injection and progressing that way. Now, at least in my research, we don't see that. It's people that have friends that are injecting already, and that's when they start.

DR. LITMAN: But do you think that there's a big decrease in the number of people that are trying to manipulate these tablets since the ADFs have come onto the market?

DR. HOFFER: Well, I think if you look historically in 2010, there was a big shift when oxy was changed, the ADF for oxy, but since then, I think, like I said before, people who want to abuse these medicines, typically, they're on a trajectory to use more potent drugs. So they might initially start out with a pill or two. Once they inject heroin once, they don't go back to pills, ever --

DR. LITMAN: Got it.

DR. HOFFER: -- and I mean ever, only when they can't get heroin, which is really, really rare for them.

DR. LITMAN: We could talk more about this in the public health version. So go on to issue 2? Any other discussion about question 1? Friedhelm?

DR. SANDBRINK: Friedhelm Sandbrink. Separate from the issue of what is an abuse-deterrent property, I feel, in particular in regard to the oral properties, we really cannot make a judgment about this drug without knowing anything about the addictive potential. We have these human abuse studies in crushed product and milled products, but what is the likeability of this drug compared to what's on the market for the majority of patients who are going to use it in its intact form?

If I know maybe, yes, it's going to be better or more favorable in regard to the IV use -- but that is not the common use. The common use is oral. The common abuse is oral. So in

order to make a comparison, I need to know what is the concern in regard to abuse, likeability, actually, of the intact formulation. If that is unfavorable, we avoid getting patients who use it as prescribed who suddenly end up starting developing an addiction.

DR. LITMAN: Thank you. We'll move on to question 2.

Sorry. Dr. Zeltzer?

DR. ZELTZER: Hi. Lonnie Zeltzer. I just want to add one sentence to what you said, and that is the likeability in the oral form of both OxyContin and this product were similar. So in the most common form that it's going to be used or misused, it's just as likeable. There aren't deterrents to the most common form in which it will likely be misused.

DR. LITMAN: Thank you.

In summary, I'm pretty confident in saying that the panel felt that there was demonstration of intravenous abuse properties and there was not for intranasal or oral, and for intranasal, there was

some concern about the higher blood levels that were achieved.

Did I miss anything?

(No response.)

DR. LITMAN: Should we go on to 2? Question 2, the applicant is requesting approval of Aximris XR as an analgesic with properties expected to deter abuse by the intravenous route. Discuss the implications of approval of Aximris XR that can be expected to deter abuse by a single route.

The way I read that is what are the implications if this were approved, and it could be deterrent in one route and not others. I think we covered that already in this previous discussion, but if anybody has anything to add, Dr. Mehta?

DR. MEHTA: I was just hoping to get some clarification around this question because I struggled with understanding the discussion specifically for this product when the other products that have been approved with the abuse-deterrent claim are not for all of the different routes; they do have specific routes

called out. So maybe some further clarification from FDA in what the nuance is here that makes this scenario different.

DR. LITMAN: Dr. Lowy?

DR. LOWY: Sure. I think there are a couple of things. First, this would be the first that would deter by only a single route. The other formulations that are expected to deter abuse have more than a single route labeled. So we wanted to understand your thoughts about a single route, as well as your thoughts about whether that single route may shift to a different route.

Does that help?

DR. MEHTA: Yes, it does. So the difference is maybe a product with a single route versus two routes because there aren't any products with all of the routes covered, right? So we're talking about whether it would be okay to have just the single route versus more than one route.

DR. LITMAN: Dr. Sullivan?

DR. SULLIVAN: I think this requires integrating some of the other understanding of the

routes of abuse. I would just comment that in this case, the deterrents for the IV route is actually the least commonly abused route, and the intranasal, where there may be some facilitation or some increased Cmax, is a more common route of abuse.

So I think that this question, really, if you think of it at the population level, if you deter some and facilitate others, that may lead to a later question about risk-benefit. But I would just say maybe it's not so clear as like is a single route okay or not, but which route is it and how does that relate to the population practice.

DR. LITMAN: Thank you. Dr. McCann, did you have a question?

