FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Tuesday, June 26, 2018

9:30 a.m. to 4:22 p.m.

Open Session

DoubleTree by Hilton Hotel Bethesda

Washington DC, Grand Ballroom

8120 Wisconsin Avenue

Bethesda, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:30 a.m.)

Call to Order

Introduction of Committee

DR. McCANN: Good morning, everybody. I would first like to remind everyone to please silence your cell phones, smartphones, and any devices if you've not already done so. I would also like to identify the FDA press contact, Jennifer Dooren. If you are present, please stand. Thank you.

My name is Mary Ellen McCann, and I am the acting chairperson of the Anesthetic and Analgesic Drug Products Advisory Committee, and I will be chairing this meeting. I will now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We will start by going around the table and introducing ourselves. We will start with the FDA on my left and go around the table.

DR. HERTZ: Good morning. I'm Sharon. I am

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

DR. STAFFA: Good morning. I'm Judy Staffa. I'm with the Office of Surveillance and Epidemiology at the Center for Drugs, FDA.

DR. WILTROUT: Good morning. I'm Lisa Wiltrout. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products.

DR. HERTIG: Good morning. John Hertig with Purdue University, their Center for Medication and Safety Advancement in Indianapolis, Indiana.

DR. BRENT: Good morning, everybody. My name is Jeffrey Brent. I'm a medical toxicologist and distinguished professor of medicine at the University of Colorado School of medicine.

DR. TERMAN: I'm Greg Terman, professor of anesthesiology and pain medicine at the University of Washington in Seattle.

DR. PRISINZANO: Good morning. I'm Tom Prisinzano, professor of medicinal chemistry at the School of pharmacy at the University of Kansas.

DR. NELSON: Good morning. I'm Lewis

Nelson. I'm a professor of emergency medicine and medical toxicologist at Rutgers New Jersey Medical School in Newark, New Jersey. And I oversee the New Jersey Poison Control center.

DR. MEISEL: Steve Meisel, director of medication safety for Fairview Health Services and the University of Minnesota Health System in Minneapolis.

DR. WANG: Yinghua Wang, designated federal officer, FDA.

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

MS. SPOTILA: Good morning. My name is Jennifer Spotila. I've lived with chronic pain for more than 20 years and have been on opioid treatments for more than 10.

MS. ROBOTTI: Hi. I'm Suzanne Robotti. I'm the founder of MedShadow Foundation and the executive director of DES Action USA.

DR. GRIFFIN: Good morning. I'm Marie

Griffin. I'm a pharmacoepidemiologist and an internist and a professor of medicine and health policy at Vanderbilt University.

DR. ZELTZER: Hi. I'm Lonnie Seltzer. I direct the pediatric pain and palliative care program at UCLA and distinguished professor of pediatrics, anesthesiology, and psychiatry at UCLA.

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

DR. GOUDRA: Basavana Goudra, associate professor of anesthesiology and critical care medicine at Penn Medical Center, Philadelphia.

DR. ZIBBELL: Good morning, everybody. I'm John Zibbell, a behavioral health scientist, RTI International, Atlanta, Georgia, and also a professor of anthropology at Emory University.

DR. CICCARONE: Good morning, everyone. My name is Dan Ciccarone. I'm a family medicine and addiction medicine specialist and professor of family and community medicine at University of California, San Francisco.

DR. ARFKEN: Good morning. My name is Cynthia Arfken. I'm an epidemiologist and professor of psychiatry and behavioral neurosciences, Wayne State University, Detroit, Michigan.

DR. HERRING: Hello. Good morning. I'm Joe Herring. I'm a neurologist and associate vice president of clinical neuroscience at Merck Research Laboratories and industry representative to the AADPAC committee.

DR. McCANN: Thank you.

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

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I will pass it to Yinghua Wang who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. WANG: 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

committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC, 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 USC, 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 service outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the

integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses and minor children, and for purposes of 18 USC, 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 022324, oxycodone extended-release capsules submitted by Pain Therapeutics with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is intended to have abuse-deterrent properties based on its physicochemical properties.

The committees will be asked to discuss whether the data submitted by the applicant are sufficient to support labeling of the product with the properties expected to deter abuse. This is a particular matters meeting during which specific matters related to Pain Therapeutics' 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. William Herring is participating in this meeting as a nonvoting 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 and Company.

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 and 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 committee of any financial relationships that they may have with the firm at issue. Thank you.

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

FDA Introductory Remarks

DR. HERTZ: Good morning, Dr. McCann, members of the DSaRM, Drug Safety and Risk Management Advisory Committee -- sorry about that -- and the Anesthesia and Analgesia Drug Advisory Committee, and invited guests. Thank you all for being here for this advisory committee

meeting.

At this joint meeting, we'll be discussing this application from Pain Therapeutics for this new extended-release intended abuse-deterrent oxycodone product. It's intended to deter abuse by the oral, nasal, intravenous, and inhalation route. The relevant indication would be management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate. This is generally the indication that we use for opioid products that are appropriate for chronic pain management.

We have heard concerns at a number of advisory committees and in other settings that the approval of new opioid analgesics may be a source of increase in the prescribing and availability of these products, and therefore may contribute to an increase in misuse and abuse.

There has been a publication, based on data reviewed by FDA, that has shown that while the number of opioid prescriptions has been decreasing

since 2012, there have been many approvals of new both innovative as well as generic products. So there really is not a correlation with new drug approvals and an increase in prescribing. So as you think about the meeting today, know that we're keeping an eye on that, but that doesn't seem to be a problem.

Over the years, we've gained a lot of knowledge and experience reviewing abuse-deterrent formulations. We've approved 10 opioid analgesics with labeling consistent with our guidance on the development of abuse-deterrent opioid analgesics, and these have included extended-release products and one immediate-release product. A number of these products have never been marketed for reasons that one would need to ask the applicants: five of the approved ADFs or oxycodone products for extended release, two of which have not been marketed, and one immediate release.

The goal, based on our guidance, is to evaluate relevant routes of administration or routes of abuse and to use a step-wise approach to

gather data, and ultimately to have postmarketing data supporting premarketing evaluations. As you are all I'm sure quite familiar, the category 1 testing is in vitro testing on methods of manipulation.

The category 2 is pharmacokinetic studies of products in the manipulated state compared to intact and other comparators. Category 3 are human abuse potential studies looking at subjective effects with appropriate controls in the context of manipulated and unmanipulated product. And then category 4 is postmarketing data that supports the conclusions from the premarketing data.

When we write labeling for these, we say that these findings can lead one to expect that there would be a reduction in abuse by virtue of the methods of manipulation that any given formulation can make more difficult. Note, I didn't say prevent abuse, nor did I mention the word "addiction." I'll come back to that in a second.

With the goal of category 4 data providing

support for the premarketing studies, we're really hoping to get that information to be able to both inform the labeling of products, but also to inform the wider community. Although there have been many publications describing potential benefits for some abuse-deterrent opioid products on the market, we at FDA have not been asked to review data to add postmarketing information to labeling by any of the companies with currently marketed products who may have some amount of data, and that always makes me wonder why we do examine data quite closely.

So at this point in time, based on the information available to us, the literature, what we've come to learn over time, it's reasonable to conclude that the utility of abuse-deterrent opioid analgesics has yet to be determined in the real world. Challenges to determining the impact of abuse-deterrent analgesics include difficulty measuring the important outcomes, abuse, misuse, overdose, and death, and then attribute any changes that are found to specific actions such as the formulation, because we have to remember that there

are numerous ongoing federal, state, and local activities intended to address the problem of prescription opioid abuse.

So it's necessary to look at the outcomes for any one product in the context of what is happening with other similar products or prior non-abuse-deterrent product. Some review articles describe decreases in abuse of a particular abuse-deterrent product following its marketing, but also generally describe a contemporaneous increase in the rate of abuse of other prescription opioids or illicit drugs during the same periods examined.

So far, many articles have concluded that there's not been an overall net positive effect of reduced abuse across the community, but perhaps more shift. One downside of the abuse-deterrent products that has emerged is a possible false sense of safety because of a misunderstanding on the part of some prescribers that these products are less addictive or cannot be abused, as they fail to understand what the limitations of abuse-deterrent

properties are, that they make a product more difficult to manipulate for the purpose of abuse or potentially making a product less reinforcing following manipulation for abuse.

As these are all analgesic products, all must be able to deliver the opioid to the patient, so they all remain abusable by the oral route in the original unmanipulated state. As opioids, these products all remain potentially addictive, and none of the reformulations into abuse-deterrent products has resulted in a change in scheduling. They all remain in the same original schedule as non-abuse-deterrent products.

In addition to the limitations in what an abuse-deterrent formulation can accomplish, there is the concern about unintended consequences. Patients early on had some problems with ADF products sticking to mucosal surfaces -- for instance, the esophagus -- at times requiring even endoscopic removal or surgery.

With Opana ER, which we brought to advisory committee last year, there were a number of

findings that were disturbing, leading to us requesting that it be removed from market: outbreaks of HIV and hep C infections because new methods for manipulation for IV abuse led to more needle sharing as well as microangiopathic thrombocytopenia related to excipients intended to impart abuse-deterrent properties, and effects of other methods developed to support intravenous abuse of that product. In addition, there were data suggesting a shift from nasal to the more dangerous IV route of abuse.

Not all ADFs have met the hoped for outcomes when studied. We have determined that when a product that can reasonably be expected to have abuse-deterrent properties, based on the formulation and studies conducted, fails to demonstrate those properties and preapproval studies, it's important for prescribers to understand this information, that the product fail to meet the stated goals so they can make informed decision about the role of the product in their practice of pain management.

There is one product that's been approved intended to be abuse deterrent, Apadaz, which is a benzhydrocodone/acetaminophen immediate-release product that, as with all these products, has been brought before these committees and failed to meet any of the usual endpoints that are considered relevant for the premarketing support for a potential abuse-deterrent effect.

There was some small early changes relative to controls that we did put in labeling that's information. we don't know that there's any clinical relevance. And in all the products that we have that have had more substantive changes in the premarketing studies, we've still yet to see the hoped for public health benefits.

We're still waiting for that data, trying to see if these products are having the intended value. So the labeling for that product includes language describing the results of these additional secondary endpoints that are not described in our guidance and for which the clinical significance is unknown.

The results of this applicant's clinical trial data in vitro physical and chemical manipulation assessments and in vivo human abuse potential studies will be presented during this meeting. You'll hear presentations from the applicant and from the agency, including results from agency chemists.

Now, what folks may not know is that our labs have been working on studying the properties of abuse-deterrent formulations for a long time now. Sometimes our results match sponsors/applicants and sometimes they don't. That's not an indicator of any impropriety in any way.

The methods for evaluating these products in vitro have not been standardized, so even if similar conditions are used, in the absence of well-established standardized methods, differences happen. And you're going to hear about some differences from our lab compared to the sponsor, but I just want to make sure that it doesn't come with a particular or even implied negative intent

or concept, that it's just a different finding in different hands.

We're going to ask you if the applicant has provided adequate support for the safety and efficacy in the intended population; for the labeling, whether the labeling should include abuse-deterrent properties, and if so, which ones; and overall if the product's benefits outweigh its risks.

Your advice and recommendations are essential in assisting us with addressing these complex and critical public health concerns associated with these products with this whole area of therapeutics, and we're grateful that you have agreed to join us for this meeting. Thank you.

DR. McCANN: Thank you.

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

presentation. For this reason, FDA encourages all participants, including the applicant's nonemployee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, 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 presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Pain Therapeutics' presentations.

Applicant Presentation - Remi Barbier

MR. BARBIER: Good morning, and welcome to the open session of the advisory committee meeting for REMOXY. My name is Remi Barbier. I'm a drug developer. I have 25 years of experience in drug

discovery and drug development.

We have a relatively full agenda this morning, and I propose that we dive right in. A few brief words about us, Pain Therapeutics is the sponsor, obviously, of REMOXY. We are a research and development company based in the college town of Austin, Texas. We've been around for a little bit over 20 years, and in that time, our research focus has been primarily on diseases and disorders of the nervous system.

Before we actually start a couple of disclosures and disclaimers, when we use the term "abuse deterrence," we are not intending to designate a medical claim, but rather a general description of properties to address the abuse, misuse, and diversion of opioids. We don't know it all, and as with any company, we use a number of consultants. We pay these consultants.

So these consultants, in our case, Dr. Crowley, Dr. Webster, and Dr. Montgomery, have a financial relationship with the company in the form of professional fees, consulting fees,

expenses, and/or equity interest that may be perceived as a conflict of interest.

As we all know, REMOXY is in registration for approval as an extended-release gel formulation of oxycodone. REMOXY has properties that are expected to deter formulation abuse, therefore, we are seeking label claims against abuse by the injection, snorting, and smoking routes of abuse. Note at this time, we are not seeking a label claim against the oral route of abuse.

The FDA guidance document defines abuse-deterrence properties as, quote, "those properties shown to meaningfully deter abuse even if they do not fully prevent abuse." So from our point of view, the design goal of an abuse-deterrent formulation, or ADF, is a robust extended-release mechanism that resists dose dumping under conditions of abuse.

To state the obvious, and as Dr. Hertz has informed us, abuse deterrence is never and can never be abuse proof. We know that oxycodone can be extracted from REMOXY or any abuse-deterrent

formulation. The question is how much time, effort, and frustration is needed relative to a comparator drug? Let me repeat that because it's a very important concept. Abuse deterrence is never abuse proof, but the question for us is how much time, effort, and frustration is needed relative to a comparator drug?

We see several potential benefits of abuse-deterrent formulations, or ADFs. For the novice abusers, we believe ADFs can eliminate the quick, easy common method of formulation abuse, such as chewing or crushing. For recreational abusers, we believe ADFs can discourage abusers from transitioning to non-approved routes of administration such as snorting, smoking, or injection. For the advanced abusers, we believe ADFs can render manipulations or drug abuse more difficult, expensive, and time consuming, thus making manipulated drug products less rewarding.

But again, as Dr. Hertz pointed out, there are some severe limitations to ADFs. Drug abuse is a very, very complex problem, and ADFs alone will

not prevent prescription drug abuse. Furthermore, ADFs do not address the long-standing issues we've had with opioids such as euphoric effects, addiction, or potential for addiction I should say, tolerance, and dependence.

To us, the persistence of opioid abuse indicates a need for more robust abuse-deterrent formulations. When it comes to ADFs, we can never rest or be satisfied with the status quo. For example, after abuse-deterrent OxyContin reached the market, one research found, quote, "Although the reformulation produced an immediate drop in abuse rates, a definite ceiling effect appeared over time beyond which no further decrease was seen" unquote.

So our overall message is that ADFs can play a critical role in the fight against opioid abuse, but additional ADF solutions are needed. Additional ADF solutions are needed to advance the science of abuse deterrence, to provide additional treatment options for physicians as well as for patients, but most of all to address certain

vulnerabilities of existing ER oxycodone products. And with that, I'd like to turn it over to Dr. Crowley for a review of our in vitro abuse deterrence.

Applicant Presentation - Michael Crowley

DR. CROWLEY: Good morning. My name is Michael Crowley. I'm a consultant to Pain Therapeutics, and my background is in molecular pharmaceutics. I'll be discussing the category 1 in vitro abuse-deterrent study results with you.

Eleven category 1 studies were conducted in accord with the FDA guidance, abuse-deterrent opioids evaluation and labeling issued in April of 2015. These studies characterize the abuse-deterrent properties of REMOXY ER, including the degree of effort required to bypass or defeat those properties.

The studies were performed according to a protocol that was submitted to the FDA for their review prior to its execution. Input from the agency was incorporated into the study design. All studies were conducted by third-party laboratories

with prior experience performing category 1 studies. Three or six replicates were performed for a given experiment, which is an industry standard.

The category 1 study methodology was based upon the physical and chemical properties of REMOXY; common methods of abuse for extended-release opioids; the FDA guidance with their input; clinical and scientific consultants; and internet sites frequented by opioid abusers.

The category 1 studies were extensive. More than 9,000 unique data points were generated from 5 oral abuse simulations, 4 injection abuse simulations, and 2 smoking simulations. All results were reported in the REMOXY NDA. Due to time constraints today, only representative results that include worst case outcomes are being presented. As a reminder, the experimental conditions are blinded, and the codes were provided in the closed session.

The FDA guidance states, "Abuse deterrent properties can generally be established only

through comparison to another product." Accordingly, OxyContin ER, Xtampza ER, and Roxicodone IR were comparators in the category 1 studies. OxyContin was commercially available for the duration of the studies. Xtampza was approved and commercially available later and was included in a smaller subset of the studies. Both intact and manipulated product states were evaluated.

REMOXY's abuse-deterrent properties were evaluated in a comprehensive battery of these studies. The studies were conducted with scientific rigor in which a physical manipulation was followed by a chemical extraction. The manipulations included simple methods using common household tools, a few procedural steps, and progressed and evolved to more complex processes using sophisticated tools, the application of stress conditions, and multiple procedural steps that require more time and effort. Extractions considered the pH, polarity, and ionic strength of the solvent. The solvent volume, agitation method, extraction temperature, and extraction time were

additional experimental parameters.

These studies simulated both intentional abuse and unintentional or accidental misuse. In some cases, the simulations required more time, expertise, equipment, and effort than a casual abuser might employ. Manipulations were directed to common routes of abuse. Oral studies evaluated the impact of tools and manipulation methodology on drug extraction at volume D.

