FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEES

Open Session

Wednesday, July 26, 2017

9:15 a.m. to 4:43 p.m.

FDA White Oak Campus

The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:15 a.m.)

Call to Order

Introduction of Committee

DR. BROWN: Good morning again. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, who is Lauren Smith Dyer, who is in the back, and she's standing up.

My name is Raeford Brown. I'm the chairperson of the Anesthetic and Analgesic Drug Products Advisory Committee, and I will be chairing this meeting. I will now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table to introduce ourselves, and we'll start with the FDA to my left and go around the table.

DR. HERTZ: Sharon Hertz, director for the

Division of Anesthesia, Analgesia, and Addiction Products.

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

DR. STAFFA: Judy Staffa, associate director for public health initiatives, Office of Surveillance and Epidemiology, Center for Drugs.

DR. TOLLIVER: James Tolliver, pharmacologist for the controlled substance staff.

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

DR. SHOBEN: Abby Shoben, associate professor of biostatistics, Ohio State University.

DR. ARFKEN: Cynthia Arfken, professor of psychiatry, Wayne State University.

DR. NOVAK: Scott Novak, director of psychiatric epidemiology and drug safety at Battelle Memorial Institute.

DR. SETOGUCHI: Soko Setoguchi, general internist and pharmacoepidemiologist at Rutgers University.

DR. GERHARD: Tobias Gerhard,

pharmacoepidemiologist at Rutgers University.

DR. HABEL: Laurel Habel, epidemiologist and associate director for cancer research at Kaiser Permanente.

DR. WARHOLAK: Terri Warholak, professor of quality and safety at University of Arizona.

DR. MEISEL: Steve Meisel, director of patient safety, Fairview Health Service in Minneapolis.

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

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

DR. LITMAN: Ron Litman. I am pediatric anesthesiologist at the Children's Hospital of Philadelphia and the medical director of the Institute for Safe Medication Practice.

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

DR. ZELTZER: Lonnie Zeltzer, distinguished professor of pediatrics, anesthesiology, and psychiatry, UCLA School of Medicine and director of the Pediatric Pain and Palliative Care program.

DR. GALINKIN: Jeff Galinkin, professor of anesthesiology and pediatrics at University of Colorado and medical safety officer at CPC Clinical Research.

DR. McCANN: Mary Ellen McCann, pediatric anesthesiologist at Boston Children's Hospital and Harvard Medical School.

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

DR. HIGGINS: Jennifer Higgins, AADPAC consumer representative.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant, patient representative and sociologist, National Coalition of Independent Scholars.

MS. ROBOTTI: Susanne Robotti, consumer representative and founder of MedShadow, and executive director of DES Action.

DR. CAMPOPIANO: Melinda Campopiano, senior medical advisor, Center for Substance Abuse Treatment at the Substance Abuse Mental Health Services Administration.

DR. KLINE: Rick Kline, drug design chemist and program lead for the National Institute on Drug Abuse drug supply program.

DR. NELSON: Lewis Nelson. I'm an emergency physician and medical toxicologist from Rutgers, New Jersey Medical School in Newark.

DR. MENDELSON: John Mendelson. I'm an internist in San Francisco, professor at the University of California San Francisco, a senior research scientist at Friends Research Institute, and founder of DXRX.

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

DR. BROWN: Good morning and thanks for coming.

For topics such as those being discussed at

today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details about this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Moon Hee Choi, who will

read the conflict of interest statement.

Conflict of Interest Statement

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

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

The following information on the status of these committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in

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

Related to the discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing,

patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application, or NDA, 209653 for oxycodone hydrochloride extended-release oral tablets, submitted by Intellipharmaceutics Corporation with the proposed indication of management of moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time.

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

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

members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Nabarun Dasgupta has disclosed that he

is a part-time employee at the University of North Carolina at Chapel Hill, where his research during the past five years has been funded by NIH and CDC. He is also a member of the scientific advisory board of the RADARS system and a part-time employee of the Denver Health and Hospital Authority, or DHHA, a political subdivision of the state of Colorado.

DHHA independently owns and operates the RADARS system, which is supported by subscriptions from pharmaceutical manufacturers for surveillance, research, and reporting services. Denver Health retains exclusive ownership of all data, databases, and systems. Subscribers do not participate in data collection or analysis, nor do they have access to the raw data.

Neither the preparation of Dr. Dasgupta's presentation nor his participation in today's meeting was supported by the RADARS system. As a guest speaker, Dr. Dasgupta will not participate in committee deliberations, nor will he vote.

We would like to remind members and

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

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

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

FDA Introductory Remarks - Sharon Hertz

DR. HERTZ: Good morning. Advisory committee members, invited guests, all here and those watching remotely, thank you for attending this meeting and taking time from your busy schedules.

At this joint meeting of the AADPAC and DSaRM, we will be discussing application from Intellipharmaceutics for a new extended-release

formulation of oxycodone, designed with properties intended to deter abuse by the nasal and intravenous routes, although the sponsor is only seeking labeling for the intravenous route at this time.

Proposed indication is the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Prescription opioid analgesics are under intense scrutiny, appropriately at present, and each new product that proposes to make claims based on labeling must have data suitable to support those claims, including claims of abuse-deterrent characteristics.

While we've approved 10 opioid analgesic products with labeling describing abuse-deterrent characteristics, there is still much we need to know about the ability of formulations to deter abuse.

In spite of efforts to carefully convey that abuse-deterrent opioid analgesics are still

abuseable, can still result in death due to overdose, and can still lead to addiction, we are learning there appears to be a great misunderstanding among some prescribers that abuse-deterrent properties mean the product is safer, abuse proof, or less addictive, all of which are absolutely not true.

As you may recall, products listed under Schedule II of the Controlled Substances Act have a high potential for abuse, which may lead to severe psychological or physical dependence. The current abuse-deterrent opioid analgesics remain in Schedule II because they have a high potential for abuse, which may lead to severe psychological or physical dependence.

The guidance for industry, evaluation, and labeling of abuse-deterrent opioid analgesics is our attempt to provide a series of recommendations for studies to be conducted to describe abuse-deterrent properties and the appropriate labeling to reflect those findings.

The results of the applicant's in vitro

physical and chemical manipulation studies will be presented during this meeting. However, no clinical studies of the pharmacokinetic effects of manipulation or pharmacodynamic endpoints were conducted as recommended in the guidance.

Because it's not possible to safely conduct human studies of manipulated oral formulations by the intravenous route, for products with physical chemical properties intended to deter intravenous abuse, we rely on the in vitro assessment of the ability to manipulate the product for extraction or to form a solution suitable for injection. However, it is possible to do clinical studies of pharmacodynamic endpoints for products by the oral and nasal routes of administration.

There are currently no data that establish clear criteria for the relationship between in vitro properties and abuse-deterrent effects for abuse by the oral and nasal routes.

Yes, we think smaller particle size may result in greater absorption of the opioid across the nasal mucosa, but depending on the properties

of the excipients, the particle size alone may not be enough to predict the rate and extent of absorption of the opioid.

Even when we have the pharmacokinetic data of the opioid from a manipulated abuse-deterrent formulation administered by one of these routes, we don't have enough data to predict whether the rate and extent of absorption will result in any meaningful difference compared to other non-abuse-deterrent or other abuse-deterrent products.

In the important pharmacodynamic endpoints of drug liking, drug high, or willingness to take the drug again; hence, the use of human abuse liability studies to establish that for the specific PK profiles observed, there is or is not an effect on these endpoints.

Basically, we ask the study subject to tell us whether they would want to abuse the drug again. We have no better alternative endpoints and generally reject arguments that small differences in the amount of drug high or liking that do not influence the decision to abuse the drug again are

meaningful.

While the development of abuse-deterrent opioid analgesic formulations is considered one important element in reducing prescription opioid abuse, the product must not create undue risk for the patient taking it as directed for the management of pain.

In April of 2010, an advisory committee was held to discuss a product that contained niacin, intended to minimize the potential for oral abuse of the opioid. In addition to the committee disagreeing with the sponsor's interpretation of deterrent effects, the committee concurred with our interpretation that it was unacceptable to subject patients to additional side effects associated with exposure to niacin.

It's also important to avoid unintended consequences for individuals who abuse prescription opioids. As discussed at the March 2017 advisory committee meeting, reformulated Opana extended-release, Opana ER, was associated with a thrombocytopenic microangiopathy and an outbreak of

HIV among individuals who were abusing the product by intravenous administration. These were unacceptable and unexpected findings.

Further, data presented at this March advisory committee suggested that the introduction of reformulated Opana ER was associated with a shift from nasal to intravenous abuse, a riskier route of abuse also unacceptable.

You will hear presentations from the applicant regarding their findings. The agency will present our approach to the development of abuse-deterrent opioid analgesic formulations based on the guidance for industry issued in 2015. You will also hear presentations regarding the safety of excipients as it relates to intravenous abuse of opioid-deterrent analgesic formulations and the behavior or effects of persons who abuse opioids and what may or may not affect those behaviors.

We do not have postmarketing data to present for the spectrum of approved opioid analgesics with abuse-deterrent labeling, and I know that's frustrating to some of you. For a number of

products, this is a result of a number of challenges in the availability of data to describe the impact of these products on abuse as discussed at our recent public meeting just a couple of weeks ago.

As well as a chicken-and-egg situation, where in the absence of data providing a rationale for the higher cost of these products, there is low market penetration. But the low market penetration limits the ability to collect the data.

However, some sponsors have enough data to publish postmarketing epidemiology studies for their products, such as Purdue, but have not yet taken the opportunity to bring their data to this setting for an open scientific discussion. We look forward to that opportunity.

So as with our prior AC meetings, we will ask you to use our best judgment to address our questions with the limited information available. Further, we are working to find out how to determine whether products that are able to deter attempts at abuse by certain routes, whether these

result in a reduction in the overall abuse problem or if they're deflecting abuse to other illicit or illicit opioids, we will appreciate hearing your discussion about whether the sponsor has demonstrated abuse-deterrent properties for their product and whether the data support labeling and, overall, whether the benefits of the product outweigh its risks, and whether it should be approved.

As always, we recognize these are difficult questions and the answers aren't easy. That's why we're here, asking for your advice. We're asking you to provide your expertise, and experience, and best insights to help us find a reasonable and responsible path forward.

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

DR. BROWN: Thank you, Dr. Hertz.

Both the Food and Drug Administration and

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

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

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

We will now proceed with Intellipharmaceutics's presentations.

Applicant Presentation - Isa Odidi

DR. ODIDI: Good morning. My name is Dr. Isa Odidi, and I am the CEO and the co-chief scientific officer of Intellipharmaceutics. I'd like to thank the FDA and the committee for allowing us to present our data today.

We're here to discuss our NDA for our oxycodone extended-release tablets that use chemical barriers and aversion technologies to discourage abuse. For this presentation, we'll refer to our product as IPC Oxy.

IPC Oxy is an opioid agonist indicated for pain severe enough to require daily around-the-clock long-term opioid treatment and for which alternative treatment options are inadequate. IPC Oxy is intended for adults and opioid-tolerant pediatric patients, 11 and older, who can tolerate a minimum daily upper dose of at least 20 milligrams oral oxycodone or its equivalent.

We have filed an NDA for IPC Oxy under 505(b)(2) drug approval pathway, using OxyContin as the reference listed drug. Our category 1 studies

compare IPC Oxy to OxyContin. The proposed dosage strengths, which range from 10 to 80 milligrams, are the same as OxyContin. Our product was designed so a patient taking OxyContin could easily transition onto IPC Oxy. Bioequivalence data demonstrated that patients will receive the same therapeutic amount of oxycodone with IPC Oxy.

IPC Oxy is also bioequivalent to itself under fasting and fed conditions. That means there's no significant food effect. Patients can take IPC Oxy without regard to meals. It's also important to note that there's no dose dumping with alcohol.

In regard to abuse deterrence, IPC Oxy and OxyContin have some similar characteristics, but IPC Oxy has additional features that provide an incremental improvement in abuse deterrence over OxyContin. Both products offer resistance to physical manipulation and chemical extraction, and both form a viscous gel on contact with liquid to resist IV injection.

However, IPC Oxy gels more quickly. Its gel

is generally 3 times more viscous than that of OxyContin. And importantly, IPC Oxy is more resistant to pre-treatment strategies featured on internet that are commonly used by abusers. IPC Oxy also contains a nasal irritant to discourage snorting. It also contains an intense staining blue dye that is released if the tablet is crushed or chewed.

On the next slide, we will show a video of what happens when both products are exposed to pre-treatment according to an internet recipe that is commonly used to defeat OxyContin. Subjected to the same conditions for the same period of time, IPC Oxy turns into a thick blue gel while OxyContin is still relatively liquid.

As you will see later in the presentation, these features result in IPC Oxy being more difficult to draw into a syringe and having superior IV abuse deterrence for common methods that abusers use to defeat abuse-deterrent formulations.

The blue color you saw in the previous slide

is released whenever IPC Oxy is crushed or chewed. The dye stains. It is difficult to remove from the hands, face, or clothes. Removing it requires intense scrubbing with a brush for about 30 to 40 minutes. We developed this feature as a potential deterrent to abusers, but for another reason as well.

When somebody becomes a serious abuser, and especially in cases of overdose and death, it is not uncommon to hear family and friends saying things like, "If only we had known, maybe we could have done something." It's our hope that the dye could discourage abusers, but also act as an early warning signal for family, friends, and coworkers so their loved ones have a greater chance of getting help for the progress to more serious abuse.

We decided to pursue the IV abuse deterrence label rather than wait for the abuse deterrence studies to be completed because we want the product to be available to physicians and patients sooner rather than later.

We believe that there's a need for innovation and improvement over currently available abuse-deterrent formulations. Data show that other ADFs, including OxyContin, are still being abused intravenously. While these products can be still taken when used as intended, they are not supposed to be injected and neither is IPC Oxy.

The difference is that our product is very unlikely to be abused by the IV route because of the difficulty in preparing it for injection. In category 1 studies, IPC Oxy showed similar or superior IV abuse deterrence over OxyContin. We think this is important because of the dangers involved with IV injection.

Excipient safety is another issue we have carefully considered. The data show that the blue dye and the nasal irritant SLS do not pose unintended safety risks when the product is taken as intended.

There are limited data to suggest that excipients are safe when taken by non-intended routes. However, like all ADFs, we will include

all appropriate warnings against injection, crushing, snorting, or tampering with the product in any way. And finally, although we are only seeking a label for IV abuse deterrence at this time, we did design IPC Oxy to deter abuse by other routes, and our category 1 data suggests that it will.

We expect that the blue dye and the nasal irritant would act as a deterrence. However, we understand the evidence concern and recognize that we will need human abuse data for an explicit label on other routes of abuse. We will collect the data in the future, and we will seek to update the label at that time.

Consistent with our current level of evidence as well as with standard ADF language, we are proposing the following label language. The in vitro data demonstrate that IPC Oxy tablets have physical chemical properties expected to deter intravenous abuse. However, abuse of these tablets by this route as well as by the oral and intranasal routes is still possible.

We also are proposing the following labeling warning. If crushed or chewed, IPC Oxy tablets release an intense blue dye that can stain skin as well as oral and nasal cavities.

Now, I want to take a moment to discuss another issue that is likely on your mind. This past March, advisory committees reviewed data suggesting that reformulated Opana ER was associated with cases of thrombotic thrombocytopenia purpura or TTP-like illness. The FDA presented data suggesting that these cases were caused by IV injection of the polyethylene oxide, or PEO, in reformulated Opana ER.

At the request of FDA, Opana was withdrawn from the market earlier this month. During that advisory committee meeting, the FDA presented data on cases of thrombotic microangiopathy, or TMA, of which TTP is a subset in Opana ER compared to various other deterrent opioids.

Because IPC Oxy is most similar to OxyContin, we will show you that comparison. The FDA found an extremely low incidence of TMA

associated with the injection of OxyContin compared to Opana ER. From the time Opana was reformulated in 2011 until June 2016, there were 59 cases of TMA with Opana ER in the U.S. OxyContin was associated with 2 cases.

This difference is even more dramatic when you can see the number of prescriptions written during that time period, approximately 750,000 for Opana ER versus 24 million for OxyContin. This translates into a rate of nearly 8 cases per 100,000 prescriptions for Opana compared to less than .01 for OxyContin.

While we don't know why the risks appear significantly lower with OxyContin, the FDA has commented that reformulated Opana ER can be readily prepared for injection. It also contains a different type of PEO than OxyContin.

IPC Oxy is even more resistant to IV abuse than OxyContin. It also contains the same PEO as in OxyContin. This information suggests that IPC Oxy's TMA-related safety profile would be similar or even better than that of OxyContin.

Here now is the agenda for the rest of our presentation. Dr. Richard Dart will present the rationale for abuse-deterrent opioid pain medications that provide incremental improvement over current ADFs as well as the need for innovative approaches to abuse deterrence.

Dr. Beatrice Setnik, vice president for scientific and medical affairs at INC Research, will discuss the clinical pharmacology of IPC Oxy. Dr. Edward Cone, a recognized world expert on the chemistry and pharmacology of drug abuse, will present the category 1 studies that demonstrate similar or superior IV abuse deterrence to OxyContin.

Dr. Edward Sellers will provide the public health perspective on abuse deterrence and IPC Oxy and close our presentation. In addition, we are joined by toxicologist Dr. William Brock to answer questions on the safety of excipients. All of our speakers' organizations have been paid for their time and expenses. No one has a financial interest in the outcome of this meeting.

Thank you for your attention. I will now call on Dr. Dart to the lectern.

Applicant Presentation - Richard Dart

DR. DART: Good morning. My name is Rick Dart, and I'm the director of the Rocky Mountain Poison and Drug Center and a professor at the University of Colorado. I'm also executive director of the RADARS system, which studies prescription drug abuse and aversion in the United States. Today, I'll explain why I feel we need additional opioids with abuse-deterrent properties on the U.S. market.

Nearly every day, the news tells us that the number of opioid deaths in the United States is increasing. It's important to realize that these increased rates are primarily due to heroin and illicit synthetic opioids like fentanyl rather than prescription opioids.

The National Vital Statistics System, or NVSS, data from CDC show that deaths in the natural and semi-synthetic opioid group, which includes oxycodone, shown in purple on this slide, have

plateaued since 2011, but they remain at historic high rates. In 2015, there were almost 13,000 deaths in this category alone.

We can't tell from the CDC data what routes of abuse were involved in these deaths. The poison centers do record the route of abuse involved in each case they receive. In the RADARS poison center program, injection was involved in 15 to 20 percent of the fatal intentional abuse cases. While poison centers receive only 5 to 10 percent of the fatalities that are reported to NVSS, the trends correlate between the programs reasonably well.

Now, we can't directly apply this proportion to the NVSS data certainly, but I think we can say that injection remains a substantial problem among the prescription opioids.

Compared to simple ingestion, the risk of death or a major adverse effect in the RADARS poison center program was found to be 2.6 times greater when the case involved intravenous injection. And of course, there are other

consequences of IV abuse as well. The CDC recorded in 2015 that 6 percent of new HIV diagnoses and 10 percent of new AIDS diagnoses were attributed to some type of IV abuse.

Injecting an opioid like oxycodone also puts the abuser at risk for other bloodborne infections like hepatitis C and endocarditis, not to mention blood clots and other problems.

The potential benefits of reducing injection can be seen in these data from the RADARS RAPID program, which show that reformulated OxyContin is still snorted and injected. RAPID is a subset of Dr. Ted Cicero's SKIP program and consists of a cohort of individuals in substance abuse treatment. These data were from 244 individuals distributed across the United States who abused OxyContin before and after its reformulation and answered the question, "Which of the following applied to your use of both new and old formulations of OxyContin to get high or to alter your mood?"

Almost 45 percent of patients responded that they switched from injecting or snorting to

swallowing. This in itself is a beneficial change. Thirty-five percent of the patients indicated that they continued to inject or snort OxyContin, so injection of oxycodone ER remains a problem.

We see the same result in epidemiologic data from the RADARS poison center program. The proportion of respondents indicating they injected OxyContin has decreased over time, but still about 15 to 20 percent of the cases continue to involve injection.

So how could an additional abuse-deterrent formulation help with this problem? There are three general types of opioid abusers, although the groups do overlap. There are of course legitimate pain patients who are simply trying to obtain pain relief. We know a small portion will go on to abuse their medication, and an even smaller number will end up with opioid use disorder.

For those just beginning to abuse, an abuse-deterrent formulation may deter them from crushing to speed up and intensify the drug effect. ADFs can present a barrier to the intranasal and IV

abuse because these patients haven't developed severe abuse behaviors yet and should be less committed and knowledgeable about overcoming the abuse-deterrent mechanism.

The effects would be similar in many novice or recreational abusers who are experimenting with opioids. An effective abuse-deterrent product could create a barrier to snorting or injection, an important feature since these routes, especially the IV route, are inherently more dangerous.

For advanced abusers, an abuse-deterrent formulation may well deter them from snorting or injecting that product, but it will not stop their larger opioid abuse problem. They will likely switch to another drug or, as we saw, switch back to oral abuse.

What these individuals need is substance abuse treatment. An abuse-deterrent product can't completely stop abuse, but it is clear from both quantitative data as well as chatrooms and blogs that these products do create significant barriers to risky routes of abuse.

So why do we need more ADF options? Well, first, the current products have not eliminated intravenous abuse of ER oxycodone, and second, improved ADF options are needed to address vulnerabilities in currently available products.

Third, the development of innovation in opioid abuse deterrence was anticipated and encouraged in the FDA guidance. IPC Oxy, which you're about to hear more about, is an example of some innovative thinking in that area. Thank you for your attention, and I'll turn this over to Dr. Setnik now.

Applicant Presentation - Beatrice Setnik

DR. SETNIK: Good morning. I'd like to thank the FDA and the panel for the opportunity to present today. My name is Beatrice Setnik, and I am the VP of medical and scientific affairs for INC Research and an adjunct professor with the Department of Pharmacology and Toxicology at the University of Toronto. Today, I'll review the clinical pharmacology of IPC Oxy, including its bioequivalence to the comparator OxyContin.

Here is an overview of my brief presentation. I will cover the bioequivalence, dose proportionality, and assessment of food effects of IPC Oxy. The studies that I will present today were conducted under naltrexone cover, and all fed states were administered as standard high-fat meals.

This graph shows the ratios and confidence intervals for maximum plasma concentrations, or Cmax, in area under the curve, or AUC values, comparing 10 milligrams of IPC Oxy to OxyContin.

Values below a least square or LS mean ratio of 100 percent indicate that oxycodone concentration was lower with IPC Oxy than with OxyContin, whereas values greater than 100 indicate higher concentrations with IPC Oxy; and FDA's criteria for bioequivalence specifies that the 90 percent confidence intervals around the ratio should fall within the range of 80 to 125 percent, which is shown by the gray shading.

This criteria serves as a basis for drug approval. As you can see, 10 milligrams of IPC Oxy

met the bioequivalence criteria under both fed and fasted conditions.

Looking at the confidence intervals of the 80-milligram dose for Cmax, AUC last, and AUC infinity, we see that IPC Oxy met the bioequivalence criteria under both fed and fasted conditions.

This slide shows the results of the Multiple Dose study. This study involved the administration of 80 milligrams of IPC Oxy and OxyContin every 12 hours for 3 days in 24 healthy volunteers. The pharmacokinetic parameters were examined at steady state. As you can see, the LS means and 90 percent confidence intervals for Cmax and AUC were contained within the 80 to 125 percent range. This demonstrates that IPC Oxy was equivalent to OxyContin at steady state.

Moving now to the dose proportionality study, this was a randomized 7-period crossover open-label laboratory-blind study. IPC Oxy was given as 7 single oral doses ranging from 10 to 80 milligrams. Blood samples were taken up to

24 hours post-dosing. The subjects included healthy male adults aged 18 to 50 years old, tested under fasted conditions, and 22 subjects completed the study.

This slide shows the results. The power estimates and 90 percent confidence intervals for Cmax and AUC were contained within the 0.8 to 1.2 criteria. This demonstrates that IPC Oxy is dose proportional between all 7 doses.

This graph provides the least square means for the long-transformed pharmacokinetic parameters of Cmax and AUC infinity for each dose. Plots of these least-square means illustrate the dose proportional responses obtained in this study.

Finally, a PK study was conducted to determine if there was a clinically significant food effect. This figure illustrates the plasma oxycodone concentrations over time, comparing fed, indicated by the gray line, and fasted states, indicated by the blue line. As you can see, the curves appear similar. In addition, the LS means and 90 percent confidence intervals for Cmax and

AUC were contained within the 80 to 125 percent range, demonstrating that there is no food effect with IPC Oxy.

In summary, IPC Oxy was shown to be bioequivalent to OxyContin. This supports the approval of the 505(b)(2) application and forms a scientific bridge to a well-established safety and efficacy profile. It was proportional between all 7 doses, and there was no clinically significant food effect. And therefore, patients can take medications without regards to meals.

Thank you for your attention. I would now like to invite Dr. Edward Cone as the next speaker.

Applicant Presentation - Edward Cone

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

on Drug Abuse.

The sponsor conducted a series of in vitro studies to evaluate the physical and chemical abuse-deterrent properties of IPC Oxy in consultation with Pinney Associates and in accordance with the 2015 FDA guidance.

In all relevant studies, OxyContin was used as the abuse-deterrent comparator. The selection of tools, solvents, and conditions followed a systematic approach. First, an exploratory phase was conducted to manipulate the products using common practices employed by abusers for different routes of abuse.

Next, we standardized and optimized conditions for inclusion in formal studies and to include worst-case scenarios. These studies include both common methods used by abusers as well as extreme laboratory manipulations that abusers are unlikely to use in the real world.

Here are the category 1 abuse-deterrent studies I'll present, experiments with various household tools to reduce the particle size of IPC

Oxy and OxyContin; syringeability and injectability studies of both drugs to evaluate resistance to IV abuse; large-volume extraction studies to evaluate resistance to chemical extraction in a variety of solvents; an in vitro study to assess the risk of alcohol dose dumping; a dissolution study to evaluate drug release of manipulated IPC Oxy and OxyContin tablets; a study to assess the ability of various solvents and chemicals to eliminate the blue dye from IPC Oxy; and finally, a simulated smoking study to assess the feasibility of smoking these products.

I'll now review the particle-size reduction experiments. Ten household tools were selected that represent the different methods an abuser might use to decrease the particle size of solid opioid dosage forms, including cutting, crushing, grating, and grinding.

Trained laboratory technicians applied each tool to IPC Oxy and OxyContin. The resulting particle-size distribution was measured by sieve analysis. On this slide, the X-axis shows each of

the 10 tools used, and the Y-axis represent the percent of particles smaller than 600 microns. Tools 2, 4, and 8 are not shown here because they were unable to reduce either product in defined particles, so sieve analysis was not feasible.

Given tablet hardness is not the primary abuse-deterrent feature of IPC Oxy, it yielded a somewhat higher percentage of small particles across the various tools in comparison to OxyContin. Tool 10 was further evaluated because adding additional tablets to this tool can produce smaller particle sizes. Particle size reduction procedure was optimal when grinding 20 tablets for 3 minutes.