DR. McCANN: Yes. Mary Ellen McCann. I guess I'm just a little bit confused. I think the question really is, does it deter nasal abuse more than the comparator; not does it deter nasal abuse. Is that the --

DR. LITMAN: No, no. I think the point of this question was what do we think about this being

the only drug that would be given in an abuse-deterrent label if it only deters IV and not nasal or oral.

DR. McCANN: Thank you.

DR. LITMAN: Because that does not exist yet on the market.

Any other comments? Sorry. Dr. Shoben?

DR. SHOBEN: This is Abby Shoben. I'm sort of conflicted here in the sense that if it were just going to deter abuse by the nasal route, I think that we'd have some concerns as a committee about that, the potential that they'd go directly from oral to IV. I hope some of the addiction experts can chime in because I am not one, but I've heard a lot about that; this sense of deterring by a single route when that single route is IV, where you see the highest risk of a lot of other potential bad outcomes is potentially okay in my mind as opposed to something that deterred by just the single nasal route.

DR. LITMAN: Dr. Suarez?

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I

would like to make the point that I made before in response a little bit to what you said. To me, the concern would be that it would increase the use of intranasal because it's easier to crush. So it wouldn't be that intranasal remains the same and intravenous is decreased. For this particular compound, that would be my concern.

DR. LITMAN: Dr. Hoffer?

DR. HOFFER: Just really quickly --

DR. LITMAN: Just state your name into the record.

DR. LITMAN: -- Lee Hoffer; I'm sorry -- I think there's a substantial amount of evidence to suggest that people who have substance-use disorder for opiates will use them in the ways they can use them. If they can use them orally, they will use them orally. If they can snort them, they'll snort them. If they can inject them, they'll inject them. But if one of those routes is cut off, if they can't inject, then they'll snort. If they can't snort, then they'll still try to inject.

I think that it's not sort of, well, if they

can't inject it, then it's safe, or if they can't snort it, it's safe. They have to ingest it some way. You can't have all three, and we're going to stick with the oral. But I think with the insufflation, there are some real challenges there. If they can't inject it, they might snort it. Just going back, I think this is a really high bar to set for the manufacturer to say, you know what, we're going to deter abuse. I think that's the real challenge in these medications.

DR. LITMAN: Thanks. Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. Based on what Dr. Hoffer just said, I tend to agree. I think the answer to this question, discussing the implications of approval of deterring a single route of abuse, could possibly be a balloon effect, which would push someone to abuse it by another route. But on the flip side, I think, as we've already heard it, it might be a holy grail in terms of having an opioid come before us that -- maybe "tamper resistant" was a better term to describe this, that deters abuse by all three routes might

just not be realistic.

So there might be a balloon effect, but I don't think we could deny the fact that we have heard evidence to show that if there was an asterisk about the abuse-deterrent properties of this medication, if it were approved, that it would refer to by just intravenous route, that that would be accurate.

DR. LITMAN: Yes, Dr. -- sorry. I can't read from here.

(Laughter.)

DR. TYLER: Linda Tyler.

DR. LITMAN: Thank you. Dr. Tyler?

DR. TYLER: Not to minimize the problem in any way, but this strikes me as a parallel to child-resistant packaging. Not for one moment will child-resistant packaging deter a determined child if you're not watching them; it only slows them down, but sometimes those few seconds are really important.

In this particular case, what I have to ask myself, and to Dr. Hoffer's point, is people who

are determined to abuse drugs will abuse drugs, and they'll figure out a way. So does this dosage form slow them down? In my mind, no.

We're having this public meeting. Everybody knows that if they can't use it one way, they'll use it another, and in fact they'll get higher concentrations faster if they use it intranasally.

So this does not slow down. This does not contribute to our decreasing people's ability to abuse drugs in our communities.

DR. LITMAN: Thank you. I'll just finish by adding, I do have a hard time calling something abuse when it's only one of the three, and it's the one that's used the least.

Can we go on to question 3 -- oh, no; summary. Sorry.

To sum up, there was probably some mixed views here. Some people felt, like I did, they had trouble with calling something abuse deterrent if it was only a single route and would cause people to -- like Dr. Sullivan said, in context, it has to be the route that's used most often.

I can't remember the other points I heard, but --

(Laughter.)

DR. LITMAN: I'm not sure there were any others. Can someone remind me?

(No response.)