Injection abuse simulations assessed syringeability and injectability, or the ability to draw the REMOXY formulation into a syringe through a needle and eject it from a syringe through a needle. In addition, injection-abuse simulations evaluated the impact of tools and manipulation on drug extraction at volumes A, B, and C. Nasal abuse simulations attempted to solidify REMOXY into a format suitable for snorting. And finally, smoking simulations measure the amount of oxycodone vaporized under heating.

Within a given experiment, 7 parameters were varied. REMOXY's abuse-deterrent properties were

evaluated using 12 manipulation methods, 24 tools, and 3 stress conditions. The extractions utilize 24 solvents, 4 different volumes, 4 different agitation methods, and 4 different extraction temperatures. This represents a total of 75 variables. As directed in the guidance, REMOXY was tested to failure to read. To reiterate Remi, abuse deterrence does not mean abuse proof.

REMOXY has unique physical and chemical properties. The high viscosity gel formulation does not flow, making it difficult to snort, syringe, or inject. In addition, the REMOXY formulation is sticky and adhesive. An abuser faces practical difficulties handling the sticky, high viscosity formulation. Manipulation methods RM2 and 8, for example, result in about a 25 percent loss of the REMOXY mass before an extraction attempt can even begin.

When subjected to extreme heat, oxycodone degrades and an excipient boils. It releases acetic acid or vinegar, and its vapors are irritating. Later, Dr. Montgomery will be speaking

with you about the safety of inhaling this material. Low oxycodone extraction from REMOXY after a manipulation and extraction is intended to contribute to its abuse deterrence.

As we mentioned, REMOXY is highly viscous. To provide you with a frame of reference, it's about 500 times more viscous than motor oil and about 4 times more viscous than Vaseline. The REMOXY formulation is also hydrophobic and does not dissolve in aqueous-based solvents. A common and simple method of abuse involves placing an intact extended-release opioid in a liquid, waiting for it to dissolve, followed by oral ingestion.

Here we present extraction results from intact REMOXY after soaking in 4 solvents at volume D and temperature B using mixing type A for time O. As you can see, 7 percent of the oxycodone dose was extracted in insolvent S1 and 49 percent of the dose was extracted in solvent S5.

Now, let's take a look at a oral abuse simulation in which the formulation was manipulated, followed by an extraction. In this

oral abuse simulation, we present the oxycodone extraction profile from manipulative REMOXY in solvent S1 at volume D and temperature B through time K. REMOXY was manipulated using 7 different methods coded RM1 through 9. Methods 8 and 9 also had stress be applied prior to the extraction. The intact, non-manipulated REMOXY extraction profile is represented by the dashed green line. As you can see, REMOXY maintained its extended-release characteristics following all 9 manipulations in solvent S1.

The extraction profiles of the comparator products are now illustrated. OxyContin ER intact is the dashed red line, and as you can see, there is little difference between intact OxyContin and manipulated REMOXY. OxyContin manipulated using method OM1 is a solid red line, where REMOXY, the immediate-release comparator, is the blue line.

OxyContin, manipulated using method 1, rapidly defeated its abuse-deterrent properties in which over 80 percent of the dose was extracted by the first time point. I want to point out that the

color scheme presented on this slide will be maintained going forward.

Solvent S5 was the most effective solvent in its class. As previous, this is the oxycodone extraction profile from manipulated REMOXY through time K at volume D and temperature B. Oxycodone extraction from REMOXY was dependent upon the manipulation method. Method 8 with stress B was the most effective method, while method 1 was the least effective method. Manipulated REMOXY maintained rate control through time K, following all 9 manipulations. By comparison, greater than 80 percent of the oxycodone was extracted from manipulated OxyContin and Roxicodone by the first time point.

As directed in the FDA guidance, REMOXY was tested to failure. Method 10 was the most effective manipulation method to defeat REMOXY's abuse-deterrent properties. This is a sophisticated manipulation procedure requiring the use of multiple tools and 6 steps. Method 10 must be performed in a certain and specific order in

order to defeat REMOXY. In solvents 1 through 5, REMOXY retained rate control for time J in 3 of those 5 solvents. By comparison, under similar conditions, OxyContin retained rate control in only 1.

Here are the results comparing oxycodone extraction from REMOXY, following manipulation methods 9 and 10 in solvent 1 at volume D. The table at the top was performed at extraction temperature B, and the table at the bottom was performed at temperature F. REMOXY's abuse of deterrent properties were defeated by method 10, which requires the use of tool 16 and 6 applications of tool 12. Again, it's a complicated and sophisticated procedure, requiring 6 steps in a certain order.

Now, let's look at extraction results from manipulated REMOXY in a different class of solvents. This figure summarizes and compares extraction results in 11 solvents, numbers 6 through 16. Of these 11 solvents, only one was capable of extracting 75 percent of the oxycodone

dose from REMOXY, while 7 solvents extracted 75 percent or more from OxyContin at time D. Similarly, at time J and K, fewer solvents were capable of extracting greater than 75 percent of the dose from REMOXY compared to OxyContin.

REMOXY's high viscosity formulation cannot be snorted like a powder. stress condition A with manipulation methods 4, 5, and 6 failed to convert REMOXY into a form suitable for snorting. Later, Dr. Webster will report the results of a category 2 and category 3 human abuse potential study in which REMOXY was applied to the nostrils of recreational opioid abusers.

Next, I'll discuss the results of IV abuse simulations. IV abuse simulations were performed to evaluate REMOXY's abuse-deterrent properties following manipulations and extractions and volumes A, B, and C. IV abuse simulations were conducted at temperature B through temperature F in solvents 19 through 24.

Here we present the extraction profile of REMOXY following manipulation using method 2 and

11, and in combination with stress B. The study conditions were temperature B and volume C in solvent 19. REMOXY resisted extraction following these manipulations and extraction conditions with less than 20 percent of the dose extracted by time H. In addition, application of stress B had no impact on oxycodone extraction from REMOXY.

Let's take a look at the comparator products and see how they fared under similar conditions. As I mentioned earlier, Xtampza was included as a comparator in a smaller subset of category 1 studies. Xtampza ER is the solid purple line and was manipulated using method XM1. OxyContin is the solid red line and was manipulated using method OM2 and stress B.

As you can see, oxycodone was rapidly extracted from OxyContin under these conditions at the very first time point. In this IV abuse simulation, REMOXY was manipulated using method 11. Stress C was applied for time D, F, and H prior to the extraction. The study conditions were solvent 24 at temperature D and volume B. So in

addition to a different solvent and different stress condition, this extraction was performed at a different temperature and a different volume compared to the prior slide.

REMOXY resisted extraction following these manipulations and extraction conditions with less than 40 percent of the dose extracted by time H. In addition, the application of stress C had no impact on oxycodone extraction from REMOXY. By comparison, you can see how rapidly oxycodone was extracted from OxyContin.

The worst case conditions in an IV abuse simulation were in solvent 20 at temperature F and volume C. REMOXY was manipulated using methods RM2 and 11 with stress condition B applied. Under these conditions, method 2 extracted about 40 percent of dose in time B. About half the dose was extracted at time H following manipulation method 11. These extraction conditions defeated both manipulated OxyContin and manipulated Xtampza. Greater than 80 percent of the dose was extracted from these two products at the first time point.

Now, let's turn our attention to syringeability and injectability studies. Syringeability studies were undertaken to assess whether the REMOXY formulation could be drawn into a syringe through a needle. Four needle gauges were tested, and all attempts to draw the formulation into a syringe failed. An injectability study was also performed in which the REMOXY formulation was backfilled into a syringe, and 4 needle gauges were tested to see if the REMOXY formulation can be dispensed from the syringe and through a needle.

In addition, the injection rate and temperature were also varied. The REMOXY formulation could not be injected from a syringe under any of the conditions that were tested. On the next slide, a video will illustrate the injectability experiment.

(Video played.)

DR. CROWLEY: Please direct your attention to the red oval. The experiment was conducted using needle size d at temperature B. As you can

see, when the plunger rod is pressed, the REMOXY formulation backflowed around the rubber stopper rather than through the needle.

I realize that may be hard to see from the back.

Now, I'll discuss the smoking abuse simulation results. Smoking is a less common route of abuse for oxycodone due to the narrow margin between the vaporization temperature and temperature where oxycodone degrades. REMOXY was heated to temperature I, and its vapors were continuously collected. The quantity of oxycodone recovered from the vapors was determined against time. As you can see in this image, REMOXY carbonizes at this temperature. Minimal oxycodone was recovered from REMOXY vapors at time D and time F. A larger quantity of oxycodone was recovered from the vapors of OxyContin, then REMOXY, under identical experimental conditions.

This concludes the results of the category 1 studies, which I will now summarize. The category 1 studies demonstrated the physical and chemical

properties, the REMOXY formulation impart abuse deterrence. REMOXY provides resistance to manipulations and extraction procedures. Its high viscosity formulation sticks to tools, making it difficult to manipulate and recover the entire quantity of the mass within a capsule. The studies also demonstrate it's difficult to syringe and inject and could not be converted into a form suitable for snorting. Minimal oxycodone was recovered in smoking simulations.

Finally, there are no visual cues to alert an abuser that REMOXY seat might be defeated or compromised. By visual cues, I mean a solution is not formed, nor a powder formed that could be snorted. Lacking visual cues, an abuser must rely upon guesswork, trial and error, or the use of sophisticated laboratory equipment such as an HPLC. To gauge the success or failure of the various manipulation methods, an abuser would also need to record their experimental procedures, what tools they used, which solvents they used, and for how long in order to identify conditions for REMOXY

abuse. The complexity, frustration, and tools needed to abuse REMOXY are intended to contribute to its abuse deterrence.

Next, Dr. Webster will discuss the category 2 and 3 in vivo abuse-deterrent studies.

Applicant Presentation - Lynn Webster

DR. WEBSTER: Good morning, everyone. I'm Lynn Webster, vice president of scientific affairs at PRA Health Sciences. My board certifications include anesthesia, pain medicine, and addiction medicine. As most of you know, I presented to you several times on abuse-deterrent formulations. I'm here today because I was the principal investigator of REMOXY's oral and nasal human abuse potential studies.

My presentation will show the results of the category 2 and category 3 assessments for both the oral and nasal abuse potential studies. The primary objective of the oral human abuse study was to compare the relative abuse potential of chewed 40 milligrams REMOXY ER versus crushed 40 milligrams IR oxycodone in solution.

The oral abuse potential study was performed prior to the FDA guidance issued in 2015. It was a single center, randomized, triple dummy, double-blind 4-way crossover design in recreational opioid abusers; 46 subjects completed the study. The study included a screening visit, the qualification phase using a naloxone challenge, a drug discrimination phase, and a treatment phase. A drug discrimination phase was used to ensure subjects could differentiate between the effects of 20 and 40 milligrams IR and placebo.

During the treatment phase, subjects were randomized to 1 of 4 treatment sequences, 40 milligrams intact REMOXY ER, 40 milligrams chewed REMOXY ER, 40 milligrams crushed oxycodone in IR in solution, and placebo. Subjects were instructed to chew up to 5 minutes. The primary objective was to compare the relative abuse potential of chewed 40 milligrams REMOXY ER versus crushed 40 milligrams IR oxycodone in solution.

The study had 4 co-primary endpoints: drug liking Emax, drug high Emax, drug liking area under

the effect curve zero to 2 hours, and drug high area under the effect curve zero to 2 hours. Drug liking endpoints were measured using a unipolar scale ranging from zero to 100. For example, overall drug liking was assessed by asking the subject, "Do you like the effect you are feeling now?" where a score of zero was not at all, and the score of 100 would be extremely. As per FDA guidance, data was generated for the 46 subjects who received all 4 study treatments.

Results of the study showed statistically significant differences between chewed REMOXY and immediate release oxycodone for 2 of the 4 primary endpoints. The two endpoints that were associated with significantly lower scores with chewed REMOXY compared to IR oxycodone were the area under the effect curve of zero to 2 hours for drug liking and drug high. However, no statistical differences were observed between drug liking and drug high Emax when comparing chewed REMOXY ER with IR oxycodone.

This slide shows the PK results of 40

milligrams of REMOXY intact, 40 milligrams of REMOXY chewed as the method of manipulation, and 40 milligrams crushed IR oxycodone in solution. The mean plasma concentration of intact REMOXY ER was statistically lower than crushed IR oxycodone at each time point following drug administration through 4 hours. However, the mean plasma concentration of chewed REMOXY was statistically lower than crushed oxycodone IR at only early time points of 30 and 60 minutes.

When examining the overall time course, there was a statistical difference in drug liking scores between REMOXY ER manipulated and oxycodone IR at earlier time points of 30, 60, and 90 minutes but not at 2 hours. Early time course effects are important as faster onset of effect has been associated with greater drug liking overall in recreational users.

The same early time course differences were observed with drug high when comparing 40 milligrams REMOXY chewed and 40 milligrams oxycodone IR at earlier time points of 30, 60, and

90 minutes, but again not at 2 hours.

In summary, the oral abuse potential steady met 2 of the 4 primary endpoints but did not meet the primary endpoints of drug high or drug liking Emax. At time points 30, 60, and 90 minutes, REMOXY demonstrated a statistical difference in favor of chewed REMOXY when compared to oxycodone IR crushed in solution taken orally, but there wasn't a difference at the 2 hours.

Now, let's look at the nasal abuse potential study. In this study, the primary objective was to compare the relative abuse potential of manipulated and intact REMOXY ER to immediate-release oxycodone. This study was conducted in 2017. A secondary objective was to compare the PK profile of REMOXY ER to crushed IR oxycodone and manipulated OxyContin ER.

The nasal abuse potential study was a randomized, double-blind, 4-way crossover study in recreational abusers. As is typical with these types of studies, there was a screening phase, qualification phase with a naloxone challenge, a

discrimination phase using 40 milligrams of oral oxycodone IR, and placebo followed by the treatment phase.

After the double-blind treatment phase, 20 subjects entered an exploratory open-labeled PK phase with manipulated 40 milligrams OxyContin administered intranasally. In the treatment phase, subjects were randomized to either intact 40 milligrams of REMOXY, 40 milligrams manipulated REMOXY, 40 milligrams crushed oxycodone IR, and placebo. Manipulation technique for intranasal administration of REMOXY ER is specified in section 3 of the confidential briefing book.

As previously mentioned, the open extension phase also used 40 milligrams manipulated OxyContin taken intranasally. As per FDA guidance, the primary endpoint was drug liking Emax comparing REMOXY ER to immediate-release oxycodone. A bipolar scale was used to evaluate drug liking PD endpoints where zero was strong disliking and 100 was strong liking, and a score of 50 was neither like nor dislike.

The statistical analysis plan was prespecified and reviewed by the FDA. Data were generated for 36 completers from the blinded portion of the study and 20 completers from the open labeled portion.

The PK results of intranasally administered drugs are illustrated in this figure. Both intact and manipulated REMOXY ER demonstrated an extended-release profile and lower bioavailability than ground oxycodone IR and manipulated OxyContin IR. Cmax for manipulated and intact REMOXY was significantly lower than for ground oxycodone IR and manipulated OxyContin ER.

This figure shows Cmax for manipulated and intact REMOXY was significantly lower than for crushed oxycodone IR and manipulated OxyContin ER when administered intranasally. The Tmax of manipulated and intact REMOXY was also statistically longer when compared to crushed oxycodone IR and manipulated OxyContin ER. As you know, the longer Tmax or time to Cmax is generally associated with more abuse deterrence due to the

delay in peak drug effect.

Now, let's look at the primary endpoint of drug liking Emax. The PD assessment of drug liking Emax used the zero to 100 bipolar visual analog scale where zero is a strong negative response, a score of 50 is a neutral response, and a score of 100 is a strong positive response. Here we show the drug liking Emax for 40 milligrams of REMOXY, both manipulated and intact, was significantly lower than 40 milligrams of crushed oxycodone IR.

Drug high Emax was measured using a zero to 100 unipolar scale where zero was no effect and 100 was maximum at the moment high or euphoric effect. Drug high Emax for manipulated and intact REMOXY ER were significantly lower than crushed oxycodone IR. Manipulated REMOXY compared to IR oxycodone showed a 46.1 millimeter lower Emax, while intact REMOXY showed a 45.2 millimeter lower Emax.

This figure shows the mean drug liking scores following nasal administration over time. It supports the observation that REMOXY manipulated and intact were less liked then crushed

IR oxycodone for 8 hours following intranasal administration.

Take drug again is another important assessment in evaluating the abuse potential of drugs. This slide shows that at 12 hours, there was a significant difference in take drug again for both manipulated and intact REMOXY when compared to crushed oxycodone IR. The difference on a bipolar scale was 28.8 millimeters for manipulated REMOXY and 24.9 millimeters for intact REMOXY ER.

Consistent with the 12-hour take drug again results, there was a statistical difference between manipulated and intact REMOXY when compared to crushed oxycodone IR at the 24-hour time point. In addition, all the secondary endpoints were statistically significant in favor of manipulated and intact REMOXY compared to immediate-release oxycodone. The objective measurement of a difference in pupil constriction was consistent with subjective PD assessments.