So the next slide shows particle-size distribution of both products using tool 10. While IPC Oxy had finer particles in both cases, 99 percent of the particles were reduced to less than 600 microns, and that's for both products. This range is suitable for snorting. However, it is important to note that the smaller particle sizes yielded by IPC Oxy actually increased gelling

and did not increase drug release or extraction.

Next, I'll discuss the studies that evaluated the potential for IV abuse. First, I'll discuss the common methods found on the internet that abusers use to prepare intact or manipulated tablets for IV injection. Abusers first crush the tablet and extract the drug in 1 or 2 milliliters of water in a spoon.

They may heat the spoon with a lighter to accelerate drug release. When ready to inject, most will syringe the material through a piece of cotton or a cigarette filter to avoid clogging of the needle or injecting particulates. Most abusers only use a 27- or 29-gauge needle, although some may use larger syringes and needles with smaller gauges.

Most abuse-deterrent formulations are designed to resist common methods for IV abuse. For IPC Oxy, we went further and evaluated common and more advanced methods from internet recipes. Both IPC Oxy and OxyContin are formulated to deter IV abuse by producing a highly viscous gel when

hydrated. IPC Oxy also has excipients to enhance the gelling feature, even when subjected to a considerable extraction volume or pre-treatment.

So in general, following the small-volume extraction procedure, we attempted to syringe the material through a small cotton filter. We started with the largest needle gauge, a size commonly used in blood transfusions. If successful, we progressively tested smaller needles that are more commonly used for injection.

We first conducted what we call standard syringeability and injectability studies that simulate common abuser practices and included some very extreme conditions. Samples of IPC Oxy and OxyContin in tablet form B were added to various volumes of solvent ranging from volume 1 to volume 6 of solvents 1 or 2. These samples were incubated for up to 30 minutes with agitation A or C and temperatures A or B.

So for the standard syringeability test, none of the conditions yielded a suitable amount of injectable oxycodone, even with the largest needle

gauge. This supports that both IPC Oxy and OxyContin have abuse-deterrent properties for the IV route.

This slide shows a representative example of the abuse deterrence of both drugs using these standard procedures. As you can see, both products gel, making the liquid preparation nearly impossible to inject. However, there are some recipes to overcome the gelling properties of these formulations.

The most typical manipulation involves pre-treatment D, so we tested both drugs by applying pre-treatment D to tablet form B under a variety of conditions. The samples were incubated for up to 5 minutes with agitation A at temperature A or B.

Turning to the data, with pre-treated tablets at temperature A at 30 seconds, we were able to recover about 20 percent of oxycodone from IPC Oxy compared to 40 percent from OxyContin. At temperature B at 30 seconds, we also recovered less oxycodone from IPC Oxy. The IPC Oxy solution in the syringe was a deep viscous blue liquid and was

difficult to expel. The OxyContin had the consistency of water. So clearly, IPC Oxy was more resistant to syringeability than OxyContin after pre-treatment.

Here's the same pre-treated tablets at temperature A across time. We used the same container and needle gauge to attempt to load the syringe, first at 30 seconds, and then at 3 minutes, and then at 5 minutes. Both products were not syringeable at 3 or 5 minutes.

From all of these IV-related studies, we concluded that IPC Oxy has either similar or superior IV abuse deterrence compared to OxyContin.

Turning to our large volume extraction studies, we used a variety of solvents to prepare the drug in solution. The abuser might then either drink the solution or it might serve as a starting point for further work in manipulations.

In these studies, the rate of drug release from IPC Oxy and OxyContin in tablet form B was evaluated in large volumes of a variety of households and advanced solvents. As recommended

by the 2015 FDA guidance, the solvents had a range of pHs and polarities as well as protic and aprotic properties. Experiments were conducted at different temperatures and agitation conditions to maximize the amount of oxycodone extracted.

This next slide shows the amount of oxycodone released at 30 minutes. Extraction was performed with volume 7 of various solvents at agitation A at temperature A. The main oxycodone release was generally similar between IPC Oxy and OxyContin for most of the solvents, particularly those very common ones that are easily ingested.

Next, I'll review the in vitro study that assessed potential for IPC Oxy to dose dump in alcohol. It's well known that some ER opioids may rapidly release when co-ingested with alcohol, possibly leading to toxicity, overdose, or death. The in vitro study provides evidence that the co-ingestion of alcohol with IPC Oxy would not lead to dose dumping.

These are the results with IPC Oxy tablets in dissolution condition A, showing the amount of

drug released over time. IPC Oxy actually released less oxycodone as the concentration of alcohol increased.

To speed the release of API in ER opioid formulations, abusers may heat, crush, cut, or grind tablets prior to ingestion. Thus, dissolution studies were also designed to evaluate the impact of different types of manipulations to defeat abuse-deterrent properties.

Dissolution of tablet form B and dissolution condition A showed that the release of oxycodone was similar between the products. In the first few hours, IPC Oxy drug release was slightly lower than OxyContin. This demonstrates that the smaller particle-size distribution of manipulated IPC Oxy did not lead to a faster release than OxyContin; rather, the smaller particles likely enhanced the gelling properties and slowed oxycodone release at early time points.

As mentioned, abusers commonly pre-treat tablets to defeat the ADF properties. This slide illustrates the dissolution profile of IPC Oxy and

OxyContin under tablet form A following pre-treatment G in dissolution C. These results further demonstrate that IPC Oxy has greater resistance against pre-treatments known to defeat currently marketed abuse-deterrent formulations like OxyContin.

Moving now to the dye elimination studies, in those tests, we tried to eliminate the dye from OxyContin with solvent extraction and photo and chemical degradation. Solvents 11, 13, 18, and 23 could not separate the blue dye from the oxycodone. Solvents 20 and 24 separated oxycodone from the dye, but the yield of oxycodone was only 38 percent or at trace levels we call zero, respectively.

We concluded that a complex multi-step procedure with considerable chemistry knowledge would be required to effectively eliminate the dye from the product.

Finally, abusers may try to vaporize the drug so they can smoke it. The common procedure for smoking opioids includes crushing or cutting tablets, placing the material on foil, and heating

the underside. Typically, the heat melts and chars the ground material and some drugs may be vaporized.

We developed two standardized procedures to simulate this form of abuse. At optimal heating conditions with a block heater, approximately 6 percent and 7 percent of oxycodone was vaporized from the two products.

Applying direct heat with a Bunsen burner yielded 8 percent oxycodone recovery from IPC Oxy and 11 percent from OxyContin. Probably neither method would be considered an efficient route of administration for either product.

So in summary, IPC Oxy was somewhat easier to crush into small particles. In most cases, oxycodone could not be separated from the blue dye with single-step chemical manipulations. IPC Oxy exhibited similar and, in most cases, superior abuse-deterrent features compared to OxyContin.

IPC Oxy also resists pre-treatments that defeat OxyContin. Large-volume extractions of IPC Oxy were comparable in most cases to OxyContin, and

IPC Oxy showed no evidence of dose dumping in the presence of alcohol.

Thank you for your attention. I'd now like to invite Dr. Sellers.

Applicant Presentation - Edward Sellers

DR. SELLERS: Thank you. Good morning. My name is Ed Sellers. I am professor emeritus at the University of Toronto. I spent my 40-year career deeply engaged in research and clinical care involving drugs that have dependence and addictive potential. My group has published and presented more than 700 scientific papers, many involving the assessment of and standards for abuse potential and abuse deterrence.

I've been asked to place abuse-deterrent formulations, and the IPC Oxy formulation in particular, in the context of the serious public health problem that exists with prescription and other opioid abuse in the United States.

The causes and remedies of the opioid abuse problem are complicated and will not be addressed by a single intervention or drug. All ER opiates

must be abuse deterrent because they contain relatively large amounts of active pharmaceutical ingredient, which makes them very tempting for tampering or abuse.

ADFs are one of the ways we can prevent the reoccurrence of the tampering and abuse that we've seen in the past. It may be useful to actually combine established ADF approaches such as gelling and including a nasal irritant with potential new ADF approaches such as the blue dye that you heard of. In addition, improving a property such as gelling, that is increasing the gelling capability, could result in more robust abuse-deterrent products than those already available.

To date, ER abuse-deterrent formulations have been approved based on formulation properties and pre-market studies. So far, none of these products have received category 4 labeling, namely shown to deter abuse. However, we have seen positive public health impact.

ER OxyContin, the comparator for the drug under consideration today, is a model for assessing

the public health impact of abuse-deterrent formulation with hardened and gelling properties. As you may recall, when OxyContin was approved in 2010, only category 1 studies were available. Importantly, the in vitro characteristics demonstrated in these studies suggested that the abuse-deterrent formulation would impact the routes of abuse being used, overall prescribing, overdoses, deaths, and doctor shopping to obtain more drug. As you can see, those category 1 studies proved to be predictive.

This chart summarizes the 10 postmarket studies conducted with the reformulated OxyContin. The words across the top indicate the measures that might change pre- and post-abuse-deterrent formulation as well as over time, abuse, misuse, addiction, overdose, deaths, and diversion. The checkmarks indicate which studies looked at the changes in rates of these measures. Often, they were assessed in comparison to other marketed opiates.

This slide summarizes the results of the

various studies. Significant and relatively large reductions were seen in prescribing, abuse, addiction, overdose, diversion, double-doctoring, and shifts away from non-oral abuse. Although not shown here, these studies also identified some increases in prescribing and abuse of some other single-entity ER and IR products and in use of illicit opiates. As you know, some fraction of abusers will always turn to other prescription or non-prescription opiates.

Some of these studies also looked at changes in routes of abuse. OxyContin showed a highly significant reduction in all abuse, but particularly in non-oral abuse shown in yellow on this slide. These data come from a variety of sources, including the cohort study in Kentucky at the top, where the reductions in non-oral abuse were especially large.

This slide also shows similar or greater reductions in non-oral abuse in the NAVIPPRO and RADARS monitored treatment programs and in the National Poison Data System Study. In retrospect,

the pre-approval category 1 data of in vitro hardening, crush resistance, and gelling with OxyContin turned out to be quite good at anticipating the postmarket effects on abuse.

The product under consideration today has many features in common with OxyContin. In category 1 studies, IPC Oxy shows resistance to crushing. With respect to intravenous abuse, when exposed to water, IPC Oxy turns into a highly viscous substance that's impossible to syringe and inject in volumes of solutions that abusers typically use.

More importantly, compared to OxyContin, IPC Oxy was much more difficult to prepare in adequate amounts for injection with typical recipes found on drug abuse websites. These recipes are the ones commonly used to defeat OxyContin. Even after applying these recipes, IPC Oxy retains high viscosity while OxyContin is basically water like. Abusers are unlikely to try to inject intravenously a deep blue highly viscous solution in my experience.

Several factors could be expected to discourage intranasal abuse of IPC Oxy. First, it's a misconception that intranasal abuse deterrence hinges on particle-size reduction only. In fact, it depends on a variety of factors, including texture, volume, what it feels like in the nose, and so forth.

So for example, when IPC Oxy comes in contact with the nasal mucosa, it's expected to form a gel that limits absorption and can drip from the nose, losing drug. We've seen this with other gelling products, and I can assure you that drug abusers are not interested at losing valuable drug in this way.

IPC Oxy also contains sodium lauryl sulfate, an irritant detergent. In studies with other products containing SLS such as Oxaydo, abusers have reported aversive nasal irritation. This makes them dislike snorting the drug.

The inclusion of the blue dye is unique. The dye is dark blue, adheres to membranes and fabrics, and is difficult to remove with usual

solvents. This should deter intranasal and oral abuse of crushed product.

In summary, in my experience, multiple ADF approaches within the same product generally result in superior deterrence. IPC Oxy has shown increased gelling properties compared to OxyContin, which has shown abuse deterrence consistent with its pre-market category 1 data. IPC Oxy is expected to deter IV abuse, and its intrinsic properties may also deter other types of abuse.

Thank you for your attention. I'll now turn the podium back to Dr. Odidi to answer your questions.

Clarifying Questions

DR. BROWN: Are there any clarifying questions from the panel for Intellipharmaceutics? When asking a question, would you please remember to state your name for the record before you speak? And if you can, please direct questions to a specific presenter. And as we did last time, if you turn your card up so that we can know who to call on, I'd really appreciate it.

Dr. Craig?

DR. CRAIG: Thank you. Maybe Dr. Odidi, I'm just curious about the amount of PEO in this particular product compared to Opana or OxyContin. Is there a percentage or is there a quantity that could be identified?

DR. ODIDI: We don't know the amount of PEO in Opana or OxyContin because of the proprietary information.

DR. CRAIG: The amount of PEO in this particular product?

DR. ODIDI: The amount of PEO in our product, of course, that we know. It's approximately between 195 milligram to 240 milligram depending on the tablet strength you're thinking of. The variation in the amount is to allow for dose proportionality given the strength of tablet or the amount of oxycodone in the tablet.

DR. CRAIG: So a higher amount of PEO correlates with a higher strength in milligram of oxycodone tablets?

DR. ODIDI: In a way, you can say that. So

I can give you the amounts if you want, if you so desire, for every tablet.

DR. CRAIG: I just was curious about the trend there. Thank you.

DR. ODIDI: Thank you.

DR. BROWN: Dr. Higgins?

DR. JONIAK-GRANT: Another question for Dr. Odidi. On slide CO-9, you state that there is a belief that there is excipient safety. What gives you that understanding? What data have been analyzed or anything been tested?

DR. ODIDI: I would like to call on Dr. Brock to answer the question, please.

DR. BROCK: Good morning, all. I'm Dr. Bill Brock. I'm a consulting toxicologist at IPC. I also hold an adjunct appointment in the school pharmacy at UNC-Chapel Hill. The question wasn't particularly specific about a particular excipient, but let me address the oral toxicity of the blue dye in particular.

There is actually considerable data on the blue dye with oral administrations. It's an

approved food additive. With long-term oral administration, there is systemic toxicity, significant systemic toxicity that is observed. It's not carcinogenic. It's not a developmental toxin. It's not genotoxic. And besides, it has very limited absorption from the GI tract with oral administration.

DR. BROWN: What about IV administration?

DR. BROCK: There are some very limited data with IV administration of the blue dye. With IV administration, there is some toxicity that occurs, but that toxicity is primarily at the injection site. There is no organ toxicity distant from the injection site that's observed. There was no systemic toxicity observed other than the local response. Thank you. And this is with single and repeated injection.

DR. BROWN: So this is eliminated through the kidneys, and there's no renal toxicity?

DR. BROCK: Right.

DR. BROWN: Or can you convince us that there have been studies which evaluated this

particular point?

DR. BROCK: The data are rather limited with IV administration, but what has been reported is that the material is eliminated primarily through the urine when injected, so the urine is actually tainted blue. There is some elimination via the feces as well excreted through the bio, such that the feces are somewhat tainted blue.

DR. BROWN: But limited data?

DR. BROCK: Pardon me?

DR. BROWN: I said, but limited data.

DR. BROCK: Limited data.

DR. BROWN: Thank you. Dr. Galinkin?

DR. GALINKIN: Yes. Jeff Galinkin, a couple of questions. The first is that all the excipients considered generally regarded as safe products. And if not, have there been testing in 11- to 18-year-olds for these for safety since this is being labeled for adolescents?

The second question is, I didn't see any drug-liking studies. Were these done, or were they not necessary because the dosing was felt to be

equivalent?

Then the third question I have, you mentioned that the blue dye may deter oral and intranasal abuse. If just the blue portion of the drug is scraped out, that defeats the sodium lauryl sulfate. So does that blue portion have a drug-liking score that is higher than regular oxycodone or OxyContin? Thanks.

DR. ODIDI: I'd like to invite Dr. Brock to answer the question as to toxicity. There are three questions there. You want to repeat the question for the benefit of Dr. Brock, please? There were three of them.

DR. GALINKIN: I'll just repeat it. So are all the excipients considered GRAS products? And if not or even if so, have they been tested in 11- to 18-year-olds for safety since this is being labeled for adolescents?

DR. BROCK: First of all, the blue dye is not a GRAS material. It's an approved food additive. There's a distinction between that. With respect to whether it's been tested in

adolescents, that's a clinical question, so I'm going to defer to Dr. Dart or Dr. Sellers to that question. I have no toxicity data in juvenile animals with that material.

DR. GALINKIN: And the other excipients, because there is others.

DR. BROCK: SLS I believe is also approved as a food additive. There are oral toxicity data with that material out to 2 years. No real systemic toxicity, not even GI toxicity, was reported with that material.

The other excipient -- there are lots of excipients here. The one that's of interest probably to this committee is polyethylene oxide or polyethylene glycol. With the PEO that's used in this particular drug product, there are some oral tox data with that material.

Once again, it is not very well absorbed from the GI tract, given its molecular weight. But there was no systemic toxicity seen in experimental animals principally because it was poorly absorbed from the GI tract.

Is there another excipient you'd like? Let me call on Dr. Dart.

DR. DART: In terms of the blue dye, I don't think there are formal in that age group specifically, of 11 to 18, but this dye is in products that that age group consumes in large volumes, for a long time, often after sporting events or that type of thing.

Does that answer the question? But I'm not aware of any formal toxicity testing in that age group for the dye.

DR. BROWN: Dr. Zeltzer?

DR. ZELTZER: Thank you. The same individual --

DR. GALINKIN: I had two other questions that were listed. I had the question about the drug liking and then also if the blue substance was actually tested alone.

DR. BROWN: I'm sorry.

DR. ODIDI: Again, the blue substance wasn't tested alone. It's incorporated in a homogeneous mixture in the core.

DR. GALINKIN: That homogeneous mixture in the core, since it's high concentration of oxycodone, was it tested by itself?

DR. ODIDI: During the attempts of what sort are you talking about? Tell me what properties, please. In the manufacturing process, you have the core made and then that core was tested.

DR. HERTZ: So let me help once again. It's Sharon Hertz. The question I believe is were there any studies about the ability to extract, or manipulate, or liking studies -- is that right, Jeff -- with the material that has blue dye in it, in the absence of the outer shell layers? Were any studies of any sort done with that?

DR. ODIDI: No liking studies were done.

DR. BROWN: Dr. Zeltzer?

DR. ZELTZER: Thank you, Lonnie Zeltzer. I guess, first because you're talking about -- really, Jeff asked part of this question. In a younger age group, going down to 11, some will be prepubescent, some will be post-pubescent. And obviously, body size and composition will be

different even within that range.

Are there any data on the effect of blue dye, even as a food additive, separate from this product in relation to risk by pubertal status or by body mass?

I guess a corollary question is, just as some food dyes, like red food dye or yellow, in a subpopulation are found to have allergenic, anaphylactic like risk, are there any studies on, just in general, the blue dye that's being used, given that it's a food additive, but in terms of anaphylactic risk?

DR. ODIDI: I would like to call on Dr. Dart to help answer the question.

DR. DART: Because it is a food additive, I guess I expect that there were some studies, but we didn't prepare that information, so I don't have it. The product I was referring to, since you can just Google it, if you Google, is Gatorade. So I forget which flavor it is. Isa, you may know, but one of the -- it's here.

Blueberry pomegranate Gatorade contains

this. So while we don't have safety data that I know, except that it's a safe food additive, it is a regularly consumed drug in that age group -- I'm sorry, product, food in that age group. I think that's all we have.

DR. ODIDI: Correct.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. These questions are regarding Dr. Setnik's presentation on slide CO-31 with respect to the dose proportionality design study. Just a few questions there with respect to why only males?

DR. SETNIK: Yes. These studies were conducted in Jordan, and the population was male only. Now, the bioequivalency studies that were conducted at 80 and 10 milligrams in fed and fasted were conducted in both healthy males and females, representing about two-thirds female. So there's data to support the bioequivalence and the food effect.

DR. ZACHAROFF: Okay. And you mentioned 22 subjects completed. Were there a significant

number of subjects that did not complete?

DR. SETNIK: Yes, there were. And the primary reasons for withdrawal at that point were due to nausea and vomiting, half of which were due to the naltrexone dose, and the other half were from when they received OxyContin. So they were removed from the analysis, and it was still powered to support the analysis based on the 22.

DR. ZACHAROFF: One last question along this line and sort of tied to what Dr. Zeltzer mentioned. Was there any standardization for body mass, boy weight, fat distribution in any of the subjects to investigate whether or not those things might impact dose proportionality?

DR. SETNIK: Not that I am aware of. The whole population of the completer population was analyzed.

DR. ZACHAROFF: Thank you.

DR. BROWN: Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson. I have two questions. One back for Dr. Setnik, I think, if that's okay. Dr. Cone presented data, I

believe, on the particle size after grinding or otherwise mechanical disruption and some dissolution data. And I wondered, rather than hear specifically about dissolution data, if there was pharmacokinetic data on what happens in people when they ingest the round particles as opposed to what happens in an in vitro system. Are the pharmacokinetics altered?

In particular, his data compared your oxy, IPC Oxy, with OxyContin in a crushed form. Is there data comparing IPC Oxy whole versus crushed and what the disruption of the abuse-deterrent mechanism does in terms of the pharmacokinetics?

DR. ODIDI: Those studies have not been conducted as of now, comparing crushed OxyContin to crushed IPC Oxy in terms of trying to understand their pharmacokinetic profiles.

DR. NELSON: What about crushed IPC to whole IPC?

DR. ODIDI: Those studies haven't been done in humans. No human studies have been done yet.

DR. NELSON: Okay. And how about in the

dissolution version? Has it been compared to crushed versus the whole?

DR. ODIDI: IPC, sure.

DR. NELSON: For IPC.

DR. ODIDI: Yes. For IPC, that's been done, and I would call on Dr. Cone to talk about that.

DR. CONE: Yes. I'll start with CD-9. We may have other slides that are pertinent. This is a dissolution of IPC Oxy, form A relative to form B. And you can see there's some speeding up of release with the form B, but it's very similar.

DR. NELSON: So form A is whole, I assume?

DR. CONE: Sorry?

DR. NELSON: Form A is whole, is a whole pill? In other words, is it whole versus crushed? What is it? I'm not sure I recall, or are these two different crushed ones?

DR. CONE: You would need to refer to your coating system. I can't divulge it in public.

DR. HERTZ: Hi. This is Dr. Hertz. So the question is can the sponsor provide data on whether there is information for crushed versus whole? Are

you able or willing to do that? I mean, that's the question.

DR. ODIDI: Yes. They asked for the dissolution data, which has just been provided. But I think what Dr. Cone is saying is that these are blinded and you have the cheat sheet to tell what form it is. This is a public open hearing. We don't want to --

DR. HERTZ: Right, but we're not asking about the specific conditions under which manipulation were conducted. That's what's proprietary. The question is, can you provide any data on the relative dissolution of intact versus some manner of crushed, presumably the method of crushing that produced the greatest disruption? That's the question.

DR. ODIDI: Yes.

DR. DART: I can partially clarify. Form A was intact.

DR. NELSON: Okay. Thank you.

If I could ask Dr. Dart a question. The data you presented from Cicero's paper that showed

that patients or users who were being admitted for treatment for addiction and abuse had indicated they switched -- we can look up what slide it is. I think it is CO-22. They switched from snorting to swallowing whole, which is presumably what could happen here as well.

There is also data in that paper that talks about switching to other drugs altogether. Could you just clarify a little bit about what those other drugs were and what the implications were?

DR. DART: I don't remember the precise percentages, but they switched to a variety of other opioids, including illicit opioids. So there was a whole spectrum, and I think the heroin might have been the highest percentage one if I recall correctly.

DR. NELSON: Thank you.

DR. BROWN: Dr. Warholak?

DR. WARHOLAK: Hi. This is Terri Warholak. The first question I have is I think for Dr. Brock. Again, with slide CO-9, I think we've asked the question a couple of times, but I just want to

clarify.

It's stated here that limited data suggests excipients are safe when taken by non-intended routes. Did you bring those data with you, and if so, can we see them?

DR. BROCK: The data that's being referred to here are published data. I'm pretty sure I have all of those publications with me, and they can be provided to the agency.

DR. WARHOLAK: Then I have a couple other questions of Dr. Cone. So did you test syringeability of IPC Oxy after taking off the coating? Why or why not? And if you did, what did you find?

DR. CONE: I'm sorry. I didn't completely understand the question.

DR. WARHOLAK: The outer coatings, did you test the syringeability by first taking off the outer coatings, and then dissolving the tablet, and then testing syringeability? Was that done? And if so, why not?

DR. CONE: We, let me start off by saying

the outer coating is easily removable with a wet paper towel. Once you do that, you have an insoluble coating that you can't wipe off. I suppose you could do other things, but it's not easy.

So when we tested in syringeability, both for the intact condition, the water-soluble coating comes off real quickly anyway. So no, we didn't do exactly what you said. We didn't remove the coating because it comes off in a few seconds.

DR. ODIDI: If you don't mind, sorry to interrupt. I just wanted to clarify that a little bit for you as the design of the product, I guess.

There are several coatings. From the closed session, I did take you through several coatings over there. The coatings that Dr. Cone is referring to that you can wash off easy is esthetic coating. And there are different esthetic coatings on all the strengths to help patients identify the color on them.

Those coatings just come off like you're soaking on jelly. But after that coat comes off,

which is a non-functional coat, the remaining coats are pretty tight the way they're put in there. And that's what he refers to as not soluble. That's going to be very difficult to dissolve or wash away instantaneously. Of course, you can always take things off if you work hard enough.

DR. CONE: Just to add to that, under the insoluble coating is all of the API and the excipients we've been discussing.

DR. WARHOLAK: May I ask one more real quick?

DR. BROWN: Can we stop here and take a 10-minute break, and come back at maybe 11:05? We will get to the rest of the questions from the panel after we hear a few more presentations, and we will get to every question before we begin to vote.

But if we could take a break now. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 11:05.

(Whereupon, at 10:52 a.m., a brief recess was taken.)

DR. BROWN: Let's migrate back to our seats so that we can get started. We are now going to proceed with the presentations from the Food and Drug Administration.

FDA Presentation - James Tolliver

DR. TOLLIVER: My name is James Tolliver. I'm a pharmacologist with the controlled substance staff within the Office of the Center Director, Center for Drug Evaluation and Research at the FDA. This morning, I'd like to briefly discuss the need for oral and intranasal human abuse potential studies for the pre-market abuse deterrent assessment for NDA 209-653.

Intellipharmaceutics Corporation, the sponsor for this application, is seeking intravenous abuse-deterrent claims for oxycodone hydrochloride ER tablets. In support of this application, sponsors submitted category 1 physical manipulation and chemical extraction studies, but no category 2, 3, oral, or intranasal human abuse

potential studies evaluating intact and manipulated product.

It should be noted that on page 8 of the sponsor's open session background document, sponsor did acknowledge the need to complete human abuse potential studies in order to obtain abuse-deterrent claims for the oral and intranasal routes of administration.

Furthermore, on page 51 of the same document, sponsor notes that these studies will be completed postmarketing and submitted under a supplement NDA 209-653 to obtain abuse-deterrent labeling for oral and intranasal routes of abuse.

