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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**DESIGNATED FEDERAL OFFICER (Non-Voting)****Moon Hee V. Choi, PharmD**

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P R O C E E D I N G S

(1:30 p.m.)

Call to Order

Introduction of Committee

1 DR. LITMAN: Good afternoon. My name is
2 Ron Litman, and I'm going to be chairing this
3 afternoon's meeting. I would first like to remind
4 everybody to please silence your cell phones,
5 smartphones, and any other devices if you have not
6 already done so. I'd like to also identify the FDA
7 press contact. Nathan Arnold.
8

9
10 Nathan, if you're here, can you stand up and
11 identify yourself? Thank you.
12

13
14 I'll now call the Joint Meeting of the
15 Anesthetic and Analgesic Drug Products Advisory
16 Committee and the Drug Safety and Risk Management
17 Advisory Committee to order. We'll start by going
18 around the table and introducing ourselves. We'll
19 start with the FDA to my left and go around the
20 table. When you introduce yourself, can you please
21 state your expertise?
22

DR. STAFFA: Good afternoon. I'm Judy

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

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

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

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

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

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

22 DR. GARCIA-BUNUEL: Good afternoon. Martin

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

4 DR. GREEN: Traci Green. I'm an
5 epidemiologist, and I'm a professor and director at
6 the Opioid Policy Research Collaborative at the
7 Institute for Behavioral Health, at The Heller
8 School for Social Policy and Management, at
9 Brandeis.

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

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

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

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

22 DR. ZACHAROFF: Good afternoon. I'm Kevin

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

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

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

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

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

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

1 Institute for Safe Medication Practices.

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

5 DR. SHOBN: Abby Shoben. I'm a
6 biostatistician at Ohio State.

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

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

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

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

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

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

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

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

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

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

22 DR. SULLIVAN: Patrick Sullivan. I'm an

1 infectious disease epidemiologist professor of
2 epidemiology at Emory University.

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

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

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

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

22 DR. LITMAN: Thanks, everybody.

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

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

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

3 **Conflict of Interest Statement**

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

16 The following information on the status of
17 these committees' compliance with federal ethics
18 and conflict of interest laws, covered by but not
19 limited to those found at 18 U.S.C. Section 208, is
20 being provided to participants in today's meeting
21 and to the public. FDA has determined that members
22 and temporary voting members of these committees

1 are in compliance with federal ethics and conflict
2 of interest laws.

3 Under 18 U.S.C. Section 208, Congress has
4 authorized FDA to grant waivers to special
5 government employees and regular federal employees
6 who have potential financial conflicts when it is
7 determined that the agency's need for a special
8 government employee's services outweighs his or her
9 potential financial conflict of interest, or when
10 the interest of a regular federal employee is not
11 so substantial as to be deemed likely to affect the
12 integrity of the services which the government may
13 expect from the employee.

14 Related to discussions of today's afternoon
15 meeting, members and temporary voting members of
16 these committees have been screened for potential
17 financial conflicts of interest of their own as
18 well as those imputed to them, including their
19 spouses or minor children, and for purposes of
20 18 U.S.C. Section 208, their employers. These
21 interests may include investments; consulting;
22 expert witness testimony; contracts, grants,

1 CRADAs; teaching, speaking, writing; patents and
2 royalties; and primary employment.

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

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

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

1 afternoon meeting and all financial interests
2 reported by the committee members and temporary
3 voting members, no conflict of interest waivers
4 have been issued in connection with this meeting.
5 To ensure transparency, we encourage all standing
6 committee members and temporary voting members to
7 disclose any public statements that they have made
8 concerning the product at issue.

9 With respect to FDA's invited industry
10 representatives, we would like to disclose that
11 Drs. Jay Horrow and Reema Mehta are participating
12 in this meeting as nonvoting industry
13 representatives, acting on behalf of regulated
14 industry. Drs. Horrow's and Mehta's role at this
15 meeting is to represent industry in general and not
16 any particular company. Dr. Horrow is employed by
17 Bristol-Myers Squibb and Dr. Mehta is employed by
18 Pfizer.

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

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

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

11 **FDA Opening Remarks - Rigoberto Roca**

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

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

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

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

1 excipients.