In summary, intranasally administered manipulated and intact REMOXY ER showed

significantly less liking when compared to nasally administered immediate-release oxycodone. Subjects significantly preferred IR oxycodone over nasal REMOXY ER at all time points. Secondary endpoints were consistent with the primary endpoints, and PD was consistent with the PK results. Finally, REMOXY ER maintained extended-release profile when manipulated, suggesting less abuse potential than the comparator.

Dr. Friedmann will now present the clinical development of REMOXY ER.

Applicant Presentation - Nadav Friedmann

DR. FRIEDMANN: Good morning. My name is Nadav Friedmann. I'm the chief operating and medical officer for Pain Therapeutics. This morning, I will discuss product profile of REMOXY, the goals of the clinical program, and the safety and efficacy of the product.

As you have seen before, REMOXY is oxycodone based in a sealed capsule. If approved, it will be available in 5 milligram to 40 milligram strength. It will be administered twice daily for the

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

The goal of the clinical program was to demonstrate the safety and analgesic effect of REMOXY administered twice daily to patients with moderate to severe chronic pain. The efficacy program was developed in close collaboration with the FDA through a special protocol assessment. A special protocol assessment is a process in which there's a declaration from the FDA that the trial design, including patient selection, clinical endpoints, and statistical analysis are acceptable for FDA approval should the study be successful, and in this case, it was.

Study PTI-821-C0 compared the analgesic effect of REMOXY ER versus placebo in a chronic patient population. It was a 12-week, double-blind, randomized, placebo-controlled multicenter in 412 patients with moderate to severe chronic pain due to osteoarthritis of the hip or

knee.

On the next slide, you'll see the schematic of the study design. Following a washout period, patients were titrated in an open fashion for 2 weeks from 5 milligrams to 20 milligrams of REMOXY ER. Following the titration, patients were then randomized in a double-blind fashion to either REMOXY ER or placebo. Placebo patients were titrated down over a 2-week period to preserve the blind.

REMOXY ER patients had the ability to either increase or decrease the dose for the first 4 weeks of the study, and then the last 8 weeks of the study, all doses were fixed. At the end of the study, again to preserve the blind, patients will tapered down.

REMOXY met the primary endpoints with a statistical significance of 0.007. The primary endpoint was the area under the curve of the pain intensity compared to placebo. REMOXY also met all secondary endpoints related to pain that were measured during that study such as quality of

analgesia, global assessment, and others. Adverse effects occurred in that study shown here that occurred at a frequency greater or equal to 5 percent of the patient population. No new or unexpected adverse events were noted in this study.

I will now address the total package that we have on REMOXY in terms of patients involuntary exposure. This slide summarizes the total exposure of REMOXY ER/ Over 2400 patients were administered REMOXY of which 469 were administered for 6 months and 381 for 1 year. Overall, the side effects profile was similar to that of other opioid drug products, and there were no new or unexpected adverse events.

In summary, in a double-blind study, REMOXY met the primary efficacy endpoint, statistically significant at 0.00-7 and all secondary endpoints related to pain. The safety profile is consistent with that of other opioid drug products. I will now ask Dr. Steve Montgomery to present excipient risk management, which are related to unintended route of administration.

Applicant Presentation - Stephen Montgomery

DR. MONTGOMERY: Good morning. My name is Stephen Montgomery, and I am a toxicology consultant to PTI. I will be presenting information on systemic exposure on the only 2 excipients and 2 decomposition products that were detected in an in vitro extraction study.

The in vitro excipient extraction study was conducted at an independent laboratory. REMOXY 40-milligram capsule samples were manipulated and extracted according to category 1 conditions. Analytical methods were developed and limits of quantitation established.

Only 2 excipients Triacetin and hydroxyethyl cellulose, or HEC, and to excipient decomposition products, acetic acid and myristic acid, were detected. The highest level detected for Triacetin was 18.63 milligrams per milliliter, and for HEC, it was 1.52 milligrams per milliliter with manipulation R11 [sic] at extraction temperature E at time J. Levels of acetic acid and myristic acid were detected at or slightly above

the LOQ, each at a single time point.

Our evaluation involved searching the published scientific literature with a focus on intravenous studies with Triacetin, HEC, acetic acid, and myristic acid. Where possible, an attempt was made to identify a no adverse effect level and to calculate a margin of safety relative to the level of the extracted excipient or decomposition product from 2 REMOXY 40-milligram capsules.

Triacetin is a triester of glycerin and acetic acid, which are rapidly hydrolyzed in tissues to yield systemic exposures to glycerol and acetic acid. The high LD50 values with IV injection indicate that Triacetin has a very low potential for systemic toxicity.

In a repeated-dose study in animals receiving 31,600 milligrams per kilogram IV as a daily infusion showed no evidence of toxicity. This is concordant with the absence of toxicity associated with high oral doses of Triacetin in repeated-dose animal studies. The margin of safety

based on the 7-day repeated-dose IV study relative to the amount quantified in the in vivo extraction study was greater than 10,000-fold.

Excipient vapors that were evolved under certain conditions of REMOXY ER manipulated, noted by a previous speaker, were identified as Triacetin. Inhalation of exposure to saturating vapors of Triacetin for 6 hours per day for 5 days showed no evidence of respiratory, nasal, or ocular irritation, indicating a low potential for local effects from evolving REMOXY ER vapors. In studies to evaluate ocular irritation, only one was suggestive of a transient irritation with direct application of Triacetin, indicating a low or a minimal risk.

HEC is a celluloid polymer similar to other cellulose-based polymers that are currently approved in other opioid ER formulations. It is listed in the FDA inactive ingredient database, the IID, for use in approved oral, ophthalmological, otic, and topical drug products. It is inert at high acute and repeated oral dose in animals.

HEC is not readily metabolized, and therefore systemic clearance slowly occurs via the reticuloendothelial system. Information on acute systemic exposure to HEC is quite limited and varied depending on the species and delivery methods. Low acute toxicity values with systemic exposures in some rodent studies has not been affirmed in non-rodent studies have longer duration.

Toxicity was not reported following a single intravenous injection of 1200 milligrams per kilogram. Repeated IV injections of HEC have been associated with hemodilution, hepatic, and renal storage, and vascular lesions in some studies. The margin of safety based on the acute IV study relative to the amount quantified in the in vitro extraction study was greater than 4800-fold.

Acetic acid is a natural constituent readily metabolized in most tissues. This is absorbed orally from intake of foods, providing for the endogenous levels of acetic acid. The level of acetic acid detected in the in vitro extraction

study was below 0.4 percent, the amount listed in the FDA inactive ingredient database for use in approved IV drug products, and therefore does not present a safety concern at the level detected.

Acute toxicity IV50 values would suggest that acetic acid may have low to moderate potential for adverse effects if given by this route of administration. However, considering a safety margin of 21,000-fold for the low level of acetic acid detected in the in vivo extraction study seemed very unlikely.

Myristic acid is a natural C14 fatty acid metabolized in the intestine and systemically via the beta oxidation pathway. Myristic acid is absorbed orally following food intake; hence, providing for the endogenous human plasma concentrations. The IV50 value of 43 milligrams per kilogram would suggest that myristic acid may have a potential for acute toxicity. However, oral studies in animals have shown myristic acid to be relatively non-toxic.

Based on the IV LD50 value, the safety

margin was calculated as 4300 fold based on the amount extracted from 2 REMOXY ER capsules. Given the endogenous plasma concentrations, it would seem unlikely that systemic exposure to myristic acid at the level detected in the in vitro extraction study would pose a safety concern.

In summary, the margin of safety for systemic exposure to Triacetin at the maximum amount extracted is greater than 10,000-fold and for HEC is 4800-fold relative to the levels detected in the in vitro extraction of manipulated REMOXY ER 40-milligram capsules. In conclusion, the results show a low risk for Triacetin, HEC, acetic acid, and myristic acid for acute adverse systemic effects with misuse.

I will now ask Dr. Michael Marsman to discuss the risk mitigation strategy for REMOXY ER.

Applicant Presentation - Michael Marsman

DR. MARSMAN: Thank you, Dr. Montgomery.

Good morning, everyone. As the slide states. my name is Mike Marsman, and I'm responsible for regulatory affairs at Pain

Therapeutics. This morning, I'd like to give you just a brief overview of our risk mitigation strategy as well as summarizing the risk-benefit profile for REMOXY ER.

As sponsor of an extended-release opioid product, we are very serious about our responsibilities to assure safe use of REMOXY once it's on the market. Accordingly, we plan to assure that strong risk mitigation strategies are in place following approval. This will include full participation in the class-wide REMS activities, a comprehensive drug safety and pharmacovigilance program, and procedures to assure safe packaging, distribution, and disposal of our product.

As indicated on the slide, Pain Therapeutics currently has observer status in the industry-wide REMS consortium, and we plan to convert to full active membership upon approval, and that will include full participation in the REMS educational activities and post-approval study activities.

To summarize the risk-benefit profile, REMOXY demonstrates a favorable risk-benefit

profile. It met the clinical endpoints in a large, well-controlled, phase 3 efficacy study. The safety profile is similar and consistent with other ER opioid products. There were no new or unexpected adverse events identified. And based on the totality of the category 1, 2, and 3 study results, REMOXY can be expected to meaningfully deter injection, nasal, and smoking routes of abuse.

In conclusion, abuse resistant or abuse deterrent formulations such as REMOXY can play an important role against prescripted opioid abuse while still ensuring appropriate access to patients suffering from chronic pain. REMOXY's unique formulation is an advancement to the science of abuse deterrence. It increases the range of available abuse-deterrent technologies. It provides another treatment option for chronic pain. It addresses the vulnerabilities that exist with some currently marketed ER oxycodone products. And it demonstrates properties that can be expected to deter abuse by the nasal snorting, injection, and

smoking routes of administration.

Finally, I'd like to express our appreciation to the committee for their attention to our presentation this morning and to thank FDA for working with us throughout the development process. Thanks to both of you. And I'll now turn the podium over to Dr. Friedmann for any clarifying questions. Thank you again.

Clarifying Questions

DR. McCANN: Are there any clarifying questions for Pain Therapeutics? Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter. Ms. Spotila?

MS. SPOTILA: Jennifer Spotila. My question's for Dr. Crowley. In your presentation, you said that design of the in vitro work was informed, in part, by recreational opioid abusers, and you mentioned internet forums. Was that your only source of information from those abusers?

DR. CROWLEY: Yes. We read several internet sites to see what the abuse community was doing to

manipulate and abuse existing commercial products.

DR. McCANN: Dr. Meisel?

DR. MEISEL: Steve Meisel, Fairview. A question for Dr. Montgomery about the toxicity. I appreciate the information you gave, but it seemed like it was focused on what happens if you would try to extract these chemicals. I want to focus on what happens when you use this drug as intended. So what is the absorption of these ingredients, plus the ingredients that you didn't mention that are in there as the excipients?

What happens when used correctly? How much of it is absorbed? What are the anticipated adverse effects of these ingredients, not when extracted and injected, but when ingested in the designed way?

DR. FRIEDMANN: We have done full toxicology on those products, and we'll try to show you what we did.

DR. MONTGOMERY: Yes, we've done a full complement of toxicology studies normally required for these individual components. Let's see if we

can get the slide up here. Basically, in running these studies with an oral administration, they're relatively non-toxic. In other words, we don't see much happening with huge oral doses, 2,000 to 4,000 milligrams per kilogram per day.

So you can see the listing over here of the number of studies -- of the types of studies, which were completed, including acute subchronic; chronic toxicity studies, which are 6 months or longer; genotoxicity studies usually in in vitro and in vivo; carcinogenicity studies; reproduction studies, which includes seg 1 [ph], seg 2, seg 3; fertility reproduction, teratology, and perinatal/postnatal studies in some cases; and other toxicity studies.

DR. MEISEL: Well, I'm not sure that really answers any detailed questions. Specifically, I just did a quick Wikipedia search on myristic acid, and it talks about the fact that it has the potential of raising somebody's cholesterol and triglyceride. And if that happens, what are the long-term impacts if you take something that raises

somebody's cholesterol and triglyceride on their cardiovascular risk factors?

DR. MONTGOMERY: Well, in these particular studies -- for example, for the chronic oral toxicity studies -- we would do a complete battery of CMC work, which would include everything from hematology, clinical chemistry, and urinalysis using rats and dogs. And when we do those, we take a look and see whether or not there are any changes in lipid values, for example, or any changes in hematology parameters, et cetera.

As said, the studies which were done, there was almost no toxicity that was associated with any of them, particularly the Triacetin.

DR. CROWLEY: With respect to your last question, myristic acid is not an inactive ingredient. It was a degradant formed following a manipulation, and small amounts were observed during an extraction.

DR. McCANN: Dr. Nelson?

DR. NELSON: Thanks. I have two questions for Dr. Friedmann. Lewis Nelson. I'll just put

them together, and you can answer them in any order you like, if you don't mind.

My first question is, as I read the efficacy study that you designed, it looks like it's an enrolled enrichment and controlled withdrawal study. And I wonder why you didn't do a study that was randomized at inception in an unscreened population, which would probably be more true to form of how things worked in the real world.

My other question is, what is the implication of the proposed indication, the last line of which says, "for which alternative treatments are inadequate," what are the alternative treatments that you're suggesting are inadequate? Are these other opioids or is this meant to be a first-line opioid that people go to when they have chronic pain?

DR. FRIEDMANN: Answering your first question, why did we do the enriched design, I have done a phase 2 study earlier, where we actually started the 10 milligram as a first dose, the 10 milligram twice a day, and the dropout was quite

high. And that's why we elected to develop the 5 milligram as a titration dose to move up. And the second study when we did the large efficacy study, the dropout was a little less and patients tolerated it better.

Does that answer the first question?

DR. NELSON: It answers the enrollment, the enriched enrollment part. But what about the controlled withdrawal? Why didn't we just start everybody from inception on medications rather than get everybody hyperalgesic or tolerant, and then stop them.

DR. FRIEDMANN: Because the dropout is going to be fairly high if you want to titrate them up to -- if you start at 10 and you go up higher, the dropout was just too high in that study.

Secondly, as I mentioned earlier, this study was designed, together with the FDA, as a special protocol assessment, and everything was agreed to. And the alternative therapy, that's classic for all the opioids basically, given to us by the FDA. And alternative therapies would be the non-steroidal,

anti-inflammatories, for example.

DR. McCANN: Dr. Zibbell?

DR. ZIBBELL: Jon Zibbell, RTI International. I know the injection abuse studies, you said that there was no syringeability and injectability. A lot of times in the real world, we don't know what other things people are going to use to be able to manipulate those. Let's say they could manipulate those and inject that formulation. Would there be any vein damage or could you see any damage physiologically if those drugs were injected? Is there any evidence for those excipients causing harm if injected?

DR. FRIEDMANN: That's a two-point answer. Number one, we have done studies where you take from oxy at special temperatures that would force [indiscernible] injection, and put it in blood, and there's no extraction. So there's no reason for somebody -- it will not be a good reason for somebody to even inject it because they're not going to get any high. That's number one.

Number two, in terms of the second portion

of your question, the extraction studies, what we try to show is how much oxycodone you will get during the extraction for an IV injection; and as you saw, very little you're going to get from the extraction.

Does that answer your question?

DR. ZIBBELL: Sure. Thanks.

DR. McCANN: Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF. This if for Dr. Webster. Concerning the human abuse potential studies, it seems that on a few of the comparators, there was both OxyContin IR manipulated -- I'm sorry, oxycodone IR manipulated and OxyContin branded ER manipulated, but not for all. I'm wondering why OxyContin ER was not used in all of those studies.

DR. FRIEDMANN: Let me answer that question. We designed the study and discussed it with the FDA. The thought was just run a study against a OxyContin. Why do a study against an IR? That's going to be our comparator. The impression that I received from the FDA was that it's probably better

to run it against the IR because there's more information available, and that's a standard that we should run against.

So the study was going to go against the IR and no OxyContin. And then as a second thought, I said, well, why don't we see how is OxyContin doing in an open stud. So the study itself was a 4-way crossover study without OxyContin, and then we took the first 20 volunteers, and we gave them OxyContin manipulated just to see the PK on that.

DR. McCANN: Dr. Arfken, please?

DR. ARFKEN: Cynthia Arfken, Wayne State University. I have two questions. What is the age range for which you are seeking permission? And the next one is, what are the demographics of the people who participated? I'm especially interested in the age range as well as that they're both women and men involved in these studies.

DR. FRIEDMANN: Which study are we talking about?

DR. ARFKEN: I'm interested in all the studies.

DR. FRIEDMANN: I missed -- well, both men and women were in all the studies. That's to answer the second question. The first question, I didn't quite understand.

DR. ARFKEN: The age range that you're seeking approval for.

DR. FRIEDMANN: Well, in the osteoarthritis study, obviously, the age range was for the older population, although we have a fair amount between the age of 30 and 40 In the abuse-deterrent population, the HIP [ph] studies, the population was younger, most men and women.

DR. ARFKEN: So are you asking for approval for the adult population only?

DR. FRIEDMANN: We're asking for approval from 18 years and older, yes.

DR. McCANN: Ms. Robotti?

MS. ROBOTTI: Hi. This is Sue Robotti. During Dr. Meisel's question, slide number 34 was put up on the screen. I think Dr. Friedmann was talking, although I don't remember. There was a note made that you did studies on reproductive

toxicity. Could you talk about those studies?

DR. FRIEDMANN: Thirty-four?