DR. LITMAN: Okay. Question 3, discuss whether you have any concerns regarding the impact of Aximris XR on public health. Take into consideration its potential effect on abuse of extended-release oxycodone as well as potential consequences of administration of this product by unintended routes.

Dr. Zaafran?

DR. ZAAFRAN: Sherif Zaafran. This kind of goes back to what was said in question number 2, that from a public health standpoint, my concern would be, will this have the unintended consequence of pushing people to a different route where it might have even more drastic effects from the intranasal standpoint? So I'm conflicted.

The holy grail is something like what we

heard attempted by another drug, where it's the molecule but not the way that you're actually taking the drug. That seems to be the way you'd actually be able to slow this down. But I would suspect that abusers are going to go down the path of least resistance, and if that path of least resistance is taking it intranasally, then that's what they're going to do, and that's what we're going to see a lot more of.

So I worry from a public health standpoint we're going to see a lot more of that, and I'm concerned that it might have that negative effect.

DR. LITMAN: Dr. Zeltzer?

DR. ZELTZER: Lonnie Zeltzer. Given its molecular weight and size, even though the IV abuse route will be the least used or least common, unintended consequences may be thrombotic events with this, as we are now maybe starting to see with the OxyContin, at least the three cases in Australia and what we saw with Opana; so I'm concerned about that.

DR. LITMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Thank you. Sonia Hernandez-Diaz. From a public health point of view, I think with the evolution of the epidemic, we have realized that probably the way to reduce deaths from abuse would be to reduce people going in the path and reduce addiction, because when things are harder, they go to heroin. Probably if we want to have an impact, we have to start reducing the number of individuals exposed to opioids at all.

However, I'm conflicted because I have the feeling that we might be changing the rules of the game for the companies as they are working on this better, so I don't know what to tell you about that. But I think from a public health point of view, working at the deterrent when you are choosing the route to abuse it, it's maybe too late to have an impact. But again, that was not what was said to the companies when they started this process, so I'm conflicted about that.

DR. LITMAN: I'd like to know a little bit more about the current status of recreational users

or addicts using this nasally versus intravenously.

Dr. Amirshahi, what's your feeling about the relative uses of these pills these days?

DR. AMIRSHAHI: My disclaimer is I work in the D.C. area, so this may not be reflective of obviously the national trends. But in my practice, I see two specific populations. Because I think there's still a significant stigma associated with intravenous drug use, I have a discrete population that is like, I have a standard, I'm not going to shoot up, and they really rely on the nasal insufflation because of that; then I have patients that are IV drug abusers and they prefer that route.

I know that you mentioned that they're going to find a way to abuse it if they can get their hands on it, but I find that my IV drug abusing population generally really prefers the IV route and will use that whenever possible. So if they have the option between intravenous and nasal insufflation, they're going to choose the intravenous route.

So I think there are really two discrete populations. In the end, if they're in a bind and they're withdrawing, they're going to take whatever they can, but people I think do have their preferences as well.

DR. LITMAN: What are they insufflating? What are they sniffing? Is it the IR forms or the abuse deterrents?

DR. AMIRSHAHI: In my current population, we have people that generally do the -- we have a lot of people that snort heroin more than anything else, but we also have people that do mostly the immediate release, and also we have a large population that does Percocet just because it's so much more widely available than a lot of these other ones.

DR. LITMAN: Thank you. Any other comments or questions about question 3, the public health implications of Aximris?

(No response.)

DR. LITMAN: To sum up, I didn't hear any pros on the public health side. I heard a couple

of cons. One is that recreational users or abusers would want to shift to other forms, and that possibly a drug such as this, which is a deterrent at the IV route, is too little, too late.

Anything else I missed?

(No response.)

DR. LITMAN: Could we go on to question 4, please? Discuss whether the benefits outweigh the risks for the proposed indication. Discuss if any additional data are needed for this application to be approved.

Dr. Higgins, you start us off.

DR. HIGGINS: Jennifer Higgins. It may be a gut reaction more than it is based logically, but I guess I feel more comfortable with the standard of meeting several routes in order to be approved. It might just be difficult for me accept one single route because it breaks from the standard. I'm also dealing with a lot of other different thoughts and feelings about the risk-benefit ratio. I'm really torn, but that's what comes to mind initially.