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

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

22 The second point will be for you to discuss

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

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

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

21 DR. LITMAN: Thanks, Dr. Roca.

22 Both the Food and Drug Administration and

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

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

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

22 We will now proceed with

1 Intellipharmaeueuties Corporations' presentation.

2 **Applicant Presentation - Isa Odidi**

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

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

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

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

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

17 The proportion of respondents indicate the
18 injected OxyContin decreased, but about 15 to
19 20 percent of the cases continue to involve
20 injection. An improved ADF that can potentially
21 address these vulnerabilities and improve upon
22 these statistics is a good thing.

1 Aximris XR was developed to address the gaps
2 in IV abused deterrence. Aximris XR represents
3 over a decade of didactic research and development
4 work involving comprehensive in vitro and clinical
5 studies. We have filed an NDA for Aximris XR under
6 the 505(b)(2) drug approval pathway using OxyContin
7 as the listed drug and comparator. The proposed
8 dose strengths range from 10 milligrams to
9 80 milligrams and are the same as OxyContin.

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

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

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

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

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

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

8 Here is the agenda for the rest of our
9 presentation. First, Dr. Aloba will discuss the
10 detailed results of the comprehensive set of
11 Category 1 abuse deterrence studies as well as
12 studies to assess excipient safety of Aximris XR.
13 Dr. Ruth Stevens will then discuss the detailed
14 results of the clinical pharmacology and Category 2
15 and 3 abuse-deterrent studies. Finally, I will
16 round up this presentation by summarizing Aximris'
17 benefit-risk profile and Intellipharma's risk
18 mitigation management and postmarket surveillance
19 plans.

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

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

6 **Applicant Presentation - Olu Aloba**

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

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

1 dangerous route of abuse.

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

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

1 method for grinding tablets.

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

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

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

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

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

1 extraction for IV abuse using common abuser
2 practices.

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

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

22 I will now provide information on advanced

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

8 On this slide, we see that a manipulated
9 Aximris XR is not syringeable in 2 mL of an
10 alcoholic solution at room temperature and elevated
11 temperature in contrast to OxyContin, where a
12 solution suitable for IV injection was obtained,
13 and the oxycodone recovery was between 53 percent
14 and 69 percent. In 5 mL alcoholic solution,
15 Aximris XR, as shown by the blue bars in the graph,
16 have markedly lower recovery compared to OxyContin,
17 which is shown in orange in different solutions and
18 different volumes. A similar trend is observed in
19 10 mL of alcoholic solution.

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

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

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

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

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

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

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

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

1 some ingestible and some not ingestible.

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

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

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

1 abuse-deterrent properties.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 effects were seen in any organ or system.

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

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

12 **Applicant Presentation - Ruth Stevens**

13 DR. STEVENS: Thank you.

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

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

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

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

20 FDA's criteria for bioequivalent specifies
21 that the PK parameters maximum concentration, C_{max} ,
22 and the area under the curve, AUC, the ratios and

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

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

15 Moving now to the multiple dose steady-state
16 bioequivalent study, this slide shows the study
17 results of the multiple-dose, steady-state study
18 between Aximris XR versus OxyContin. The multiple
19 dose steady state looked at 80 milligrams of
20 Aximris XR versus 80 milligrams of OxyContin every
21 12 hours. The three primary PK parameters were
22 examined at steady state. As demonstrated, the 90

1 percent confidence intervals and their ratios for
2 Cmin, Cmax, and AUC were contained within the 80 to
3 125 range. This demonstrates that Aximris XR was
4 bioequivalent to OxyContin at steady state.

5 The dose proportionality study was conducted
6 with Aximris XR 7 dosage strengths. A power
7 analysis model was applied and showed that the
8 slope estimates and 90 percent confidence intervals
9 for Cmax and AUC were contained within the 0.8 to
10 1.2 criteria. Aximris XR demonstrated dose
11 proportionality among all 7 dosage strengths.

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

22 Aximris XR demonstrated dose proportionality

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

8 I'll now discuss Category 2 and 3 studies
9 conducted by in Intellipharmaeueutics. The Category
10 2 PK studies were combined within the Category 3
11 human abuse potential studies. These studies were
12 designed in consultation with the FDA. OxyContin
13 and oxycodone immediate release were used as the
14 comparators.

15 I will now present the results of the
16 intranasal HAP study. Thirty subjects completed
17 the treatment phase and they each received
18 5 treatments in a crossover design. The intranasal
19 HAP study manipulated Aximris XR and OxyContin by
20 grinding them and comparing them to a crushed
21 oxycodone IR product.