The 2015 final guidance for industry abuse-deterrent opioids evaluation and labeling document notes the need to understand the potential for abuse of abuse-deterrent formulations by multiple routes of administration such as oral, intranasal, and intravenous. This allows for better understanding of how the formulation may be abused following approval.

Furthermore, this document discusses in

detail the conducting of category 2 and 3 clinical studies as part of the overall abuse-deterrent assessment. These studies provide information that cannot be gleaned from category 1 studies.

Category 2 studies focus on the effects of product manipulation on pharmacokinetic parameters of the active pharmaceutical ingredient of the formulation. Subjective reinforcing effects are not generally collected, while other effects such as nasal tolerability data may be obtained.

Category 3 studies focus on the effects of manipulation on subjective reinforcing effects as well as generally including collection of pharmacokinetic data on the API for the formulation.

Again, other pharmacodynamic data such as nasal tolerability may be obtained. The totality of data collected from the category 1, 2, and 3 studies obtained during the pre-market assessment is to be considered in allowing abuse-deterrent claims in the label with respect to oral and intranasal abuse.

One important function of category 1 studies is to assist in developing protocols for the category 2 and 3 studies, particularly with respect to selecting the proper manipulations for the test formulation and positive control.

It should be noted that oxycodone hydrochloride ER tablets are under development at dosage strengths ranging from 10 milligrams to 80 milligrams of oxycodone hydrochloride with compromise of the extended-release of the oxycodone hydrochloride. Due to one or more types of physical or chemical manipulation, considerable amounts of oxycodone hydrochloride may become immediately available for purposes of oral or intranasal abuse.

If in the course of conducting category 1 physical and chemical manipulation studies, oxycodone hydrochloride ER tablets demonstrate susceptibility to particle-size reduction and compromise of the controlled release properties for oxycodone hydrochloride. And the potential exists for the abuse of the manipulated product by oral

and intranasal routes. Category 2, 3 studies, even abuse potential studies, are warranted.

Category 2 and 3 clinical studies provide important information that cannot be gleaned from category 1 studies alone. These studies allow for the examination of the effects of manipulation and routes of administration of a drug product in the non-dependent opioid-experienced population, on the pharmacokinetic parameters of the API of the formulation, and on subjective reinforcing effects such as drug liking, high, take drug again, and overall drug liking.

They allow for assessing food effects on the pharmacokinetics of the APIs and on subjective reinforcing effects following oral administration of abuse-deterrent formulations. Furthermore, they allow for determination of the percentage of a dose-manipulated product that individual study subjects are able to insufflate.

For each subject, this percentage can be further correlated to subjective reinforcing effects. Experience is demonstrated that strong

subjective reinforcing effects can be documented in subjects who are able to insufflate only a fraction of the total manipulated dose for opioid products.

Additional information obtained includes the effects of particle size on pharmacokinetics of the API of the formulation and on subjective reinforcing effects following insufflation. For example, fine versus coarse particle size produced by different manipulations may be compared.

These studies also allow for investigator- and subject-rated assessments of nasal tolerability as a function of time following insufflation of manipulated products. This would include evaluation of nasal irritants intended to serve as aversive agents to deter intranasal abuse. In such studies, nasal tolerability scores may be correlated to changes in ratings of subjective reinforcing effects as a function of time.

Currently, the sponsor has not submitted to the agency any study reports examining the possible oral or intranasal abuse-deterrent effects attributable to the dye present in the formulation.

Later today, you will have the opportunity to discuss possible approaches to this new area of research.

In conclusion, in support of a deterrent claims to intravenous abuse for oxycodone hydrochloride ER tablets under NDA 209-653, category 1 physical manipulation and chemical extraction studies were provided.

According to the 2015 guidance for industry, abuse-deterrent opioids evaluation of labeling document, the pre-market abuse-deterrent assessment should cover multiple routes of administration such as oral, intranasal, and intravenous.

Category 2 and 3 studies provide important information for the evaluation of abuse-deterrent formulations with respect to oral and intranasal abuse that cannot be derived from category 1 studies alone. These studies have yet to be provided with respect to oxycodone hydrochloride ER tablets.

Finally, the totality of data generated from category 1, 2, and 3 studies will be necessary to

assess the deterrent effects of oxycodone hydrochloride ER tablets to the oral and intranasal routes of abuse. Thank you.

I would now like to introduce Dr. Jennie Wong, who will discuss the utilization trends of oxycodone ER and other ER/LA opioid analgesics.

FDA Presentation – Jennie Wong

DR. WONG: Hi. Good morning. My name is Jennie Wong. I am a drug utilization analyst in the Division of Epidemiology in the Office of Surveillance and Epidemiology. I will be presenting drug utilization trends for oxycodone ER and other extended-release long-acting opioid analgesic, or otherwise known as ER/LAs, from 2012 through 2016 to provide context for today's discussion.

The focus of this presentation is to show recent drug use patterns of oxycodone ER in the outpatient retail market. The outline of the presentation will be as follows. First, I will discuss national sales distribution of oxycodone extended-release products followed by prescription

utilization of selected opioid analgesic products in the outpatient retail setting.

I will then present our findings on top prescriber specialties as well as diagnoses associated with the use of oxycodone ER and will end my talk with limitations and summary of findings.

Our analyses focused on oxycodone ER products and also included other ER/LA opioid analgesic products to provide context for the utilization of oxycodone ER within the ER/LA opioid analgesic market. Additionally, immediate-release oxycodone was also included to provide comprehensive analyses of oxycodone utilization.

Before going into the utilization analyses, I would like to point out opioid products approved by the FDA with properties designed to deter abuse. For brevity, I will use the term ADF for the rest of my presentation to reference to these products.

Currently, there are 10 opioid products approved of properties designed to deter abuse. Of these, 4 are extended-release oxycodone-containing

products. Currently, only 2 of these products, OxyContin and Xtampza, are being marketed. Targiniq and Troxyca have been approved, but are not on the market yet.

For today's discussion, we focus our analyses on the outpatient retail setting, which is the primary setting of care of where oxycodone ER analgesic products are sold from manufacturers to various channels to various channels of distribution in the U.S. To conduct these analyses, we use several different databases. I will describe each of those databases briefly before presenting the results of each analysis.

To obtain the prescription utilization data, we used the quintiles IMS Health National Prescription Audit Database, which measures the volume of prescriptions from retail pharmacies into the hands of patients via formal prescriptions in the U.S. The data are nationally projected and can also be stratified by prescriber specialty.

This figure shows the nationally estimated number of dispensed prescriptions for single-

ingredient oxycodone from U.S. outpatient retail pharmacies. Shown on the green line, prescriptions dispensed for oxycodone ER decreased 23 percent from approximately 5.1 million prescriptions in 2012 through 3.9 million prescriptions in 2016. During the same time period, prescriptions dispensed for single-ingredient oxycodone IR products increased 26 percent from approximately 14.1 million prescriptions in 2012 to 17.8 million prescriptions in 2016.

Focusing on ER/LA opioid analgesic products, this graph displays the nationally estimated number of dispensed prescriptions for ER/LA opioid analgesics from U.S. outpatient retail pharmacies. As seen in the previous graph, the utilization of oxycodone ER products decreased over the study period. Utilization of other ER/LA products such as morphine ER and transdermal fentanyl has remained fairly steady while utilization of other products such as methadone has declined.

In 2016, oxycodone ER, as shown in the figure as a dotted green line, accounted for the

third-most utilized of the ER/LA opioid products in the outpatient retail market. This figure shows the nationally estimated number of dispensed prescriptions for ADF opioid analgesic products. Prescriptions dispensed for ADF products decreased from approximately 5.1 million prescriptions to 4.3 million prescriptions in the outpatient retail setting.

Of the total ADF prescriptions, the vast majority of prescriptions were dispensed for reformulated oxycodone ER, as shown by the blue line, throughout the examined time period. As noted in the earlier slide, there are a number of opioid products that have been approved by the FDA with properties designed to deter abuse. However, quite a few of them are not in the market during the study period.

We now move on to prescriber specialty data for single-ingredient oxycodone ER products. Based on dispensed prescription data for 2016, primary care provider such as family practice, general practice, and internal medicine were the top

prescribers for single-ingredient oxycodone ER processed at 26 percent of dispensed prescriptions followed by mid-level practitioners at 23 percent and anesthesiologists and osteopathic medicine doctors at 11 percent each.

Now, we will transition to our analyses of diagnoses associated with the use of oxycodone ER. To determine this, we use a database that contains data from monthly surveys of 3,200 office-based physicians representing 30 different specialties across the U.S. who report on all patient activity during one typical workday per month. These data are nationally projected by physician specialty and region and are helpful in characterizing the use of drug products in clinical practice.

Based on physician survey data, the top group of diagnoses associated with the mentions of single-ingredient oxycodone ER products reported were for conditions related to disease of the musculoskeletal system and connective tissue such as back pain or knee pain. This was followed by conditions related to disease of the nervous system

such as hereditary or idiopathic neuropathy followed by pain related to neoplasms.

As with all studies, there are limitations. Only outpatient utilization was assessed. No inpatient or mail order data were included in the prescription analyses. However, this setting accounted for the majority of utilization and may have less healthcare provider oversight than utilization in other settings such as inpatient or nursing homes.

Diagnoses data are not linked to dispensed prescription data. Rather, the data presented were mentions of a drug at a physician visit based on survey data of a sample of physicians. The diagnoses data were derived from surveys of office-based physicians and may not have captured prescribing patterns of physicians who practice in other settings of care such as hospice care, pain, cancer, or urgent care clinics. Our findings do not include data from prescribers such as dentists and mid-level practitioners.

In summary, outpatient retail utilization of

oxycodone ER products decreased while prescriptions dispensed for oxycodone IR products increased in the examined time period. Oxycodone ER products were the third most-frequently dispensed among the ER/LA opioids in 2016.

Of the ADF opioid products, the majority found in the market are extended-release oxycodone products. Please note that although FDA has approved 10 ADF opioid products, over half are not marketed.

The top prescribers of oxycodone ER were primary care providers followed by mid-level practitioners. The top group of diagnoses associated with the use of oxycodone ER were conditions related to disease of the musculoskeletal system and connective tissue.

That concludes my presentation. Thank you. Now, I will turn it over to Dr. Fields, who will be presenting on excipients and oral opioid analgesics and IV abuse.

FDA Presentation - Ellen Fields

DR. FIELDS: Good morning. Today, I am

going to give a brief presentation on the regulatory aspect of excipients in opioid analgesics intended for oral administration and how these relate to abuse of these products by the non-oral routes. And I expect my talk to raise more questions than give answers.

At previous advisory committee meetings, we heard from some committee members about concerns regarding the safety of excipients in oral opioid analgesics that are abused by non-oral routes. As you know, there have been unintended consequences of abuse-deterrent formulations that have had negative effects on the public health such as the recent experience of Opana ER and the TTP-like illness in persons abusing it by the IV route.

I will review the major excipients in oxycodone ER tablets as previously presented by the sponsor, then discuss the agency requirements for the assessment of excipients in drug products. I will talk about labeling with regards to excipients and unintended routes of administration. And I will conclude my talk with a brief mention of

trends in IV abuse of prescription opioids.

As the sponsor noted, oxycodone ER tablets are formulated to resist chemical extraction, dose dumping with alcohol to form a viscous hydrogel when in contact with an aqueous environment and to deter nasal and IV abuse.

They stated that the excipients intended to convey the abuse-deterrent properties include polyethylene oxide, which is a gelling agent, sodium lauryl sulfate, which is a nasal irritant, and a blue dye that stains skin and clothing. There are numerous other excipients in the formulation that are proprietary.

As stated in chapter 3 of the USP, excipients in all drug products should have a specified intended purpose. Excipients that do not serve a specific purpose for a product only result in unnecessary exposure to the materials. We are still reviewing the safety of the excipients of oxycodone extended-release tablets for the intended oral route.

The current formulation contains excipients

that may present risks by parenteral routes of administration, and parenteral administration of excipients extracted from the product could result in adverse local and potentially systemic effects.

As per FDA guidance for industry non-clinical studies for the safety evaluation of pharmaceutical excipients, excipients in drug products are assessed for safety for the intended routes of administration.

According to USP chapter 1, drugs intended for parenteral administration cannot contain coloring agents such as dyes. That said, the agency does not require that oral drug product excipients be assessed for safety for intravenous and other unintended routes of administration.

Now, I'll move to labeling. We have routinely included labeling language specific to risks of abusing a drug with regard to excipients and disease transmission in section 9.2 of the label, which is the abuse section, under the heading Risks Specific to Trade Name.

A number of opioid products contain

excipients with known risks in the setting of parenteral abuse. Many products contain talc as an excipient, and it has been known since the late 1970s that injection of talc is associated with serious risks.

For example, MS Contin and Kadian are examples of opioids that have labeling regarding talc, and the labeling is as follows. Due to the presence of talc as one of the excipients, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, et cetera. And there is also a sentence that talks about the transmission of infectious diseases.

Morphabond, which is a morphine sulfate extended-release tablet, and OxyContin, oxycodone extended-release tablets, have similar labeling regarding risks associated with the excipients in parenteral abuse as well as the spread of infectious disease. I'll let you read that.

Lastly, Opana ER, oxymorphone extended-release tablets, has been shown to have specific risks associated with abuse by the IV route due to

its formulation. I'll let you read the wording for the Opana ER risks that are specific to that formulation. That part of the label also includes the warning about infectious diseases.

Things we know. Just saying excipients are in the solution doesn't appear to deter abuse. People inject solutions made from products intended for oral use even when labeled as dangerous to do so. And people who abuse opioids over time often move from less dangerous routes, such as oral abuse, to more dangerous routes such as injection.

An injection may be the most dangerous route of abuse as it is associated with substantial health consequences such as injection-related endocarditis, infectious disease transmission, increased risk of overdose, emergency department visits, and death.

A recent publication in the Journal of Drug and Alcohol Dependence presents a study that assesses trends in treatment admissions, reporting oral injection, smoking, and inhalation abuse of prescription opioids and examined the

characteristics associated with non-oral routes of prescription opioid abuse in the U.S.

Data are from over 19 million treatment admissions reported in the 2004 through 2013 treatment episode dataset, or TEDS, public use files. TEDS, reported annually by the Substance Abuse and Mental Health services administration, provides demographic and substance-use characteristics of substance-use treatment admission among people 12 years of age or older to state-licensed or certified substance abuse treatment centers that receive federal public funding.

TEDS represents a compilation of data collected through individual data collection systems of the state agencies for substance-use treatment. The data are publicly available and primarily include substance-use and demographic measures.

Prescription opioid abuse treatment admissions for 2004 to 2013 were used to calculate counts and percentages of prescription opioid

treatment admissions, reporting oral injection or smoking and inhalation abuse.

In this figure, the black lowest section of the bar, each bar, represents oral abuse. The dark gray middle sections represent smoking or inhalation, and the light gray sections at the top represent abuse by injection. From 2004 to 2013, oral abuse decreased from 73.1 percent to 58.9 percent. Injection abuse increased from 11.7 to 18 percent, and smoking and inhalation abuse increased from 15 to 23 percent.

This study found large shifts from oral abuse of prescription opioids towards non-oral routes of abuse among admissions to substance-use treatment during the time period assessed. The largest percentage change occurred among treatment admissions reporting injection as their usual route of prescription opioid abuse, increasing from 11.7 percent of primary prescription opioid abuse admissions in 2004 to 18.1 percent of admissions in 2013, a 55 percent relative increase.

There are some limitations to the study.

First, TEDS comprises a significant proportion of all admissions to substance abuse treatment in the U.S., however, it does not capture all admissions. Second, the primary, secondary, and tertiary substances of abuse reported to TEDS are those substances that led to the treatment episode and not necessarily a complete enumeration of all drugs used at the time of admission.

Third, in many states, TEDS data may include multiple admissions for the same patient. But despite these limitations, this appears to be the first study to examine in-depth national-level trends and characteristics associated with non-oral routes of prescription opioid abuse.

In summary, excipients in drug products are assessed for safety only for the intended routes of administration. It is reasonable to believe that abuse of oxycodone ER tablets via intravenous administration of extracted materials could result in adverse local and potentially systemic effects.

Opioid analgesic labels include risks of misuse and abuse with regard to excipients, but

this has not effectively mitigated these risks, and rates of abuse via injection of prescription opioids have increased.

The agency needs to consider how to approach the issue of excipients, particularly as abuse-deterrent formulations of opioid analgesics, may increase the opportunity of exposure to new excipients with unknown and unintended consequences.

I'd like to make two more additional comments. First, references to the use of dyes in food, including drinks, as evidence of safety is potentially misleading with regard to non-oral routes and with regard to the relative amount.

For example, blue dye in Gatorade, by a quick Google search, is approximately 1 to 10 milligrams per liter, which may not be relevant to this product. And second, it is also important to understand that not all blue dyes may be the same with regard to the many compounds that they are made of, including metals that may be present in the dyes.

I think next is Dr. Dasgupta, our guest speaker, or do we have questions?

Clarifying Questions

DR. BROWN: Dr. Fields, we're going to allow the panel to ask some questions of the FDA and then move on to Dr. Dasgupta.

If there are any questions to clarify the presentations that you just heard from the FDA, let's entertain those at this point. We'll come back to questions for the presenters earlier this morning a little bit later.

Any questions? Ron?

DR. LITMAN: Ron Litman. This question is for Dr. Wong. I'm trying to figure out from the great slides that you presented and the data that you called from Quintiles INS if the percent of ADFs are rising or not. It appears I have to combine slides 7 and 9.

Slide 9 shows that from 2012 to 2016, the oxycodone prescriptions have gone down. Maybe I'm looking at the answer right here. These are abuse-deterrent labeling prescriptions, but how does that

compare relative to slide 7? Are we to assume that all prescriptions for oxycodone were abuse-deterrent labeled from 2012?

DR. WONG: Yes. For that particular slide, we included ADF and ADF single-ingredient oxycodone.

DR. LITMAN: Slide 7 is both?

DR. WONG: Yes, slide 7 is both. And then the one inside 9 only includes the ADF products.

DR. LITMAN: So I am trying to understand, the ratio of ADF to non-ADF oxycodone, has that been going up, down, or the same? I just can't tell looking at these slides.

DR. HERTZ: This is Sharon Hertz. Perhaps I can help with that question. I believe that most of the oxycodone extended-release market is still predominantly OxyContin.

DR. McCANN: Yes

DR. LITMAN: Non-ADF?

DR. HERTZ: No, ADF, yes, because [inaudible] switched it over.

DR. LITMAN: From what year was that?

DR. WONG: I believe it was 2010 that they did that, and it was April 2010.

DR. HERTZ: Let me just follow up with a question. Do we have any information about the other marketed extended-release oxycodone Xtampza in terms of numbers? Were we able to get that from IMS?

DR. WONG: Yes. I believe it's in the background or we have a table in there with the prescription numbers for each of the ADF products.

DR. HERTZ: So it's still fairly small if you go back and look at that.

DR. LITMAN: I think that's helpful. So if you assume that, on slide 7, all oxycodone ER is ADF, that's actually been decreasing over the years for whatever the reason.

DR. WONG: Yes.

DR. LITMAN: Thank you.

DR. BROWN: Dr. Meisel?

DR. MEISEL: Steve Meisel, a question for Dr. Fields. On slide 4 -- call that up -- I just want to get some clarity about the first bullet

point here. It says excipients should have a specific intended purpose, and those that don't have a specific purpose have unnecessary exposure.

Does that mean that if there is an excipient that's got a purpose, but a purpose for which the applicant is not seeking approval at this time, does that mean that that particular excipient shouldn't be there, that that's a consideration for disqualification of that particular excipient?

DR. FIELDS: That's an excellent question. I think that's part of what we're going to be discussing when we ask you questions. This is not a law, so I believe it's one of the questions we're asking you during the discussion, and you can certainly have more discussion about it.

DR. MEISEL: Sure. I just wanted to understand whether that was a regulatory requirement or standard, or not.

DR. FIELDS: I mean, from our perspective, a product should have -- the excipients in the product need to have a purpose. There's no reason to expose patients to something that has no

purpose, either for them or for the public health, which is the abuse-deterrent nature of these drugs. We take in that consideration as well.

DR. MEISEL: Thank you.

DR. BROWN: Dr. Mendelson?

DR. MENDELSON: Yes. I'm surprised there's not more data available on the excipients, at least in the toxicity databases, with LD50 data and other parenteral administration, particularly for metals. I mean, there must be some recorded literature some place on aluminum toxicity when put into parenteral nutrition solutions. And I'm sure it's not good for you. I'm pretty sure it's not something you would seek to add to your TPN solution.

So I'm surprised there's not more toxicity data. Did you guys search for that or is that available?

DR. FIELDS: Some of the excipients that are in this product are proprietary and so can't really be discussed. But I will say that our toxicologists are certainly looking into the relevant data for anything that's in this product

and are reviewing it in terms of safety for both patients and safety in terms of the public health. And I did say in my talk that we are still reviewing that.

DR. MENDELSON: Do we have a dose in milligrams for the blue dye versus what was available in the Gatorade?

DR. FIELDS: The sponsor would have to respond to that.

DR. BROWN: Dr. Fields, Ellen, when you said that the agency is continuing to evaluate excipients, at what point will we have some understanding of the toxicities?

DR. FIELDS: The NDA is under review, so when we take our action, whatever that may be, you can look at the reviews.

DR. HERTZ: Part of the problem is that some of the proprietary information that we need to review with regard to the makeup -- you know, dye is not a substance. It's a number of different compounds that are mixed together, and it's usually a DMF, a drug master file. And that information is

not publicly releasable in terms of all the different information. It's proprietary.

So with regard to the current situation, we're still looking at the safety of the dye and the other excipients, the other proprietary pieces, with regard to the intended use.

So the unsatisfying answer is, we'll never be able to give you the details, but we will be doing that review, and that will be part of our risk and benefit assessment when we think about whether the product should be approved or not as part of the action that we take.

DR. BROWN: Dr. Zeltzer?

DR. ZELTZER: Thank you. As the FDA is reviewing, in this moving-forward period, the safety of excipients, is there any consideration to looking at not just adult weight and height, body composition, but also -- especially since you're going down to age 11 in a lot of these products or indication for age 11 and up, that the 11 to 16, 17 is still a big group of individuals in terms of pubertal status and potential toxicity, developing

organs, et cetera.

Also, are there data within that age group, the data that were presented in terms of increasing abuse potential in the IV routes of non-intended IV medication for that adolescent, early adolescent, mid-adolescent age group?

So the question is, as you move forward in looking at this, is there consideration or planned consideration to looking at both pubertal status as well as body composition?

DR. FIELDS: We do take into consideration, and our toxicology reviews take into consideration, effects of excipients on pediatric patients. And if a drug is going to be approved in a pediatric group, there's often non-clinical juvenile animal studies and such that are conducted.

Does that answer your question?

DR. BROWN: Dr. Nelson?

DR. NELSON: Thanks, a question for Dr. Wong or Dr. Fields. As Dr. Hertz commented on at the beginning, we're talking about abuse-deterrent formulations, but obviously a big part of the

problem that we see in opioid use in the country involves non-abuse-related addiction.

You presented some data on treatment admissions in your talk, Dr. Fields, about excipients and Dr. Wong about utilization. Is there any sense of how we should approach this issue as a committee and try to look into the issue of addiction?

Do you have any data to show whether there's any role of ADFs or any of these new formulations in reducing the risk or increasing the risk and rate of addiction?

DR. HERTZ: As I cited in my intro, there is no reason to believe that these products or other products that are abuse deterrent, based on differences in the physical chemical behavior, would affect the risk of addiction from exposure to an opioid.

In a very broad sense, there's a lot of different avenues of evaluation of abuse-deterrent formulations, and some are actually trying to look at other aspects. Some are trying to limit the

exposure to the opioid if you take more than you're supposed to, even of the intact product, by mouth.

So the exposure may be limited, and that could potentially have some additional impact in terms of trying to ramp up or increase exposure. Some are also using other very novel and interesting approaches, some of which might actually impact the abuse liability of the active drug substance.

But if the active drug substance is a Schedule II opioid, and the formulation is not being reassessed because of the potential for lowering the scheduling and changing the scheduling to a different schedule, for instance Schedule III or IV, and if it's going to remain Schedule II, there's really no reason to believe that the exposure and the risk for addiction would change.

If it's Schedule II, it has the same risks as a Schedule II product. There may be some differences in risk across different opioids, but that's not really the question. For any given opioid in a formulation, for any one opioid, in

this case oxycodone, this product is delivering oxycodone. It will be in Schedule II. It will remain a product that could be associated with addiction.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: Yes, just a quick question for Dr. Fields. On slide 13, when you were looking at routes of abuse among the patients entering treatment, that was for all opioids, not just the ER opioids. Correct?

DR. FIELDS: Yes. They did not differentiate between ER and IR.

DR. SHOBEN: Thank you.

DR. BROWN: Are there any other clarifying questions for the FDA prior to us moving along to our featured speaker?

(No response.)

DR. BROWN: If not, we will now proceed with the guest speaker presentation from Dr. Nabarun Dasgupta.

Guest Speaker Presentation - Nabarun Dasgupta

DR. DASGUPTA: Good morning. My name is

Nabarun Dasgupta, and I'm an epidemiologist at the University of North Carolina in Chapel Hill. I thank the agency for giving me the opportunity to speak today.

So you've heard my disclosure already, so I won't belabor that. Over the next 20 minutes, I want to give you an overview of what is historically known about excipient harm and tampering, followed by a deeper look at one salient example, and conclude finally with the framework of how we might conceptualize tampering and harms.

Let's start with a quick review of the history drawn primarily from the published peer-reviewed literature from the 1960s going forward. I could have started even earlier, actually. Talc granulomas were observed in patients who injected tablets as far back as 1933. The one citation on the next slide has a review of the earlier findings if you're interested.

It might be a surprise to start talking about Paregoric, which was still sold as a tincture of camphorated opium in the 1960s. The specific

report in this article involves a 32-year-old woman. The harm actually stems from the second component of Blue Velvet, namely the antihistamine, tripelennamine.

Magnesium silicate, or commonly known as talc, was the excipient of concern in tripelennamine. She had been injecting for nearly two years, but had been experiencing shortness of breath, cough, and lower extremity edema for 3 months when she presented.

After 2 months in the hospital, she died at 9:00 a.m. May 5, 1963. Despite her relatively young age, autopsy revealed pronounced atherosclerosis, and angio occlusive lesions, and pulmonary vasculature.

You can see in the image on this slide the dark and central mass is a cross-section of the accumulated and crystalline deposits in the pulmonary artery. In their discussion, the authors pointed out that the parenteral forms of tripelennamine contained lactose as a bulking agent instead of talc, implying that parenterally safer

excipients may have prevented this death.

A point here in addition is that a single safer formulation, theoretically Paregoric, may become intimately linked with another less safe one based on the way that it's actually abused on the street, but the attributable harm is often described in terms of the combination of both products.