DR. LITMAN: Thank you. Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. This question would be for the FDA with respect to just clarification. When we say the risks and benefits for the proposed indication, do we mean including abuse deterrence?

DR. ROCA: You're asking whether actually indicating in the label that it has the terms with respect to abuse, whether that actually has benefit-risk or are you just asking as to whether if it gets approved, and we know that they have data that shows that it cannot be abused through intravenous even if it's not mentioned, whether that has benefit-risk? Are you asking us to whether it would be labeled or whether it would just be the indication?

DR. ZACHAROFF: I'm really only asking about the indication. So we're talking about someone who needs medication around the clock, can't be treated successfully with other means, and can we just think of this as the proposed medical need indication for this medication or do we need to

include medical need plus the abuse deterrence in answering this question?

DR. ROCA: I think if you think of it from that standpoint, putting aside for the moment whether it actually gets labeled as to whether it's abuse deterrent or not, but just looking at it from that standpoint as you just described for that particular indication, I think you would still need to put it into your process as to the potential public health implications of having it approved, knowing what the product can and cannot do.

DR. ZACHAROFF: Okay. Thank you.

DR. LITMAN: I don't see any other names, so I'll weigh in a little bit. Sorry. Dr. Shoben?

DR. SHOBEN: Abby Shoben. To me, the comparison here, the relevant comparison here, is if this product were to replace all of the existing abuse-deterrent OxyContin, what would be the potential benefits and what would be the potential risks from a public health perspective?

The benefits I see are what I alluded to earlier in terms of potentially better abuse

deterrence by IV, and that's balanced against less abuse deterrence for the nasal route; that at least OxyContin has some crushed-resistant properties that this product does not. It's relatively easily manipulated for nasal abuse.

Then there's also the unknown risk of what happens if you're injecting it by IV. We can expect that it might be similar to how OxyContin behaves, but we don't actually know that, whereas there's at least several years of data of people unfortunately injecting the current OxyContin, and we know what that does.

DR. LITMAN: You think there's a favorable or unfavorable benefit-risk ratio, after all that?

DR. SHOBEN: I was just articulating my opinion.

(Laughter.)

DR. SHOBEN: So you're going to put me on the spot.

DR. LITMAN: Yeah.

DR. SHOBEN: That's what the vote is for.

(Laughter.)

DR. LITMAN: Ms. Robotti?

MS. ROBOTTI: Suzanne Robotti. I don't think that there is any unique benefit compared to what's already on the marketplace. It's a pain medication. It's going to work exactly the way that oxycodone does. So there are no new benefits and there are no new risks. It's going to have the same risks when used as prescribed. It's just like what's already there.

So the only question, really, is the benefits of its abuse-deterrent properties; are they a unique benefit that outweighs the unique risks of its abuse deterrent? In my opinion, I'm always most concerned about unintentional misuse that leads to addiction and abuse, somebody who chooses it by mistake and gets that hit or takes 2 too quickly and becomes confused and takes 3 and ultimately gets addicted.

So the oral route to me is by far the most important deterrent because that's where, if you're going to become an abuser of opioids or other products by mistake, it's going to come that way.

If you're intent on becoming addicted to something, if you wake up one morning and say I'm going to get addicted, that's not it. But most people who come through the opioid passageway of addiction, I believe do it inadvertently, and it would be through the oral. So to me that's the most important deterrent route.

DR. LITMAN: Dr. Sandbrink?

DR. SANDBRINK: Friedhelm Sandbrink. Going back to my concern about the addictive properties, what I would need is, really, some kind of studies about the liking or the drug take again for the intact product when it's taken as intended. Considering that we do have what is considered an abuse-deterrent formulation already for OxyContin, we need to compare to that. I just want to make sure that this isn't more likeable than what we currently have.

DR. LITMAN: Dr. Shoben?

DR. SHOBEN: I just wanted to make the comment that it's bioequivalent to the existing OxyContin, so I would expect that if you're taking

it intact the way it's prescribed, that it would be very similar to the existing drug.

DR. LITMAN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. My discussion on this question would be that I believe the benefits would be equal to what products are already on the market as we've heard. But taking into account more than just patient level of risk, I think that, based on all the discussion we've been having for all these questions, the public level risks probably in my mind outweigh the potential benefits. Thank you.