DR. ROBOTTI: It's not from the original presentation; it was from when Dr. Meisel asked a question. That's not the slide.

DR. MONTGOMERY: Well unfortunately, I didn't do the study, so I can't really speak to them very much. IT's the one before this. And my colleague who did do them is, unfortunately, recovering in the hospital for back surgery, so I would be happy to talk with you a little bit later perhaps about exactly what was done.

DR. ROBOTTI: Will it affect the guidelines or the labeling? Will you have information for pregnant women or lactating women? Am I misunderstanding what reproductive toxicity is? What is reproductive toxicity?

DR. MONTGOMERY: I'm sorry?

DR. ROBOTTI: What is reproductive toxicity?

DR. MONTGOMERY: These are studies that are done --

DR. KLUETZ: Microphone, please.

DR. MONTGOMERY: Reproductive toxicity studies are done to assess the effects of the drugs or the inactive ingredients on fertility and reproductive, on teratology, and on -- in some cases, we'll also look at perinatal/postnatal development.

DR. ROBOTTI: So I'm just asking if that will come into play during the labeling.

DR. MONTGOMERY: Yes.

DR. ROBOTTI: I'm not sure if that's a --

DR. MONTGOMERY: It would come into play.

DR. ROBOTTI: So information on that would be helpful. Thanks.

DR. HERTZ: This is Sharon Hertz. I think the question is, are we going to be able to discuss this part of the labeling today, and we don't typically. So I think the next question -- I don't want to tell you what questions to ask the sponsor, but we're not planning to present toxicology data. So if you have questions about the results of the studies and how it may affect labeling, we're not going to have that information either.

DR. ROBOTTI: Okay, because use of opioids during pregnancy and lactation, there's often not a huge amount of information. So if there were studies done on this and that information's going to be on the label, that would be -- that should be discussed. The information should be available to the panel.

DR. HERTZ: Right. So you might want to query the sponsor more.

DR. ROBOTTI: So that's my question. Are you requesting -- are you going to be asking to put information on pregnancy and lactation use on the label? And if so, will you give us that information?

DR. FRIEDMANN: We're not asking for it.

DR. McCANN: With that --

DR. HERTZ: This is Sharon Hertz again. Sorry. There are several sections that are required as part of labeling, and information about sex from reproductive toxicology studies are a part of that. If you want more information on that, perhaps the section of labeling that's relevant

might be displayed. I just feel like there's a disconnect between the questions and the discussion right now, so I'm just putting that out there, if the sponsor would care to display the proposed label, the relevant sections to the repro-tox.

DR. FRIEDMANN: I'd just like to mention that all the studies we have done on the excipients of toxicology was done according to guidance for the excipients and for REMOXY. We also have done a study with the complete formulation in guinea pigs.

DR. McCANN: So we have about 5 or 6 more questions to go, but what I'd like to do at this point is take a very short break and come back by about 11:18. Then we'll start with the FDA and get to the questions after the FDA's presentations. Thank you.

(Whereupon, at 11:07 a.m., a recess was taken.)

DR. McCANN: We will proceed with the FDA presentations.

FDA Presentation - James Tolliver

DR. TOLLIVER: Good morning. My name is

James Tolliver. I'm a pharmacologist for the controlled substance staff within the Office of the Center Director, Center for Drug Evaluation and Research at the FDA. This morning, I would like to briefly discuss oral human abuse potential study B4501016, submitted under NDA 22324 for REMOXY ER capsules. I also intend to make a few comments regarding the category 1 smoking study conducted with REMOXY ER.

The oral study is a randomized, double-blind, triple-dummy placebo and active controlled single-dose, 4-way crossover design utilizing an evaluable population of 46 non-dependent recreational opioid users. Treatments included placebo; REMOXY ER capsules, 40 milligrams intact swallowed; REMOXY ER capsules, 40 milligrams chewed for 5 minutes; and oxycodone hydrochloride IR 40-milligram tablets crushed and placed in solution as the positive control.

Statistical analyses of pharmacodynamic measures were conducted by the CDER, Office of Biostatistics, using where possible a mixed-effects

model. The primary comparison was that of REMOXY 40 milligrams chewed versus oxycodone hydrochloride IR, 40 milligrams crushed.

The pharmacodynamic measures of interest will include the zero to 100-millimeter unipolar visual analog scales, or VAS, for drug liking high, take drug again, and overall drug liking. The 3 unipolar scales of drug liking, high, and overall drug liking were anchored on the left by zero, not at all, and on the right by 100 extremely. In the case of take drug again VAS, the anchor on the left was zero, definitely not, and on the right by 100, definitely so.

Drug liking VAS and high VAS are at the moment subjective measures taken at selective time intervals following start of treatment. In the case of drug liking, subjects are asked to respond to the statement, "At the moment, my drug liking for this drug is." For the high VAS, subjects are asked to respond to the statement, "I am feeling high."

Take drug again VAS and overall drug liking

VAS are taken at 24 hours after dosing when the drug effect has largely subsided. Subjects were asked to reflect back over each treatment. In the case of take drug again VAS, subjects are asked to respond to the statement, "I would take this drug again." For overall drug liking, subjects are asked to respond to the statement, "Overall, my liking for this drug is."

There were four primary endpoints in the study, including maximum effect designated Emax for unipolar drug liking and high, and in addition, cumulative experience of drug liking and high out to 2 hours post-dosing, designated area under the effect curve or
AUE zero to 2 hours.

The results for the primary endpoints are provided in the table on this slide for all four treatments. Treatments constituting the primary comparison, namely REMOXY chewed versus oxycodone hydrochloride IR crushed in solution, are provided in the yellow columns. What I would like for you to notice about this slide is that for both of

these treatments, the resulting mean values for Emax and area under the effect curves out to 2 hours for both drug liking and high were higher than that produced by either placebo or REMOXY swallowed intact.

This slide provides the statistical analyses for the primary comparison. The Emax and drug liking for REMOXY chewed was not smaller than that produced by the comparator oxycodone hydrochloride IR crushed. In addition, the Emax of high was statistically smaller for REMOXY chew compared to oxycodone hydrochloride IR. However, there was a failure to demonstrate a minimum of 5 percent reduction in mean Emax of high for REMOXY chewed compared to oxycodone hydrochloride IR crushed. REMOXY chewed resulted in limited but statistically significant reductions at area under the effect curve out to 2 hours compared to oxycodone hydrochloride IR crushed for both drug liking and high VAS.

The slide provides the secondary endpoints for the Emax of take drug again and overall drug

liking VAS. Again, the treatments constituting the primary comparison, namely REMOXY chewed versus oxycodone hydrocodone chloride IR crushed, are provided in yellow. Note that following these two treatments, least squared mean Emax, for both measures were in the range of 60 to 65 millimeters, which are well above the means values produced by either placebo or REMOXY swallowed intact.

Statistical analyses for the primary comparisons for Emax unipolar take drug again and unipolar and overall drug liking are provided in this slide. Numerically, the mean differences of Emax for take drug again and overall drug liking, produced by REMOXY chewed, was lower by 1.5 and 3.8 millimeters, respectively, compared to that produced by oxycodone hydrochloride IR crushed. These small differences were not statistically significantly different. As such remarks, REMOXY chewed when compared to oxycodone hydrochloride IR crushed was not associated with a lower Emax for either take drug again or for overall drug liking.

This slide provides some conclusions

regarding the oral study. There were three findings of this study when considering the primary comparison. First, REMOXY chewed compared to oxycodone hydrochloride IR crushed was not associated with significant reductions in Emax for the unipolar visual analog scales for drug liking, take drug again, or overall drug liking.

Secondly, although statistically significant, the reduction in Emax of unipolar high VAS produced by REMOXY chewed versus oxycodone hydrochloride IR crushed was limited, raising the question of clinical relevance.

Third, early drug liking and high experience reflected in the area under the effect curve out to 2 hours post-dosing was lower but limited for REMOXY chewed compared to oxycodone hydrochloride IR crushed.

When considering these findings together, we conclude that there are no data to support that limited differences in the early drug liking or high experience over the first 2 hours are clinically relevant findings consistent with

possible abuse-deterrent effects, especially considering that the Emax analyses for drug liking, high, take drug again, an overall drug liking in this study failed to demonstrate abuse-deterrent effects of REMOXY.

I'd like to turn for a moment to the category 1 smoking study, which was conducted under protocol coded V1. Under this protocol, the percentages of labeled dose of oxycodone from manipulated REMOXY 40 milligrams and 40 milligrams of the active comparator recovered from vapor were 3.8 and 10.7, respectively. Overall, this percentage difference reflecting 2.76 milligrams of oxycodone was limited.

The 4.28 milligrams of oxycodone quantitated in the total collected vapor from the active comparator might be expected to produce subjective effects in non-dependent recreational opioid drug abusers if all the vapor was inhaled. However, the methods used to collect and assay, the oxycodone and vapor was artificial and does not reflect the real-world experience. Considering that

individuals would most likely capture only a limited percentage of the vapor, it is not clear whether subjective effects would be obtained using the positive active comparator.

Finally, my last slide, I would like to comment on the assertion that Triacetin, an excipient found in the REMOXY formulation, might serve as a deterrent to smoking the REMOXY formulation. This substance may be volatilized, and the resulting vapor may serve as an irritant to the respiratory track and eyes. However, any consideration of Triacetin serving an abuse-deterrent effect to smoking of REMOXY would require confirmation of significant irritant effects as documented in human subjects smoking REMOXY.

At the same time, based upon ethical considerations, the administration of REMOXY to human subjects by smoking for purposes of evaluating irritant or subjective effects cannot be done. Considering the limited amount of oxycodone recovered in the vapor it is not clear that the use

of Triacetin as a potential aversive agent would be warranted. Thank you.

FDA Presentation - Mallika Mundkur

DR. MUNDKUR: My name is Mallika Mundkur. I'm a medical officer within the office of Surveillance and Epidemiology, and I'll be reviewing the recent epidemiologic data on use, misuse, and abuse of oxycodone. Aligned with recommendations from a 2017 report released by the National Academies of Sciences, Engineering, and Medicine, FDA continues to consider public health throughout the life cycle of opioid products. Public health considerations include both unintended consequences as well as use in non-target populations.

In that context, the purpose of this review is to provide the committee with a relevant public health framework to consider alongside other data. Our two objectives are as follows: first to review high-level data regarding the utilization of oxycodone products; and second, to review epidemiologic data on misuse and abuse of

oxycodone-containing products and comparator drugs.

Of Note, many of the data sources we reviewed do not distinguish between extended-release versus immediate-release products. Thus, we describe data more generally and provide product-specific information when available. Additionally, to date, no postmarket data have been submitted to the FDA that support a meaningful effect of ADFs on reductions in abuse, misuse, or related adverse clinical outcomes in the community. Therefore, published studies attempting to evaluate these outcomes will not be presented.

We will begin by presenting data on utilization extracted from IQVIA national prescription audit. The specific questions we sought to answer were the following: How frequently are specific oxycodone products dispensed in the U.S.? Among extended-release and long-acting products, which are the most frequently dispensed products? Among products intended to deter abuse, which are the most frequently dispensed? And finally, what are the trends in

dispensing for any of the above?

This figure shows the nationally estimated number of dispensed prescriptions for oxycodone-containing products from U.S. outpatient retail pharmacies over the period of 2013 to 2017. Overall levels of dispensed oxycodone prescriptions peaked in 2015 at $56 million and have decreased to $50 million by 2017. The vast majority of oxycodone prescriptions in 2017 were either combination or single-entity oxycodone immediate-release products, while fewer than 8 percent were for an oxycodone extended-release product.

In contrast with the previous slide, this figure includes not only oxycodone but other products as well for comparison. Among extended-release and long-acting opioid analgesics, morphine ER accounted for the largest proportion in 2017 at approximately 33 percent, followed by fentanyl at 22 percent, and oxycodone ER at 20 percent of all dispensed ER/LA prescriptions.

Here we see yearly estimates of

prescriptions dispensed for opioid analgesic products specifically formulated with properties intended to deter abuse. Reformulated OxyContin ER, delineated here by the green line, accounted for 88 percent of ADF products dispensed in 2017. The other oxycodone ER product currently available on the market, Xtampza ER, is delineated by the purple line at the bottom. There has been a downward trend in prescribing for reformulated OxyContin with 4.9 million prescriptions in 2013 and 3.4 million in 2017.

In summary, in 2017, approximately 50 million prescriptions for oxycodone were dispensed at outpatient retail pharmacies in the U.s. Among ER/LA opioids, oxycodone ER constituted 20 percent of all dispensed prescriptions, and among ADF products specifically, 88 percent of dispensed prescriptions were for reformulated OxyContin ER.

The second component of this review will focus on misuse and abuse of oxycodone-containing products and comparator drugs. With the second objective, we will address a number of questions,

including the following: What is the current scale of misuse and abuse of prescription opioids? Which are the most frequently abused opioids? What are the most common routes of abuse for opioids, including available abuse-deterrent formulations? And finally, what is the magnitude of morbidity and mortality associated with oxycodone-containing products versus comparator drugs?

The definitions of misuse and abuse used for the majority of this review are consistent with what FDA has previously issued in guidance to industry. Misuse is defined by FDA as the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse. Abuse is defined as the intentional non-therapeutic use of a drug product or a substance, even once, to achieve a desirable psychological or physiological effect.

We used a number of data sources that are described in detail in the background information provided. As we go through the results, we will provide a brief description of the relevant data

source.

Scale of misuse and abuse. According to the National Survey on Drug Use and Health, NSDUH, a federally funded household survey of individuals 12 and older in the United States, the most frequently misused opioid products in the general population were hydrocodone and oxycodone, with misuse defined by NSDUH to include use of a drug in any manner other than as medically directed, including but not limited to abuse.

In this figure, we have the Y-axis on the left indicating the number of individuals in thousands who reported past year misuse of the drug, and the Y-axis on the right represents this number as a percentage of the total population. You can see there is no significant change in levels of oxycodone misuse from 2015 to 2016, and the total number of individuals reporting misuse of oxycodone in 2016 was 3.9 million or approximately 1.5 percent of the total population.

In this figure, we have data from the National Poison Data System, a national network of

poison centers receiving calls from the public or healthcare workers. One strength of this data source is that it collects more detailed information on product formulation, and may be more accurate in that regard than other data sources.

This figure demonstrates that over 3,000 calls per year reported intentional exposure to an oxycodone-containing product over the period 2012 to 2016, with calls reporting exposure to IR products being much more frequent than those for ER products. A total of 50,000 calls reporting intentional exposure to an oxycodone product were placed over the entire time period, while by comparison, 75,000 calls were placed for hydrocodone, 9500 calls for morphine, and 24,000 calls for heroin. In NPDS, intentional exposures include misuse, abuse, self harm, and other unclassified reasons for exposure.

Relative frequency of abuse; specific products. According to the Radars Treatment Center program, a surveillance program that includes surveys of individuals entering treatment for

opioid use disorder, 35 percent of individuals reported past month abuse of oxycodone.

This chart shows the percentage of respondents in the RADARS Treatment Center program who reported past month abuse of various opioid products with products grouped together on the X-axis by active pharmaceutical ingredient. In this population, oxycodone was the most frequently abused prescription product, though heroin was the most frequently abused overall.

Formulation-specific data from RADARS suggest more frequent abuse IR than ER products, though as noted here, 15 percent report past month abuse of an oxycodone ER product specifically.

When accounting for prescription volume, the relative frequency of oxycodone abuse compared with other products appears to change. This chart shows the rate of past month abuse per 100,000 dispensed dosage units by active pharmaceutical ingredient. Here we see that some of the more potent agents such as fentanyl and oxymorphone are abused more than other agents relative to what will be expected

from their overall levels of availability. Formulation-specific data in this case suggests that when adjusting for utilization, oxycodone ER appears to be abused more frequently than oxycodone IR.

Routes of abuse. We reviewed a number of articles that discussed routes of abuse for prescription opioids with the key results summarized in this table. From left to right, the columns for this table are the study author, data source used, the category of opioids assessed, and specific routes of abuse assessed in the study.

Two of these studies reported data on abuse of ADF products specifically. The Cassidy study, based upon data from the surveillance system NAVIPPRO, a system like RADARS, which surveys individuals entering treatment facilities for substance-use disorder, 60 percent of individuals reported oral abusive ADFs, 20 to 30 percent reported snorting, and 30 percent reported injection.

The Severtson analysis, a quarterly report

released by the RADARS Treatment Center program, reported similar numbers, though additionally providing data on chewing and smoking of ADFs products, endorsed among 25 percent and 5 percent of individuals, respectively. A study by Butler and colleagues, also using data from NAVIPPRO, though focused primarily on oxycodone ER, reported higher rates of oral abuse, similar rates of snorting, lower rates of injection, and similar rates of smoking as the prior studies.

Finally, a study by the Vietri and colleagues, identified by the sponsor, used a small sample of patients from the Kantar Health U.S. National Wellness survey and assessed abuse of all prescription opioids. This study reported very different numbers, potentially explained by the more heterogeneous category of opioids assessed, the smaller sample size relative to the other studies, or that the population in the Vietri study may represent patients with less advanced opioid use disorder. Another key difference is that the Vietri study assesses abuse in the past 3 months,

while the other studies assess abuse in the past month only.