The second example comes from Texas in 1976. The x-ray here depicts the lung of a 33-year-old woman who had been injecting methamphetamine pledgets for 4 years and experiencing respiratory symptoms for one year. Pulmonary hypertension was confirmed by open lung biopsy.

At the time, these inhalers contained wads of cotton that were soaked in methamphetamine that was intended to be inhaled as a vapor, like an inhaler you can get over the counter for a cold now. She had been squeezing the liquid out of these pledgets and injecting it. Stray cotton fibers and talc from other tablets accumulated in lung tissue to the point where the authors observed

"interstitial fibrosis, greatest around arterial, some of which were completely obliterated." You can see normal vasculature in the top right quadrant, anatomical right quadrant, in the slide, but the three other dark quadrants are dark due to extensive vascular damage.

The paper goes on to detail 3 additional cases involving other stimulant inhalers, heroin and barbiturates. In most cases, injection had been occurring for 2 to 4 years before presenting for care, giving us a rough timeline at least for this kind of excipient harm.

It is also worth noting that despite the documented harm from injection of stimulant inhalers containing levomethamphetamine and purple hexedine, both of these products remain on the market and are over the counter, in fact. And while there are sporadic reports of tampering on use, the outrage seems to have dissipated while the drug remains available.

I can't quite explain this other than to consider that abuse and tampering may be somewhat

an inherent property of any given drug, but it's just as likely to have an interaction between that given drug and everything else that's available on the market.

Moving on to the early 1980s, there was a well-documented outbreak of pharmaceutical injection triggered by a sudden decline in heroin supply in Chicago. The Ts and Blues episode subsided soon after it started as heroin returned to the streets.

Ts and Blues were a combination of pentazocine, another opioid analgesic, and tripelennamine. Much has been written about this phenomenon, but this paper documented similar symptomology of presenting excipient harm as we saw in the earlier examples.

In this figure from the paper, focused on the shaded bars, compared to heroin injectors, those injecting the 2 tablets had much higher respiratory problems stemming presumably from pulmonary occlusion from talc deposits.

Perhaps the most traumatic excipient harm of

recent memory happened in the United Kingdom, largely in Scotland. The benzodiazepine temazepam had been reformulated, making it harder to inject. I'll go into this in more detail in a moment, but injection of the ADF version of the product led to very concerning gangrene and limb loss.

I'll also point out in this particular photo the temazepam gel cap had been stored in poor conditions outside the sanctioned supply chain, leading to the ND dissolving and the capsule leaking. As I'll discuss in the framework section, storage conditions after diversion are one of the dimensions of understanding risks from tampering and injections.

In the early 2000s in Malaysia, buprenorphine tablets had been on the market for a few years as treatment for opioid dependence. They were subsequently reformulated to include the antagonist naloxone, putatively making it less desirable to inject when crushed. While it's not an excipient, the naloxone was supposed to be sequestered when taken orally.

This study, relying on interviews with active drug users before and after reformulation, documented increasing frequency of injection with abuse-deterrent formulation, thereby increasing risks for bloodborne pathogen transmission. And again, despite increased injection frequency, the naloxone-containing product remained on the market as it does in the United States.

Increasing injection frequency was also noted in a more recent ADF reformulation, which I suspect the committee is well aware of at this point. Extended-release oxymorphone, Opana ER, was reformulated to make it harder to crush. The injection deterrence was incomplete enough to have resulted in a documented increase in injection episodes with more injections per episode.

This is believed to have contributed to an HIV outbreak in Indiana. Excipient harm was noted as well with cases of thrombotic thrombocytopenic purpura-like illness, TTP, being documented by CDC.

Since this drug has been extensively discussed already, I won't go into more details,

but you can see the epidemic curve on the left there for context. On page 21 of the briefing materials for this meeting, the sponsor suggested that excipient harm is not an issue because one of the excipients, polyethylene oxide, is of a similar molecular weight as to that and the reference listed drug, OxyContin.

But I would like to point out that TTP has been documented with the same reformulated OxyContin in Australia. In that report, a 29-year-old female had been injecting immediate-release oxycodone and original OxyContin for a year prior to reformulation, but had switched to the reformulated OxyContin in the 2 months preceding admission for treatment. The authors of that study hypothesized a yet-unidentified genetic susceptibility.

Mixed exposures such as this are the norm, making etiology even more difficult to judge. So higher molecular weight PEO in Opana ER does not alone explain the causal connection to TTP, nor is its lower molecular weight of PEO totally

protective from TTP.

So it appears that it would be reasonable to expect cases of excipient harm with the formulation under discussion today or any formulations that come out that contain PEOs with different molecular weights.

Now, let's return to the temazepam case study from the United Kingdom. This is an episode that is still talked about today and has shaped drug policy in that country to this day. In the 1980s, liquid-filled gel caps were commonly prescribed, the yellow rugby balls you saw in the earlier image.

The liquid could be drawn up easily with a needle into a syringe. In response to reports of injection, the manufacturer reformulated it with a higher molecular weight crystalline wax. In 1989, the reformulated product was already being called abuse resistant. A noticeable reduction of intravenous injection followed, but all was not well.

A couple of years later, reports emerged of

intraarterial injection. The capsule could be boiled and the melted wax extracted. Public outcry intersected with reports that a widely adopted recent technological innovation was being used to melt the wax, namely the microwave oven. When injected intraarterially, the wax would harden, resulting in severe damage with amputations in extreme cases.

It's important to note that there were a few dozen of these documented cases, and it was fairly localized, but it was enough to have the drug withdrawn from the market.

This example also makes us pause to ask if the proposed labeling is accurate to describe intravenous injection specifically as a phenomenon unique from intraarterial or subcutaneous injection. Does intravenous-deterrent labeling signal to those interested in tampering that other forms of injection are viable? I think this is an open question. It doesn't seem like that's the intent, but it seems a little bit confusing to me.

Now let's turn to how we can synthesize this

information into a practical framework for putting excipient harms into context. I emphasize that this is my own work and conceptualization, and I welcome others to contribute or criticize.

When speaking to people who inject drugs about injection harms, I tend to divide each injection episode into pre-exposure and consumption phases. In the pre-exposure phase, I tend to ask questions about the manner in which the drug is acquired and prepared.

In the consumption phase, I examine the manner in which it was administered and the specific harm that was experienced. Of course, above all of this is the choice of drug. I'll briefly walk you through the series of questions in these five categories and practice in assessing a specific case of harm. I will start with the harm and work backwards through these categories, but it's more logical to introduce the concept going forward in time.

For the drug itself, the physical design of the formulation is relevant as we've discussed

already, and it's also important to know if other drugs use the same drug delivery platform. But there's also a dimension of misclassification that can occur that influences self-reporting in surveys, just something to be aware of for observational studies.

It's also important to note that many of these concerns are outside of the control of the sponsor, so there's only a limited amount that any one party can do.

In terms of the acquisition category, the sourcing social dynamics can actually modify the risk associated with a product, not always for the better. Some difficult-to-extract ADFs can be purchased in already-extracted form such as a powder with a price premium reflecting the labor.

Logistics of the acquisition can also be important, although often overlooked. Even the legitimate market faces pressures of pedigree and expiration dates, and the black market is no exception. For naturally derived drugs like heroin, contamination with microorganisms is very

common. We don't know how much this affects prescription drugs.

There are practical issues, too. Small numbers of pills might get stashed into the coin pockets of jeans. I've seen cringeworthy tablets covered in pocket lint that weren't very well cleaned before injection.

Again, these are aspects that are well out of the control of any given manufacturer or federal agency, but are relevant for the public health harms; so again, outside of control for many of these things.

Before we go into the preparation aspect, let's review the basics of injection equipment so we're on the same page. A tourniquet isn't always necessary, but many choose to use one. I'll try to point that there. Syringes can have fixed needles like this one or detachable needles, syringes with detachable needles like this one.

Sterile water is nice to have, but any water source will be actually used in practice, even puddles or water from the toilet bowl. This is a

particularly nice looking cooker on the bottom of the screen there with a handle, but bottle caps or spoons are commonly substituted as the place where the pulverized pill and liquid substrate are combined.

In some countries and within certain drug user networks in this country, it may be common to add something to help the drug dissolve regardless of whether it actually does so. In this case, we are looking at packets of USP grade citric acid distributed by harm reduction programs in the United Kingdom.

In the U.S., we generally don't have much of an additive culture, but it isn't that exceptional to hear talk of adding lemon juice and vinegar. Obviously, microbial contamination is definitely a risk.

Finally, filters of many kinds are used, placed at the tip of the needle when drawing up the drug prepared in the cooker. Cigarette filters often have fiberglass, but Q-tips, cotton balls, and tampons are also used.

So on the topic of filters, there are commercially available filters in other countries that fit on the tip of a syringe which effectively eliminate the most harmful-sized particles, the small ones that get stuck in the finest of capillaries.

I don't know that these are taking hold in the U.S., though, but it would further demonstrate that excipient harms are a worldwide problem being addressed with different approaches in different countries.

In the preparation step, each of the implements used for injection can modify health risks either up or down. In terms of the methods of extraction, heat, either added or removed, has a long history of being used to manipulate tablets.

Chemical extraction techniques will emerge, possibly disseminated on the internet. And while they often dazzle us in their sophistication, it is hard to know how widely they are actually used. In speaking to injection drug users about this, the single dimension that was consistently described

was time, how long does it take to go about getting the dope out of the pill?

I don't know that this is a routinely measured dimension in trials, but we've clearly heard from experts who have tried many of the online recipes that are available to look at.

I think there's also a level of nuance of ritual and belief that influence harm, that don't come across online. Let me show you an example from a study we did, which included drug use observations, which were conducted with permission. These are actual images of tampering of an older 80-milligram OxyContin before it was reformulated.

In the bottom frame, you can see the lighter that is being used to crush the tablet inside a dollar bill on the top frame. You can see the powder that emerges, and I don't think currency is the cleanest of services, and you can extrapolate some harms right away.

But this individual was really interesting because he highlighted the importance of beliefs about drugs and rituals. You can see the white

streaks almost on this slide -- you can see the white streaks on his blue shirt. Just before this picture was taken, he had put the pill in his mouth and let it sit there for a dozen seconds.

When I asked him why he did that and why he was wiping it on his shirt, he replied that he was "getting rid of the time release" by dissolving the green-color filum coating on the tablet. So usually, extended-release tablets have most of the active ingredient embedded in a matrix deeper inside the tablet. So the superficial tampering in this example really just introduced oral flora into the injection and didn't actually get rid of the time release as the belief was at the time.

I won't go into the full details of administration since they are relatively well known, but I will point out that knowing the toxicity and release of a drug from adipose tissue is pretty important, but is often overlooked.

Some people will inject into fat, especially for steroids, if veins are unavailable. But more commonly, veins are missed, and the drug may end up

in adipose tissue surrounding the blood vessel.

Dissolution from and toxicity in this tissue may have consequences worth studying. I was a bit surprised that the background material seemed to focus on intravenous route, and as we've already seen, intraarterial, subcutaneous, and other routes may play an important role when it comes to severe excipient harm.

So while the labeling is specific to route of administration, we have to acknowledge that the harm by any route could be of public health concern, maybe a slightly different dimension on this from the regulatory perspective.

Finally, I show you a short list of injection-related harms. I'm sure you can add more. The point of this list and the way I use this framework is to start with a specific harm that was experienced and work my way backwards to the previous four categories, and this way, you can start to string together the chain of causal events that led to the drug harm. Oftentimes, by the time you get to the first drug category, the product

itself becomes largely irrelevant because the harms are associated with the steps in between.

The focus of excipient harm studies, then, is to take the interceding factors into account and put them in context of existing practices and isolate the effect of the drug formulation itself.

I'm not privy to the pre-approval testing done by the manufacturer of the drug in question today. I would expect that an ethical drug development campaign would include animal testing of excipient harms when the product is tampered with.

This example from Israel provides a suggested path forward when gangrene was suspected in a 37-year-old man from injecting codeine tablets. This angiogram shows a complete block of the arteries in the hand. The physicians wanted to isolate which excipient led to limb loss. They injected dogs with the various excipients from tablets that had been injected by the patient and were able to specifically isolate that microcrystalline cellulose had caused the

pathology.

Similar studies have been conducted in rabbits and rats, and those citations are summarized in a Danish study published in 1987, which I don't have on the slides, but I'll give you the details of, analyzing 33 consecutive fatalities among injecting drug users in Copenhagen.

In this rather remarkable paper, the authors were able to differentiate between excipients in organ tissue from histologic sections. The different excipients were talc, potato starch, corn starch, microcrystalline cellulose, magnesium stearate, siliciumoxid, and cotton fibers.

The excipients were consistently sequestered in histocytes causing granulomatous reactions throughout the body. Specific excipients were able to be linked to specific branded products. Nearly all of the decedents, regardless of cause of death, showed birefringent material deposits, most prevalently in the lungs in 94 percent of decedents; spleen, 76 percent of decedents; liver, 55 percent; lymph nodes, 40 percent; bone marrow,

24 percent; and so on.

My apologies for not including this on the slides, but for the transcript, the PubMed ID number for this paper is 3036675.

A more recent animal study comes from Russia in 2004. Rats were injected with high molecular weight PEO over fairly high-dose ranges, resulting in thrombocytopenia, anemia, and other outcomes. This was conducted well before human concerns emerged with Opana ER or OxyContin.

I'm waiting on a human translation of the article from the Russian, but the point is that animal studies of excipient harm have been published and the precedent exists for conducting them.

In conclusion, one thing that nags at me when I think about excipient harm is it's unclear why certain injectors experience them and others don't. We've heard in the literature about questions about genetic predispositions, but what those specific genetic markers are is unknown. The Danish study I mentioned suggests that excipient

damage may be accumulating silently among people who inject pharmaceuticals that are meant for oral use.

Opioid analgesic injection has been concerningly widespread in the U.S. for two decades. We do not know what it will take to tip background levels of excipient build-up into a new public health crisis. Hence, I think the needs for animal testing are paramount.

To date, these kinds of safety studies have not been required, and if they were suddenly to start being required, even for one drug, how far back and how far afield they should go will need to be established in a fair manner.

Perhaps excipients approved for parenteral administration are a starting point for safer formulations, as alluded to a half-century ago. I emphasized that it has only taken a handful of cases of severe excipient harm to have drugs pulled off the market.

At the same time, drugs with documented excipient harms remain on the market and can even

be found over the counter. There's a lot we don't know and don't understand about excipient harm, so it's hard to generalize to every new case that comes up.

In conclusion, I note that the discussions of excipient harm have played out in the pages of major scientific journals over a span of decades. It almost feels like there are no unintended consequences when it comes to tampering and injection of controlled substances.

We know that ADF mechanisms will be tested on the street, and we know that they're not perfect. The question is only a matter of which specific harms will come of tampering and whether we would be able to detect them. Thank you for your time.

DR. BROWN: Thank you, Dr. Dasgupta.

Are there any questions for Dr. Dasgupta at this point? We're going to ask that the panel only ask questions about the information within this particular presentation. Are there any questions for this very nice presentation?

(No response.)

Clarifying Questions (continued)

DR. BROWN: If there are not, thank you again for coming up from Chapel Hill, and we certainly appreciate your presentation.

We'd like to move ahead now to answer some of the questions or to allow you to ask some of the questions that we were going to get to.

Dr. Warholak, is there a question?

DR. WARHOLAK: Sure. This is for Dr. Cone. Looking at the syringeability studies, I recognize that you said that you tested with the most common agents that people use, but you looked at solvents only 1 and 2, and I wondered if there are other common solvents that you looked at, and if so, what those results were.

DR. CONE: We chose the two most common solvents that we are aware of. Primarily because of that, we didn't look across other broad-ranging solvents that are much less common. We did include a variation on the saline or that particular solvent. We looked at what we call hypertonic

saline.

If I may, I'd like to clarify something about the coating one more time. It seems like there was a little bit of confusion. If you cut the tablet in half, it's a very rigid matrix, so you can't scoop it out. If you try to do anything to it, it crushes the tablet.

So in essence, all of the gelling agent is in the core. So in testing syringeability, when we crush the tablet, we were testing it with the core material.

DR. BROWN: Dr. McCann?

DR. McCANN: Mary Ellen McCann, Boston. I have a number of questions about the blue dye, so I guess, for Dr. Odidi or Dr. Cone. One is, are we allowed to know the name of the additive, which specific blue dye it was or how many blue dyes were included in the formulation?

DR. BROWN: Dr. Hertz, are we allowed to know the --

DR. HERTZ: The sponsor can answer that if they wish. We can't. But if it's proprietary and

they choose not to, that would not be unreasonable as well.

DR. ODIDI: To help the committee out, I would make the exception and answer the question. The blue dye is FD&C Blue Number 1.

DR. McCANN: Okay. Is the blue dye dose proportional for the oxycodone dose, meaning if you take the 80-milligram tablet, you're getting the same amount of blue dye as the 10-milligram, or does it go up with the oxycodone dosage?

DR. ODIDI: The blue dye in the different strengths are approximately the same, but they range from 3.6 milligrams to 4.8 milligrams.

DR. McCANN: That was my other question. How much was in it?

DR. ODIDI: How much was -

DR. McCANN: You said it's 3.6 milligrams per tablet. Right?

DR. ODIDI: Approximately.

DR. McCANN: Approximately. Okay. And when I Wikipedia'd blue dye number 1, it says 95 percent of it is excreted fecally, which I presume that

implies anyway that 5 percent is absorbed. Is that your understanding about how blue dye number 1 behaves?

DR. ODIDI: We haven't done experiments in humans to understand how the blue dye behaves in terms of metabolism. But generally speaking, in the literature it says that it undergoes limited absorption and the majority is excreted.

DR. McCANN: Then finally, the same Wikipedia -- so I apologize for that -- says that the daily -- the FDA recommendations I believe for blue dye number 1 are 0.1 milligrams per kilo per day. So if you're looking at a 35-kilo individual, which I know is half the size of an adult, that would be one tablet.

So if you're looking at somebody -- I mean, wouldn't it be quite easy for somebody who took, say, 4 of these tablets a day to exceed the FDA-recommended amount of blue dye number 1?

DR. ODIDI: Did you conclude by saying it would be easy or not easy? Sorry. I didn't hear you well.

DR. McCANN: You didn't hear me. So if the FDA-recommended guideline for ingestion of blue dye number 1 is 0.1 milligrams per kilo per day, then wouldn't it be easy if somebody had, say, 4 tablets a day to exceed that recommendation if they were a small adult?

DR. ODIDI: Thank you. The average daily intake reported by the FDA in 2011 is 12 milligrams per kilogram per day for FD&C Blue Number 1, 12 milligrams per kilogram per day. Our product contains, as I said, a 3.6-milligram tablet.

To put it in perspective, we talked about Gatorade, and it came up many times. Gatorade contains about 10 milligrams per bottle and our tablet contains 3.6 milligram. Again, I agree with the FDA. This is not a surrogate for determining the toxicity of this product when used intravenously, but from the other point of view, I guess you can draw some conclusions there.

DR. McCANN: Thank you.

DR. BROWN: Dr. Mendelson?

DR. MENDELSON: I'm fine. No more questions

at the moment. I got it answered.

DR. BROWN: Dr. Robotti?

MS. ROBOTTI: Suzanne Robotti. I'd like to ask about the question of the removal of blue dye from skin. There was a passing comment that you would have to rub for 30 minutes with water. Did you do any tests on using any of the substances to remove it, Vaseline, detergent, makeup remover, anything like that?

DR. ODIDI: No. We didn't do those studies. We just used the common solvent, water.

MS. ROBOTTI: Then I have a question for Dr. Setnik. There are 22 subjects who completed the proportionality study. They were all men between the ages of 18 to 50. And I missed how many, but quite a few did not finish this study. Were any of those people who were removed from the study women?

DR. SETNIK: No. So for the dose proportionality study, it was all males. And the reason that they predominantly withdrew was due to vomiting when they either received the naltrexone,

the cover, or the naltrexone plus the opioid.

MS. ROBOTTI: Is there a reason you chose men over women who, actually, there are more women in the population than men?

DR. SETNIK: The study was conducted in Jordan, and there the predominant subjects are male.

MS. ROBOTTI: In Jordan?

DR. SETNIK: In Jordan, yes, the country of Jordan. So it's culturally the males who would participate in such studies. Earlier, I had mentioned the bioequivalency studies had been conducted in healthy females and males. So those studies, looking at the food effects at the 10- and 80-milligram doses included females in those populations, and they're representative in the datasets.

DR. ODIDI: And the studies were conducted in Canada.

DR. SETNIK: Yes.

MS. ROBOTTI: Okay. Thank you.

DR. BROWN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. This question is directed to Dr. Sellers with slide 71. It was mentioned very briefly that there may be a deterrent with the intranasal abuse because contact with nasal mucosa turns it into a gel. And then it just says, "Causing leakage."

Were any studies done looking at this? And also, what happens to the gel that doesn't leak out?

DR. SELLERS: So first of all, the basis of the very viscous gel, or the studies that Dr. Cone presented, even though this product can be reduced to small particle size, when you do this, what you trade off is small particle size against faster and more extensive gelling. And you end up with a material that is more viscous than, for example, the comparator here.

It takes very, very little moisture to make this gelling happen. Some of the studies here use volumes that are very typical of what abusers would usually use. Some of the large-volume studies are lots of fluid, but IV abusers or intranasal abusers

who also use IV, if they ever use liquid, they're going to use tiny amounts, like an mL or something of this sort.

So that's then the basis of the fact that -- and again, Dr. Cone showed a blob that would be with typical volumes, and that is impossible to get into a syringe. And that's what abusers normally would do.

So that's the intravenous abuse, why there's this big obstacle. And obviously the material is dark blue as well, which abusers find -- they don't like colored things, and they don't like things that they are going to inject that have particulate matter. Now, of course, there are some individuals who will take that particular risk.

So does that answer your question, or do you want to go a bit further?

DR. JONIAK-GRANT: Yes. This was more about the internasal abuse, not involving liquid, because it was mentioned that the contact with the nasal mucosa would cause it to gel. So I'm sort of envisioning, if individuals snorted it, then it

would start to turn into a gel, and then you'd have leakage.

So how much leakage and what happens? Could it turn into a gel and stay in the body?

DR. SELLERS: So with internasal abuse -- and I've done quite a few of these studies with PEO types of products. Now, this one is unusual because of these very small particles and the rapid gelling. But I think we can take a general lesson from this, that when they take the particles in through the nose -- and these particles are not so small that they can take them all the way back. They actually get stuck in the nose. As soon as they hit the mucosa, you start to get gelling.

It happens -- it depends, this product, probably very, very quickly. But when it does, the nose starts to get stuffed. They start to feel irritated. They want to blow their nose as the gelling goes on. Then you see it starting to drip out.

Now, of course, this product also contains

sodium lauryl sulfate, which is irritating to the nose. And we've done studies with other products that contain SLS. If you're interested in what those studies look like, I can certainly show you those. But there are a couple of things going on here. One is the gelling. The gelling will happen rapidly.

When the gelling occurs, this actually impairs the absorption from the gel material because some of the active drug is stuck in the gel. And then you start to have some of it leaking out, and with this product, because the SLS is in there, this will be irritating.

What we've seen in previous studies with SLS is that the intranasal abusers report irritation, burning, nasal flushing, and they uniformly say they don't want to take this particular kind of product intranasally. And of course, the product has got this blue dye, so whatever is --

DR. HERTZ: But the question was, were any studies done with this product? Because we know, for instance, that OxyContin, which gels, is

nasally abused in spite of all the things that you said.

So were studies done with this product, I believe was the question.

DR. SELLERS: I interpreted the question as to what are the rationale for this, but of course, I understand --

DR. HERTZ: But were studies done?

DR. SELLERS: For this particular study, for this particular drug, intranasal studies have not been done, as the sponsor has indicated.

DR. BROWN: In further looking on the internet, Brilliant Blue 1 is the subject of quite a bit of information. And it reports here that it's been banned in France and Finland. I'm just interested from the FDA if that comports with your understanding of that excipient.

DR. HERTZ: I can't really discuss that. I can't discuss the details of the excipient at this meeting.

DR. BROWN: Can you just answer this question, then?

DR. HERTZ: I'll try.

DR. BROWN: Blue number 1 that's in our food, has it been banned in France and Finland?

DR. HERTZ: I don't know. I mean, is that what you're seeing online? I am not familiar with how different countries have regulated the different dyes and how that pertains to the dye here. Sorry.

DR. ODIDI: Can I just give some clarification? Did I hear you say Brilliant Blue? Because the dye we have is different from Brilliant Blue. It is FD&C Blue Number 1. So is that what was banned in France?

DR. BROWN: Yes, it seems to be

DR. ODIDI: Brilliant blue?

DR. BROWN: Correct.

DR. ODIDI: We are not using Brilliant Blue in this product. We have used blue number 1.

DR. BROWN: Dr. Meisel?

DR. MEISEL: Thank you. I've got two questions, first for Dr. Setnik. Referring to the bioequivalent studies, I think the slide is 28 and

30, I understand the FDA 80- to 125-percent tolerance limits. But am I correct to assume here, as I look at these slides, that there are statistical differences here between the two products on this particular slide?

In a fed state, the IPC is about 10 percent less well absorbed, but in a fasted state, it's about 6 or 7 percent more absorbed. That is statistically true?

DR. SETNIK: So the way the analysis is done, it does the LS means within a certain range, so there are some variations between the Cmaxes that are acceptable if they are within those limits.

DR. MEISEL: I understand the 80 to 125 tolerance for bioequivalence, but based on the look of this, the confidence limits don't cross that center lane for most of these. So would I be correct to assume that there are, if not clinically relevant differences, statistically relevant differences? Is that true?

DR. SETNIK: So the statistical analysis in

terms of a p-value, comparing the Cmax directly, I don't recall those having been conducted.

DR. MEISEL: I see the same phenomenon on slide 30.

Then I have got a question for Dr. Sellers on slide 70. Am I correct to assume, as I read these graphs, that in the Kentucky survey, with the reformulated OxyContin, the percent of intravenous use or abuse went down by 100 percent and that snorting went down by almost 100 percent? Is that correct?

DR. SELLERS: That is correct. This was a cohort study, so this was a group of abusers who were tracked as to what was the effect of the introduction of the reformulated OxyContin. And this is the report that they gave as to how they were using the drug.

DR. MEISEL: Then, in the other three studies, you talk about oral versus non-oral. In the non-orals, can that be split out by IV versus inhalation versus who knows what?

DR. SELLERS: These data are derived from a

paper. Paul Coplan is the first author and published in 2016. And the paper does not contain the break-out between, say, snorting and IV. That's why I didn't put it on the slide.

DR. MEISEL: If you believe that Kentucky survey, it would be hard to get better than that, wouldn't it?

DR. SELLERS: In the Kentucky survey, because it was directed at a cohort, where they're being asked what route it was, it is specified in that particular part of the array of different studies that were done.

DR. MEISEL: Right. But in all the other ones, the reduction is at least 70 percent.

DR. SELLERS: Could you repeat that?