DR. LITMAN: Thank you Dr. Garcia?

DR. GARCIA-BUNUEL: Martin Garcia-Bunuel. I've been obviously listening and appreciate all the comments, and will kind of put this in some clinical context to understand from the indication. One way that I guess I put it out there for folks to think about is if I think about what I'm trying to do for a patient, and if I have a patient who needs, and there's an indication for a medication that provides an analgesia 24 hours for someone

with chronic pain, I already have the tools there.

Would a patient come through that I'm so concerned about their ability to abuse a drug like this in IV formulation that I would choose this medication because it has this deterrence that's better than the current product of OxyContin? No. This is not a medication that I know if I had a patient that I was that concerned about them injecting the drug, that I'd say I'm going to still use this because I think it's so hard for you to abuse it or misuse it.

So therefore, in my mind, practically speaking, I would never see using this medication to solve a problem in the care of a patient who needs it. Secondarily and lastly, really the question we seem to be asking is what about all those other people who may use this drug who we don't prescribe it to, which is other discussions this committee has had about naloxone and other things. We're putting a drug into the community and what are the effects of that to others?

In that situation, what I'm hearing from

Dr. Hoffer and others is that there are so many options for our patients and community members who are going to misuse and especially abuse drugs who have a substance-use disorder. I don't see this formulation as one that's going to impact that profoundly, and I think we're at a place, too, where I'm very, very concerned about adding more prescription opioids into a system, especially with all these unknowns, when we still have a long way to go in redefining how we treat pain.

DR. LITMAN: Thank you. Dr. Hoffer?

DR. HOFFER: Lee Hoffer. I think my struggle here is with the additional data needed. I want to get back to Dr. Hernandez-Diaz's comment, are we changing the rules here for ADFs? This company seems to have taken care of the IV route, and we all agree on that, but now we have a standard for people sniffing the drug.

So I think that it's tricky as to what additional data -- do we need data on all of the different routes and all of the possible combinations. There are lots of combinations for

people to abuse these drugs, so I think it's tricky to ask, well, what additional data do we need here?

DR. LITMAN: Thank you. Dr. Green?

DR. GREEN: Traci Green. I think I would have to say on the balance of the risk and also with the benefits, I think the benefits are similar to many of the medications that we have already in this extended-release formulation that we have. I'm worried about the additional risks, however, especially with the intranasal pathway being one for misuse and abuse, one of the more common ones, and the idea of having a known pathway for many of the people that I work with and study, who began misusing prescription opioids orally, started snorting, and some of them started injecting until they couldn't afford it anymore, and then heroin was more available.

This story has changed dramatically with ADFs and with prescribing restrictions, that the pathway may be, sure, you can snort a little bit, and then you move quickly to heroin, with the idea that this medication is actually quite easy to

insufflate, and it's also pretty easy to manipulate; to think about the concern about ADF status for one route, feeling this safety feature and being hard to communicate to the public, therefore, the intranasal route being seen as a safer one and misuse happening more in this route of administration, and then it would make very little population [indiscernible] risk; actually a difference in that.

So the sum of all parts suggests that the public health risks are greater by moving a medication like this into the marketplace. That's without even considering some of the injection-related risks that we know from the excipients and some of the data that are starting to come forward in Australia and other places and the unknown information around the molecular weights of the compounds.

So I think that in terms of the additional data, the thing that struck me that I'm still scratching my head around is the PK and the PD on the insufflation. I just don't understand

how -- to understand what's happening here, the disconnect between the Cmaxes being so high and the liking being so different with OxyContin and the PD data. But otherwise, I think the concerns around risks and benefits are tipping potentially in the area of greater risk for the public health.

DR. LITMAN: Thank you. Dr. Meisel?

DR. MEISEL: Steve Meisel. First of all, as an aside, I want to compliment the sponsor here. Two or three years ago, this committee reviewed the drug and declined to approve it, and they went back and worked with the FDA, did their homework, and did everything the FDA asked them to do, and I give them a lot of credit for that.

In terms of this question, would a physician look at this drug and say I want to prescribe this instead of OxyContin, or Xtampza, or whatever, I don't think that's realistic because if this drug were to be approved, the differences amongst the various ones that are out there will be opaque to individual providers. Nobody's going to be differentiating them to themselves.