The findings from these studies can be summarized as follows. For a sample of patients entering treatment for opioid or substance-use disorder, oral abuse was the most common, followed by snorting and injection, with smoking as a very infrequently reported route of abuse. For a sample of patients from the general population, data on routes of abuse for specific products such as oxycodone or not available, though for prescription opioids as a whole, oral abuse is much more common with snorting, injection, and smoking also reported as frequently attempted routes.

Finally, morbidity and mortality. According to the National Electronic Injury Surveillance System, NEISS-CADES, a database of a nationally representative sample of emergency department visits in the U.S., during 2016, there were nearly 300,000 estimated ED visits for harms from prescription opioid products of which approximately 40 percent involved oxycodone-containing products,

specifically.

This table summarizes ED visits moving from left to right, with the left column indicating opioid ingredient, then the number of cases in the sample, the weighted number of visits projected at the national level, and the percent of the total visits involving prescription opioids for each intent of use. The red box highlights that an estimated 50,000 ED visits in 2016 involved non-medical use of oxycodone, with non-medical use defined to include pharmaceutical abuse, therapeutic misuse, and overdoses without indication of intent.

This table highlights that among ED visits associated with non-medical use of oxycodone, approximately 40 percent or an estimated 22,000 visits resulted in admission, transfer, or observation. As noted here, oxycodone was frequently adjusted with other agents, including prescription opioids, benzodiazepines, and most notably, illicit drugs or alcohol.

This graph shows the proportion of ED visits

associated with non-medical use of oxycodone that were associated with specific categories of adverse outcomes. Among the visits with non-medical use of oxycodone, nearly 20,000, resulted in patients experiencing a serious adverse outcome such as cardiac arrest, unresponsiveness, or respiratory failure and distress, collectively represented by the lighter blue section of this chart.

National data on drug-involved mortality were made available to the agency by the National Center for Health Statistics. Drug-involved mortality, DIM, combined the cause of death, demographic, and geographic information from the National Vital Statistics System Mortality, NVSS-M files, with information extracted from the death certificate literal text, allowing for more a granular analysis of specific drugs involved in deaths.

In this figure, we see the number of deaths involving various opioids over time. Included on this graph are oxycodone, the solid black line; hydrocodone, the lighter solid, brilliant gray

line; morphine, the darker dashed line; and heroin, the lighter dashed line.

Analysis of the NVSS-M and DIM linked databases found that in a 6-year period, from 2010 to 2015, oxycodone involved desks remained relatively unchanged with between approximately 5[000] to 6,000 deaths per year. In contrast, a sharp increasing trend was observed for heroin-involved overdose deaths over the same time period, rising from approximately 3,000 in 2010 to over 13,000 deaths in 2015.

In summary, to review the data we've presented on misuse and abuse, with respect to scale, in 2016, 3.9 million individuals in the general population reported past year misuse of oxycodone-containing products defined by NSDUH to include both misuse and abuse. Greater than 3,000 calls per year have been placed to poison control centers, reporting intentional exposure to oxycodone-containing products, and 35 percent of individuals entering treatment for opioid-use disorder reported past month abuse of

oxycodone-containing products. In terms of abuse of specific products, past month abuse of oxycodone IR products was more frequent than for oxycodone ER products. However, when adjusting for prescription volume, past month of use of oxycodone ER products appears to be more frequent.

For routes of abuse, abuse-deterrent ER/LA opioid analgesics are abused by multiple routes, where 60 percent of respondents in one study reported oral abuse, 20 to 30 percent reported abuse via snorting, while 30 percent reported abuse by injection. Finally, with morbidity and mortality, 40 percent of ED visits in 2016 that involved non-medical use of oxycodone-containing products required admission, hospitalization, or transfer. Nearly 20,000 ED visits with non-medical use of oxycodone-containing products involved patients experiencing serious adverse outcomes such as cardiac arrest or respiratory failure. Over the period of 2010 to 2015, over 30,000 deaths involved oxycodone.

Here, we highlight some key limitations of

the data sources we used, but these are described in more detail in the background information provided. NSDUH is affected by biases typical of most surveys, including recall response or social desirability bias. NPDS under-captures serious outcomes and may not provide a reliable picture of trends.

For the RADARS and NAVIPPRO systems, data on routes or patterns of abuse may not be nationally representative. This is a specialized population that's entering treatment. Additionally, product misclassification can occur as patients are identifying these products themselves through the surveys.

NEISS-CADES doesn't include cases that result in death before or during ED evaluation. This is certainly a limitation. There's also the potential for misclassification of products, which is done at the practitioner level. NEISS-CADSES also only includes acute opioid harms resulting in ED visit. It doesn't include visits for opioid withdrawal, seeking treatment, detox, or inadequate

therapy, so it's sort of an underestimate of the true burden of morbidity. NVSS-M and DIM rely on the literal texts of the death certificate and are likely to miss the cases of drug-involved deaths where the drug is not listed on the certificate.

In conclusion, oxycodone-containing products are frequently dispensed in the U.S. with oxycodone ER products representing the majority of the ADF market. Oxycodone-containing products are the most frequently misused and abused prescription opioid products per population with high levels of abuse possibly driven by the wide utilization in the general population.

Products intended to deter abuse such as reformulated oxycodone ER are commonly abused by several routes, though most commonly oral followed by snorting and injection. And finally, despite the growing popularity of illicit opioids, oxycodone-containing products continue to be involved with high morbidity and mortality in the U.S.

Thank you. I want to acknowledge the other

members of the FDA review team who've all contributed substantially to the content presented today.

FDA Presentation - Lisa Wiltrout

DR. WILTROUT: Good morning. My name is Lisa Wiltrout. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. I'm going to provide you with a high-level, multidisciplinary review of the REMOXY ER new drug application. I will address the following in my presentation today, the aspirational goals for abuse deterrent opioid formulations, also known as ADFs; the current reality with ADFs; a brief summary of the clinical trial data and what data pertaining to abuse deterrence show; and lastly, FDA's approach to the evaluation of excipient safety with ADFs and what this means for REMOXY ER.

The goals for a successful ADF are twofold, consistent and effective delivery of an opioid dose when the ADF is used as labeled and either an expectation of or achievement of a reduction in

abuse by making the ADF more difficult to abuse by one or more relevant routes.

Goals are nice, but let's look at where we are today with ADFs. We know that ADFs are not abuse proof and do not prevent addiction. The FDA has approved 10 opioid analgesic products that are labeled with abuse-deterrent properties in accordance with the FDA guidance entitled, Abuse Deterrent Opioids: Evaluation and Labeling Guidance for Industry. Abuse-deterrent labeling is based on data from premarket studies. There are three categories of premarket studies, category 1, which are in vitro; category 2, which are pharmacokinetic; and category 3, which are clinical abuse-potential studies.

Abuse-deterrent labeling is located in section 9.2 of the prescribing information. All approved ADFs have postmarketing requirements to conduct additional category 4 studies. As stated in the FDA guidance, the goal of postmarket studies is to determine whether the marketing of a product with abuse-deterrence properties results in

meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting.

Published studies evaluating ADFs in the post-approval setting exists, however, to date, no postmarket data have been submitted to the FDA that support a meaningful effect of ADFs on reductions in abuse and misuse in the community.

The applicant has met the evidentiary standards for a reformulated opioid analgesic. The applicant used the 505(b)(2) pathway referencing Roxicodone, which is an immediate-release oxycodone-containing drug product. We required the applicant to conduct one adequate and well-controlled phase 3 clinical trial to support the efficacy of REMOXY ER given the change in dosing interval from every 4 to 6 hours for an immediate-release product to twice a day for an extended-release product.

Study PTI-821-CO, described earlier by the applicant, was conducted under special protocol and provided substantial evidence of efficacy for the

proposed indication. We required additional clinical data to support the safety of REMOXY ER given that it is a reformulation of oxycodone. The applicant conducted a second phase 3 clinical trial, study PTI-821-CM, to support the long-term safety of REMOXY ER. In the available clinical trial data, REMOXY ER has an adverse event profile typical of an extended-release opioid.

Now, I will summarize the abuse-deterrence findings with REMOXY ER by route of abuse. As discussed earlier by Dr. Tolliver, the oral human abuse potential study fails to demonstrate an effect on abuse deterrence. Additionally, in vitro data demonstrate that oxycodone, suitable for oral abuse, can be extracted from REMOXY ER using manipulation method RM10 in study conditions solvent S1, volume D, and temperature F.

As discussed earlier by the applicant, the intranasal human abuse potential study meets current standards for intranasal abuse-deterrent labeling. Subjects in this study experience less drug liking and less willingness to take drug again

with REMOXY ER than with the immediate-release comparator under the conditions tested. Based on an analysis of available epidemiological and in vitro data, we do not consider smoking a relevant route of abuse for oxycodone.

As I will discuss in more detail on the following slide, category 1 studies conducted by the FDA lab generated results that were different than those presented by the applicant. The clinical implications of these results are concerning. The FDA lab performed a set of manipulations and extractions using the same conditions as those described by the applicant to replicate some of the applicant's category 1 data. In the next two slides, I will summarize the most relevant results.

The table presented here shows that up to 72 percent of oxycodone content was extracted from REMOXY ER with no pretreatment using manipulation method RM11 in study conditions solvent S20, volume b, time H. A relatively simple process yielded as much as 15 milligrams of oxycodone. And

the table on this slide shows that more oxycodone content, up to 83 percent, was extracted from REMOXY ER with pretreatment C and temperature G, again using manipulation method RM11 in study conditions solvent S20, volume B, and time H. A slightly more involved process that is not beyond the scope of an experienced IV drug user yielded as much as 29 milligrams of oxycodone that was syringeable.

We recognize that there are limitations to category 1 studies. There are many variables at play, and the methodology used in these studies is not standardized. Nevertheless, the take-home message is that fairly basic manipulation and extraction methods generated high yields of oxycodone suitable for injection. Moreover, these manipulation and extraction methods are presumed to be readily available in the community.

The implications of the FDA lab findings are clear. Oxycodone suitable for IV use can be extracted from REMOXY ER. The amount of extracted oxycodone and the extraction volume may lead to

sharing among IV drug users. Given what happened with Opana ER, other important public health consequences are to be expected.

The previous slides show some troubling data from the limited perspective of oxycodone available for injection following extraction. Drawing on our experience with Opana ER, it is necessary to discuss the unintended consequences of excipients when manipulated and administered by an unintended route. We routinely require an adequate assessment of excipient safety for the intended route or routes of administration.

We have a guidance entitled FDA Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients. Prior to certain key events, we did not require any assessment of excipient safety for oral drug products being abused by the IV route or other unintended routes.

ADF opioid development and use has presented a learning experience for both FDA and industry. Postmarket experience with ADFs has yielded some

unanticipated outcomes when ADFs are abused by unintended routes. Based on the available data, parallels can be drawn between Opana ER and REMOXY ER. Opana ER, much like REMOXY ER, showed some abuse deterrence by the nasal route.

In the case of Opana ER, data suggest that persons abusing the drug shifted from one route of abuse, nasal, to another more dangerous route of abuse, injection. This shift from non-parenteral to parenteral use of Opana ER was consequential. Some IV drug users experienced thrombotic microangiopathy with IV use of manipulated Opana ER, which an investigation showed was due to injection of the PEO excipient. Additionally, the method used for preparation of Opana ER for injection resulted in a solution that could be shared. We saw an increase in transmission of blood-borne diseases, HIV and hepatitis C, in IV drug users who were sharing manipulated Opana ER.

Not all of the parallels between Opana ER and what we currently know about REMOXY ER are directly related to the excipients. However, given

the thrombotic microangiopathy and PEO experience with Opana ER, the FDA is now much more interested in understanding the potential risks associated with IV exposure and exposure by other unintended route to excipients in oral drug products.

We require sponsors to submit a safety assessment of the potential adverse effects associated with abuse of the final drug product. The safety assessment is needed to determine the complete risk-benefit profile of the drug, and we included potential excipient related adverse effects from abuse of ADFs in section 9.2 of the label.

The applicant has already provided a review of their approach to assessing excipients safety with potential IV abuse of REMOXY ER. We note the following limitations of the applicant's safety assessment. The applicant only looked for known REMOXY ER excipients and the expected degradants. The extraction conditions employed were basic typical forms of manipulation.

The IV abuse simulation conditions that

yielded the largest amount of extracted oxycodone, termed the worst case IV abuse simulation conditions by the applicant, were not employed in the excipient safety assessment. Therefore, excipient safety utilizing the conditions most likely to be replicated by a person seeking to manipulate REMOXY ER, extract oxycodone, and inject it remains unknown. It is also important to remember for all ADFs, that we cannot predict everything that could happen with the drug product once it is marketed. Case in point is Opana ER.

In summary, the applicant's data support the safety and efficacy of REMOXY ER as an extended-release, long-acting opioid analgesic for the proposed indication. The applicant's abuse-deterrence data for REMOXY ER meet current standards for abuse-deterrent labeling by the nasal route. However, the abuse-deterrence data do not meet the current standards for abuse-deterrent labeling by the oral route. We generally do not consider smoking a relevant route of abuse for oxycodone based on an analysis of available

epidemiological and in vitro data.

Results of category 1 studies conducted by the FDA lab demonstrate that oxycodone suitable for IV use can be extracted from REMOXY ER under certain conditions. Given this information about REMOXY ER's vulnerability to manipulation and abuse by the IV route under specific conditions, the applicant safety assessment of excipient risks from abuse of the final drug product is incomplete. Thank you.

Clarifying Questions

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

DR. GOUDRA: Dr. Goudra from pain medicine. Maybe this question was answered by Dr. Lisa Wiltrout. How common and how relevant is drug manipulation used as insufflation or inhalational purposes? Is it really that big of a problem in the country?

DR. WILTROUT: I'm sorry. Could you repeat the question for me?

DR. GOUDRA: Yes. How relevant is the problem of drug manipulation for the purposes of nasal insufflation or inhalation, or smoking or nasal use?

DR. WILTROUT: I'll defer that to Dr. Hertz.

DR. STAFFA: This is Judy Staffa. I think in Dr. Mundkur's presentation, you saw that it was around 30-ish percent of how people are abusing this, that they would have to manipulate it in order to then be able to snort it.

DR. GOUDRA: I guess my question was slightly different.

DR. STAFFA: Okay. Then we're not understanding it. My apologies.

DR. GOUDRA: In terms of the number deaths that have occurred in the USA, so 19,000 or something, how common have people used the drugs in alternate route? Was it, say, overdosing by oral, or intravenous, or something like that?

DR. STAFFA: Thank you for clarifying your

question. Those kinds of data are not easily obtained.

DR. GOUDRA: Okay. Thank you.

Sorry. In fact, I have another question. In terms of the REMOXY data that's presented, is there anything anybody can do or take -- I'm not mentioning the excipients, which are already there. Can somebody manipulate the pH in the stomach or intestine by taking something else to influence the drug absorption and increase the pharmacodynamic availability?

DR. HERTZ: This is Sharon Hertz. We only have data on methods that were described during the closed session. Other standard evaluations include food effect, so we do have data on that. We didn't present because we don't always present things that don't raise questions. So we didn't have a concern that, for instance in this case, the food effect altered absorption in a meaningful way. But we don't have anything else other than what you saw this morning.

DR. McCANN: Dr. Zeltzer, please?

DR. ZELTZER: Thank you. Lonnie Zeltzer, UCLA. So one of the issues in terms of differences between FDA findings and the pharmaceutical company's findings have to do with certainly risks for manipulation for IV administration, with all the downstream potential consequences of making a drug -- another drug entering the market able to go the IV route. And the company's data talked about the complications because of viscosity and other characteristics that made it so difficult for IV administration.

I don't know who to ask to sort of explain some of the differences.

DR. HERTZ: This is Sharon Hertz. I'll start. When we do the in vitro studies to evaluate the ability to manipulate for the purpose of intravenous abuse, there are a series of different types of manipulation. We ask for the most direct approach of getting drug into syringe, and those are the syringeability or injectability studies. And those are the studies that were described by the sponsor, where they just couldn't do that,

based on the nature of the material.

Then we look at small-volume extraction. Within the in vitro manipulations, we do a variety of things because, as the sponsor said, we ask them to keep pushing until they defeat the product. It's not a surprise that all products have some ability to be defeated because if you couldn't get the drug out of them, well, what good are they? So it's a progressive approach to see how far one needs to go.

The trouble is the data available -- and I'll use our quotes. "The data available on manipulation is not a static text." What we know is that -- well, we learned a lot of this with Opana, is that individuals who have a particular product available to them will do what they can to attempt to defeat that product. So what happened with Opana was surprising, the methods that were used, the combination of conditions, the results that differed by location. So it's not even as if one can assume the same methods to get the drug out will be the same across the country.

So we have laid out in guidance, and through discussions with the agency, we asked for a variety of things. The sponsor conducted them. And then the difference, the big difference is that even using some of the same categories, the same types of manipulations, our lab yielded more. And like I had mentioned, this is a phenomenon that we know about.

With chemistry method standardization is quite important because there are a large number of variables that can impact the outcome. And part of the reason why our labs do studies is to understand the formulations better, as well as to see how the results compare.

So that's really where the difference is. It's not the injectability or syringeability, but the ability to extract the oxycodone from the product using a variety of conditions that you heard about this morning.

DR. McCANN: Ms. Griffin? Dr. Griffin? Sorry.