DR. MEISEL: In the other three, the reduction in non-oral abuse from the OxyContin reformulated version is at least 70 percent.

DR. SELLERS: There is reduction in both oral and non-oral, but a greater reduction in non-oral. So the NAVIPPRO and RADARS are individuals who are in treatment programs and they're being

asked what routes are you using or have you been using with, for example, in this case the reformulated OxyContin.

DR. MEISEL: Thank you.

DR. BROWN: Can I just comment on that? If you could put that slide back up, that does not imply that the frequency of intravenous abuse in Kentucky has dropped. And in fact, the import of heroin into especially eastern Kentucky has risen dramatically, coincident with having OxyContin ADF on the market.

DR. SELLERS: That's correct. These are the data for the change of the pattern of use of OxyContin and illustrate that the pattern of abuse for the product per se has changed.

DR. MEISEL: Going back, somebody made the comment early on in one of your presentations that, if you're an abuser, you'll just switch to something else. That's what you're getting at. Right? They switch to heroin or something.

DR. BROWN: Dr. Arfken? Dr. Campopiano? She asked me to ask the following questions. Does

the sponsor have data in which the sponsors studied any relationship of this drug to GI distress, constipation, diarrhea associated with the excipients and if there's a dose-related response?

DR. ODIDI: The answer is no.

DR. BROWN: Dr. Kline?

DR. KLINE: I buy that adult patients may not want to be stained blue, but I think my question is more about a diversion issue, and that is with the current rave culture, has there been any thought given to the fact that there might be youngsters that would actually like to look blue and might be taking this for that actual status symbol, of having a mark that they're using this illegally?

DR. ODIDI: We haven't conducted any studies, but I think it's important to put this in perspective and what we're trying to do with this blue dye.

A blue dye in this product is basically a two-pronged approach. First it acts as a deterrent, which you are saying for those

youngsters, perhaps trend seekers may not think this is a deterrent, but something good to do. And also it acts as an early warning system to alert families regarding abusers or who would be abusers like these youngsters who try to indulge in this process.

I think, if they do abuse because they like the color, then that obviously will be revealing and will tell easily that they have tried to abuse this product, and hopefully family members and friends will try to intervene.

DR. KLINE: I think my concern, though, about the diversion is that unless the adults know to look for this as a sign -- unless this is a well-publicized fact that you're looking for the blue color to see if they're using this, that this blue color isn't going to raise any concerns in adults unless they're educated.

The kids, as I am the father of teens, they will also be very inventive on being able to get rid of the blue color and how they do that, so just thoughts.

DR. ODIDI: I'd like to call on Dr. Sellers to give a perspective on this.

DR. SELLERS: A couple of practical points, I certainly thought of the kind of situation that you proposed, but I think you have to look at this product as a whole because it's got these other properties. It does form this gel. It contains the SLS. And it has a blue dye.

The blue dye is going to be predominantly effective in individuals who have not progressed to kind of cult-like behavior and are deeply engaged in a drug-abusing situation. The impact on early diversion, crushing of the product, obviously these are going to be the most important things.

Among all of the things, some of which have been presented today, these kind of observations, like a small group of kids who might think having a blue mouth is really cool and it's part of a culture, tend to be fads. They tend to be localized. They tend to be kind of clusters of cases. They don't get huge amounts of traction. The Opana Kentucky experience is an example of a

localized area in which something happens or something a bit different.

So I think you're right. There probably will be, but in the big picture of what this sort of blue dye is meant to contribute, I think that it's going to have a much bigger effect than just thinking about how it could become a weird kind of endorsed behavior.

DR. BROWN: Dr. Litman?

DR. LITMAN: Thanks. Ron Litman. I have a couple of hopefully simple quick questions, and then one more significant one after that.

Dr. Setnik, I just think everyone here is thinking it. I just wanted to ask because of my own ignorance. Why Jordan?

DR. SETNIK: I think that one would have to be answered by the sponsor.

DR. ODIDI: Why Jordan? I think what happened is that we had several studies to do, and we determined that we had a time span to do them. And we looked for sites that would be FDA-approved sites to do the studies. We looked at the U.S., we

looked at Canada, and we looked at Jordan, and we looked at India. In India, we couldn't get permits to take the products there. In Jordan, we have permits.

So that was it. That's what informed those studies done in Jordan. But a lot of the studies were done in Canada, actually. But in order to get everything aligned to apply, the decision was taken.

DR. LITMAN: Thank you. So the next question I have is for Dr. Brock. I was just looking up what happens when you inject this blue dye intravenously. And there's this great picture on the internet of this mouse with blue nose, and ears, and paws.

One of the things that concerns me is, as I look through the public comments that pertain to this meeting, people who are representative of the addicted community are very concerned about public shaming.

So if you inject this intravenously, will you turn blue, I mean, to say it directly, and for

how long?

DR. BROCK: I can't really address the public shaming part of this, but I can address the toxicology data that do exist with IV injection in animals. There is some data that were published by Gross in the early 1960s. In this study, they did repeat IV injection to cats. Why cats, I don't know, but they used cats.

Systemically, they didn't see anything, but when they started doing repeat subcutaneous injection into mice -- that's probably what you found on the internet because I found the same thing, is that, yes, at the injection site, both IV and subQ, the injection site turns blue. And when they gross-necropsy the mice, the organs are blue, the urine is blue, the feces is blue.

The elimination of that blue dye from the injection site from after systemic administration does take time, and it's dependent upon the dose of the blue dye that was used. It's dependent upon the regimen of injection of the blue dye. The longer you inject an animal, the longer it's going

to take for that blue dye to be eliminated, visually eliminated, after the final injection. It's just the biologies of this.

Pharmacokinetically, there are no PK data with injection. The only PK data I have is following oral administration, if it's absorbed. It was stated earlier that it has low absorption, and that's true.

So with oral administration, very little of it is absorbed. The majority of it is eliminated in the feces.

DR. LITMAN: Thank you. I'm sure that, if and when the product ever hits the market, we'll have pictures on the internet within days.

One last question for Dr. Odidi. One of the most important things we're discussing here today is whether or not the category 1 studies are sufficient for ADF labeling, but I haven't really heard a very explicit explanation as to why that would be okay to forego the category 2 and 3 studies for labeling or at least for IV deterrence.

DR. ODIDI: We understand your concerns. As

shown in the core presentation, this product represents an improvement in IV abuse deterrence over existing products. And we've also shown that it's bioequivalent to OxyContin. Thus, we think it's safe and effective from that point of view for its intended use.

It offers a very specific advantage toward deterring abuse by injection. I think we tried to show those data today. And we believe it has other properties, as we said. But we'll be exploring those.

As a matter of fact, we just had an approved protocol for human abuse potential study for the intranasal route, which we'll be studying in a month or two, so beta protocols and discussing with the FDA for what we call a focus group study, looking to assess the impact this blue dye will have on behavior and whathaveyou with abusers.

So again, like I said, we do understand your concern, but I think, given the physical chemical properties of this product, the presence of the blue dye, the presence of SLS, which is a known

nasal irritant, we think that it's important. We suggest that this product be made available to physicians sooner rather than later.

DR. LITMAN: So just for the purpose of today's meeting, the blue dye and the SLS are to discourage mostly nasal, but they really don't have anything to do with --

DR. ODIDI: There are other properties which Dr. Sellers alluded to, which is the superior gelling property of this product.

DR. LITMAN: Thank you.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: Jeff Galinkin. So I guess I'm worried about unintended consequences. If you're taking this long term, you've already mentioned that the urine turns blue. As an anesthesiologist and worried about resuscitation, when we give methylene blue, the pulse ox changes.

If somebody is taking an overdose of this medication or is even taking multiple pills of this over long periods of time, do the nail beds start to turn blue? Do you get the blue dye type effects

that you do with methylene blue? And if somebody was going to be resuscitated after this, it could cause them to have a different resuscitation if their pulse ox is reading much lower due to the fact that this methylene blue is altering it.

Did you do any studies looking at that?

DR. ODIDI: Thank you very much. We understand your concern, and I think we've got to be clear. This is not methylene blue. It's again FD&C Blue Number 1. It's well known.

DR. GALINKIN: I understand that it's not methylene blue, but that's not it. The point is, if you change the color of your nail beds -- this is why we do not allow people to wear nail polish, especially blue nail polish, when we're doing an anesthetic -- it will change your pulse oximetry reading.

DR. ODIDI: Again, I think I should ask Dr. -- thank you.

DR. DART: First, could I clarify the question? You're concerned that, when taken orally as directed --

DR. GALINKIN: Yes, when taken orally over long periods of time, you get that bluish tinge to your blood that other blue dyes can cause. When you resuscitate somebody and they're blue, you'll have a low pulse ox, which won't change.

DR. DART: There's no evidence that I'm aware of that it accumulates, so I don't think it would be an accumulation problem, and it is in multiple products now. The one I mentioned earlier was Gatorade.

DR. GALINKIN: Gatorade does not turn your urine blue that I'm aware of.

DR. DART: But I think --

DR. GALINKIN: They said that this does turn your urine blue.

DR. DART: Dr. Brock was talking about under testing of toxicity conditions, where you're giving a very large dose compared to the body weight.

So when we're giving a few milligrams to adolescents or adults, I think, for that matter, people who already take products that have it in it to the same degree at the same amount in there, we

heard those numbers, up to 10 milligrams per bottle. I think it's a liter of the Gatorade, actually.

So these numbers aren't that different. I don't know if we need to make a separate presentation on that because that wasn't anticipated, but really, to me, we have a natural experiment that has gone on here for quite some time in Gatorade and other products as well, and we haven't seen that.

So I don't think there's a concern there, but that's the best we can do.

DR. GALINKIN: Not everybody takes one pill. You might have people taking 4, 5, 6 pills at a time, I guess is my concern, twice a day.

DR. DART: Right. It's a BID medication that the person will be titrated to the dose. The dose is in there, so they can get to the right dose and have one pill twice a day.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. I have two questions. One of them, unfortunately, is dye

related. I do understand the comments about the pulse oximetry and the dose relationship to that, but if I also think about the fact that this is intended to be a long-term administered medication, that the likelihood is, if somebody's taking it twice a day, while there may not even be visual change in the urine color, it's likely that there will be dye in the urine, whether it's visual or not.

What I'm wondering is if there's been any testing done to see if this can affect in any way urine drug testing results.

DR. ODIDI: No, to answer your specific question.

DR. ZACHAROFF: Because I would think I would not want to know the answer to that question. I don't know that Gatorade, if somebody consumes 2 bottles a day every day for 3 months or longer if it could potentially impact urine drug testing results, but without question, candidates for this medication are going to be subjected to urine drug testing of some kind. And I would think it would

compel us to know if it's possible that the dye could potentially impact the results.

DR. ODIDI: I think we do intend to discuss with the FDA to address issues such as those, labeling for example, a warning on labeling.

DR. ZACHAROFF: I think it is an important fact to know. I see you shaking your head no, Dr. Brook [ph]. I don't know if you want to make a comment with respect to that or not.

DR. BROCK: Specifically, I can't comment on whether the blue dye would interfere with urine drug testing. I don't think even methylene blue does. So just by analogy, it's unlikely from my perspective. I'm not an expert in that, but that's my perspective.

The other thing that I think we're getting lost in here is -- and Dr. Dart pointed it out -- when I was talking about the urine being blue, the feces being blue, and so forth, I mean, we're talking about doses in animals that are two orders of magnitude or more above what the actual human dose would be with this drug product.

The level of the blue dye that's here is higher than what's in the inactive ingredient guide, FDA's inactive ingredient guide, so I had to look at this from the perspective of qualification. And in order to do that relative to the intended clinical route, oral, I had to go back and look at all of the oral tox data that's available for this, and there's a fair amount of it.

So even in those studies, where it was orally administered, there was some blue dye tint to the urine and the feces, as I've said before. Most of it is actually eliminated in feces anyhow. But the GI mucosa was not tinted on gross necropsy or histopathology.

But to compare this, again, the dose that one might take of this blue dye could be up to 156 milligrams a day in humans. And that is, from my calculations, about two orders of magnitude below where we see this blue discoloration.

DR. ZACHAROFF: I understand. It just has to do with the science of urine drug testing, how they measure absorption of light and whether or not

it's been tested, so everything taken.

The other question is that I've heard discussed a couple of times by different members representing the sponsor about cutting the pill in half, and I'm wondering if any testing has been done on pills cut in half taken orally to see if it affects in any way the pharmacokinetics.

So if someone cuts the pill in half, because it sounds like you can, and then takes it orally, does it affect the extended-release mechanism, and do you have any data with respect to the answer to that question? Has any testing been done

DR. ODIDI: No testing has been done in humans for that, but we do have dissolution data.

DR. ZACHAROFF: Thank you.

DR. ODIDI: I'd like to call on Dr. Sellers to try and throw some perspective on the last discussion before your question. I think that's important.

DR. SELLERS: Just in response to Dr. Zacharoff's question about the urine testing, most of these of course are immunologically-based

tests, and the blue dye will not cross-react with opiates and other drugs of abuse that are looked for in these tests. So I think that's a very, very remote likelihood that would ever be a problem.

DR. BROWN: We are now going to break for lunch. We will reconvene again in this room in one hour from now at 2:00 p.m. We will get to the rest of everybody's questions prior to the time that we go to discussion and voting.

Please take any personal belongings you may want with you at the time. Please remember that there should be no discussion of the meeting, during lunch, amongst yourselves, with the press, or with any member of the audience.

(Whereupon, at 12:58 p.m., a lunch recess was taken.)

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

(2:00 p.m.)

DR. BROWN: Before we start the open public hearing portion of our meeting, Dr. Staffa had some clarifying comments that she wanted to make.

DR. STAFFA: Thank you, Dr. Brown.

This is Judy Staffa from FDA. I guess, as a follow-up to some of the comments this morning about the epidemiologic data that were presented by the sponsor, that were published by Purdue about the impact of the abuse-deterrent OxyContin, I just want to caution the committee on interpreting those data.

We just had a public meeting a couple weeks ago where we talked about the many methodologic- and data-related concerns we have with the ability of us, or sponsors, or anyone to adequately evaluate the impact of abuse-deterrent formulations right now.

So I don't want to go into all the details, but if you look at these publications with a critical eye, they can look rather appealing at

first blush, but for example, what was presented was really just the decreases in OxyContin, but there were many other things going on in 2010, 2011 as well. There were a lot of decreases in a lot of the abuse of other products, too.

So we continue to struggle with this, and we continue to try to provide sponsors the best possible advice we can on how to do their postmarketing required studies. But there's a reason why none of the products has labeling yet, because we're trying to figure out how do we get rigorous scientific data to show that.

So I just wanted to throw that out there to make sure the committee understood our stance on that. And Dr. Hertz had alluded to that in her comments as well. So thank you.

Open Public Hearing

DR. BROWN: Thank you, Dr. Staffa.

We're going to begin the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To

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

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

For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The

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

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

As an addition to that, each of the speakers has been allotted a specific amount of time, and we would appreciate it if everybody would try to keep to that time.

So will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a senior fellow at the National Center for

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

The development of opioids formulated to prevent abuse is a public health priority, and we support the FDA's efforts to encourage their development. The FDA states that a product that has abuse-deterrent properties means that the risk of abuse is lower than it would be without such properties.

The in vitro testing demonstrates that compared with reformulated OxyContin ER, IPC Oxy displayed similar and, in some cases, superior abuse-deterrent properties. For example, IPC Oxy was more difficult to get into a syringe for typical recipes used to abuse reformulated OxyContin ER. However, please keep in mind the comparison to a so-called abuse-deterrent opioid currently on the market does not necessarily set a

high standard.

The FDA states that the development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Based on this criterion, the results of in vitro testing provide promising evidence that IPC Oxy provides incremental improvement to deter intravenous abuse over reformulated OxyContin ER. However, with no data from pharmacokinetic and clinical abuse potential studies, it is difficult to make assumptions about IPC Oxy's effects in the real world.

Proving whether IPC Oxy's abuse-deterrent properties are effective in the real world will require data from categories 2 and 3 studies. For example, as mentioned during discussion today, the blue dye intended to deter abuse could be novel or intriguing for teenagers. It is also unclear from the available evidence how much is known about whether this ADF could have unexpected health effects when used long term or abused.

We know from previous experience that once opioids designed to deter are on the market, they tend to be abused more extensively than laboratory studies suggest. That is exactly what happened with reformulated Opana ER, which FDA recently decided should be taken off the market.

Although the available data suggests that this drug will be less likely to be abuse intravenously, individuals who are addicted are highly motivated to overcome those deterrents.

Opioid addiction is an epidemic in the U.S. and labeling a drug as abuse deterrent influences doctors, patients, and family members. We commend the FDA for making it a priority to find ways to adequately explain risks in the label, including distinguishing between the risk of abuse and the risk of addiction.

At the FDA's recent public workshop on opioids, Commissioner Gottlieb said, "We don't want to improperly convey a perception that a product that is resistant to manipulation and abuse is somehow also less prone to fueling addiction, when

that is simply not true." We strongly agree with Commissioner Gottlieb's statement. Unfortunately, many doctors think abuse deterrent means an opioid is less addictive.

To be a part of the solution rather than part of the problem, the FDA should require sufficient evidence that this drug's abuse-deterrent properties result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes.

The two FDA-approved abuse-deterrent single-ingredient oxycodone opioids included pharmacokinetic and clinical abuse potential studies before receiving the abuse-deterrent designation. The FDA should not use a lower standard for approval for IPC Oxy as abuse deterrent.

It is important for this panel and the FDA to make approval decisions based on good science and strong data. Do the current data represent rigorous evaluation of IPC Oxy's impact? Do we know enough to determine the real-world impact of

this opioid formulation intended to be abuse deterrent?

To reduce the opioid epidemic, FDA must hold pharmaceutical companies to a high standard with clear evidence. We do not believe IPC Oxy should be designated as abuse deterrent unless that is clearly proven, as we are concerned about unexpected impacts of the formulation without pharmacokinetic and clinical abuse potential studies.

We urge the committee to vote that there is not sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration.

In order to be labeled as abuse deterrent, we urge you to recommend that data from categories 2 and 3 studies be required to provide evidence that IPC Oxy is abuse deterrent. If there is a reason that this data is not necessary, there needs to be sufficient justification so that a lower standard is not set for approvals of future

abuse-deterrent formulations.

Thank you for the opportunity to share our perspective.

DR. BROWN: Thank you. Could speaker number 2 step to the podium and introduce yourself?

DR. COHEN: Thank you. My name is Dan Cohen. I'm the chair of the Abuse Deterrent Coalition. I do not have a financial relationship with the sponsor. I am an officer of a competitor innovator, KemPharm, and I'm a board member of the Mid-Atlantic MedStar Hospital System.

The Abuse Deterrent Coalition was formed as a talk forum of ADF innovators, patient and issue advocates, and research groups to educate the public, policymakers, and the FDA on the importance of developing and expanding ADF technologies. The 19 innovators in the AD Coalition have produced all 10 ADF-labeled opioids and Intellipharmaceutics is an original member of the coalition.

Is it reasonable to approve Intellipharmaceutics's oxycodone hydrochloride extended-release tablets with abuse-deterrent

features focused on the ability to deter IV abuse?

As this panel is aware, existing products with ADF labeling have largely attempted to make products more resistant to tampering or less rewarding to abusers. This product does that as well, but it also attempts to discourage abuse by making abuse efforts themselves visible and noticeable.

One can imagine that the blue dye shows evidence of an abuser's effort to chew, snort, or inject the product will impact abusers and potentially discourage intranasal and intravenous abuse.

But focused on their request, preventing injection with prescription opioids has been one of the primary public health goals of abuse-deterrent formulations, because IV abuse is associated with more severe health consequences.

Data from recent peer-reviewed papers offered by the RADARS poison control center suggests that the relative risk of death or major adverse event for IV abuse routes is over 2.6 times

greater than abuse by oral methods alone. IV abuse was also associated with 6 percent of the new HIV diagnosis and 10 percent of all new AIDS diagnoses in the U.S. in 2015.

As this panel prepares to respond to today's voting questions, it is important to ensure that we are using appropriate and similar terms for the discussion. As our members and the agency, along with expert panels such as this one, have grappled with the fundamental issues, one key concern has been nomenclature.

Having different understandings of the terms being used will yield a faulty decision and not appropriately address the question. Those terms include core concepts such as abuse deterrence and who is the customer or the target of ADF technology.

There are many real and potential attributes of what is ADF. What is not under consideration today is IPC's oxycodone hydrochloride capabilities as an abuse prevention formulation or APF. There is no APF. Products with ADF technology do not and

are not expected to prevent abuse of scheduled products, only to lower through deterrence the abuse potential of the products.

To save lives, we must adopt the science that is possible today and not wait for what we hope will be a technology tomorrow. As we achieve therapies for patients while making abuse, misuse, and diversion of important medications as difficult as possible within the bounds of known science, ADF will get more effective. But we cannot get to future innovation by failing to approve current discovery.

But to give full meaning to this as well, it is important to agree on another term. Who is the customer for ADF? Most of the discussion, data, and anecdotal stories reviewed, including today, have focused primarily on the addicted and/or the criminal abusers of drugs, but little focus has been on the misusers.

Abuse deterrents are best understood as a technology that reduces the risk of misuse and diversion by focusing primarily to the point of

exclusivity on the opiate-naïve and early-stage recreational abusers.

ADF is not a technology capable of effectively deterring a professional manipulation, a desperate addict, or highly experienced abuser. ADF is an early-stage intervention designed to reduce prescription drug abuse. It is a lone tree in a large forest that plays a key role in deterring people, children, from progressing on the path to addiction. It is not a silver bullet that can solve the entire problem.

There is room for incremental improvement offered today by IPC Oxy to deter abuse via the IV route. 2015 FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids acknowledges that the FDA expects the market will foster iterative improvements in products with abuse-deterrent properties.

IPC Oxy was developed to address the public health need for incremental improvement in abuse-deterrent technology, particularly for the IV route, which is the most dangerous route of abuse.

To sum up, as you consider your recommendations this afternoon, I urge you not to seek to make the perfect the enemy of the good. Oxycodone hydrochloride is a common target of abuse with relatively high rates of intranasal and IV routes of abuse. The data presented this morning demonstrates that IPC Oxy is a product that can be expected to offer both abuse deterrence and a similar safety and efficacy profile to its comparator product, the pure definition of an ADF.

Overall, these results demonstrate that IPC Oxy would be an effective extended-release opioid analgesic with incremental improvements in abuse deterrence via the IV route. Thank you.

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

DR. CICHON: Good afternoon. I'm Charlie Cichon. I'm the executive director of the National Association of Drug Diversion Investigators, NADDI, and I have no relationship with the sponsor.

NADDI is the leading drug diversion training organization in the U.S., with the largest

networking platform of professionals involved in the field of pharmaceutical drug diversion. Our platform provides the opportunity to bring diverse viewpoints, education, supports, and resources to the individuals facing the challenges in the fight against the misuse and abuse of pharmaceutical drugs.

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

NADDI's organization works to develop and implement solutions to the problem of prescription drug abuse, misuse, and diversion. We advocate for the responsible use of prescription drugs by people who need them.

Our primary focus is training and education

for our members, which include law enforcement personnel, regulatory agents, healthcare professionals, healthcare fraud investigators, and the pharma industry.

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

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

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

The new drug application under review of oxycodone hydrochloride extended-release oral tablets has been formulated with the intent to deter abuse. Adding new physical and chemical features to prescription opioids to deter abuse could also reduce misuse of these drugs and sometimes, unfortunately, the deadly consequences. These products can be part of a comprehensive approach, which should include prevention, interdiction, prosecution, and substance abuse treatment.

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

In short, I believe that abuse-deterrent formulations of opioids can interrupt the abuse trajectory for these medications by preventing manipulation for nasal and intravenous abuse.

This is true whether the drug is obtained by

prescription or is diverted to an unintended user. NADDI supports expanding access to ADFs in order to reduce prescription drug abuse, misuse, and diversion.

Due to the ongoing problems with the pharmaceutical drug abuse, misuse, and diversion in the U.S., we are a strong proponent of new abuse-deterrent medicines that make it more difficult for an abuser and reduce law enforcement involvement in healthcare. Thank you again for allowing me to provide testimony before the committees. Thank you.

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

DR. BRASON: My name is Fred Brason from Project Lazarus, and I have no disclosures this morning. Thank you, Committee, for giving me the opportunity to share today with the slides that I'm sharing. I'm letting you know that we all are in a place today in the United States, in our communities, where we've never been before, so when the music changes, so does the dance. We all have

to do something different from the FDA to the manufacturer to the community. And that's what Project Lazarus does to help.

We took a comprehensive approach, and it all is necessary to combine everything together in what we can do to make a difference to stop and prevent overdoses, but also to present responsible pain management that is safe for the patient, family, and caregivers, but also to promote substance-use treatment and support services.

So it takes a comprehensive approach that's facilitated within our communities, but we have social issues that bring about a lot of the problems that we're having. And as Malcolm Caldwell said, "Epidemics are sensitive to the conditions and circumstances of the times and places in which they occur."

Sadly, I report from my own community, Wilkes County, North Carolina, we began with moonshine a long, long time ago, and, unfortunately, it's still there, too. But then we moved into marijuana, methamphetamine, and then

medicine, are issues we have within our company largely because of the social determinative factors that we have within our community.

This shows you on this slide the amount of people that are pulled into round-ups from selling mostly prescription pain medications and benzodiazepines within our community, mostly gained from outside the community because they can no longer find it from within.

But it just shows you the number of people because of the economic factors and the poverty factors, the depression factors that we have. And most of these are diverted and they are not abuse-deterrent formulations that are.

In 2007, we were the third worst county in the United States for prescription medication overdoses. From 2000 to 2014, by the Pew Charitable Trust, that study showed that Wilkes County was number two in the country for income loss. Is there a correlation? Absolutely.

When we work with prescribers, they not only just look at the pain of what the individual is

experiencing and the reasons for that, they have to look at the genetic factors, the cultural factors, the substance-use factors, the mental health factors, and the environmental factors.

That patient can be the perfect patient, taking everything correctly, making sure that it's stored securely, but in the environment that we now live in, unfortunately, in many of our communities, there's somebody else that's looking for that medication, somebody else that's seeking to buy that medication, or to steal that medication, or the substance-use issues history of that individual.

All of that has to be weighed before writing that prescription from our prescribers, and abuse-deterrent formulations at least stops and deters the diversion of that product.

When we worked with the military, we found the same thing in the co-prescribing of naloxone and working with the shoulders there that unfortunately were experiencing overdoses. Now, in Fort Bragg, in the Army, every refill is an abuse-

deterrent formulation to ensure that diversion does not take place. It lessens that probability.

We also learned from the Massachusetts Division of Public Health preliminary study that at least 2 out of every 3 people who die of an opioid overdose had been prescribed an opioid between 2011 to 2014. But at the time of death, only 8.3 had an active opioid prescription.

Therefore, that tells us that the majority came from diverted medications that they received elsewhere either bought, stolen, or freely shared, again just showing us the prominence of diversion and the force behind that, what is occurring within our communities.