The decisions will be made by UnitedHealthcare and Prime Therapeutics, and Medicaid programs, and all of those to decide whether we're going use product A, B or C. Part of that calculus will be on the basis of cost, but part of it will be on the basis of which one is going to give us the best chance of combating the opioid crisis.

If I'm in the position of UnitedHealthcare, or Prime, or a Medicaid program, and I've got two products, and one of them will be labeled for both nasal and IV, and another one is IV only, that's a no-brainer. I'm going to pick the one that's labeled for both. So a product like this, which would not have the nasal labeling for that, wouldn't even be considered in a situation like that.

So whether or not we approve it, I think the market share of it would end up being trivial because the people who would be in the position of making those evaluations would be the only ones that would see the differences, and it wouldn't be

individual providers. So I think in that sense, it's not the benefit-risk, it's that the benefit is not there compared to that of other products, so it wouldn't be used. That's the way I'm looking at this.

DR. LITMAN: Thank you. Dr. McCann?

DR. McCANN: I would also like to bring out if I were an insurance company, I might go for the cheaper product. Obviously, we don't evaluate that here, but I think that might be what they would think about.

But I just want to go back to slide 4 that the sponsor put up. The last point was, "FDA guidance anticipates innovation and incremental improvement of opioids with abuse-deterrent properties." I don't think this drug is an incremental improvement over what's already out there. I do think it's unfortunate for the sponsors that the game does change what we expect, but I think the FDA has let people know that if there's a better product out there, your product has to be slightly better.

DR. LITMAN: Thank you. Dr. McAuliffe?

DR. McAULIFFE: I was thinking about the novice versus the more experienced abuser, and I think that the risks of this are actually higher for the novice abuser. I'm thinking about the adolescent who is going to utilize PEO opioids and then crush them. I know that we say that the deterrence there may cause congestion and cause some irritation in the nose, but that may actually, by some adolescents, prove that the drug is working; that is the drug that they think it is, and they kind of work through that. People smoke cigarettes, and it's irritating, and they still smoke, or they smoke marijuana, and it still is irritating.

So I think for the novice abuser, instead of decreasing the risk of opioid abuse, I think it may actually increase the risk of opioid abuse.

DR. LITMAN: Thank you. Dr. Roca, did you have your name up? Did you want to comment?

DR. ROCA: Yes, a comment, but I wanted to wait until everybody was finished because it's sort

of not related to the discussion. I wanted to make sure that everybody was done.

DR. LITMAN: Are there any other comments?

(No response.)

DR. LITMAN: If not, I'll add mine before I sum up. I do not believe that the benefits outweigh the risks. There are two salient features here that we've heard today that are worrisome. Number one is it's only the IV route. That doesn't seem to be the most important route of abuse. Number two, I think the high concentrations, even though the PD appeared to be the same in their studies, just needs to be hashed out a little bit.

The obvious tests that would need to be done is what happens if you take more than just that amount? Well, you can't think of a way that you could do that ethically in humans. I'm not quite sure that would be a study that you could do with naloxone protection. That sounds kind of dicey to me. But I would certainly look into some kind of existing PK/PD, whether there are case reports, things like concentrations that have been found in

people's bloodstreams who have had respiratory depression and that sort of thing.

Do you want me to sum up before you give a comment, or do you want to comment first?

DR. ROCA: Actually, you can sum up because you addressed my comment.

(Laughter.)

DR. LITMAN: Excellent.

In speaking about the benefit-to-risk ratio, I did not hear anyone here in the room come up with a favorable benefit-to-risk ratio. Most everyone that spoke were concerned that it was too risky for a variety of reasons, at both a public and an individual label.

I did hear, as far as the additional data needed, that it would be difficult at this point to ask the company to go back and do something that they knew that the FDA had requested of them, and people were concerned about changing the rules. So overall, I just heard mostly an unfavorable benefit-to-risk ratio from our committee.

Did I miss anything?

(No response.)

DR. LITMAN: Okay. Let's keep going then.

Next is the vote. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are 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. Moon will then read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

DR. ZACHAROFF: Kevin Zacharoff; just a

clarifying comment. There's nothing in this vote or question about abuse deterrence, and I'm just bringing that out there.

DR. LITMAN: That's a good point.