DR. GRIFFIN: Marie Griffin. I'm wondering

if you could take that one step further. So if you can extract it, then should there be injectability studies of that extracted material, or is that possible to do further studies?

DR. HERTZ: Traditionally once extracted, it's going to be in a liquid form, so we don't usually have concerns about the viscosity. Now, it may have a lot of nasty material accompanying the oxycodone, which is why we've been adding these evaluations of what comes out, again, having been finding out about problems with other products along the way. So it's been a learning experience for us, for industry, as more and more products are evaluated, and then we see what actually happens.

We can't possibly anticipate all the conditions that will be attempted by the community seeking to abuse these products by different methods. We ask for a lot, but there are limitations. So the idea behind it, if we take a few steps back, these products are trying to deter so that if somebody decides they want to abuse it,

there are obstacles in their way for readily manipulating the product to do what ER products can do, which is dose dump under certain conditions readily; so starting from no resistance and then how much can these attempts be forced to escalate in effort and sophistication.

DR. McCANN: So we're fortunate that the real chairman of this committee, Raeford Brown, I understand is online and wants to communicate with the group. So I would ask him to introduce himself, and then make his comments.

(No response.)

DR. McCANN: Maybe he's not online. Right? All right. We're going to go to our next person, Dr. Goudra.

DR. GOUDRA: Dr. Goudra from pain medicine. This question concerns the only study, which is PTI-082-10. I'm just curious to know why did you guys choose patients with osteoarthritis or [indiscernible] knee. It's I don't think a typical case where patients use opioids. Those patients have surgical options for these. And low back pain

probably is [indiscernible].

DR. McCANN: I think we're still doing FDA questions, Dr. Goudra.

DR. GOUDRA: Okay.

DR. McCANN: We're still at the FDA part. Sorry.

Are there any questions left for the FDA?

(No response.)

DR. McCANN: Then we will go on to the sponsor and Dr. Goudra's question.

DR. FRIEDMANN: There are a lot of pain models for acute pain, but not a lot of pain models for chronic pain. Normally you use either low-back pain or osteoarthritis? At the time we did the study, these were the classical models. That's why we used one of them.

DR. McCANN: I had a question for the sponsor. Mary Ellen McCann. My question was -- and maybe this gets to what Sharon was saying a little bit earlier. But in my experience as a pediatric anesthesiologist trying to get med sedatives into young children that have neither and

IV or unwilling to swallow a medication, we often give these medicines sublingually or intranasally but not snorting. When I first looked at this medication, my inclination was if I had a medication that was like super thick Vaseline, why don't I just put it on my finger and smear into my buccal mucosa and see what happens.

Did anybody at your company try that?

DR. FRIEDMANN: Somebody in the company tried the placebo into their nose. But as you have seen, we have done the nasal study, and you don't get the blood levels. So why would you want to do that?

DR. McCANN: But the nasal study was trying to basically make it into particulate and then sort of blow it in --

DR. FRIEDMANN: No, no. There were two. One was manipulated REMOXY and one was REMOXY intact, and neither one provided any significant levels.

DR. McCANN: Thank you.

So our next question is Dr. Brent.

DR. BRENT: Thank you Jeffrey Brent here. I have a question for Dr. Friedmann, and it is about your phase 3 efficacy study. Just so we fully understand the design of the study, were your patients who had chronic osteoarthritic knee pain using opioids before they were enrolled in the study?

DR. FRIEDMANN: Yes, they were.

DR. BRENT: And they were then withdrawn from their opioids, the washout period.

DR. FRIEDMANN: That is correct.

DR. BRENT: So basically all the patients had to go through a period of opioid withdrawal before being put on --

DR. FRIEDMANN: No. That isn't correct. Not all patients were on opioids before they started this study. Some were opioid naive. So the starting dose of the study for those that were naive was the 5 milligrams.

DR. BRENT: Right.

DR. FRIEDMANN: Patients who were at the higher dose initially, they were given equivalent

dose of oxycodone.

DR. BRENT: Equivalent dose.

DR. FRIEDMANN: Yes.

DR. BRENT: So the study population was a mixed population of opioid-dependent and opioid-naive patients?

DR. FRIEDMANN: That is correct.

DR. BRENT: Okay. And then when they went through the protocol, you then went through a tapering period at the end of the study?

DR. FRIEDMANN: Yes.

DR. BRENT: What percentage of the patients during that time went through withdrawal?

DR. FRIEDMANN: I do not have this. I don't think very many. The withdrawal period was based on the presumed dose -- since it was blinded, we don't know what dose they were, so we way to assume those a particular dose that they were on. And based on that, the number of days they were withdrawn varied. But I do not recall many people in withdrawal.

DR. BRENT: So you had people that were

receiving -- what was the maximum dose that was given? Was it the 40-milligram dose?

DR. FRIEDMANN: Yes.

DR. BRENT: Right. So you had people that were given the 40-milligram dose for 12 weeks, and then when you stopped it, you say you don't believe they had withdrawal?

DR. FRIEDMANN: No. They were tapered down over 2 weeks blindly.

DR. BRENT: Right. Okay. Yes.

DR. FRIEDMANN: So if they were on 40, they went to 30, to 50, and I forget the exact numbers, then to 5.

DR. BRENT: Okay. And you don't think they withdrawal symptoms?

DR. FRIEDMANN: I don't recall any.

DR. BRENT: Okay. Thank you.

DR. McCANN: Dr. Hertig?

DR. HERTIG: John Hertig, Purdue University. My question is for Dr. Marsman related to the postmarketing safety initiatives. One of the initiatives mentioned is drug disposal, and as many

of us know, still the biggest route of abuse is oral, especially with diverted medications. So drug disposal becomes a really important issue.

Can you talk to me just a little bit about what the plan drug disposal program is and how it may work with current disposal technologies that are available that are designed to sequester medications?

DR. MARSMAN: Yes. We're still in the process of exploring that. We're starting to talk to distributors and third-party vendors to try to -- and this is a discussion that also goes on with some members of the REMS consortium as well, to try to find the best mechanism to do this. I don't have details to give you now because we're in a preliminary research of looking at this.

DR. HERTIG: Thank you.

DR. McCANN: Dr. Terman?

DR. TERMAN: Sure. It sounds like most of the questions I had have been asked. I will clarify, the irritant smoking, that's theoretical, right? There's no data from the company.

DR. FRIEDMANN: That's correct.

DR. TERMAN: The phase 3 was very interesting to me. Did you look at any of the outcome measures except at the end? Did you look at them after randomization, for instance, to see whether there were differences between groups?

DR. FRIEDMANN: In terms of what?

DR. TERMAN: Pain, function. Were there any differences before -- when you randomized and before you started to taper the placebo, were there any differences between the groups at that state?

DR. FRIEDMANN: Before we randomized, there were no differences because that's how we randomized them. We randomize not only -- by pain scores twice at the beginning of the study and then at the randomization. So when we randomized, the high pain scores were randomized into one group and the low pain scores were into one group. So that's the best we could do on the randomization.

DR. TERMAN: But that doesn't really answer the question of when you finished randomizing, whether there were differences between the groups.

I mean, yes, higher.

DR. FRIEDMANN: I don't think we looked into it.

DR. TERMAN: Okay. The other question of course would be what happened to the pain scores or function in the people that you tapered down? That would be useful information as well, but you didn't look at that.

DR. FRIEDMANN: No, it was not done.

DR. TERMAN: So mostly all of those outcome measures were at the very end of the studies.

DR. FRIEDMANN: You're right, at the end of the study. That's correct.

DR. TERMAN: Okay. And I'm not sure whether FDA or you would be best to ask this question. Do you know whether OxyContin has been looked at in terms of the 5-minute chewing sort of approach? It wasn't in the OxyContin information that was given to us. A study like that wasn't done as far as I can tell.

DR. FRIEDMANN: I do not know that -- would you like to answer that

DR. HERTZ: This is Sharon Hertz. We took all that to advisory committee a long time ago, and there were chewing studies and there were other studies for oral route of abuse, and they did not succeed in getting a labeling claim. So the studies were not able to meet the criteria for success from an oral deterrent effect.

DR. TERMAN: Okay. So hard to know how that would look in comparison to the chewing failure here as far as I'm concerned, so failure --

DR. FRIEDMANN: Well, I don't think it's a failure on REMOXY because if you look at the blood level, on REMOXY, it was 65.9 nanograms per mL. Xtampza intact is over 62 nanograms per mL. So REMOXY chewed compared to Xtampza intact, it's about the same level.

I think the failure in that study was the failure of the immediate release. The immediate release was 75 nanograms per mL. This is one of the lowest numbers that I have seen in many studies that I reviewed on immediate release. Xtampza, when they presented to the committee, study number

17, the IR was 116 nanograms per mL. If we had 80 nanograms, we would have been significantly different than they the IR.

DR. TERMAN: Okay. But it certainly appears on page 48 that there was a significant difference. I don't know how clinically significant, but in terms of your chewed and unchewed product --

DR. FRIEDMANN: Clearly.

DR. TERMAN: -- there was a very big difference.

DR. FRIEDMANN: No question, yes.

DR. TERMAN: And that can cause some concerns if that's the way abuse is taking place.

One last question. Apart from the smaller dose, which is a difference from other products on the market, what would you say is the benefit? Apart from the abuse deterrent issue, what would you say is the advantage of this product?

DR. FRIEDMANN: Oxycodone is oxycodone, so it's going to be better. It's really the formulation. We presented category 1 data much better -- that REMOXY performed much better than

the immediate release, or OxyContin, Xtampza, that can be defeated very quickly at 80 or 95 percent. The FDA presented data on REMOXY, but they did not present data on the comparator on the same conditions. So it's hard for us to judge what really happened in that regard.

DR. McCANN: I understand Dr. Raeford Brown is now on the line. We'll give him a second try.

DR. FRIEDMANN: Wait. I didn't finish. I didn't finish the question.

So the formulation is one thing. The other thing is the PK data. REMOXY PK data is very different -- we have a slide for that if you'd like to see it. It's very different. The PK and the steady-state kinetics are very different for REMOXY than the other products.

The steady-state state kinetics for REMOXY is 66 nanogram per mL. The steady-state kinetics for Xtampza and OxyContin is 76. The minimum effect for both of them is around 20 nanogram per mL. For REMOXY it's 25. So they've peak to trough fluctuation is about 50 percent different; not

quite, but just about 50 percent between REMOXY and the other two products.

DR. TERMAN: Okay. Thank you.

DR. McCANN: I think we're done with that question.

DR. FRIEDMANN: Okay.

DR. McCANN: We're going to go on and give Dr. Brown a third try.

DR. BROWN: Hi. This is Rae Brown, and I am a professor of anesthesiology and pediatrics at the University of Kentucky. This has been a very interesting conversation, and I have question for the FDA. And it relates to the formulation of REMOXY relative to the agents that were tested by the sponsor but not tested by the FDA. The medical officers presented some very good data that suggested that all oxycodone formulations are problematic, and one wonders whether or not this directs us to look more closely at the safety of oxycodone on the market.

DR. HERTZ: This is Sharon Hertz.

DR. BROWN: That question is for the FDA.

DR. HERTZ: Hi Rae. This is Sharon Hertz. I didn't quite catch the full question. I believe you referenced the in vitro data that we had, and what is the question based on that?

DR. BROWN: The medical officers presented data about the relative risk of having oxycodone in general on the market, whether it be in any ADF formulation. So my question is, does the FDA feel like there is sufficient evidence to warrant putting another ADF oxycodone on the market?

DR. HERTZ: I believe the question is -- just to sort of paraphrase and make sure that I've got this right -- we presented -- this was actually our epidemiology group, presented data on the current availability of oxycodone products on the market, including the ADF products, and are there data to support putting another ADF on the market or this ADF on the market?

Was your question specific to this or in general?

DR. BROWN: Well, it's really a question in general, but since we're talking about this ADF,

it's an opportunity to raise the question.

DR. HERTZ: Okay. I'm not going to answer the specific question because that's what we're going to ask you guys to vote on. But in terms of general, if we ask the question, how many versions of a product are appropriate to be on the market, I would say the answer is as many as meet adequate criteria for marketing.

We don't have a limit on how many abuse-deterrent formulations of a particular drug substance should be marketed at any one time. So going back something I mentioned in my introductory comments, there is concern that the approval of new products might expand the market, might expand the use of opioids. And it's sort of a subtext kind of question in terms of how many ADFs should be on the market of any given product.

This was published in Anesthesiology. Was it 2017 or 2018? 2017, and we can put the citation somewhere for folks to get.

(Crosstalk.)

DR. HERTZ: Oh, there you go. It's in our

backgrounder. So the availability of opioid analgesics is not currently limited by the products available. The amount on the market is based on the number of prescriptions being filled. So with new approvals, what we found was the number of approvals, both innovator and generic -- and there are many more generic approvals than innovators. If you look at that over time and then you look at the number of prescriptions over time, they intersect, meaning the -- well, of course, depending on scale. But they have opposite slopes.

The number of new products, new innovators, new generics, is rising, is increasing. The number of opioid prescriptions is decreasing over that same time period. So we don't limit the number of a given kind of drug. What we try to do is create a standard for them. And then if products start to exhibit differences in efficacy or safety, we look at that in the context of public health, relative risk, that sort of thing, which of course are all very difficult to measure or quantitate.

DR. BROWN: Sharon, I appreciate that.

However, this is not a single variable issue, and the problem with the paper that you presented to us in the backgrounder is that it appears to presume that this is a single variable issue, and that is that the only variable is the increase in the number of ADFs on the market and the decrease in the number of prescriptions. I won't push this any further, but I think it's food for thought in your deliberations after this meeting.

DR. HERTZ: This is Sharon Hertz. Thank you for that. Rae. I'm sure we'll have some conversations about that.

DR. McCANN: With that, we have three or four more comments, but I'm afraid of bumping into the open public hearing. So we're going to adjourn for lunch and get to the comments after the open public hearing.

I would like to say we will reconvene here at 1:30 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst

yourself, with the press, or with any other members of the audience. Thank you.

(Whereupon, at 12:42 p.m., a lunch recess was taken.)

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

(12:42 p.m.)

Open Public Hearing

DR. McCANN: We're going to begin the open public hearing session.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

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

to advise the committee if you do not have any such financial relationships. 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 on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only one recognized by the chairperson. Thank you for your cooperation.

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 on behalf of the National Center for Health Research. I am Dr. Megan Polanin. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from industry, so I have no conflicts of interest.

We strongly support the FDA's efforts to encourage the development of opioid analgesics that deter abuse. As with any other drug, the FDA evaluates these opioids should be held to a high standard for approval to maximize the probability that the risk of abuse is actually lower than it would be without properties designed to deter abuse.

We all know that oxycodone is one of the most highly abused opioids. For example, from 2012 to 2016 calls to poison control centers indicated that intentional abuse of oxycodone was only surpassed by heroin. RADARS and NAVIPPRO databases both found that oxycodone was the second most

highly abused opioid. In addition, oxycodone was the second most commonly reported abused drug among patients entering treatment for opioid-use disorder.

With this context in mind, please consider these two questions as you evaluate REMOXY's patient and public health benefit-risk ratio. Has the sponsor shown that REMOXY has properties that will deter abuse by oral, nasal, and intravenous routes of administration? If REMOXY can prevent abuse through all three known routes of abuse, that would be a very positive step for preventing further misuse and abuse and initiate a higher standard for abuse deterrent drugs.

That is not the case with this drug. Category 1 studies showed that REMOXY's physical properties successfully deterred abuse via injection, snorting, and smoking. Human potential abuse studies indicated that REMOXY might deter intranasal abuse. For example, when compared with oxycodone IR, REMOXY was more difficult to use intranasally and less likable for abusers.

However, we're concerned that results from the oral human abuse potential study showed that chewed REMOXY did not deter abuse compared with crushed oxycodone IR tablets for half of the primary endpoints. And as the FDA stated, the significant findings may not be clinically relevant. In addition, the FDA's category 1 studies showed that oxycodone can in fact be extracted from REMOXY. Finally, excipient risks have not yet been adequately tested.

It is well known that abusers of the drug can be very creative in finding unique ways to overcome deterrence. Because oxycodone is a highly abused drug, we are concerned that this drug could still be abused orally and intravenously.

Finally, we want to point out that REMOXY was compared with oxycodone and oxycodone IR drug and not compared with current abuse-deterrent oxycodone ER/LA products on the market. What are the potential unintended harms of REMOXY in the real world? We know that patients continue to abuse ER/LA oxycodone with abuse-deterrent

formulations and that oxycodone ER tablets are particularly vulnerable for abuse.

In the laboratory setting, REMOXY appears to meet the FDA's current standards for determining intranasal and intravenous abuse. Whether its abuse-deterrent properties are effective in the real world is a much more difficult question that will require postmarketing data. We know from previous experience that so-called abuse-deterrent opioids are sometimes abused more widely than current laboratory studies suggest. Opana ER is one example.

To reduce the opioid epidemic, the FDA must hold pharmaceutical companies to a high and truthful standard. REMOXY did not meet the FDA standards for oral abuse, and it may be able to be abused intravenously. The safety of the excipient is also in question. Please carefully consider the risks of putting another drug with abuse-deterrent labeling on the market that could result in misuse and abuse in the real world. We urge this advisory committee to vote that the

benefits of this drug do not outweigh its potential risks. Thank you for the opportunity to share our perspective.