22 The table presented here contains PK

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

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

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

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

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

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

1 statistically significantly different and appeared
2 to be the same.

3 Moving next to how subjects rate the ease of
4 snorting, subjects rated ease of snorting 5 minutes
5 post-dose on a VAS scale where 0 indicated the drug
6 was very difficult to snort and 100 very easy.

7 This bar graph shows the mean ease of snorting VAS
8 scores. Aximris XR was rated to be statistically
9 significantly more difficult to snort compared to
10 treatment shown.

11 Moving next to look at how subjects rated
12 local irritation effects and the reporting of
13 treatment-emergent adverse events collected during
14 this study, the subject rated assessment of
15 intranasal local irritation effects used a scale of
16 0 to 5; 0 indicating no effect and 5 the most
17 severe.

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

1 treatment-emergent adverse events were observed
2 with Aximris XR.

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

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

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

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

6 Turning now from the PK results to the PD
7 endpoints, here the PD endpoints drug-liking
8 VAS-E_{max} and take drug again VAS-E_{max} were not
9 statistically different between Aximris XR and
10 OxyContin in the manipulated state. Both Aximris
11 XR and OxyContin did not have statistically
12 significantly lower abuse potential compared with
13 oxycodone IR.

14 In summary, the findings from the intranasal
15 PK study, Category 2 data showed that Aximris XR
16 has higher C_{max} and partial AUCs, but similar
17 overall exposure to the active treatments. The
18 intranasal PD study Category 3 showed that Aximris
19 XR drug liking VAS-E_{max} and drug take again
20 VAS-E_{max} are not statistically significantly
21 different from that of OxyContin. Aximris XR was
22 rated more difficult to snort compared with

1 OxyContin and also displayed local irritating
2 effects.

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

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

13 **Applicant Presentation - Isa Odidi**

14 DR. ODIDI: Thank you, Dr. Stevens.

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

1 well-established safety and efficacy profile.

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

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

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

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

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

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

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

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

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

22 Evidence for this is the fact that a number

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

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

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

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

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

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

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

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

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

9 **Clarifying Questions**

10 DR. LITMAN: Thank you, Dr. Odidi.

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

19 Dr. McAuliffe?

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

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

6 DR. ALOBA: With respect to small volumes,
7 we were using volumes up to 10 mL of the different
8 solutions, solvents, that were used. That's
9 typically the volume that would be used by an
10 abuser for the purpose of intravenous injection.
11 The higher volumes were targeted at -- we used
12 30 mL for the multiple tablet extractions, and the
13 large-volume extractions, which were like 100 mL
14 and 200 mL, were geared towards oral abuse
15 preparatory to other types of manipulations that
16 would be typical in an abuse situation.

17 Did that answer your question?

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

22 DR. ALOBA: Yes. Could you please put up

1 slide 35?

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

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

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

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

3 I don't know if that answers your question.

4 DR. McAULIFFE: That does. Thank you.

5 DR. ALOBA: Thanks.

6 DR. LITMAN: Dr. Zeltzer?

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

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

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

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

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

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

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

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

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

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

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

6 DR. LITMAN: Dr. Sandbrink?

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

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

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

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

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

1 you put up OR-8, please?

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

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

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

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

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

18 DR. LITMAN: Dr. Tyler?

19 DR. ODIDI: Thank you.

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

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

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

5 DR. STEVENS: Yes?

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

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

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

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

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

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

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

16 DR. TYLER: Right.

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

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

22 DR. TYLER: Thank you.

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

5 Lee, please?

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

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

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

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

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

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

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

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

14 DR. LITMAN: Thank you.

15 We will now proceed with the FDA
16 presentations.

17 **FDA Presentation - Matthew Daubresse**

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

1 oxycodone and other opioids.

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

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

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

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

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

11 Immediate-release combination and
12 single-entity oxycodone prescriptions, in the
13 dotted lines above, made up the bulk of
14 prescriptions dispensed, whereas extended-release,
15 single-entity and combination oxycodone
16 prescriptions, in the solid lines below, make up a
17 much smaller proportion of total oxycodone
18 prescriptions dispensed.

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

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

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

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

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

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

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

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

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

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

1 opioids. Data from the National Vital Statistics
2 System and death certificates shows that the rate
3 of overdose deaths involving heroin and fentanyl
4 increased substantially from 2011 to 2016. The
5 rate of overdose deaths involving oxycodone
6 decreased from 1.8 per 100,000 people in 2011 to
7 1.6 in 2013, then increased to 1.9 deaths per
8 100,000 in 2016. Overall, the rates of overdose
9 deaths involving oxycodone appear to have remained
10 stable during this time period.