Dr. Roca?

DR. ROCA: With respect to whether it would be labeled, et cetera; is that what you're asking?

DR. LITMAN: Yes. So the way it reads right now, there's no abuse-deterrent labeling in the vote.

DR. ROCA: Part of the thing we want to do is find out whether you think the product should be approved, period; then as to whether there's any labeling in it, we can certainly discuss that internally. But the question on the table is whether everything that you've heard makes you feel that this product actually should be approved.

DR. LITMAN: With an abuse-deterrent labeling? Maybe or maybe not is what you're saying.

DR. ROCA: Correct.

DR. LITMAN: Okay. So I'll read the

question or what we're voting on into the record.

Do you recommend approval of Aximris XR, oxycodone extended-release tablets, for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?

Please vote.

(Voting.)

DR. LITMAN: Everyone has voted, and the vote is now complete. Moon will bring it up and read off the votes to us.

DR. CHOI: For the record, we have 2 yes, 24 no, and zero abstentions.

DR. LITMAN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted as you did into the record. I think today, because Dr. Suarez, you needed to leave soon, we can start on this side of the room if that's okay with everyone.

Dr. Tyler? I remembered.

DR. TYLER: Thank you. Linda Tyler. I voted no. There's no question that for a new product to come on the market in this space, it has a high bar and it has to provide some advantages compared to what's on the market. I did not feel this offered any advantages and perhaps offered some disadvantages in that it is easy to manipulate the tablets. I was concerned about the nasal concentrations as I talked about before.

So while it may deter the IV dosage form and be dose deterrent in that way, the intranasal may in some ways be more concerning.

DR. MARSHALL: Brandon Marshall. I voted no for many of the same reasons that Dr. Tyler mentioned. I don't think I'll elaborate, but I agree with you on all points.

DR. SULLIVAN: Patrick Sullivan. I voted no for the same reasons as were described.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted no for the same reasons.

DR. ZAAFRAN: Sherif Zaafran. I voted no

for the same reasons.

DR. SANDBRINK: Friedhelm Sandbrink. I voted no for the same reasons.

DR. PISARIK: Paul Pisarik. I voted no for the same reasons, too.

DR. AMIRSHAHI: Maryann Amirshahi. I voted no for the same reasons as well.

DR. BLOCK: Laura Block. I voted no for the same reasons.

MS. ROBOTTI: Suzanne Robotti. I voted no for the same reasons.

DR. HIGGINS: Jennifer Higgins. I voted no because I don't believe the benefits outweigh the risks, but I feel like it's a very novel mechanism of action and product and does really represent sort of the camel's nose under the tent and may influence the production of new ADFs going forward.

DR. MEISEL: Steve Meisel. I voted no for reasons previously stated, and I'll just use this as an opportunity to once again implore the agency to come up with more objective guidelines for industry and for these committees in this space. I

think it's highly unfair for sponsors to put the time, effort, and money into developing these sorts of products based on what they think would be acceptable and approvable, only to find out that we've sort of changed the definitions as we go along; we make them up along the way.

I think it's incumbent upon the agency to be much more specific about what is and is not a -- what abuse deterrence means. Is it manipulation deterrence? Is it abuse deterrence? What are we really talking about here and how does one achieve that threshold?

DR. SHOBEN: Abby Shoben. I voted no. I think I struggled with this decision more than some of the others on the panel because I really do think there is a benefit in the improved IV deterrence with this product. In the end, my concern was around the nasal route and both the potential for the ease of accidentally stumbling into what happens if I try to insufflate it and the potential of the message getting out there that the nasal route is safer than the IV route, and that

that might cause some public health concerns.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no for the reasons stated in the discussion, and I second Dr. Meisel's points to the FDA.

DR. LITMAN: Ron Litman. I voted no. There are two components here. Number one is what we had talked about before with Dr. Zacharoff, and that is can this be approved with no abuse-deterrent labeling? I voted no on that because I'm concerned about the nasal route. If you want to consider the abuse deterrence, I'm not comfortable with just 1 out of the 3, especially the one that's hardly -- well, I shouldn't say hardly because I don't know the numerators; the one that's the least chosen for abuse.

Yeah. One of the two who watered. Yes.