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

MR. THOMPSON: Good afternoon. I'm Edwin Thompson, president of Pharmaceutical Manufacturing Research Services. For full disclosure, I have submitted all supporting documents from this presentation to the FDA docket. They are publicly available.

2016 and 2017 are the first two consecutive years, since the flu epidemic in 1925, that life expectancy in the United States has declined, driven by the opioid epidemic. The opioid epidemic is an iatrogenic and preventable. But the FDA's solutions offered do not identify or address the root cause.

The United States opioid epidemic is in its 23rd consecutive year with an increasing number of

deaths each year. The root cause of the opioid epidemic is the illegal FDA approval of opioids for the treatment of chronic pain. FDA is asking this committee for a recommendation on your approvability of REMOXY. You're being asked to continue to fuel this epidemic. The answer is unquestionably no. Your individual vote and committee recommendation will tell us if you're the clean-up committee or the cover-up committee.

REMOXY has been submitted as a 505(b)(2) product, relying on the data submitted in the 1995 OxyContin FDA approval. Your vote today will either affirm or reject the OxyContin data.

This slide is the FDA cover sheet for the integrated summary of efficacy for OxyContin, completed in June 1995 by Dr. Curtis Wright and reviewed by Dr. Douglas Kramer. There were 6 double-blind studies, only 2 of which are placebo controlled. The FDA approved OxyContin on a single one study, adequate and well-controlled study 1102.

Study 1102 is a 10-milligram, 20-milligram, and placebo-controlled study in osteoarthritis for

14 days. The FDA conclusion, quotes, "This double-blind, parallel group, dose-response study provides substantial evidence of the short-term analgesic efficacy of controlled-release oxycodone 20 milligram in patients with this chronic pain model."

Also in Dr. Wright's review, he states, quote, "Oxycodone 20 milligrams separated from placebo within a week with an effect size of about 0.4 or 0.6 or two-thirds SD." The 10 milligram was not effective -- not effective -- but provided information as a half-dose control. This data is not adequate by itself to support an OA indication, but is a very helpful trial in a non-oncologic chronic pain model.

This is the single adequate and well-controlled trial, study, identified by the FDA to approve OxyContin. This is an osteoarthritis study that the FDA stated is not adequate by itself to support an OA indication.

Let me say this again. One of the 2 doses used, the 10 milligram, was not effective, and the

20-milligram dose provided substantial evidence of the short-term analgesic efficacy. The 40-milligram dose was not studied. The FDA knew OxyContin should not be approved, but they approved OxyContin 10 milligram, 20 milligram, and 40 milligram.

Let me show you how I know the FDA knew the approval of OxyContin was wrong; wrong. By 2000, the FDA reported on OxyContin abuse in the opioid epidemic. These are FDA slides. The FDA knew that OxyContin should not have been approved, and the FDA was at a crossroads. Revoke the approval of OxyContin or cover up the approval.

This slide is the FDA minutes from a July 14, 2001 meeting between the FDA, this division, and Purdue. Dr. McCormick is the director of this division. Let me quote and read the minutes. Dr. McCormick stated that the labeling -- started -- "began the labeling discussion by expressing the agency's concern about the clinical trials section. The trials currently in the label are pain models in artificial settings

with regard to the appropriate use of the product. The agency's position is that neither the osteoarthritis --" that's the 1102 study used to approve this drug -- "nor the single-dose postoperative pain study provide adequate data for a claim in the label."

How can you approve a drug if you don't have adequate data for the label?

"The studies as they were performed and described in the label are in contradiction to the indications we have inserted in the label. The sponsor believes that since the studies are placebo-controlled, they should be allowed to be remaining. Dr. McCormick stated that the studies must show separation of the study drug from placebo in the intended population and that the studies, which enroll patients based solely on their disease state rather than their pain status, and their use of, and the failure of other non-opioid medications, send a misleading message regarding the appropriate use of this drug."

Surprised we have an epidemic? There is no

question that OxyContin should have been revoked in 2001. OxyContin should have been revoked in 2001. Instead of revoking OxyContin, FDA decided. without any additional clinical data, not one additional data submission, to change the label. They restricted the clinical trial section to the single adequate and well-controlled trial 1102.

Remember that when you vote today. Remember, this is trial 1102, a 14-day trial in osteoarthritis, comparing 10, 20 milligram, and placebo. Again, in the FDA's own words, "The 10 milligram failed. The 20 milligram provided substantial evidence of the short-term analgesic effect. And the 40 milligram was not studied. The OA study is not adequate to support an OA indication."

On this single efficacy study, the FDA has proceeded to approve 10, 15, 20, 30, 40, 60, 80, and at one time 160-milligram tablets of OxyContin. This is illegal, and somebody needs to be held accountable. The FDA's response to the opioid epidemic was to change the indication to management

of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. There is no clinical evidence to support that indication or the approval of OxyContin.

The opioid epidemic begins in 1995 with the FDA approval of OxyContin, and you have a decision today. You can become the clean-up committee or continue to be the cover-up committee. Thank you.

DR. McCANN: Would speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. KOLODNY: My name is Dr. Andrew Kolodny. I'm the co-director of the Opioid Policy Research Collaborative at Brandeis University, and I'm the director of Physicians for Responsible Opioid Prescribing. I have no financial relationships to disclose.

There's been a fair amount of discussion today about abuse-deterrent formulations. I'd like to call your attention to what I believe is a more

important issue, and it's an item you'll be voting on at the end of the day, which is the efficacy of REMOXY. It's not just my opinion that this is an important topic that you should be asking yourselves, have I been presented with substantial evidence of efficacy for the intended population; it's not my opinion that this is something you really need to seriously consider. It's the law. It's what the law says, the law on adequate and well-controlled studies for new drug applications.

And it says, quote, "Adequate and well-controlled investigations provide the primary basis for determining if there is substantial evidence to support the claims of effectiveness." So what information have you been presented with to make that determination?

I'd like to point your attention to page 58 of the briefing document that you received, and I'd like you to look at the area that's highlighted. What you'll see is the highlighted sentence is referring to safety and efficacy on the basis of bioequivalence to Roxicodone. FDA is suggesting

that based on bioequivalence to Roxicodone, there's reason to believe that there's safety and efficacy.

That's a strange sentence because, by definition, an extended-release opioid is not bioequivalent to an immediate-release opioid. But putting the bioequivalence question aside, I think this would sort of make you wonder what happened in the Roxicodone NDA, what was the study that was done to demonstrate efficacy of Roxicodone.

So if you look at the Roxicodone new drug application and the medical review for it, what you would find out is that Roxane Laboratories was not required to produce an efficacy trial. Roxane Laboratories was given permission to bridge to Percodan, which is a combination product with two active ingredients that was on the market before FDA required efficacy studies. So there was no efficacy trial done for Roxicodone.

This is the next sentence in the briefing document. It refers to just one study that was done to provide information about efficacy. This is the Lynn Webster study. This is a poster for

that study, and this study was presented to you earlier today. I want to draw your attention -- this is a chart in that study. And I'd like to just describe this study in a little bit of detail.

The study enrolled 558 patients with moderate to severe osteoarthritis of the hip or knee. That is not the intended population for this drug. The label for this drug, the intended population, is quote, "Pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate."

That's not who the drug was studied, and showing that a drug is efficacious for patients with moderate to severe osteoarthritis pain is not the same as showing it's efficacious for patients with severe pain who have failed all other options. But it really gets worse if you look at the methodology that was used in this study. Some people call it enriched enrollment, randomized withdrawal. I think a better term for this type of

methodology is cooking the books.

The patients enrolled began by taking REMOXY titrated to 20 milligrams BID. That's equal to 60 milligrams morphine per day, and they took that for 2 weeks. By the end of the 2 weeks, 146 patients who didn't tolerate REMOXY, or didn't get adequate pain relief, or violated protocols were removed. That left 412 patients, the enriched sample. It was those 412 patients that were then randomized to either stay on REMOXY and be titrated up or to be switched over to placebo.

Anybody with clinical experience prescribing opioids would recognize immediately that there's a real problem here because if you take patients who are on 60 milligrams of morphine a day, and over 2 weeks taper them down to placebo, the patients will experience worsening pain. Complaints of pain, pain hypersensitivity, and patients being withdrawn from opioids is extremely common.

Tapering people over 2 weeks is rapid. The clinical recommendations from CDC and other organizations are to taper patients by 10 percent

each week. Some recommend 10 percent a month. These are patients who should have been tapered off of 60 MME over several weeks or several months, not over 2 weeks. One would expect that these patients would have significant pain.

It's very difficult to describe this as a double-blind trial because the patients who were switched over to placebo after taking a strong opioid for 2 weeks to be given the sugar pill, the patients would probably know it, any of them. And these study clinicians would probably know it because those patients would be experiencing withdrawal symptoms. So this was also not a true double-blind study.

So in summary, the NDA for REMOXY does not include an efficacy trial in the intended population, not one. The only efficacy trial included in the NDA was performed on patients who are not the intended population, moderate to severe osteoarthritis pain. The only efficacy trial included in the NDA was not adequate and well controlled, which is required by the law.

If this is something that sounds strange to you, that FDA would move in this direction, you're in good company. At the request of Commissioner Califf, the previous FDA Commissioner, the National Academy of Sciences issued a report where they urged FDA to overhaul its opioid policies, particularly the way that it's approving new opioids.

Commissioner Gottlieb immediately endorsed the report. A year later, though, we've seen very little action, which has led to frustration, particularly among the National Academy of Science's panel members who have written a letter to the docket available to you to read, expressing concern about approval of opioids for chronic pain when we lack evidence of benefit, yet have significant evidence of harm.

A federal review has found the same. Fortunately, Purdue Pharma announced in February that it would cease promoting OxyContin for chronic pain. This is good news because despite recent declines in oxycodone prescribing, we are still

massively overprescribing. This is how we compare to oxycodone prescribing in Europe. The United States is blue. Europe is red.

Here's what the picture looks like today. You can see this is all opioids, and you see the prescribing really took off -- [microphone turned off].

DR. McCANN: Would speaker number 4 please come to the podium?

MS. HOLTUM: name is Lexi Reed Holtum. I am the executive director of the Steve Rummler Hope Network. I'm sharing my time today with Michael Daub, and I don't have any financial disclosures. I have 4 minutes to tell you the kind of destruction that this kind of pill does on the market, and I can't imagine -- and let me say thank you to all of you for giving me the time today. And I can't imagine that all of you who don't know someone that this has impacted the way in which our country has had its prescribing practices for opioids for the last 20 years. So I'm going to try and be really succinct, but I'm telling you, it's

impossible for me to tell you the story of Steve Rummler in 3 minutes.

Steve suffered an injury to his back in 1996, and in 2005, he was prescribed time-released opioids. That started his journey into hell. He literally lost his life because he was prescribed opioids. In the beginning, he felt like it was a lifeline because somebody believed him that he was suffering with chronic pain, and they treated him. Very quickly after that, he became addicted. And in 2011, rather than planning our wedding, I ended up planning his funeral.

The namesake of our foundation is not alone in the journey that he walked. He was prescribed opioids to treat his pain. His doctor was taught that that was the right thing to do, and it killed him. And he like hundreds of thousands of Americans -- you know, as I listen today to the things that are being said, and I listen to the questions that you really intelligent people asked, one of the things that I walk away with is that the question could not be answered, what happened to

those patients that were in the study? What happened to those individuals afterwards? Did anyone follow up to see were they seeking opioids in some other form or fashion? Because that's what's happening across our country, is people are being prescribed into addiction, and 4 out of 5 individuals that overdose and die from heroin started with prescription pain pills.

I beg of you, please do not -- do not approve any more opioids to market. We are working hard to clean up the problems that impact every social economic class in our country today, not just the individual, but the people that are left behind. We cannot afford to have another opioid go to market that has not been adequately, scientifically tested and proven that the benefits outweigh the risks.

I thank you for your time today. I'm happy to answer any other questions. And I just really appreciate the time to share. And please, we have to stop doing harm before we can create solutions. We are in a country that has a shorter life

expectancy because of our prescribing practices. And it is literally the definition of insanity to keep doing it the same way and expect different results. Thank you.

DR. DAUB: Good afternoon. My name is Michael Daub. I'm on the board of directors of the Steve Rummler Hope Network, founded in the aftermath of the death of our namesake in 2011. We're from Minnesota. Our efforts led to the passage of what's called Steve's Law, which gave first responders the ability to carry naloxone on emergency calls and protect individuals who call 911 from criminal prosecution. We're advocates of legislation to hold big pharma accountable. We provide overdose training throughout the state of Minnesota and offer prescriber education to the medical profession.

Almost 20 years ago, I became involved in a community of people who had recovered from substance-use disorders. I began mentoring men and women seeking to recover. I began volunteering at facilities, treating these people, and began trying

to help them overcome substance-use disorders. All of my efforts have been on a voluntary altruistic basis. I have no financial stake in any of this business.

I've been on the front lines. We call it being close to the flame. I need your help on your end. I believe I speak here today for people all across America who are lost, who feel that the deck is stacked against them. I also believe I speak for all of those who have suffered and are continuing to suffer. We've experienced an outpouring of support from our community simply because they know we're here today to speak up and to carry this message.

When I was a kid, I remember being in a grocery store. Over the loud speaker, the manager announced, "Clean up in aisle 3. Bring them up." The drug companies have made billions of dollars. They've made slick presentations. We're the people that are cleaning up the mess, and they fight us every step of the way. We tried to get some legislation passed this year, and they hired teams

of lobbyists to oppose our legislative efforts. They make enormous contributions to political campaigns. They pay tribute to lawyers by the truckloads to defend lawsuits brought by the hundreds, by governmental entities trying to recover monies that it's cost the taxpayers, again, to clean up the mess they created. It's a juggernaut. They need to be stopped. Someone, something needs to stand in the way.

The opioid epidemic is engulfing the United States. I've watched with great pleasure recovery successes, but I've observed far too many people fail, succumbing to addiction again and again. Barely a week goes by where I don't get a call that someone's died of an overdose, sometimes two, sometimes three.

I had a discussion the other day with a OB-GYN doctor about neonates, and how the neonates end up in ICU. These are our sons. These are our daughters. These are our friends. These our neighbors. These are our co-workers, good people failed by a pernicious, unforgiving, relentless

malady. It annihilates all things worthwhile in life. It engulfs all whose lives touched the sufferers. It brings misunderstanding, fierce resentment, financial insecurity, disgusted friends and employers, more lives of blameless children. Children without parents is a big issue the last few weeks. We can tell you all about children whose parents have died.

Americans everywhere are affected. Communities are overrun by despair. Suicide is more prevalent than ever before. I've read the National Academy of Science's report, which is quoted in one of the letters that you've received. Years ago, I remember watching the movie, Thank You for Smoking, and they called the lobbyists the merchants of death.

Well, why do I feel that life is imitating art? These people are pariahs. They've pulled the wool over your eyes time and time and again. They're a bunch of liars, thieves, and scoundrels dressed up in business suits. They've stolen the soul and dignity of billions of millions of

Americans. They've decimated family values. They've robbed the economy of billions of dollars of productivity. They have cost counties, cities, and states billions of dollars. Trying to regulate them and do business with them is like trying to herd cats. Please forgive me. I'm a cat lover. They shake your hand, and at the same time, the knife you in the back. They've been fined millions of dollars, but they keep moving forward.

I've read a little bit lately about this constitutional claim that they can disseminate health claims about their product without first submitting their claims to the FDA. They are challenging your authority is how I look at it. That's how far they've pushed the FDA and the American people, and thousands of people have died as a result. I can't believe we're sitting here having a conversation where there's been collateral damage that's cost 200,000 or more lives. We went to war because 3,000 people died back on 9-11. So what are we going to do about 200,000 people? Is that just a drop in the bucket?

I can't talk on the level of the experts. I'm not a doctor. I can't deal with it from a technical level. But I have this other memory as a kid. What did they teach us in the third grade? In 1937, Congress passed the Food, Drug, and Cosmetic Act in response to the death of 107 people who died from an ingestion of an adulterated elixir. The defining moment of the FDA occurred in the case of thalidomide, thanks to the perceptiveness and determination of a single new reviewer at the FDA, Dr. Frances Kelly [sic - Kelsey]. The drug was denied approval.

So I ask you this. Thalidomide was kept off the market, and American people were protected. What would Dr. Kelly [sic] do today? Thank you.

DR. McCANN: Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WOLFE: I'm Sid Wolfe, Public Citizen health research group. I have no financial conflict of interest. I will briefly go over the

first couple of slides because the points have been made by the FDA previously. The first, the main point is that between 2010 and 2015, there were a total of 32,000-plus deaths associated with oxycodone, and the number per year really stayed the same. And this was stated by FDA correctly as a reason to think about as we consider another opioid being approved, whether there may be some net harm as opposed to any net benefit.

The next slide, again from the epidemiology presentation, simply pointing out, and I think everyone knows, that oral abuse is the most common form of abuse leading to treatment, deaths, and so forth. And within that, ER/LA oxycodone makes up about a good chunk of these, and 60 percent are with abuse-deterrent properties, so-called -- and again, the FDA has said there has never been a study submitted, really, based on good epidemiologic evidence showing that abuse deterrence works.

This to me was the most striking slide or piece of information in the whole briefing package

back last Friday, and it really shows the bottom line is intact REMOXY, and the middle Line is chewed REMOXY. And I can't think of any easier way of misusing or abusing -- as it may turn out to be, starting out with misuse -- and turning an ER, long-acting product into an instant one.