When we look at North Carolina, the injecting use that is going on, it's been on an upswing for years. And we're hoping to abate the HIV and hep-C issues that compound all of that. So we're working on that.

But again, anything that can deter that from occurring is very beneficial. I just talked with Washtenaw County. We work with a number of places

in Michigan. As injection drug use accelerates the patient severity of opioid addiction, it is important that we continue to monitor injection drug use.

This comment was made. "Seven percent of Washtenaw County Middle School students identify having used a needle to inject illicit drugs." I had to make a phone call when I got that and said give me some more information; where is this coming from?

Well, it comes from self-reporting surveys within the schools, no particular drug indicated. They checked their last year's survey. They checked their county comparables around them, and they all came up with similar numbers. This tells us the extent to what we're dealing with, and, again, any deterrent from moving people into that is beneficial.

This is an individual on my own staff as a peer recovery specialist, who is now in long-term recovery and working with those looking for it. But she described her experience when she first

experienced a prescription medication. "I remember what I was wearing, what everything smelled like, even what the weather was like outside." She added, "A friend of mine gave me a 30-milligram. That was when I was first introduced to it. I crushed it up and snorted it" -- she had never done anything with prescription medications until that time -- "and the immediate result was complete and total euphoria on a level that I had never experienced in my life.

"It was. It was bliss. It was a contentment that I had never known. It was instant. I was in love. I felt beautiful and like I belonged. From that first pill, that one teeny tiny pill, I was totally overwhelmed."

Not everybody is escalating from oral to snorting to injection. We are seeing more and more going right to injection within our communities. And any way that we can deter that from occurring is going to be beneficial. Thank you very much.

DR. BROWN: Will speaker number 5 step up to the podium and introduce yourself?

DR. TWILLMAN: Good afternoon. My name is Bob Twillman. I'm the executive director of the Academy of Integrative Pain Management. I have no conflicts of interest to declare.

The AIPM is a multi-disciplinary organization to pain care clinicians, including members from just about every healthcare profession you can imagine. We espouse a model of integrative pain management, recognizing the important role played by traditional biomedical treatments for pain such as medications and procedures, but also advocating for additional treatments that may supplement, compliment, or even replace them in the service of providing maximal improvement in pain and functional status for people with pain.

The AIPM is keenly aware that opioid pain relievers and other controlled substances have become controversial because of their prominence of prescription drug abuse. We've been extremely active in a variety of policy advocacy efforts related to the two major public health issues of concern, inadequately-treated pain and prescription

drug abuse.

One subject of these efforts, which is the purpose of today's meeting, is the development and uptake of so-called abuse-deterrent technology for controlled substances. We believe that this technology represents a significant advance in protecting people from unintentional overdose resulting from their efforts to abuse opioid analgesics by altering their native forms to facilitate insufflation and/or injection.

The experience to date with the one product that has sufficient history to use to permit evaluation demonstrates that ADS may very well prevent a significant number of individuals from engaging in this dangerous behavior, thus providing a meaningful benefit.

But let's be clear, though, about what we should expect from these products. These products by themselves will not solve the problem of prescription opioid abuse. To expect that they would do so would be comparable to expecting that the introduction of the Tesla would solve global

warming.

These products are designed to prevent alteration of the native drug form so as to facilitate insufflation and injection. In the case of the current product, the manufacturer is only requesting labeling reflecting its ability to deter injection. These outcomes should be the criteria by which their effectiveness is measured.

We are grateful to FDA for its efforts to support the ongoing development of ADF technology. We also recognize, as I'm sure everyone else here does, too, that this is not a static process with a well-defined endpoint. People who tamper with these products in order to abuse them are very creative, and history has shown that they are adapted, overcoming efforts to thwart them.

Thus, we find ourselves in a sort of continuing arms race, needing to constantly develop newer and better technologies in order to stay even a few steps ahead. For that reason, we want to take this opportunity to encourage both manufacturers and FDA to continue innovating in the

ADF space, developing new approaches that may be even more impervious to or discouraging of alteration, even if those new approaches only buy us a few years of relative success.

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

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

It's patently unfair that this happens, and

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

We'll continue working on this issue in federal and state legislative bodies and regulatory agencies, hoping that more will emulate success as seen to date in Massachusetts and Maryland.

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

Thank you very much for the opportunity to speak today.

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

(No response.)

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

DR. JOHNSON: Thank you. My name is Mike Johnson. I'm an internist and a primary care doctor, and I'm here representing myself and my personal concerns about the safety of this drug. I don't have any financial interests in this company, but I do own stock in several competitors.

The concern that I have about this drug is not the PEO and it's not the oxycodone. It's the blue dye. And I learned more than 10 years ago that blue dye is a nasty biochemical with some significantly toxic properties.

I don't want to spend a lot of time. I have approached this like I do any problem in my practice with evidence-based medicine. So I've prepared a lot of slides for you, where I boiled it down to the evidence, and I hope you'll spend some time looking at my slides because they answer directly some of the questions that the committee members that have been asking about blue dye today.

The FDA has a responsibility to certify every use of every use of every color. There's no certification for blue dye to be used to intensely color the mucosa of the mouth, or of the nares, or of the hands. That has to be applied for. There has to be a safety review, and it has to be listed for that use.

There are only 7 colors that are approved for ingested drugs, and only 2 of them are blue. I suspected before today, confirmed it, that Rexista contains Aluminum Lake Blue Number 1 based on the patent information that's available.

In the patent on the overdose protection system, there were 34 examples, 6 of which contained ingredients for a dye, and all 6 of them used Aluminum Lake Blue Number 1. The minimum amount was 12.1 milligrams. The maximum amount was 18.6 milligrams. And the amount that corresponded to the example that was oxycodone 80 milligrams had 15.27 milligrams of Aluminum Lake Blue Number 1.

This is another question that was brought up earlier. Brilliant Blue is a common name for FD&C

Blue Number 1. It's a petroleum product. It was originally derived from coal tar. Coal tar is that murky substance that results when you try to break down coal into coal, gas, and coke. And it contains a lot of organic chemicals, including all of the artificial dyes, which were originally derived from coal tar.

Blue Number 1 is known to cross the blood-brain barrier. The acceptable daily limit of Blue Number 1 based on the FDA information is entirely on animal studies. There are no human studies to support this number, and the animal studies that were done were all done in animals that had healthy guts.

So the animal studies all pre-date the 2003 FDA advisory that I'll talk about, that warned about possible systemic toxicity when systemic absorption of blue dye occurs in patients at risk for intestinal permeability changes.

This is just an example here of the uses that have to be certified by the FDA. In 1969, Blue Number 1 was certified for ingested drugs in

food, but it wasn't until 1982 that it was certified for external use as a cosmetic. And even that use, there was a carve-out for the eye area. There were no safety studies to support its use around the eye, so it wasn't allowed.

Blue Number 2 is still not allowed to be used in the eye area because there are no safety studies. But we're going to allow it to be used to intensely color the mucous membranes in the nares when we won't even allow it around the eye.

This picture is also from the patent, so it's not in color, but it serves the purpose. You can see that the blue is not on the outside of the tablet. The blue dye is not being used to color the tablet. It's all homogenous on the core.

So it's clearly not there to color the tablet, and if it were there, it wouldn't qualify for good manufacturing practices. If your intention was to make a blue tablet and that's what you came up with, you wouldn't keep your GMP certification for very long.

The FDA advisory says that blue dye is used

to color food products at generally parts per million, but the patent says that the core of Rexista is 4 percent blue dye. That's parts per hundred. That's 4 decimal places. That means that Rexista delivers blue dye at a concentration that's hundreds of times good manufacturing practices for food products.

This is the point of chronic therapy, which is M&Ms. I messed up this slide because I said 77 blue M&Ms every day, but it's 77 every dose. And that's assuming that there's 6.1 milligrams of straight blue dye. Actually, there's 3.1 according to Dr. Odidi, so it's pretty close then, 77 blue M&Ms every day to get the amount of blue dye that a Rexista user gets.

It's Aluminum Lake, and Aluminum Lake is not stable at low pH, like in gastric pH. You get color bleeding, and that straight blue dye bleeds from the alumina substrate.

This is an active ingredient. It changes the user. It has direct effects. It's meant to act as a deterrent and an early warning sign. This

is not an inactive ingredient. It's not an excipient. It fits every definition of the FDA's definition of an active ingredient.

Not only does it have an effect on disease, but it also has biological activity. Brilliant Blue and all of the triphenyl methane dyes have significant inhibitory effects on the ADP/ATP translocase, which is a very important protein in the inner membrane of mitochondria. It makes up 10 percent of the inner membrane of the mitochondria and uses 30 percent of the energy created by the energy transport chain.

When you have --

DR. BROWN: Dr. Johnson, could you finish up, please, sir?

DR. JOHNSON: I will. I want to point out that the FDA in 2003 issued an advisory that said we should not be putting blue dye in tube feeds. There were 12 reported deaths with blue dye. The Canadians issued a similar alert.

What they said was that there was significant risk for patients with increased gut

permeability from trauma, shock, celiac sprue, inflammatory disease. This is what happens when you turn blue with dye. When dye is put in your tube feeds, you can turn blue, and you can die from refractory hypotension and acidosis.

DR. BROWN: Dr. Johnson, could you please finish up?

DR. JOHNSON: I will. I will. This is what it looks like when it accumulates in the gut. This is Blue Dye Number 1 at autopsy.

DR. BROWN: Dr. Johnson, I appreciate the fact that you've put this together, but your time is up.

DR. JOHNSON: [Inaudible - off mic].

DR. BROWN: Thank you very much.

Presenter number 8?

DR. WOLFE: Sid Wolfe. I've put on the front slide the most important thing -- other than that, I don't have any financial conflicts of interest -- is that this product has not been adequately studied.

These are the direct questions that you're

going to be asked to discuss this afternoon. Just look at the underlined one, which is whether it's appropriate to consider labeling this product for abuse-deterrent properties for a single route without complete assessment of all relevant routes of abuse.

Dr. Tolliver nicely reviewed the idea that the guidance says that you need to do not only the tampering phase 1 study, but also the abuse-related pharmacokinetic/pharmacodynamic and the human abuse potential studies, and the company has only done this one.

This is a slide taken from the FDA data, and it's looking at all of the 9 other -- prior to the one today -- abuse-deterrent drugs that were put on the market. The common denominator is that all of them, before getting any kind of abuse-deterrent labeling, had human abuse potential studies. I believe they all had also the pharmacokinetic/ pharmacodynamic studies as well. This is from 2009 to 2017.

The FDA has never approved an abuse-

deterrent labeling in a product that did not have all three of these categories of studies. The initial approval of OxyContin did not have an abuse-deterrent labeling, and only got it when they had done all of these three kinds of studies.

The promise by the company was if you approve this for IV abuse, then we will do the studies that, unstated, we should have done before coming to you, as in the category 2 and category 3. Upon completion of those studies, then they'll try and get an indication on the label for reduced intranasal and oral abuse.

But that's really no way to regulate, and I think that if this ever got approved under these kinds of circumstances, this is a terrible message to the rest of the industry that you don't really have to follow the guidance, which has been in effect for two years now.

This is something that wasn't discussed before. The excipient issue obviously involves polyethylene oxide and blue dye, Brilliant Blue Number 1, as you just heard, and the sodium lauryl

sulfate, a nasal irritant. But there has not been any discussion of the inactive ingredients.

This is the current labeling on OxyContin. "It can be expected, if used parenterally, to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury."

I have no idea, and we have not heard any discussion, of what the inactive ingredients there are because since it is likely there will be some kind of IV abuse, parenteral abuse, it would be nice to know what is going on; another incomplete, as were a number of other questions asked. The company hadn't done a lot of these.

These are towards the end of the discussion questions. The second and third, I'll just mention. Again, this is on the excipients without really knowing about potential risk of exposure via these non-IV routes of abuse that have not been shown and are not intended to contribute to the proposed -- the FDA is essentially saying, why has this stuff, which is in there, a dye, whatever

else, why has it not been adequately studied. And I think this essentially links with the idea that you have to do all three categories of studies.

The last one, discuss whether it is possible to determine an acceptable level of risk for excipients that may be toxic by unintended routes of administration. There aren't any data on that, and so the answer I believe is no.

This is up again just to remind people that this would be precedent setting to agree to approve a drug with abuse deterrent that had not had all three categories.

Finally, the voting questions, has the applicant demonstrated the oxycodone extended-release tablet has properties that can be expected to deter abuse by the IV routes of administration? I would say clearly no, one, because to get the bigger picture of abuse, you need to do all three categories of studies, and secondly, there are no data on parenteral use risks of inactive ingredients or the excipients, both categories, meant to deter oral and/or nasal use.

The third one is, should it be approved or not. And since I don't believe there is a consideration to approving it with no abuse deterrent, because I don't believe there are oxycodone products on the market with that, it's in reality a question about approval without any abuse-deterrent labeling.

I don't think that this is allowed, and I certainly disagree with the idea of approving this drug. It needs to go back to the drawing board. I have no idea what it would show. Certainly, in previous drugs, the human abuse potential studies revealed things that were very important to consider in terms of the overall picture of abuse deterrence. Thank you.

DR. BROWN: Could speaker number 8 step to the podium and introduce yourself?

DR. THOMPSON: It's number 9.

DR. BROWN: Excuse me, number 9.

DR. THOMPSON: Hello and good afternoon. I'm Edwin Thompson, president of Pharmaceutical Manufacturing Research Services. Beginning with

the relabeling of OxyContin in 2001, the FDA has unlawfully allowed extended-release opioids to be marketed with chronic use labeling, despite a lack of evidence to support the chronic use indication.

Even today, there remains a lack of evidence that prescription opioids are effective or safe in the chronic pain setting. Indeed, the lack of evidence to support the efficacy of prescription opioids in the treatment of chronic pain has been recognized by the CDC.

The CDC guideline is the culmination of almost three years of work by the world's experts in epidemiology. The CDC is the ultimate authority on the opioid epidemic, having combined the resources and knowledge of top experts in the field, numerous rigorous studies, and a multitude of panels.

Some of the CDC's recommendations and conclusions in the guidelines include the few randomized trials to evaluate opioid efficacy for longer than 6 weeks, not chronic, 6 weeks, had consistently poor results.

The science of opioids for chronic pain is clear. For the vast majority of patients, the known serious and too often fatal risk far outweigh the unproven and transient benefits. The CDC is telling you efficacy is unproven.

Former director of the CDC, Dr. Thomas Frieden, and Dr. Debra Houry have provided perhaps the best summary of the consequences of the use of opioids for the treatment of chronic pain.

"Beginning in the 1990s, efforts to improve treatment of pain failed to adequately take into account opioids' addictiveness, low therapeutic ratio, and lack of documented effectiveness in the treatment of chronic pain."

The former director of the CDC is telling you there is a lack of effectiveness. Whereas the benefits of opioids for chronic pain remain uncertain, the risk of addiction and overdose are clear. We know of no other medication routinely used for non-fatal conditions that have killed patients so frequently.

Since the beginning, wrongfully approved

treatment of chronic pain, it is estimated that opioids have killed over 200,000 people. IPC Oxy must not be approved for the treatment of chronic pain in the face of this growing epidemic. The risks far outweigh -- far outweigh -- the benefits.

Furthermore, the CDC has observed that overdose risk increases in a dose-response manner with higher doses producing significantly higher rates of patient overdose and death. The risk at least doubles at 50 to 99 morphine milligram equivalents per day and increases up to 9 times at 100 or more morphine milligram equivalents per day as compared with doses below 20 morphine milligram equivalents per day.

One of every 550 patients started on opioid therapy died of opioid-related causes in a median of only 2.6 years after their first opioid prescription. For patients receiving doses of 200 morphine milligram equivalents or higher, the rate of patient death was as high as 1 in 32. With strengths as high as 80 milligrams per tablet, IPC Oxy dosed BID will deliver 240 morphine milligram

equivalents per day. This daily dose is expected to significantly increase the odds of both addiction and death.

You cannot in good conscience recommend a drug that kills 1 in 32 patients to treat non-fatal conditions. No healthcare professional can recommend the approval of a drug with this benefit-to-risk ratio. Before you firmly approve or vote on this matter, you must also be able to demonstrate substantial evidence of efficacy.

Although this is not one of the questions before the committee, it is your obligation and duty to consider the safety and the effectiveness of this drug.

The FDA has abdicated its responsibility on this matter by bringing before you yet another opioid indicated for chronic treatment. You cannot support the approval of IPC Oxy, putting it in the hands of physicians and their patients without evidence of efficacy. Thank you.

Clarifying Questions (continued)

DR. BROWN: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comment.

Prior to the time we do that, however, I want to take a few minutes and allow the members of the panel to ask some of the questions that they have been waiting patiently since this morning to ask. Dr. Habel?

DR. HABEL: Yes, thank you. I had a question about slide 15 that had to do with the expected TMA-related safety profile of the IPC Oxy versus OxyContin. And it really has to do with the greater gelling properties of IPC Oxy.

Even though the PEO is the same in the two products, I'm just wondering to what extent you have data that would indicate that there's no reason to believe that the extra gelling properties might not pose risks when the product is injected.

I don't know. Dr. Odidi?

DR. ODIDI: Yes, thank you very much. I would like to, with your permission, clarify three points that were discussed this morning, and one of those will be related to your question.

The first one has to do with the blue dye. This is to clarify that the blue dye in this product is Aluminum Lake FD&C Blue Number 1. And in the product, it contains between 13 milligrams and 16 milligrams.

Aluminum Lake FD&C Blue Number 1 consists of aluminum oxide and Blue Number 1 dye. The aluminum [indiscernible] is about 20 percent content, and the blue dye is about 31 percent content. But the compound, Aluminum Lake FD&C Blue Number 1, is between 13 milligrams and 16 milligrams in our product. So I wanted to clarify that.

I also want to call on -- in view of that, I will call on Dr. Bill Brock to just say one or two things. Then I will go to the next two things to talk about on aluminum toxicity and the blue dye.

DR. BROCK: So the question that I have just been asked to discuss is regarding aluminum

toxicity as it may dissociate from the Aluminum Lake blue dye.

The first thing we need to keep in mind is, as Dr. Odidi said, with the dissociation to aluminum, that would result in about 34 milligrams of aluminum if someone took 13 pills. To put that into perspective, the typical body burden of aluminum on a daily basis is about 30 milligrams. So it does exceed, but the daily intake from aluminum through the diet is about 3 to 5 milligrams per day.

Moreover, to put this in further perspective, if one is taking an antacid like Maalox -- I do that occasionally -- the dose of aluminum from that is about 4 grams per day. So there is a great deal of variation in exposure to aluminum.

Now to the toxicology, the salt form here is aluminum hydroxide, and it's reacted with the dye to form the lake. So aluminum hydroxides are not well absorbed from the GI tract compared to other aluminum salts, like I think aluminum citrate is

pretty well absorbed.

Now, with respect to aluminum chloride, with respect to if absorbed, it is eliminated fairly rapidly from the plasma. Indeed, in IV administration of aluminum to humans, the clearance is about 15 minutes from the plasma. Now, there is some that remains, and actually, with radiolabeled aluminum, it can be detected out to 4 months.

Now, with respect to the specifics on administration to experimental animals, there have been some studies, repeated IV administration studies in dogs and rats. And in these studies, the doses were for dogs about a mg per kg per day out to 5 weeks. In this case, there was in fact aluminum deposition in the bone and osteomalacia.

In the rats with a similar IV administration, a 2-hour infusion at 40 mgs per kg, they do see increases of plasma calcium levels, all suggesting that there is aluminum deposition in bone and release of calcium.

DR. ODIDI: Thank you very much.

I want to talk on the second point. I

wanted to clarify earlier this morning, and it also leads to the question that you asked earlier on. I'd like to call on Dr. Ed Cone to discuss the impacts of these excipients and viscosity.

DR. CONE: Yes. I think this relates to the question that was just asked by the panel about viscosity and gelling. That's probably the most important factor in deterrence of IV injection.

IPC just recently acquired a viscometer that really accurately measures very viscous solutions, and we have that data. It's not been submitted to the FDA yet, but I think it'll shed some clarity on the real differences between the products. And I'd like to ask for permission to show just two slides.

Thank you. This is an illustration of the differences in viscosity. Viscosity is measured in CP, centipoises, on the Y-axis. And if you start out with a very small solution, you can see that the viscosity of IPC Oxy is over 2 times that of OxyContin. But viscosity is a very dynamic thing. If you start diluting the product down for injection to get it into a form that could be drawn

up into a needle and injected, you see on the far right, that's one of the larger volumes we used. And of course, when you dilute, the viscosity goes down. But even with this fairly large volume, we're at 8,800 centipoise compared to 1,000 for OxyContin, that's now 8.8 times more viscous.

A little perspective, I measured the viscosity of honey in the lab, and the particular brand we had was 8,000 centipoise. Water is 1. So I tried to syringe honey. You can't do it with the largest needle gauge we used. This is all with untreated material, and the real strength of IPC Oxy is the pre-treatment that overcomes the gelling properties of OxyContin, and that would be the next slide.

This is pre-treated by the common internet recipe for overcoming OxyContin, same product, same conditions. IPC Oxy retained a viscosity of 9,000 compared to 3 for OxyContin. 3 is close to water, as you saw in that video. So now, in this case, after pre-treatment, it's 3,000 times more viscous than OxyContin.

This relates to your question. Almost in all circumstances -- or always, not almost. In all circumstances, when we were trying to syringe these products, treated or not treated, the viscosity was huge for IPC Oxy in relation to OxyContin.

So the real value in this product is, under almost all circumstances, it's too viscous to load into a syringe. We only found a few conditions where you could load even a little bit of IPC Oxy into a syringe. So I hope that clarifies a little something.

DR. ODIDI: Thank you very much.

You heard what Dr. Cone had to say. Is there a follow-up question?

DR. HABEL: But I guess my question is, if you are able to load it into a syringe and inject it, would that higher viscosity pose risks for thrombotic events or other kinds of -- I mean, you're kind of saying that it's almost impossible to get into a syringe, so we don't need to consider the conditions under which it can be injected.

DR. BROCK: If you continue to dilute, and

dilute, and dilute, you'd have this large volume of solution, and it could be drawn into a syringe. But by that time, there would be very little drug in comparison to what a drug abuser wants to inject.

DR. ODIDI: I'd like to call on Dr. Dart to discuss how likely it is that anyone would try to inject this because I think this is where all this is leading.

DR. DART: I think Ed stole my thunder, really, so I will keep it brief, which is, this is incredibly hard to aspirate into a syringe. It's not like the situation that Dr. Dasgupta was mentioning with the waxy temazepam, where you could heat that, and it actually would easily go into the syringe, and then you injected it quickly, not realizing it was just going to harden again when it hit the bloodstream.

So this one's hard, much more difficult to do that. So far, in every condition -- correct me if I'm wrong -- that they've tested, they can't find a condition where this isn't better than

OxyContin in terms of syringeability.

So there's kind of a decision analysis question here, which is, if I'm going to have that product available, would I not rather have another product that was more difficult to syringe than the one that's currently available? Personally, that's why I'm here, because I think that would be a good choice to make, but that's your decision to make.

In the end, there's still the issue about safety and, well, what if they somehow get this into the blood somehow? I can't figure out how they're going to do that, but let's say they do. But actually, the testing that's been done on this product is the same that's been done on any product.

So I know it's easy to focus on that, but really, all the products out there have things in them right now that are being injected that you don't know about and I don't know about. So that I think is a wash, where you have this product that's very hard to syringe.

DR. ODIDI: Finally, I would like a thought

clarification to do with education. I think a few questions came up about educational concerns of kids handling this. I want to emphasize that our company commitment to postmarketing activities and physician and patient education is paramount as we move into this area.

In addition to our label warnings, which I talked about, and participating in the REMS program, we will do long-term detailed monitoring of unusual issues and occurrences. That's our commitment. We are formulating a plan to educate parents, high school counselors, paramedics, pharmacists, and other healthcare providers on the blue dye and what it might signify.

Finally, because our product is unique, we will work closely with the FDA to design product-specific category 4 epidemiological studies.

DR. HERTZ: Since we just saw some new data that FDA hasn't had a chance to see before, I'd like to follow up with a question because there's a little bit of a difference of understanding, I

guess, based on the viscosity data and the syringeability. And I'm going to look at my people to make sure that I'm not speaking incorrectly. This is Sharon Hertz.

My understanding from the syringeability studies is that up to 40 percent of the API could be syringed under certain conditions. Is that correct? 51.8 percent? So there are conditions in which it is actually syringeable, independent of its comparison to OxyContin. Is that correct?

DR. ODIDI: Dr. Cone, please.

DR. HERTZ: It just looked like from the data that were just presented, that it's not syringeable, but when you're not comparing it to the conditions under which OxyContin is syringeable, there are still conditions in which this can be syringed. Is that correct?

DR. BROCK: Yes. Let me show you the slide I think you're referring to. This is a pre-treated product, and if you syringe at a very early time, you can get -- it hasn't quite gelled yet. So if you can syringe within this very short time frame,

you can pull some up into the needle. When we looked at it at later times, it was not syringeable.

So in this special case, you're absolutely right. We got 20 percent of the oxycodone early, at which time we got 40 percent of OxyContin now.

DR. HERTZ: But I think we also have data that show as much as 40 percent of the API from the product under review.

DR. BROCK: That may be possible. I don't have that slide in front of me. But again, it was most likely at the early time frame, when gelling hadn't completed.

DR. BROWN: Dr. Setoguchi Iwata?

DR. SETOGUCHI: My question was answered. Thank you.

DR. BROWN: Dr. Zeltzer?

DR. ZELTZER: Thank you. I guess I'm understanding a little better the differences when you're comparing the two, the long-acting deterrent conditions in terms of the viscosity. And obviously, you're saying it's not 100 percent, but

compared to the product that's out there, it's much better than the product that's out there. So there's the issue about the risk for embolism, et cetera, for the subgroup that can be injected, done quickly.

The other is, I haven't seen the data or the rationale, other than it seems like it would be a good idea as a deterrent, to add the dye because that's also what's different about your product or the product being discussed today versus the product that it's being compared to.

Are there data that show that if somebody knows they're going to have dye on their nose, that that's enough to outweigh potential risks even though the risks may be low? We don't know. But if we're weighing benefit and risk, unintentional consequences, the added value of the blue dye hasn't yet, at least with data, suggests that it's a reasonable and important component to add beyond the viscosity. At least, I haven't heard that yet. Maybe it's there.

DR. ODIDI: I'd like to call on Dr. Rick

Dart to discuss this issue and perhaps follow up by Dr. Sellers based on their experience in the field regarding the blue dye, and if it will have an impact or not, absent of any experiment done so far.

DR. HERTZ: The question was whether there were data.

DR. ODIDI: We haven't done that work yet. We have protocol with the FDA for which we will do that going forward.

DR. DART: I would agree with Dr. Hertz. There's, I think, a solid rationale, but we don't have data that that actually averts abuse.

Is that the question?

DR. ODIDI: Yes. That is the question.