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

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

1 misclassification can also occur due to
2 self-report.

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

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

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

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

4 **FDA Presentation - Jaime D'Agostino**

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

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

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

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

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

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

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

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

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

1 studies.

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

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

16 The mixture was injected either as a single
17 dose or every 1.5 hours for a total of
18 5 injections. The plasma levels of PEO measured in
19 the animals were similar to predicted human plasma
20 levels based on the amount of PEO extracted from
21 Opana ER, indicating that the doses used in these
22 studies were human relevant. Animals dosed with

1 the PEO mixture demonstrated anemia, thrombotic
2 microangiopathy, and acute kidney injury consistent
3 with the adverse events observed in people.

4 Interestingly, these effects did not appear to be
5 due to a direct lack of blood compatibility.

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

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

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

4 PEO polymers are complex molecules of
5 different molecular weights depending on the number
6 of repeating units. Low molecular weight PEO
7 polymers under approximately 100,000 daltons are
8 often referred to as polyethylene glycols.
9 Polyethylene glycols of about 600 daltons or less
10 are liquids and are used in FDA-approved products
11 for IV administration. PEO polymers of
12 100,000 daltons or higher are often referred to as
13 polyethylene oxides.

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

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

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

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

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

1 7 compounds that were unique Aximris XR and 10
2 unique to OxyContin. Permissible daily exposures
3 were estimated from existing literature toxicology
4 data and compared to the levels detected in the
5 syringeable material. The analysis suggested a
6 relatively low risk for any given compound.

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

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

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

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

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

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

10 Here is the FDA's overall assessment of the
11 risk following IV exposure for Aximris XR.
12 Injecting any manipulated oral drug can result in
13 significant toxicity. Based on the limited data
14 available, Aximris XR is likely to have a similar
15 risk profile for unintended IV exposure as
16 OxyContin. If the high molecular weight PEO in
17 Aximris XR is able to be extracted into a syringe
18 and injected, we would expect similar results as
19 with Opana ER, such as thrombotic microangiopathy,
20 and it would be expected that these effects would
21 occur in a dose- and duration-dependent manner.
22 FDA cannot rule out the possibility that

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

7 **FDA Presentation - James Tolliver**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 recovery.

2 Under cycle 2, the focus was on heat
3 pretreated 80-milligram Aximris XR and
4 80-milligrams OxyContin tablets, whole and
5 manipulated. This was at the request of FDA, so
6 keep in mind what the difference is now. We're
7 talking about heat pretreated tablets, whereas in
8 the previous slide, I was talking about non-heat
9 pretreated; no pretreatment. A common solvent was
10 examined at starting volumes of 2, 5, and
11 10 milliliters.

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

18 In this study, intravenous infusion over a
19 1-minute time period of a solution containing 4.9
20 milligrams of oxycodone into non-dependent
21 recreational opioid users resulted in maximum
22 scores of 96.4 and 94.4 for drug liking and high

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

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

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

1 1.3 milliliters of solvent, which, upon analysis,
2 contains 16.3 milligrams of recovered oxycodone for
3 a concentration of 12.5 milligrams per milliliter.
4 Based upon the results of Colucci et al., such a
5 solution could very likely be used for intravenous
6 abuse in non-dependent recreational opioid users.

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

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

1 compared to OxyContin.

2 This slide provides some general comments to
3 come out of the table just shown. For heat
4 pretreated manipulated tablets, the volume and
5 milligrams of oxycodone recovered were less for
6 80 milligrams Aximris XR compared to 80 milligrams
7 OxyContin. For heat pretreated whole tablets, the
8 volume recovered and the milligrams of oxycodone
9 recovered were more similar between 80 milligrams
10 Aximris XR and 80 milligrams OxyContin with use of
11 a longer extraction time.

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

1 part.

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

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

22 Category 1 intravenous studies, as conducted

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

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

14 Generally, fluid in oxycodone recovered was
15 lower following use of 80-milligram manipulated
16 Aximris XR tablets compared to following
17 80-milligram manipulated OxyContin tablets. This
18 may suggest an incremental improvement of heat
19 pretreated Aximris XR tablets over heat pretreated
20 OxyContin tablets in deterring intravenous abuse.
21 However, again, it should be kept in mind that
22 OxyContin is a more difficult product to manipulate

1 than is Aximris XR. Thank you.