DR. GOUDRA: I'm one of the two who voted yes. In fact, I was no until the last second. I changed my vote after hearing from the FDA that it's up to them to do the proper labeling.

DR. ZELTZER: Hi. Lonnie Zeltzer. I voted

no because I saw it as a washout; maybe less likely to be used via the IV route; maybe more likely for the intranasal and crushing it. In the end, it's another opioid, and I'm not sure we need yet another opioid, even if it's not labeled opioid resistant.

DR. McAULIFFE: I also voted no, and I think the increased risk of potential nasal abuse is not offset by the potential decreased risk in IV abuse.

DR. ZACHAROFF: Hi. Kevin Zacharoff. I'm the other yes. Like Dr. Goudra, I was probably a no until the answer to my question about the labeling because I think that as a non-abuse deterrent formulation, this drug holds its own compared to other drugs that are already on the market.

I guess the other piece of it for my yes vote is the fact that if we take the approach that we don't need another opioid on the market, then we don't have to have any meetings about new opioids on this committee as far as I'm concerned. I think that I would hang the sign out to prospective

sponsors saying "no more opioids."

I do believe that there was probably an incremental step in the right direction taken with this medication with respect to its ability to discourage intravenous abuse, but I don't ever personally think that a reason I'm going to vote no is because the last thing we need is one more opioid on the list. Thank you.

DR. McCANN: Mary Ellen McCann. I voted no for the same reasons that other people have stated.

DR. SETOGUCHI: Soko Setoguchi. I voted no for the same reasons.

DR. MICHNA: Ed Michna, and I voted no.

DR. HOFFER: Lee Hoffer. I voted no for the same reasons. I just wanted to state that I think the balance is just off here, the risk-benefit balance. I appreciate the comments about just saying no to any opiate. I also want to reiterate Dr. Meisel's point, but I also want to talk about Dr. McCann's point in that this is a shifting space when we're talking about abuse-deterrent formulations. What was abuse-deterrent formulation

in the past isn't necessarily what's going to be the same abuse-deterrent formulation in the future, and I think FDA needs to think about that.

DR. GREEN: Traci Green. I voted no for many of the reasons that my colleagues on the committee here articulated. I also would encourage a revisitation of the properties of abuse deterrence and some of the guidance that's provided to the sponsors and to the communities so that we have a better understanding of what we mean and what we're looking for. Is it the holy grail or is it something for public health, and how attainable is it, and what metrics we want to hold the sponsors to?

DR. GARCIA-BUNUEL: Martin Garcia-Bunuel. I voted no; overall, lack of new clinical utility to benefit patients. I did not appreciate that from the presentations. In terms of the bigger picture, I do appreciate the comments about what the scientists and the staff put into developing these agents. I think the mechanism, clearly there is something about that mechanism and its deterrents

for manipulating it and for the IV form. I don't want my no to be interpreted as wanting to squash that.

Having said that, I think, once again, from the FDA's perspective, I do think context matters. I think context continues to shift. I'm not sure about the level of communication that occurs between the FDA and industry about framing context and how do you anticipate context when the pipeline can take a long time. But I do think we do need to clarify some messages at the level of the FDA of what we're looking for to impact overall healthcare in the United States.

So unless there is some clarification, yeah, I'd probably say don't throw another opioid on the table because if these are the levels of increments that we're expecting to shift what we're attempting to do here, I would agree. I don't think it'd be worth anybody's while, and I don't think it's really going to benefit the healthcare system as a whole.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips.

I voted no, and I can echo some of the conversations that have already been had. Reading the FDA's latest draft guidance from June on the risk-benefit assessment, I think it acknowledges some of the struggles that FDA is having with this ongoing issue.

DR. LITMAN: Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. ROCA: Just to thank you for your time and your input. We really do appreciate it. Thank you.

Adjournment

DR. LITMAN: We kindly ask that all attendees dispose of any trash or recycling in the proper receptacles in the hallway and not leave any waste items on the floor or tables. Panel members, please remember to take all personal belongings with you, as the room is cleaned at the end of the meeting day. Please leave your name badge on the table so that it may be recycled. All other meeting materials left on the table will be

disposed of. We will now adjourn the meeting. Thank you.

(Whereupon, at 5:05 p.m., the afternoon session was adjourned.)