DR. BROWN: That is the question.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: So first off, just to address Dr. Hertz's comment that there were two instances where it was syringeable, one was at 4 hours, and that was with adding agitation A and pre-treatment A. So there were a couple studies

with tablet B that were syringeable.

Then the other comment or question related to really ask about these deterrence studies with the dye, the first thing I thought when I read this and saw blue dye was Breaking Bad and Walter White. And among drug-using populations that I've been around, there is a myth of purity when it comes to blue dyes, such that there was crystal meth that was going around that was being called "smurf dope," and it was basically dealers were injecting blue dye into it to make people believe that it was more pure because that was the whole basis of Breaking Bad.

So there is sort of a cultural thing among certain groups where they believe colors indicate purity, which could increase use. So I just think that was important to point out.

Has the sponsor looked at any of the research? You might not have studies that show that it's a deterrent, but have you looked for research that shows it may be an attractant?

DR. ODIDI: No. Dr. Sellers would like to

comment, I hope. Dr. Sellers, please? Dr. Ed Sellers?

DR. SELLERS: No, I don't believe the sponsor has looked at this, as they just indicated. But in answer to a previous question, obviously you're aware of how in some restricted circles and small groups of individuals, that fads and fashions and so forth get started.

So it is a possibility, but of course, you'd have to trade that off against a more common-sense kind of idea that getting blue on your clothes, or your face, and having it stick there for a long time, for many people, when they hear this and when I heard it, gee, that's pretty interesting. I sort of checked around with a few people, and they sort of said, "No, no. I wouldn't want to have anybody see that I was doing this."

I mean, this is anecdotal, of course, but I am sure that there could be some examples where it could take on some special status or meaning and might get characterized as bearing a specific drug or specific purity, as you suggest.

DR. BROWN: Dr. Sharon Hertz is going to now provide us with the charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: We're done with questions. So you've heard a lot today about this product and about our current standards for excipients for the assessment of abuse-deterrent products. And as we go through the questions, we'll be asking you to -- I'm just kind of thinking of how Sid answered them for us already, Sid Wolfe.

But we'll be asking you to tell us whether or not you think there are adequate data to support any abuse-deterrent characteristics for labeling, whether it's possible and acceptable to assess and agree on an amount of risk associated with excipients that are intended to have a purpose that may not have yet been shown and ultimately whether or not we should approve this product.

So I'm just going to turn it back over now for the formal presentation of the questions. But let me just say thank you. I'll thank you at the end, but I want to thank you now for your time,

taking out of your busy schedules.

The response to the questions is important, not just with regard to the yes/no vote, but we look at the discussion in great detail as we review the results of these advisory committees. I take pretty extensive notes because I will personally be referring back to this repeatedly over time.

So thank you very much for what will be, I'm sure, an interesting discussion.

Questions to the Committee and Discussion

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

So question 1 is a discussion question. We'll put that up. Question 1, the applicant submitted only category 1 in vitro studies to support labeling of oxycodone HCL ER tablets for abuse deterrence and is seeking labeling for abuse-

deterrent properties only for the IV route of abuse.

The product contains excipients that are intended to deter abuse by other routes. Discuss whether it is appropriate to consider labeling this product for abuse-deterrent properties for a single route without a complete assessment of all relevant routes of abuse.

Is this question for discussion clear to all the members of the panel?

DR. GALINKIN: Can I ask a clarifying question?

Sharon, in pre-meetings with the company, did the FDA give indications that just having one route, a category 1 approval, was all that was needed for approval, or did you want category 1, 2, and 3?

DR. HERTZ: No, we provide advice that's consistent with the guidance.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Toby Gerhard, Rutgers. So to me, this is a pretty straightforward answer. I

think, for good reason, the guidelines ask for both data that's not limited to category 1 studies and for data that looks at all routes of abuse simultaneously because we've seen in past meetings, certainly, that these aren't independent.

Sometimes, changes in one route of abuse can affect how the drug is used in other routes of abuse. And sometimes while oftentimes the category 1 studies line up with the results for category 2 and 3 studies, there certainly can be a difference. And I believe we have seen that in the past, so they don't necessarily extrapolate from in vitro into the human experience.

Therefore, I believe these data are, for good reason, required, and therefore, the product shouldn't be considered without the full breadth of the data being available.

That being said, obviously improved gelling features are, everything else being equal, in advance, and that should be acknowledged. But without evidence that shows that there aren't any unintended consequences in the other routes of

abuse and unexpected results in category 2 or 3 studies, I think it's just premature at this point to move ahead with this product.

DR. BROWN: Dr. Schmid?

DR. SCHMID: I apologize if this is a naïve question, but I was under the impression that you label a drug when it is being sold or, in other words, to give instructions to the prescriber and to the patient. But I assume you're not approving this drug at this point because you haven't got all the studies in.

So what's the purpose of this label before things are completed, or am I not understanding something?

DR. HERTZ: We have not made a decision on approvability. That's why we're here, because we wanted to find out from the committee if the committee thought that there was sufficient support for approval or not. We'll be asking you that as a question.

So it's not safe to assume that we have concluded that we would not approve it. But you

are correct, the label, that would be part of an approval and the labeling. Yes.

DR. BROWN: Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. So I think this would be a departure from all the other drugs that have been approved with ADF labeling for a couple reasons. Number one, I think that, up to this point, ADF labeling meant that it was deterrent in both routes. Well, I shouldn't say both, anything except oral. I think about it as nasal and IV, but I guess there's smoking and chewing, whatever else.

So this would be a departure, and I'm not sure whether that would impact prescribing, if physicians or other practitioners who prescribe opioids are used to thinking about an ADF labeling as deterrent in all the routes.

The second thought I had is when I think about whether or not it's appropriate to consider this without -- I'm reading this, obviously -- a complete assessment -- I'm not worried about category 3 data. Category 3 data, to me, is very

artificial, and those results really just don't come out until whatever postmarketing you can get.

But category 2 to me is pretty important. We don't know that there's bioequivalence for effect. And I could envision a situation where whatever, the blue dye or whatever it is, mixing with the oxycodone, when you take it, it's not going to give you the same amount of analgesic activity.

Now, you could argue that that's not really true because if you show that the PK is the same in the category 1 -- but like I say, it's hard for me to imagine approving this without the category 2 data. Category 3, I'm not --

DR. BROWN: Dr. Arfken?

DR. ARFKEN: It's Arfken. I do substance abuse research, so I work with people, whether it's teenagers that are trying something new or people who are on the street that have used it for a long time, they're going to use it all different ways. And I cannot think of voting on approving something without research on the safety in all the different

ways it's used.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. The first thing I jotted down this morning when the meeting, the open session, began, was what patient type would be an appropriate candidate for an opioid analgesic that was intended to be an abuse-deterrent formulation for a potential IV abuser and not one who would nasally abuse the medication.

We have heard people mention today that there's confusion at the front line of what even abuse deterrence means. And very many people think it prevents addiction, it prevents aberrant drug-related behaviors, so on, and so forth.

I imagine it would be extremely difficult in a clinical setting for a prescriber to forecast the likelihood that a patient would abuse a medication intravenously and not nasally, or vice versa.

So in line with adhering to the FDA guidance, I'm not 100 percent sure of what the label could do to guide clinicians to decide who was an appropriate candidate for a medication that

has only been shown to potentially deter intravenous abuse.

I'd rather they be able to predict with a higher likelihood the likelihood of an aberrant drug-related behavior altogether, which has even been shown to be problematic.

So I actually don't think it's appropriate to consider labeling this product for abuse-deterrent properties for a single route of abuse because of the added confusion it would create.

DR. BROWN: Dr. Warholak?

DR. WARHOLAK: So I'm a safety person, so the first thing I think about is, is there the potential for the medication to do more harm than good. And I have to tell you, with what I've seen today and what I've read, I just don't know that we have the data yet.

It may be an incremental advance. I just don't think we're ready. We don't have the evidence. We don't know what's going to happen with the blue dye. We don't know what's going to happen with the additional viscosity and the

syringeability of the PEO. If we have additional viscosity, does that mean more TTP? We don't know. And then without the category 2 and 3 studies, we don't have information on that, either.

So I think that it's a start, but I don't think we have enough information, or I don't have enough information to say that we should approve.

DR. BROWN: Dr. Nelson?

DR. NELSON: I actually put my tag down and up again because I think a lot of what I was going to say has been said. But I do really believe in a nutshell that we -- I don't see any reason to go around the guidance that has already been very clearly stated that you need to have contributions from all three categories in order to allow something to take on the abuse-deterrent name.

If you think back to the original term, tamper resistant, before it became abuse deterrent, there was that second part, which required real-world epi studies to show that something had abuse-deterrent potential.

I know we seem to relegate in and out of the

postmarketing category 4 data, which makes me very uncomfortable because there's just so many unintended consequences that we've already talked about and I didn't really want to rehash, that in the long run, the small potential benefit of reducing IV use by a small amount when it really represents a relatively small contribution in the overall abuse and addiction problem -- we saw data that said about 15 percent or so patients present with IV use. That means the vast majority of people present with oral use, or intranasal use, or some other use potentially.

I think that without knowing what's going to happen to the oral use and, to some smaller extent, the intranasal use, it makes me very concerned by allowing simply one route of deterrence. And without complete assessment of all routes and all their potential unintended consequences, I find it to be a very concerning approach to allowing something to take on the name of being abuse deterrent.

Again, as has been stated, the

interpretation of that by the medical community and the public is very unclear. I think many people put a lot more weight in that term than we do sitting here at this committee. I think we have a full understanding of it, but I think many people, as we've seen in survey data, show or believe that it is actually much more encompassing than it is.

DR. BROWN: Dr. Zeltzer?

DR. ZELTZER: I also think you need step one and step two analyses, approval, and this is not ready for prime time with potential risk. Also, it seems like there's an assumption that, first of all, somebody who's been abusing opioids for a long time is going to use opioids, and they'll find another opioid.

So this often is aimed at the prescriber to some extent. And at least I know that adolescents who have athletic injuries are often given by the orthopedist a short-acting opioid. And depending upon what else is going on for a subgroup, this can lead to other uses of the opioid if they're distressed, et cetera.

Because there's an assumption that, for example, you add blue dye -- by definition that sounds, who wants blue nostrils, et cetera, who is going to use it -- but that's making broad assumptions for a large heterogeneous population. And in some populations, that may be a turn-on rather than a turn-off. And even if it's short term, it may become an increased use within a subgroup of potential users who are prescribed opioids by their physician, even though we're talking long-term opioid, long-acting.

So I just think the data aren't there yet to warrant approval for just phase 1/step 1 testing and approval.

DR. BROWN: Dr. Meisel?

DR. MEISEL: So a couple of points here. First of all, in terms of the perverse impact of making it more attractive, I'm just reminded of a large southeast Asian population that chews on betel nuts, and their teeth, and their tongue, and their mouth turns red permanently, and their teeth fall out. And that's a badge of honor for some of

them, just like this blue dye may end up being a badge of honor for some. That may be a perverse outcome.

To more focus on the specific question, somebody else mentioned the fact that it's hard to differentiate IV versus all the other kinds of routes of potential abuse, so should we approve it just for this and leave the other two aside?

We have already heard today in this room lots of words using speculation, "we think, it might, doesn't it make sense, it's logical." I can envision, if we were to approve this with the one indication with that stipulation, once we get out into the real world of sales reps and everything else, talking about these data, "Well, it's not approved for this, but you can imagine, you can think, you can see," we end up with a product that is going to be sold as if it were approved for all three, even though the disclaimer is there because it's very hard to differentiate that. And the lure of the blue dye, and the SLS, and all that other sort of stuff is really hard to overcome.

So I think if we're going to approve a product like this, it's got to be for all three. And to be for all three, it's got to have the level 2 studies.

DR. BROWN: Dr. Kline?

DR. KLINE: I put my placard down, but I think incremental increase or incremental improvement is not enough to set a precedence like this. And I want to echo the last comment that the implication would be bigger, I think, than the approval or lack of approval.

DR. BROWN: Are there any other comments from the panel before we move ahead?

(No response.)

DR. BROWN: Let me try to summarize a bit and say that these guidelines were begun to be worked on in 2012, and they're very well written. They had been commented on by hundreds of clinicians and scientists across the country. They're very clear.

the panel believes, and I believe, that the guidelines need to be followed. I think the

committee feels uncomfortable in providing a signal that it's all right to present incomplete data and expect a positive outcome. Perhaps there are iterative improvements in some of the functions of this drug, but we don't have enough information to determine whether this drug is safe or effective or safe and effective.

Is that what everybody heard?

(Affirmative nods.)

DR. BROWN: So let's move on to discussion question number 2. It's rather long, so I'm not going to read all of it. I'm going to ask that the committee reads through the first portion of it.

As presented earlier today, excipients in a drug product must have a purpose, and many oral formulations have excipients that pose health risks if injected. As discussed at previous advisory committee meetings, there have been concerns raised that the presence of excipients in abuse-deterrent formulations of products intended for oral use have resulted in additional toxicity to those who abuse these products by non-oral routes.

This product contains a nasal irritant, SLS, and a blue dye that according to the applicant are intended to deter abuse by the nasal and oral routes, however, no data have been provided to support these claims.

So question A would be, discuss any concerns you may have regarding this product and the presence of excipients that have been included to deter abuse. Question B, discuss whether it's acceptable to include excipients in this product that increases the potential risk to those who may abuse the drug via certain non-IV routes of abuse and that have not been shown or not intended to contribute to the proposed IV abuse-deterrent claim.

Question C, discuss whether it is possible to determine an acceptable level of risk for excipients that may be toxic by unintended routes of administration for this product.

Are these questions that the panel feels comfortable evaluating and answering? If so, Dr. Mendelson?

DR. MENDELSON: Yes. Hi. I think this is the most important question for the day.

Excipients, you generally think of as not very harmful and not really part of the drug process. They're not really there to either enhance or change the behavior of the drug in a person. However, in this case, these are active drug products. These are products designed to actually achieve a behavioral outcome that's specific and planned.

Therefore, I wouldn't qualify them as excipients in this case. I'd qualify them as drug products, and they should be tested in the way all drug products are for safety and efficacy. The dose needs to be addressed.

How much blue do you need to have a blue nose that deters people from doing something? I don't know the answer to that question, and I don't want to find out personally, but I think someone should.

How much of -- they got into this with the gelling; they've begun this with a scientific

process. But really, if you're going to make claims, you need to actually have a dose-response function for the active pharmacologic ingredients. And in this case, the blue dye and the nasal irritant are active pharmacologic ingredients and should be subjected to the same rules and thinking as other active pharmacologic ingredients.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: Melinda Campopiano. To elaborate further on what was just said, I'm very concerned, apart from the guidance and where this presentation and the product falls and how it aligns with the guidance, that it contains this blue dye that's of no therapeutic benefit to the intended patients, we've seen no evidence of proven deterrent effect, and it doesn't support anything that's being asked to be put on the product label. There's also no real study of harm or the risk of harm to either people who ingested because they were prescribed it for pain or who misuse it.

I'm also really kind of repulsed at the willingness to just accept a punitive and shame-

based approach to deterring behavior that's related to a mental illness. Other people may be thinking that, but I think it needs to be said for the record that I think it's kind of mean and gross in a very non-scientific kind of way. And to put it out there with no assessment for potential for harm or effectiveness is really kind of offensive. It's as if people who use drugs don't have a mental illness. Did we forget that somewhere along the way?

I am uncomfortable with the idea that we would be putting a product out that is potentially possibly effectively -- I'm not totally convinced -- going to deter IV drug abuse, which we know tends to shift people off to either other drugs, or more importantly in the case of focusing on this product, other routes of abuse, and we have no knowledge about whether it really provides any deterrent for abuse by those other routes.

So we're just shifting from, frankly, more dangerous, but nevertheless still dangerous pathological behavior to misuse it intranasally or

by taking large doses orally.

Much has been made about the dramatic, and from a strictly lab geek kind of way, and really impressive increase in viscosity and the promise that this seems to suggest for deterring use of this drug by injection. But there's no study of the tolerability of this increased viscosity for the intended patient, which is the pain patient, or whether this increased viscosity might have any untoward effects on that person, who presumably is ill and suffering, or wouldn't be having this medication prescribed, and do we want to subject them to some unknown risk of GI distress?

The fact is that this substance, despite the increased viscosity, does remain syringeable in some situations, which means that in at least in some cases, people will successfully inject this drug, and we have no idea what it does in their bodies once it is introduced.

Nothing has been presented about that. The only answer that I've heard so far, unless I missed something, is that it's very unlikely that anybody

will do that. I'm not really comfortable with that.

We also know that there's real harm associated with some forms of the polyethylene oxide potentially with this or a very similar form of it that may have happened outside the United States. I think the only reason we discovered the polyethylene oxide problem related to another opioid formulation was because it happened in a limited geographic area in a cohort that was taking care of limited medical resources and happened to be identified. There are most likely trends happening in much more diverse geographically dispersed populations that we've yet to detect.

So I'm uncomfortable just using a product that we know harmed some people and putting it forward as an incremental advance in improving abuse deterrence, but it might harm some people kind of under the carpet.

Sorry I didn't organize it by A, B, and C, but that's kind of my response to question 2.

DR. BROWN: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. On A, I'm not convinced that this product is safe when used as prescribed. I get the abuse issue, but the blue gel -- the issue is, this is a drug that is intended to be used around the clock every day for chronic pain, and this is a large amount of blue dye. It's a small amount of blue dye. I don't know. But we don't know what the effect is in various different bodies.

We need long-term studies to tell us what the effect will be. Will it turn people blue? Will the gel be a problem when it hits the gastrointestinal system? It's just that we don't know that it is even effective.

The blue dye, if it is abused and shows up on people's skin, we have no studies to prove that it can't be washed off with soap, or with vinegar, or with makeup remover, or whatever. So we don't know its long-term effect, we know very little about a short-term effect, and we don't even know if it is effective. So on that basis alone, I have a significant problem.

On C, is it possible to determine an acceptable level of risk for excipients that may be toxic by intended routes? Sure. If we were in a health crisis with a virus that's killing people, and we need to put out a drug to help keep people alive, and have no alternative, sure.

This is not that case. This drug is not a breakthrough drug, and I can't support this. I'm uncomfortable. Thanks.

DR. BROWN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. So I've already mentioned my concerns that some of the excipients might attract users, but I think it's important to echo Suzanne Robotti's comments because we have to ask about the safety for patients who are using it appropriately.

Patients requiring these drugs can be assumed to be in a more physically fragile state, perhaps on multiple medications with chronic conditions. With the different medications, I know a lot of us, me included, have to be very careful with our GI systems.

We're on all types of preventative drugs because a lot of the medications sort of rip up your system slowly over time. And having that increased intestinal permeability and being on multiple meds, I think it's even more critical that we really need to establish the safety of the ingredients that are being consumed. I think that's something that's really important to consider in all of this.

DR. BROWN: Dr. Higgins?

DR. HIGGINS: I concur with much of what has been said or I think all of what has been said. I think what really struck me the most was during the public hearing and just hearing from the physician that the blue dye can indeed cross the blood-brain barrier. And it does have elimination concerns that I think are real. And there's just so little safety data, that I'm just uncomfortable with the notion that it would be somehow marketed.

DR. BROWN: Dr. Galinkin?

DR. GALINKIN: Yes. I'd like to actually follow up on Dr. Mendelson's comment -- I think it

was Dr. Mendelson. But I think since there are multiple active products in this, in the 11- to 18-17-year-old age group, we really do need to think of this as a different compound in some ways than OxyContin ER because if it's a different compound, you really need to study it in this age group to make sure it's safe, especially since, as Dr. Zeltzer pointed out, these are prepubescent patients.

The second piece is, I would also like to see some chronic exposure studies since none of the studies that I saw went past 3 days, to see if it does affect nail beds and things like that, and affects pulse oximetry data because these patients sometimes do overdose and will need to be revived. And if they have problems with their pulse ox, this needs to be a warning in their label.

DR. BROWN: Dr. Schmid?

DR. SCHMID: I was very confused early on when we started talking about the blue dye, and somebody brought up the point that it had been banned in three countries. So I went and looked it

up. And then I think somebody said, well, that's not the same blue dye. It is the same blue dye that was banned in three countries. It is the Brilliant Blue dye, which I think at one point was said this wasn't Brilliant Blue dye.

Then I was trying to follow along with how much is actually safe, and there were a lot of numbers being thrown around, whether it was in Gatorade, or bubble gum, or whatever.

I think these studies have to be done, and I think there needs to be -- I mean, for a panel like this to make a decision, we have to have some numbers in front of us. I'm a statistician, so I like to see numbers.

But I really had trouble following what was safe and what wasn't, their milligrams per kilogram and all this. I was trying to do these calculations in my head. I'm pretty good with mental arithmetic, but I wasn't really able to do it. I agree with what everybody said, but I think when this is presented, there have to be numbers there that we can actually look at.

DR. BROWN: Are there any other comments or discussion points to be made before we move on?

(No response.)

DR. BROWN: If there are not, I think it's pretty clear that the panel believes that the issue of the excipients in this compound and in all of the drugs that we discussed are very important. In this drug formulation, they're perhaps more important and rise to the level of an active drug product.

As such, as was said by many people on the committee, they should be evaluated as independent drug products. We should have all the toxicity data, long term and short term, that we would expect from an individual drug were it not being used as a dye.

The excipients themselves have not been studied vis a vis toxicity. And just as importantly, some of the issues relating to the appropriate use of this drug have not been well presented. And that gets to the issue of the viscosity of the agent and its possibility for

effect on the GI tract.

So I think that there was general agreement that this sort of testing on what are the causes of the viscosity, what are the results of the increased viscosity when drugs are used as directed should be done before this drug will be ready to go to market.

I would also like to just mention one thing so that our friends from the FDA note it. And that is the issue of some of these excipients actually attracting abusers. We don't need to attract abusers. The fact that several of the experts on the panel have mentioned this means that either the FDA or the sponsor should provide us with some information about the effects of drug color on the use of this compound.

Does that pretty much get it? Everybody happy with my mumblings?

(Affirmative nods.)

DR. BROWN: Let's go to discussion point 3. Although the applicant is not currently seeking a nasal or oral abuse-deterrent claim, discuss the

type of data that would be necessary to support a claim that blue dye has deterrent effects for the intravenous, nasal, or oral routes of abuse for this product. Discuss if it is acceptable to predict intranasal or oral abuse-deterrent effects from category 1 studies alone for this product.

Does this question comport? Does everybody feel good about being able to answer this question? Is it clear to everyone?

DR. MEISEL: Is it's acceptable to expand the question to include the sodium lauryl sulfate? We talked a lot here about the blue dye, but that's only one of the additional ingredients here that are intended to --

DR. BROWN: I think that would be acceptable, but we're discussing the entire process, the entire formulation.

DR. HERTZ: Yes-ish. The intent of this question was because the blue dye is novel and because we don't yet have assessments of whether it would have deterrent effects for nasal, oral, or parenteral of any type, we're trying to get a

little bit more on if anybody has thoughts on how that could be assessed. But additional thoughts on the sodium lauryl sulfate or other aspects, sure. We can always add that, but we do want to specifically try to get some advice on the dye concept.

DR. BROWN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: I think one of the best ways to try and see if it has deterrent effects is to maybe do some interview studies, talk to the people who use the drugs, talk to the people who abuse drugs.

I know being around drug-using populations, I'm an ethnographer, so I'm actually with them in the field. I mean, the things on the hands, you wear gloves. The snorting up the nose, you use a straw and you do little amounts at a time, so just the inside of your nose is there. Crushing, you don't chew it. You crush it outside your mouth.

So there are ways to get around it. And then if you do have little bits of blue, it could be you had a Slurpee because it's only on your

tongue, things like that.

So I think really talking to the people who use these things would be the ideal way to find out if it is a deterrent rather than us sitting around going, "I think it would be for me." Right? So that's what I would highly recommend.

DR. BROWN: How can the industry test for toxicity in effects? I'd like to hear from some of our friends who are chemists and medicinal chemists. How would that work?

Dr. Mendelson, do you have ideas about that?

DR. MENDELSON: I was going to comment on the testing, and I completely agree you need experts, people who actually abuse drugs. And you have to give them first some surveys, then you have to have them actually test the product and see if they can defeat it. And you need an effective dose of blue dye.

But obviously, the pathway for pre-clinical assessment, it doesn't appear this dye has been injected into animals in a dose-response function to see what the outcomes are and looking

specifically for organ toxicity that would be amplified in people who have had a history of either intravenous drug abuse or have a history of diseases associated with addiction would be a logical place to start.

This is not complicated animal research. We don't use rats in our studies anymore. We use lawyers because there are more of them, but it's something you could do easily.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. So I think that the initial question, whether category 1 studies can assess the effects, I think is clearly answered with no. It's a novel approach. We really don't know.

Importantly, however, beyond the question of how the effectiveness and safety can be determined, I just want to reemphasize Dr. Campopiano's point that beyond the potential difficulty in establishing this, I think there is a point beyond this where we should think about whether this shame-based approach is actually something that

should be considered.

I think the argument that was made that this would bring the abuse to light and maybe the individual would receive help sounds like a plausible story line where that could be helpful, but I think one can easily imagine situations where that's not the path that that would take, where shaming an individual with a clear mental health issue could have very problematic consequences.

You could think of situations where that could lead to self-harm or even suicide. And I think it's a bigger question than just the pure immediate point of how safe is it and how effective is this, and how can we quantify it. There's really a bigger issue here that should be, I think, carefully considered before that approach is taken.

DR. BROWN: I'm going to try to clarify a little bit this because I know that the agency wants to get a handle on what kind of data would support the evaluation of this particular drug product.

Would it be possible in the circumstances of

looking at this drug product, that is, the blue dye, for us to ever get the data that are needed? Dr. Galinkin?

DR. GALINKIN: I think you do need to do standard drug-liking tests and things like that. That would be very helpful in determining -- even with the blue dye, you can crush and have people do that, those studies, and see if the drug liking is higher or lower. Those would be one thing.

DR. BROWN: Dr. Nelson?

DR. NELSON: Thank you. It's Lewis Nelson. Along those lines, years ago, we evaluated an opioid product that contained niacin. Many will remember that. And one of the things we were impressed with at the committee level was that when they did the trials, I think it sort of pre-dated the categories that we talk about now. But there was data that said that several of the participants in those clinical trials actually not only weren't deterred by the niacin effect, but actually enjoyed the effect they got from that supposedly deterrent irritant substance.

So it would be great to look at what people feel in focus group efforts and see if they were deterred by something. But even if they just came forth with plain old category 2 or 3 data, where they actually use human beings, and assessed, whether it's liking or even how they felt about the effects of this supposedly deterrent additive, they might actually not only not be deterred, they might actually like it.

So I think that independent of the opioid per se assessment in standardized human studies, the effects of these deterrents would be probably reasonable to look at. Again, just if they came forth with standard testing, we might have been able to look at this issue.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: Melinda Campopiano. I agree with everything that's been said. I think that maybe talking, having a focus group, or surveying, and other formal sorts of ways, asking and evaluating, talking with people in recovery, people who are actively using, maybe families,

treatment providers, psychiatrists, about how this type of scarlet letter approach to deterring substance use, whether it could be harmful, how it might be harmful, if there's any way to mitigate the harm, and so on.