2 **FDA Presentation - Elizabeth Kilgore**

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

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

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

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

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

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

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

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

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

22 Abuse-deterrent opioid formulations are

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

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

20 DR. LITMAN: Thank you.

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

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

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

9 (No response.)

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

12 (No response.)

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

16 (No audible response.)

17 **Open Public Hearing**

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

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

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

6 For this reason, FDA encourages you, the
7 open public hearing speaker, at the beginning of
8 your written or oral statement to advise a
9 committee of any financial relationship that you
10 may have with the sponsor, its product, and if
11 known, its direct competitors. For example, this
12 financial information may include the sponsor's
13 payment of your travel, lodging, or other expenses
14 in connection with your attendance at the meeting.

15 Likewise, FDA encourages you at the
16 beginning of your statement to advise the committee
17 if you do not have such financial relationships.
18 If you choose not to address this issue of
19 financial relationships at the beginning of your
20 statement, it will not preclude you from speaking.
21 The FDA and this committee place great importance
22 in the open public hearing process. The insights

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

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

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

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

1 conflicts of interest.

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

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

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

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

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

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

1 compared to oxycodone IR tablets.

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

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

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

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

3 DR. LITMAN: Thank you.

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

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

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

16 We want to do clarifying? Thank you. Sure.

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

21 Do you still have clarifying questions?

22 Jay, you do?

1 DR. HORROW: Very quickly.

2 **Clarifying Questions (continued)**

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

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

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

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

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

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

4 So here you have the value of 600,000 for
5 Aximris. When you extrapolate, it is a zero shear
6 rate versus less than 300,000, between 250,000 and
7 300,000 for OxyContin. We didn't put up results
8 for 5 and 10 mL. We had for 50; I think it's in
9 the briefing document. The more liquid you use to
10 try and extract the product, the more viscous the
11 product is compared to OxyContin. So that's what
12 this was trying to show.

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

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

1 what that means.

2 DR. HORROW: Thank you very much.

3 DR. ODIDI: You're welcome.

4 Oh, you want to add?

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

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

1 DR. HORROW: Thank you.

2 DR. LITMAN: Dr. Amirshahi?

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

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

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

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

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

18 DR. AMIRSHAHI: May I?

19 DR. LITMAN: Absolutely, of course.

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

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

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

10 **Charge to the Committee - Rigoberto Roca**

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

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

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

19 **Questions to the Committee and Discussion**

20 DR. LITMAN: Thank you.

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

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

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

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

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

1 it actually favors intranasal abuse.

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

14 Dr. Meisel?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 Dr. Staffa?

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

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

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

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

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

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

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

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

14 Let's go on. Dr. Suarez?

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

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

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

14 DR. LITMAN: Thank you. Ms. Robotti?

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

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

8 DR. LITMAN: Dr. Shoben?

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

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

22 DR. LITMAN: Thank you. Dr. Hoffer?

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

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

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

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

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

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

1 DR. LITMAN: Got it.

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

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

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

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

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

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

9 Sorry. Dr. Zeltzer?

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

18 DR. LITMAN: Thank you.

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

1 some concern about the higher blood levels that
2 were achieved.

3 Did I miss anything?

4 (No response.)

5 DR. LITMAN: Should we go on to 2? Question
6 2, the applicant is requesting approval of Aximris
7 XR as an analgesic with properties expected to
8 deter abuse by the intravenous route. Discuss the
9 implications of approval of Aximris XR that can be
10 expected to deter abuse by a single route.

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

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

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

4 DR. LITMAN: Dr. Lowy?

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

13 Does that help?

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

20 DR. LITMAN: Dr. Sullivan?

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

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

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

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

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

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

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

4 DR. McCANN: Thank you.

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

7 Any other comments? Sorry. Dr. Shoben?

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

21 DR. LITMAN: Dr. Suarez?

22 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I

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

8 DR. LITMAN: Dr. Hoffer?

9 DR. HOFFER: Just really quickly --

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

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

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

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

11 DR. LITMAN: Thanks. Dr. Zacharoff?

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

1 just not be realistic.

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

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

11 (Laughter.)

12 DR. TYLER: Linda Tyler.

13 DR. LITMAN: Thank you. Dr. Tyler?

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

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

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

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

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

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

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

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

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

3 (Laughter.)