I think it's a double-edged sword. I think the road to hell is paved with good intentions. I can see Smurf parties and blue lollipops suddenly becoming very popular. So it's always a balancing act.

I guess the only other thing about the blue dye, especially since pills are often shiny and pretty colors on the outside -- and I don't necessarily know exactly how you would assess this, but whether the might be more attractive for small children to pick up if they find on the floor.

So I'm concerned about the accidental pediatric exposure being somehow made more likely because it's a colorful attractive product, especially if somebody's been cutting it, or mashing it, or something, and revealed the inside color so that a child could come by and put it in

their mouth.

So that would be something else. I guess I would suggest that we try to see if there's a way to quantify.

DR. BROWN: Dr. Arfken?

DR. ARFKEN: I think we also have to think beyond is it something you like, to think of it as something like GHB, where you would do it to someone else as a way of revenge. So if there's something that someone did that they didn't like, they could give this to them, and then see the blue on them.

DR. BROWN: Dr. Schmid?

DR. SCHMID: I think the interviews are really important, but I think we should also keep in mind that while we're thinking about this as being a way to have helpful family members or friends recognize there's a problem.

There's also the sense that there's a lot of families where somebody would be totally embarrassed and upset that their child, let's say, was doing this, and they might take it out on them,

so that it might actually have the opposite effect, which is that if your kid comes home and he's all blue, it's like, "I can't believe you're doing drugs; I told you that," and it might make the problem a lot worse.

So I think that needs to be considered. So I think it's really important when you're doing these interviews to go into a lot of different types of environments to assess all those possibilities.

DR. BROWN: Dr. Nelson? Dr. Gerhard?

DR. GERHARD: Sorry, just didn't put it down.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: Just one other quick comment about if you really want to go down this route of evaluating the blue dye, I would like to see the standard category 1 studies related to it, so how easily can you actually get it off your hands, not just the anecdotal soap and water takes 30 minutes.

Is it possible to get it out of your mouth pretty quickly? Is it possible to get out of your

nose? Is it possible to erase the mark on your skin? That sort of thing, to have actual data to support those claims, not just the pretty pictures.

DR. BROWN: Dr. Zeltzer?

DR. ZELTZER: Yes, just one last quick comment. I think when we're thinking about next-step testing -- and this has already been brought up -- to remember that the end potential individual who might be put at risk is not one kind of individual in one mold.

We talked about the person who may be abusing medication, and abusing opioids, and obviously is doing that out of desperation, because they're not getting whatever, they're struggling.

But also -- and again, I'm just going to speak from my domain of experience in terms of adolescents. You have adolescents who are living on the street, adolescents who are in abused homes. There are a lot of reasons that adolescents may be using opioids to get some kind of relief from their stress and support, and there are also adolescents who are in school.

If you survey even higher socioeconomic school districts and you look at middle school students and high school students, and you ask if they're getting drugs from peers on the street, there's a fairly high and increasing percentage of adolescents who are passing drugs on as a social phenomenon.

So I guess what I'm saying is when you're looking at the user end, think of some different subpopulations where the reasons may be different in the different populations. So what might be a deterrent in one population, for example, you may not have an indication for adolescents, but you may after good testing have an indication for an older population.

So I'm saying that the end user isn't the same group.

DR. BROWN: Dr. Warholak?

DR. WARHOLAK: So I agree that category 2 and 3 studies would be crucial here, and I agree with Dr. Shoben that we need to have better data on not only what takes off the blue dye, but also

other perhaps solvents and things that people would use.

But I also agree that we do need to be really careful if we're going to do focus groups and other kinds of studies or interviews about stratification and making sure that the sample selection is truly representative of the scope of the patients not only who use it. You might even ask the patients who use it for an illegitimate indication just because those are the patients who maybe at some point someday might slip into an abuse pattern. That might be good to know.

But I was thinking, too, that if this was my grad students, I would say, "It's time to go back to concept elicitation." How do we know that blue dye would be a deterrent at all? And as some people have pointed out, have we asked abusers what would be a deterrent. And especially considering all the different strata and the different types of abusers, what would be a deterrent, or what would make them go and get help, for the bigger question.

DR. BROWN: Dr. Meisel?

DR. MEISEL: So along those lines, back 40 years ago, I used to work with the Indian Health Service in northeast Arizona. And we had to dispense aspirin tablets that were green because the white tablets didn't work. Only the green tablets were perceived to work by the population that we were serving.

That gets into a little bit of what Terri was saying, but also a little bit about the fact that if we know it's blue, we know it's pure. And would we have a perverse impact of increasing abuse of this particular product because we can now prove to the buyer that this is pure oxycodone, whereas everything else will be clear, and colorless, and you don't know quite what you're getting. And could this actually have a perverse impact of increasing sales and abuse because now it's known to be a pure product.

I think we have to have some data and some research to, A, get into the issue about what does the color really do, but also, does the presence of the color actually reduce its use or have a

perverse impact of increasing the perception of purity, and therefore increasing its use.

DR. BROWN: Are there any more discussion points to be made about this particular question before we move on?

(No response.)

DR. BROWN: If not, I'm going to summarize by saying that the sense of the group is that it's not acceptable to predict intranasal or oral abuse-deterrent effects from category 1 studies alone for this product and that the best way to evaluate for the deterrent effects is to actually use the guidances provided by the FDA, which is crystal clear on this.

Dose-response curves were also mentioned. Drug-liking studies, focus groups, surveying were also mentioned. But the strongest goal should be to provide the studies that the FDA has recommended in the guidance.

One of the issues that was brought up by one of our panelists, or many of our panelists, is the issue of shaming to reduce abuse in patient with

known mental illness. And that's wrong on so many levels. I just can't -- that's wrong on a lot of different levels.

Does that pretty much get to what was said? Anybody else want to add?

(No response.)

DR. BROWN: I am going to give the panel the choice of taking a short break now or moving with these two voting questions and finishing up.

(Affirmative replies to continue.)

So the first voting question is, has the applicant demonstrated that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration?

Anyone? The floor is open for discussion.

MS. ROBOTTI: I don't like the phrasing on this question. It is what it is. But it's as if it's demonstrated, not proven. And it can be expected to deter abuse; sure, probably. It's following the same pattern as OxyContin, and OxyContin seems to be deterring. The numbers show

that.

So I'm just saying I don't like the phrasing on the question.

DR. BROWN: Dr. Schmid?

DR. SHOBEN: I guess my question is very similar. The way I read this is, can it be expected to deter abuse. But then there's a lot of other things that we've brought up, so there's pros and cons.

So I could say, yes, it's going to deter abuse, but it's going to do a lot of other bad things. So I don't know how to answer that question. I'd like some clarification from the FDA on that.

DR. HERTZ: This is Sharon Hertz. So the language was chosen because it reflects how we phrase the language in the labeling. So will we consider these studies that are done pre-marketing not as proof of a deterrent effect, but as data that suggests there can be an expectation for some deterrence?

So that's where the "can be expected to

deter" language comes from. And then we hope to get postmarketing data to determine if those projections came true.

Another way of saying it or to try and clarify what we're trying to get at with the question, has the evaluation for intravenous deterrent effects been sufficient to consider just in isolation whether that part of the evaluation is adequate.

DR. BROWN: Dr. Meisel?

DR. MEISEL: Oh, sorry.

DR. BROWN: Dr. Kline?

DR. KLINE: In my very linear chemist mind, I think this is the same question we just answered a bit ago, not without category 2 and category 3. I don't think they've proven deterrence with just cat 1 for the IV abuse.

DR. BROWN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: I would say that in the briefing argument that we got from the FDA, it said, for each relevant route of administration, basically looking at how work should be based on,

what causes the highest release of the opioid

What caused the highest release of the opioid was actually solvent 3. You got about 100 percent dissolution at 15 minutes. And it was said that it was the most effective solvent to extract oxycodone from extended-release tablets, but there was no data given about the mean percentage recovery of the oxycodone in that 100 percent dissolution, and I didn't see anything in terms of syringeability. Syringeability just stayed with solvent 1 and solvent 2, and not this solvent 3, which gives me pause.

DR. BROWN: Dr. Zacharoff?

DR. ZACHAROFF: Hi, Kevin Zacharoff. Looking at this question in a vacuum, and in light of all the discussion we've had with respect to the lack of category 2 and category 3, and just thinking about the syringeability, I would say yes, in my opinion, the likelihood is it can potentially deter abuse by an intravenous route. But I don't think you could really look at this in a vacuum at the end of the day, but just looking at that one

factor, I would say yes.

DR. MENDELSON: I just would like to respond to Dr. Zacharoff if possible.

DR. BROWN: Sorry?

DR. MENDELSON: I was going to respond to Dr. Zacharoff and just say you can get 20 percent of the material syringed, so that's not so good.

DR. BROWN: It sounded like you said 20, but what I heard Dr. Hertz say was up to 40.

DR. MENDELSON: On slide 49 of the presentation, it shows 20 percent of the IPC OxyContin, syringeable, released at 30 seconds, and therefore obtainable by syringe.

DR. ZACHAROFF: My comment was with respect to guarantee. I think it would be potentially a deterrent, but again, I would never look at it in a vacuum.

DR. BROWN: Dr. Kline?

Any other comments before we move to a vote? One more comment.

DR. GALINKIN: Sorry. Jeff Galinkin. Maybe Sharon, this is a question for you. Compared to

what? Compared to the OxyContin ER currently or compared to just a plain OxyContin tablet?

DR. HERTZ: So how about if I try it this way? If everything else were in order, would there be adequate data to support abuse-deterrent labeling? And in terms of what it's relative to, it's relative to the data that you have.

If you were to conclude that everything else were in order, and this was one of the series of questions that we ask when we have the different routes, so the next one could have been nasal, the next one could have been oral, if we were going to do all of that, are the data sufficient to support that type of labeling?

DR. BROWN: During our discussions, if we could refrain from saying how we were going to vote, it would please many people.

We will now proceed. We will be using an electronic voting system for this meeting. And once we have begun to vote, the buttons will begin flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, and the designated financial officer will read the vote from the screen into the record.

Next, we will go around the room, and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in this same manner until all questions have been answered or discussed.

(Voting.)

DR. BROWN: So everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 4 yes, 19 no, and zero abstentions.

DR. BROWN: So we will start down with Dr. Mendelson, and go around the room, and explain

our vote.

DR. MENDELSON: I'm usually the contrarian in this committee. But I think my reasons were well outlined previously. They haven't demonstrated safety. They haven't demonstrated efficacy.

DR. NELSON: Lewis Nelson. I voted no. And I believe that, without the additional category 2 and 3 studies, they will not be able to demonstrate that this formulation has the ability to deter abuse.

DR. KLINE: Rick Kline. I concur. I think without category 2 and 3, they're not going to be able to make that label.

DR. CAMPOPIANO: Melinda Campopiano. I voted no. I agree that the absence of the category 2 and 3 data is a problem, but I'm also concerned about the one solution that is able to extract the drug fairly effectively not being tested, not being subjected to additional testing around syringeability.

MS. ROBOTTI: My name is Suzanne Robotti. I

voted yes. And I voted because I was asked to look at the question exactly as it stood, not in the full context of the drug.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I voted no. I believe we need category 2 and 3 studies. I'm also, as I expressed earlier, concerned that syringeability was only looked at for those two solvents and not the ones that did better extraction.

DR. HIGGINS: Jennifer Higgins. I voted no.

DR. CRAIG: David Craig. I voted no primarily because of lack of human studies. I think it's great to have studies, which we saw, but I think that there's just no evidence in human subjects or folks actually with addiction disorders using it in real-life situations.

DR. McCANN: Mary Ellen McCann. I voted no. I agree with everybody else that we really need the category 2 and 3 studies.

DR. GALINKIN: Jeff Galinkin. I voted yes. It is definitely difficult to syringe, so when you look specifically at this question, I think the

answer is yes. I do think they need to do category 2 and 3 studies before it gets approved, however.

DR. ZELTZER: Lonnie Zeltzer. I voted no because I do think that category 2 and 3 studies are needed, and we also don't quite know the risk yet. And there might be the law of unintended consequences for subpopulations who might increase their use.

DR. ZACHAROFF: Kevin Zacharoff. I ultimately voted no for two reasons. One is because a lot can happen in 30 seconds if somebody wants to inject it before it becomes unsyringeable; and, two, because they haven't demonstrated compared to what other medications have needed to demonstrate in the abuse-deterrent formulation class.

DR. LITMAN: Ron Litman. I voted no for all the above reasons that we talked about, even Jeff's. And I'm also concerned about setting precedent. I'm also concerned about the blue dye. We discussed it.

I'm actually not that worried about it being toxic, but it is a drug. And if you consider the FDA's definition of a drug, that it changes the body in some way, it changes, I don't know, the way you think about the drug. And that's a chemical reaction. I think back to Kessler's question of intent with smoking, and to me, that qualifies.

DR. BROWN: This is Rae Brown. I voted no, and I voted no because I think that the demonstration of the effect has to come within the realm of safety and overall efficacy of this drug. There are so many things that we don't know from the data that were presented to us that, in reality, I don't think that we can answer the question at this time.

DR. HERTZ: Steve Meisel. I voted yes because the way the question is phrased, does it have properties that can be expected to deter abuse, and it does. It's highly viscous. It forms this gunk. That should be expected to deter, not necessarily prevent, but deter abuse.

At the same time, I think it's a terrible

question. The question is phrased quite poorly, and I think the consensus of this group is that this drug isn't ready for prime time and shouldn't be approved, but that wasn't the question.

DR. WARHOLAK: Terri Warholak, and I voted no for the reasons that most everybody's mentioned. I feel like the data are just not there yet. We don't have a preponderance of evidence yet. We have some pieces, but much is missing, especially category 2 and 3.

DR. HABEL: I'm Laurie Habel. I voted no. I actually agree that it probably does deter IV use, but I voted no because I think we need categories 2 and 3. And I'm particularly concerned about the safety issues.

DR. GERHARD: Toby Gerhard. Like Dr. Brown, I voted no. And I believe the question can't really be answered in isolation from the safety and overall approvability of the drug.

DR. SETOGUCHI: Soko Setoguchi Iwata. I voted no. I agree with Dr. Zacharoff, [indiscernible], again, seems to be long. And I

want to see some data that it's actually too short to do anything with it. And also, I think we need human data.

DR. NOVAK: I'm Scott Novak, and I voted no, although I really agree with some of the folks that have said yes in terms of intuition. It's gunky, it's blue, it seems like it would be very hard to abuse via intravenously.

However, I think abusers are a very special and unique population. They're very creative. And I think without the human population studies, as much as we think that something might deter, I think you really need to get it into the patient population and the abuser population to really definitively and empirically answer that question.

DR. ARFKEN: I'm Cynthia Arfken. I voted no because we need more data from humans and we need safety data.

DR. SHOBEN: Abby Shoben. I voted yes, again, sort of strict interpretation of the question. I think it is an incremental improvement over the current OxyContin in terms of its ability

to be syringeable and prepared for IV abuse, and that's the strict interpretation of the question as I read it.

DR. SCHMID: Chris Schmid, and I voted no. Again, I was trying to wordsmith as well. I could have voted yes if it had read "could have properties," but when it says expected, it's a little bit higher level for me. So expected to me means that I'm pretty sure about this, and I'm really not given the lack of information on some things.

DR. BROWN: We will be adding a sixth question for those of you who thought that you were going to be able to get out of here after five questions, so don't run away after the next one.

Question number 5, if we can put that up, are there sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration?

Is that a clear question to everyone? Is there any discussion of this?

MS. ROBOTTI: Sue Robotti. Can we know what question 6 is? I just want to know how long to opine after this.

DR. BROWN: No. No.

DR. CAMPOPIANO: I want to vote a particular way, so I want you to give me the right question.

DR. BROWN: Don't look at me.

DR. HERTZ: Question 6 fell off our version. Control was a little soft on this, but it's just about whether we should approve the drug.

DR. BROWN: Is there any discussion, anymore discussion?

(No response.)

DR. BROWN: In that case, we will again be using the electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in, will be displayed, and the DFO will read the vote. And then we will go around the room again just as we did with the last one.

So if we could vote at this point on question number 5.

(Voting.)

DR. BROWN: So everyone has voted. Can we have the results?

DR. CHOI: For the record, we have zero yes, 23 no, zero abstentions.

DR. BROWN: So can we start with Dr. Schmid and go around the room?

DR. SCHMID: Chris Schmid. I voted no for the reasons I've stated.

DR. SHOBEN: Abby Shoben. I voted no here. My interpretation here would be about supporting the label claim, and I would want to see more safety data about some of the things that were included before you could have a label claim for abuse deterrence and then go forward, marketing it that way.

DR. ARFKEN: I'm Cynthia Arfken. I voted no because there's not sufficient data.

DR. NOVAK: Scott Novak. I agree. I voted no. I just don't think the data are there to support it.

DR. SETOGUCHI: Soko Setoguchi. I voted no. I think I passed the consistency test.

DR. GERHARD: Toby Gerhard. I voted no, nothing to add to my previous comments.

DR. HABEL: Laurel Habel. I voted no for the same reasons as the last question.

DR. WARHOLAK: Terri Warholak. I voted no for the reasons stated previously.

DR. MEISEL: Steve Meisel. I voted no. I think all has been said.

DR. BROWN: Rae Brown. I voted no for the same reasons as the last question.

DR. LITMAN: Ron Litman. I voted no, same.

DR. ZACHAROFF: Kevin Zacharoff. I voted no for reasons already stated.

DR. ZELTZER: Lonnie Zeltzer. I voted no for reasons that have continued to be stated.

DR. GALINKIN: Jeff Galinkin. I voted no this time because you still need to have the category 2 and 3 studies before you can make any determinations.

DR. McCANN: Mary Ellen McCann. I voted no, same reason as the question before.

DR. CRAIG: David Craig. I also voted no for the same reasons as the previous question.

DR. HIGGINS: Jennifer Higgins. I voted no.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I voted no for the previously stated reasons.

MS. ROBOTTI: I'm Suzanne Robotti. I voted no for similar reasons as to why I voted yes before. But to put something on the label, you need human studies. You need complete information. We don't have that.

DR. CAMPOPIANO: Melinda Campopiano. I voted no for reasons already stated.

DR. KLINE: Rick Kline. I voted no, ditto.

DR. NELSON: Lewis Nelson. I voted no, no additional comments.

DR. MENDELSON: John Mendelson. I voted no.

But if you keep asking the question, I can come up with some more reasons, but I've got enough already.

DR. BROWN: Thank you very much.

Question number 6, should this drug product, oxycodone HCL ER tablets be approved? Is that question clear to everyone on the panel?

DR. HIGGINS: May I just ask, approved for IV abuse deterrence only or what do you mean by approved?

DR. HERTZ: Should we approve it at all? Should it be approved at this time?

DR. BROWN: Any discussion?

(No response.)

DR. BROWN: If not, if we can use our system again, please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the

vote is closed.

(Voting.)

DR. BROWN: Everyone has voted.

DR. CHOI: For the record, we have 1 yes, 22 no, zero abstentions.

DR. BROWN: Dr. Mendelson?

DR. MENDELSON: I voted no, and I still don't have any more reasons.

DR. NELSON: Lewis Nelson. I voted no for the reasons we stated. And in this case, I'm still very concerned about unintended consequences of the availability of this drug. And in fact, I'm concerned about the entire line of ADFs as they're currently marketed.

DR. KLINE: Rick Kline. I voted no.

DR. CAMPOPIANO: Melinda Campopiano. I voted no.

MS. ROBOTTI: Suzanne Robotti. I voted no. I am glad that Intellipharmaceutics is attempting to add on and improve on ADF technology. I don't think that they're there yet. I have significant concerns about the blue and the gel that I've

expressed already.

There are alternatives for patients on the marketplace. There is no reason to skip category 2 and 3 studies at this point. I guess that's all I have to say. Thanks.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I voted no. I believe there's not sufficient data on safety. I am unconvinced that this is necessarily a deterrent and that it could possibly serve as an attractant to certain populations. And I believe there are alternatives on the marketplace that can fill the gap in the meantime.

DR. HIGGINS: Jennifer Higgins. I voted no. As the consumer rep, I have serious concerns about the safety of the product.

DR. CRAIG: David Craig. I also voted no, primarily I would say to concerns about PEO, about the blue dye, about the gelling, about the 30 seconds, about lack of data, et cetera.

DR. McCANN: Mary Ellen McCann. I voted no. I have concerns about the safety and efficacy data for this drug.

DR. GALINKIN: This is Jeff Galinkin. I voted no. Further, I would like to see the FDA ask for specific studies in 11- to 17-year-olds to demonstrate safety.

DR. ZELTZER: Lonnie Zeltzer. I voted no for all the reasons stated, including what my neighbor over here indicated. Thank you.

DR. ZACHAROFF: Kevin Zacharoff. I voted no for all reasons stated and for the lack of my ability to really determine a good risk-benefit ratio, taking into account the excipients and also taking into account the lack of data from swallowing a manipulated pill.

DR. LITMAN: Ron Litman. I voted no for all the reasons. But I do want to just make a comment to the FDA. I don't really think it matters if you approve this drug. I think in the scheme of things, one more drug on the market as an ADF is not going to affect anything.

There are a couple things, like addiction will never go away. Opioids probably won't ever go away. And even if every single opioid out there

was an ADF, I just can't imagine it affecting much of anything.

I mean, one of the things that impressed me the most today was Dr. Wong's slides where the ADFs of oxycodone went down, but yet Dr. Dart's slide of the heroin going up.

So I just don't think ADFs are -- if they are an answer, it's just so small. And I don't think they're going to affect the opioid crisis very much at all. But certainly this drug is not going to matter, but I voted no for the reasons we stated before.

DR. BROWN: This is Rae Brown. I voted no for many good reasons. First, the analysis from the sponsor was incomplete. This extends to the toxicities of excipients as well as the lack of human abuse potential studies. Many explanations were given for this and many promises were made. I don't think that should ever be acceptable to the agency.

Let me be clear. These medications, so-called ADFs, contain large volumes of opioids.

They can be abused as Dr. Hertz said. Patients can become addicted to opioids with these drugs in much the same way they do with morphine or any other non-ADF.

Those findings will occur in some patients. We know very little about the true efficacy of the ADFs because the pharmaceutical industry has chosen not to provide this information, though it is clearly required by FDA regulation. The sponsor chose to include excipients that are known to be problematic at high concentrations.

The iterative process of improving the products as they come to market is very important, but equally important is to use new information to assure that we are protecting the public health.

The charter of the agency is to protect the public health, and in this regard, that means receiving and acting on positive information relating to safety and efficacy. Many people ask us to give support to products because of the need for more and better opioids.

All of us endorse the concept of providing

safe, efficacious products that assist in the safe treatment of pain, but I cannot endorse products that are not adequately tested or that we can predict could be toxic when they come to market.

DR. MEISEL: Steve Meisel. I voted no for all the reasons that Dr. Brown just mentioned.

DR. WARHOLAK: Terri Warholak. And I voted no largely for lack of data, especially on safety concerns. And to be honest, it kind of disturbs me that the sponsor came to the FDA with such incomplete data.

DR. HABEL: Laurel Habel. I also think there's a lack of both safety and efficacy data, and that's why I voted not.

DR. GERHARD: Toby Gerhard. I voted no, and Dr. Brown eloquently summarized my rationale.

DR. SETOGUCHI: Soko Setoguchi. I voted no. In addition to what I said before, for the drug to be approved, I'd like to see efficacy data for the blue dye, and then also safety data for blue dye, and then also PEO.

DR. NOVAK: This is Scott Novak, and I voted

yes. I think I agree with everything that everyone is saying. I also agree with what Dr. Litman had to say about putting too much faith in these medications to move the needle.

Do I think that this drug is any less safe than an existing drug that's on the market now, OxyContin? And the answer to that is no. And I don't think that -- the issue is -- from a free-market standpoint, I think that if the data are truly as incomplete as some of the more maybe biologically learned, my colleagues, are, I would hope that the FDA would rectify that. But I just didn't see the major concerns with the blue dye.

I don't see that's going to be a major deterrent. It may not find any traction or value on the street. I was thinking about the dye, and it's sort of like the dye packs that the bank robbers get. And how much do those dye packs really stop bank robbers from robbing a bank?

Also, how much do we actually think about -- when a bank robber has that dye on his hands, do we think that that's sort of a need for

treatment, or need for somebody to get a job or something?

So we just literally can't put too much faith in these medications. And we know that traction is not occurring in the marketplace because of patient value. It's because insurers are not covering the medications, and they're not being put in the hands of patients.

So I think there's a lot of other things that are being conflated into this conversation, all of it is very, very important. But again, I think that, for me anyway, it just comes down to the equivalence to OxyContin. And I just didn't think that the drug was -- I don't think it's going to be any more effective, but I also don't think it's going to be any less effective.

DR. ARFKEN: Cynthia Arfken. I voted no for the reasons Dr. Brown stated.

DR. SHOBEN: Abby Shoben. I voted no basically for the reasons Dr. Brown stated. I think you can't put things in the product intended to deter routes of abuse by intranasal and oral,

and then not evaluate them or claim you're going to evaluate them in the postmarketing setting. I think that sets a very dangerous precedent.

DR. SCHMID: Chris Schmid. I voted no. I was struck throughout the day by the lack of answers that the sponsor had to certain questions it seemed fairly obvious that we would ask. And I would ask if they were to come back, that they would think about this and the kinds of questions that we would ask, so that we would have this information available.

I'll just emphasize again, the dye is a big part of the product. You should know everything about the dye and everything we're going to ask about it, including having numbers there for us to be able to evaluate it properly.

DR. BROWN: Dr. Herring, do you have any closing comments?

DR. HERRING: First of all, thank you, Dr. Brown, for putting me as the only obstacle between the door for the group. No. But I do appreciate the opportunity. And I think today's

been a difficult and challenging conversation, but it's been a robust one. We've addressed some important issues.

I think, if there are three learnings for industry, they would be that we have to keep in mind the level of evidence required for inert excipients that may be added as innovations in abuse-deterrent formulations. And then, as we've learned from the discussion about the blue dye, it's also important to recognize if you have non-inert ingredients in your product, it may require a higher level of evidence to support efficacy and safety of the approach.

Then lastly, and I thought this was an interesting part of the discussion, abuse-deterrent formulations may be bounded philosophically by the clinical implications of the approach, as we've discussed today. So thank you for the opportunity to comment.

DR. BROWN: Thank you very much.

Dr. Hertz, would you like to make any closing comments?

DR. HERTZ: Not much, just my final thanks, and appreciate your time.

Adjournment

DR. BROWN: This meeting is adjourned. Please take all your personal belongings with you, as the room is cleaned at the end of the day and all the materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that they can be recycled.

I'll now adjourn the meeting. Thank you very much for being here.

(Whereupon, at 4:43 p.m., the open session was adjourned.)