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

6 (No response.)

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

14 Dr. Zaafran?

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

22 The holy grail is something like what we

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

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

13 DR. LITMAN: Dr. Zeltzer?

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

22 DR. LITMAN: Dr. Hernandez-Diaz?

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

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

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

1 or addicts using this nasally versus intravenously.

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

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

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

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

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

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

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

20 (No response.)

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

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

5 Anything else I missed?

6 (No response.)

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

12 Dr. Higgins, you start us off.

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

1 DR. LITMAN: Thank you. Dr. Zacharoff?

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

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

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

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

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

12 DR. ZACHAROFF: Okay. Thank you.

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

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

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

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

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

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

15 DR. SHO BEN: I was just articulating my
16 opinion.

17 (Laughter.)

18 DR. SHO BEN: So you're going to put me on
19 the spot.

20 DR. LITMAN: Yeah.

21 DR. SHO BEN: That's what the vote is for.

22 (Laughter.)

1 DR. LITMAN: Ms. Robotti?

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

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

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

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

8 DR. LITMAN: Dr. Sandbrink?

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

19 DR. LITMAN: Dr. Shoben?

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

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

3 DR. LITMAN: Dr. Zacharoff?

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

13 DR. LITMAN: Thank you Dr. Garcia?

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

1 with chronic pain, I already have the tools there.

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

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

22 In that situation, what I'm hearing from

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

11 DR. LITMAN: Thank you. Dr. Hoffer?

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

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

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

3 DR. LITMAN: Thank you. Dr. Green?

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

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

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

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

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

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

7 DR. LITMAN: Thank you. Dr. Meisel?

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

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

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

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

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

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

6 DR. LITMAN: Thank you. Dr. McCann?

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

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

1 DR. LITMAN: Thank you. Dr. McAuliffe?

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

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

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

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

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

3 DR. LITMAN: Are there any other comments?

4 (No response.)

5 DR. LITMAN: If not, I'll add mine before I
6 sum up. I do not believe that the benefits
7 outweigh the risks. There are two salient features
8 here that we've heard today that are worrisome.
9 Number one is it's only the IV route. That doesn't
10 seem to be the most important route of abuse.

11 Number two, I think the high concentrations, even
12 though the PD appeared to be the same in their
13 studies, just needs to be hashed out a little bit.

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

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

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

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

7 (Laughter.)

8 DR. LITMAN: Excellent.

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

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

22 Did I miss anything?

1 (No response.)

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

3 Next is the vote. We will be using an
4 electronic voting system for this meeting. Once we
5 begin the vote, the buttons will start flashing and
6 will continue to flash even after you have entered
7 your vote. Please press the button firmly that
8 corresponds to your vote. If you are unsure of
9 your vote or if you wish to change your vote, you
10 may press the corresponding button until the vote
11 is closed.

12 After everyone has completed their vote, the
13 vote will be locked in. The vote will then be
14 displayed on the screen. Moon will then read the
15 vote from the screen into the record. Next, we
16 will go around the room and each individual who
17 voted will state their name and vote into the
18 record. You can also state the reason why you
19 voted as you did if you want to. We will continue
20 in the same manner until all questions have been
21 answered or discussed.

22 DR. ZACHAROFF: Kevin Zacharoff; just a

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

4 DR. LITMAN: That's a good point.

5 Dr. Roca?

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

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

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

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

21 DR. ROCA: Correct.

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

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

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

8 Please vote.

9 (Voting.)

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

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

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

1 Dr. Tyler? I remembered.

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

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

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

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

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

22 DR. ZAAFRAN: Sherif Zaafran. I voted no

1 for the same reasons.

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

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

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

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

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

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

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

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

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

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

1 that might cause some public health concerns.

2 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.

3 I voted no for the reasons stated in the
4 discussion, and I second Dr. Meisel's points to the
5 FDA.

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

17 Yeah. One of the two who watered. Yes.

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

22 DR. ZELTZER: Hi. Lonnie Zeltzer. I voted

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

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

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

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

1 sponsors saying "no more opioids."

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

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

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

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

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

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

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

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

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

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

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

22 MS. SHAW PHILLIPS: Marjorie Shaw Phillips.

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

7 DR. LITMAN: Thank you.

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

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

13 **Adjournment**

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

1 disposed of. We will now adjourn the meeting.

2 Thank you.

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

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