Essentially what happens here is that it takes 4 or some hours for the intact one to reach its maximum, whereas the chewed one is less than a half an hour, maybe 20, 25 minutes. I didn't do the exact calculations. So the slope, the rapidity of increased blood concentrations and relief from pain and so forth, is infinitely higher with the chewed version. Chewing something is not a big deal. You extract it with your mouth. There was a question asks about transmucosal absorption. I'm sure that once you chew it, some of it gets in that way; some of it gets in through the stomach.

The next slide is just a little more detail on this, and I would like to focus on the bottom line, the area under the curve. And what you can see is that translated into English at an hour is

about 8 times more chewed REMOXY getting into the body than the unchewed. And because the last slide is linear, this actually starts out right at the beginning. So with even 10, 20, 30 minutes, you already are getting much more, about 8 times more, into your body with the chewed one than with the intact one.

These are just briefly some of the findings from the oral abuse study, particularly before 501-016. I mentioned before that the maximum concentration for REMOXY, unchewed and so forth, is at 4 hours -- it occurs at 30 minutes with the chewed version. And then in another study, there's a threefold increase in the concentration of REMOXY when it was chewed as opposed to not being chewed.

This one is simply talking about -- it's middle bar -- chewed REMOXY 40 has a statistically significantly larger -- meaning Emax, and these are liking measures -- than intact REMOXY. And the FDA's conclusion, stated I think mildly, in the briefing package was, "The earlier Tmax," time of maximum concentration, "and the high relative of

bioavailability compared with the intact indicate that the proposed product may not deter oral abuse by chewing."

This is the question, and this is not asked in this kind of way at all in the briefing package. But the question is, does the United States need another oxycodone product? Dr. Hertz correctly said that if a product, whether it is the 4th or 5th or 10th, meets the FDA criteria, having one more needs to be acceptable, I suppose. But these are data from the most recent report from the U.N. International Narcotics Control Board, the narcotics drug report. It comes out annually. It came out about six or seven months ago.

"Consumption of oxycodone was concentrated in the United States where 72.9 percent of the world total was. Global consumption was 79.6 tons, meaning 58 tons of oxycodone were consumed in the United States that year." How much is this? And I just did some sort of simple calculations.

Fifty-eight tons is 58,000 metric tons or

58,000 kilograms, which is 58 billion milligrams. And since the accepted dose, which is about 2 of the extended-release REMOXYs, is 75 milligrams, according to the U.N.'s calculations, this means that there are 773 million daily doses of oxycodone in the United States, which is by far the world leader in oxycodone consumption. In fact, it's the world leader in total opioid consumptions also.

If you look at all of the other countries, all but 6 of the 166 other countries that are measured by the U.N. have less than one-quarter the amount of population adjusted opioid as the United States does.

So on to the discussion questions, oral route of administration. And the question is, has it been expected to deter abuse? It will likely increase this predominant form of abuse, increase, and misuse also -- because you might say that when a doctor gives out a prescription for this drug, and says please don't chew it because if you do, more will be released, you'll get sooner relief from your pain and so forth. I mean, this kind of

conversation is really unacceptable, which is why this drug I think is unacceptable.

So the answer is it will not deter abuse. It will likely increase misuse and abuse, and thus it's abuse or misuse enhancing, not deterring. I had not seen, until today, the FDA's look at the IV abuse and pointing out that it really cannot be said to be IV resistant, IV abuse resistant.

Finally, the last question is, do we have concerns regarding the impact on the public health? Yes. For reasons stated by the FDA and discussed today, impact on increased oral abuse is very likely if not certain. And finally, should it be approved? No. Since neither your committees, nor the FDA, want to further increase U.S. oxycodone abuse, a likely if not certain outcome of REMOXY is approved.

The idea that there are no alternative -- [microphone turned off].

Clarifying Questions (continued)

DR. McCANN: Thank you. That concludes the open public hearing portion of this meeting, and we

will no longer take comments from the audience. What we'd like to do right now is finish up with the comments for the questions for the sponsors, and I believe we have at least four questions. So we'll start off with Dr. Zeltzer.

DR. ZELTZER: This question, I'm not sure whether it's for Pain Therapeutics or really for you, Sharon. If we think about unintended consequences, we can almost assume that even though there is not an indication should this get FDA approval for use in children, adolescents will likely access and use the drug, misuse the drug, abuse the drug.

I guess in terms of even safety -- I mean, let alone all the other issues, but safety data -- given that the studies were done in adults -- and I guess the closest -- while pharmacodynamics and pharmacokinetics are different in children than in adults -- they're not just little adults -- the closest thing you would have, at least in the HIV population tested, are smaller body weights, at least for some of the population.

Was there any data looking at body mass index in outcomes just in terms of the basic safety of the product, let alone all of the other parameters? Again, I'm thinking of more basic safety questions given that if this is given -- if this is out on the market and given FDA approval for the indications requested, it will be used by adolescents, who are different.

So I don't know. -- they're really probably several questions within that.

DR. HERTZ: This is Sharon Hertz. I'm not quite sure what the final question is.

DR. ZELTZER: So the final question for Pain Therapeutics is, are there, I guess, adverse events and SAE data, just to get to this point, in smaller, significantly less than 50-kilogram adults, given that you only looked at adults? And using the HIV population, there might be at least enough of a subcohort that might be more pediatric size even though there are a whole lot of differences; so just as a basic risk factor, let alone the risks of the different components that

are in there.

So that's probably one question, and then maybe address that, and then, Sharon, I can ask the FDA question.

DR. FRIEDMANN: This product is not intended for children. We collected BMI data, but we have not analyzed to look at outcome versus BMI data. We probably can discuss it with the FDA if they need it.

DR. ZELTZER: So, Sharon, the broader question?

DR. HERTZ: Every NDA is required to have a pediatric plan, a pediatric study plan, by the time -- well, certainly by the time they file an NDA, and there are other time criteria within there. Deciding which products should be studied in children and when to study them is always challenging, particularly when it comes to an opioid.

To that end, we've had some discussion of this at two advisory committee meetings. We introduced the concept at a meeting of the

Pediatric Advisory Committee and followed that up with an advisory committee meeting specifically dedicated to the evaluation of opioid analgesics in children.

Children need pain management as much as other age groups. Early-life exposure to pain can have long-term effects. Children have needs for analgesics that are different than adults, particularly when it comes to chronic pain conditions. So yes, opioids need to be available, but as mention, we also heard during that same advisory committee -- it was a very elegant talk by a clinician whose name I cannot bring to mind immediately, but who described the effects of exposure of the adolescent brain to substances that may have abuse potential, opioids included. And that creates a variety of risks and potential downstream problems.

So then the question is, when should an adolescent even be treated with an opioid? And the answer may be much more infrequently than currently occurs. So when to study an opioid in a child,

it's challenging. With the abuse-deterrent opioids, some of the limitations are based on formulation and being able to achieve dosages that are appropriate for smaller bodies, for weight-based dosing. A number of them have failed. Also, is there a chronic pain population for whom they're even appropriate?

So have I kind of covered the issue? I'm sort of skirting whether or not this product should specifically be studied. There are a series of questions that have to be answered by the applicant with regard meeting their requirements for pediatric studies that everybody has. We take all of those pediatric study plans to the pediatric research committee and discuss them there.

I can tell you that we have been constantly monitoring the outcome of one of the more recent pediatric approvals for OxyContin. That data so far have actually shown that in contrast to concerns expressed, prescribing of OxyContin has decreased in children not increased. That might be, in part, because of a number of factors

completely unrelated to the action, as well as narrowing the indication for pediatric patients for that drug beyond what had already been the standard of practice.

So that's what I have to say.

DR. ZELTZER: Thank you. I just felt like we needed to have that piece of it discussed. Thanks.

DR. McCANN: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. A question for Pain Therapeutics. I'm not sure to whom directly to address. What was the effect on fertility that you found in your study? You had a study on fertility.

DR. FRIEDMANN: In animals.

MS. ROBOTTI: Sure. What was the effect?

DR. MONTGOMERY: Well, there hasn't been any [inaudible - off mic.]

DR. McCANN: Use the microphone, please.

DR. MONTGOMERY: As far as we know, there's been no effects on fertility or reproduction for these excipients, because that's all we're really

talking about.

MS. ROBOTTI: For the excipients, not for the opioid itself.

DR. MONTGOMERY: No. We haven't done any studies ourselves on the opioid.

MS. ROBOTTI: You didn't study that at all?

DR. MONTGOMERY: No.

MS. ROBOTTI: And did you bring your pregnancy and lactation label? Can you show us that?

DR. MONTGOMERY: I'm sorry?

MS. ROBOTTI: The pregnancy and lactation label, did you bring that? Can we see that?

DR. MONTGOMERY: No.

DR. HERTZ: This is Sharon Hertz. I'm going to introduce Dr. Dan Mellon. He's our supervisory pharmacologist/toxicologist and has done a fair amount of work in this area, and has also supervised the review of this application in the nonclinical work.

Dan, can you just give an overview of the nonclinical data, and in particular some of the

data regarding repro-tox?

DR. MELLON: Sure. Again, this is Dan Mellon, a pharm-tox supervisor in DAAAP. This program is relying upon an agency previous finding for another product. And as a result from the opioid perspective, the product will be labeled identically to the product that is currently marketed.

In that program, they had what's referred to as segment 1 and segment 2 studies that were completed in rats and rabbits. The studies are designed to try to understand the impact of the opioid during organogenesis. There were also, if I'm not mistaken, some fertility studies that were done.

The effects are pretty much what you see for most opioids. There is always a little bit of a signal on some fertility endpoints with opioids at higher doses in animals. The translation of that into the clinical setting is still a very complex issue and is not entirely clear. But the product will be labeled identically to the reference

product with respect to that.

The primary tox program here that was put together was with respect to several novel excipients that were being utilized for this particular formulation. And when we reviewed the overall tox program for this, we felt that we had all of the information that was necessary to appropriately evaluate the safety of the excipients.

And just for your own edification, any time a new novel excipient is being utilized and proposed for a drug product, they actually are required to do all of the exact same studies that you would do with a new molecular entity. So we evaluated that program, and we believe that we have adequate safety margins for the intended route, and even for an opioid-tolerant individual.

MS. ROBOTTI: Just to follow up, so a pregnant woman would be able to get clear direction from her doctor, obstetrician; or a woman who's planning on being pregnant, she could get clear direction from her doctor about using an opioid.

There's information that's useful and appropriate.

DR. HERTZ: There is information that describes the nonclinical findings. There is some information that describes some of the clinical concerns. There are warnings about neonatal opioid withdrawal syndrome. Those are in the opioid labels. Whether or not a woman who is pregnant should be managed on opioids is a huge question; opioids for pain. Let's be very specific, because opioids for management of addiction is a very different risk-benefit.

So that discussion should take place in the context of what is the woman's situation with regard to pain, what other alternatives are available, and knowing that there will be some concerns about risk, how does that individual balance the risk with the concern for pain management.

MS. ROBOTTI: And my point would be that this is a large population, a recurring new population every year, that doesn't really have clear direction on it. And I mean when prescribed

and used appropriately. I'm not talking about an abuse or misuse situation. And I know that the directions in REMS says that the bar should be raised every higher; that simply because a REMS solution was appropriate five years doesn't mean that we shouldn't hold a new applicant to a higher standard.

So I would suggest that going forward, we should be getting information on all populations who use this drug: seniors, pregnant women, and anyone else is a subpopulation.

DR. McCANN: In the interest of time, we're just going to take the last three questions that were submitted before; not people who are coming up with new questions. I apologize, but I don't want people to miss their transportation home.

So we have Dr. Prisinzano, please.

DR. PRISINZANO: Tom Prisinzano, University of Kansas. I guess my question is for the sponsor, probably most appropriately, Dr. Crowley. So can you give me your perspective on the differences that we see between the studies that you presented

versus the studies that the FDA had approved in terms of the amount of compound that's extracted?

DR. CROWLEY: So the question is commentary on the differences between the work done at our third-party labs and what the FDA found in theirs. We have not had an opportunity to speak with the agency to see how they did do their studies. In looking at one of the tables, it was performed at a different temperature, a higher temperature, than the highest temperature that we did.

We stand by our data. It was performed at two different laboratories that have done category 1 studies before. The FDA data is real data. There are going to be differences. I suspect that there were some differences between the way in which ours were done and the way in which the FDA did do theirs.

DR. PRISINZANO: Thank you.

DR. McCANN: Ms. Spotila?

MS. SPOTILA: Jennifer Spotila. It's a question for PTI. I just want to get some final clarification on phase 3 and the study cohort. You

were asked about age. I think you said over 40. You were asked about gender. You said male/female, but you didn't give us a breakdown.

What about co-morbid medical conditions and other medications, and especially in the subjects who were on the open-label trial for 6 and 12 months? Can you give us a characterization of those?

DR. FRIEDMANN: Not offhand. All the information is NDA. Patients were on multiple drugs. There were no drug interactions. They are, I would guess, 50 to 100 different products that they were on. We did not see any issues.

MS. SPOTILA: And co-morbid medical conditions?

DR. FRIEDMANN: I don't recall issues.

DR. McCANN: Dr. Hertig?

DR. HERTIG: John Hertig, Purdue University. Just a practical scenario question. So say a patient is prescribed this. If approved, they have trouble or difficulty swallowing, so they good intentionally cut open or otherwise get into the

capsule, and then scrape out the inside and put that on applesauce or whatever modality. What do you expect in that situation that the patient would experience in terms of drug effect and any adverse outcome?

DR. FRIEDMANN: I do not expect an issue. As I mentioned earlier -- and you can put one of the slides -- the Cmax that you get with REMOXY chewed is the same Cmax that you're going to get with Xtampza intact. So from a safety point of view, I don't see an issue. Okay?

First of all, if they take it from the capsule, you're going to lose a lot of material. They won't be able to get a hundred percent of the capsule out, as Dr. Crowley said. You're probably going to lose 10 to 25 percent. Beyond that, we have not done the study, so I cannot tell you what to expect, but I don't believe there are going to be issues.

DR. HERTIG: Thank you.

DR. McCANN: So that concludes our questions to the sponsor. The committee will now turn its

attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

So Dr. Sharon Hertz will now provide us with a charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: Do opioid analgesics work? Do they work for chronic pain? Do enriched randomized withdrawal designs demonstrate efficacy? Yes, to all of them. We have data. We have data for all of them. We have clinical studies in which patients who have been managed on opioids for months and years go into a randomized withdrawal treatment study design, and then after 12 more weeks, we can show that compared to the group not on the active agent, there's efficacy.

They work. This whole debate about absence of evidence being evidence of absence has really gone entirely too far, and patients are currently being harmed as a result of a complete breakdown in scientific thinking and data application when it comes to this topic.

The question isn't do opioids work and can they treat chronic pain when we're talking about public health. Who is the intended population for opioids? That's one of the important questions for public health. Why do we have an opioid epidemic? Why do we in this country use 90 percent, or whatever the figure is, of the world's opioid analgesics? Why are so many prescribed in the U.S.? Why is there no opioid crisis in Europe? They have the exact same drugs approved. The same drugs are marketed. So do we want to blame the drugs? There's got to be something else.

Who's responsible for the opioid crisis? Sponsors? Distributors? Prescribers? Pharmacists? Patients? Who's responsible? I don't think there's one targets. Are we responsible? There's no one target.

Maybe the question we should be asking is, what is the appropriate management of chronic pain and how can we deliver that to patients? I don't think anybody in this room would argue that simply prescribing an opioid analgesic in the absence of a

comprehensive pain management treatment plan is appropriate, adequate management for chronic pain.

So what is appropriate management for chronic pain? Is it accessible to the patients who need it in this country? What is available to patients in this country?

There's an AHRQ technical brief from 2011. It's technical brief number 8, Multidisciplinary Pain Programs for Chronic Non-Cancer Pain. I recommend everybody read this. It's a very important and interesting review on the status of this evidence- based approach to managing chronic pain in the country as of 2011, and there's no reason to think it's gotten any better. And I'm going to give you a few quotes from this article, and then I'm going to get us back on track to the questions at hand.

These are quotes from the article. Some of them are re-quotes from sources, but I'm not going to identify all of these right now.

"The goal of chronic pain treatment has evolved from eliminating pain to managing pain to

an extent that patients' physical and emotional functioning is restored and overall quality of life improved. This is the model of care provided by the Multidisciplinary Pain Program. There is no single protocol for treatment in MPPs. There is general agreement on some included methods."

One of the findings of this report was that there's been a decline in the number of MPPS in the United States, and in parentheses, "the number in other countries may actually be growing." There are dichotomies that have been identified in this report from some of the contributing sources that have held the MPP back from being the recognized standard care in the United States; its disciplinary collaboration in MPPs versus discipline segmented organization of major medical centers; and collaborative care in MPPs versus the fee-for-service model of health care payments.

"Rehabilitative treatment in MPPs focused on individual assessment and patient behavior change versus the curative medical model of treatment. In each of these dichotomies, the MPP model runs

counter to the prevailing architecture of American healthcare, financing, and provision. According to the experts consulted, the treatments most likely to be carved out from MPP are physical therapy and psychological behavioral therapy."

This goes on for a very um, important and detailed discussion. And one final quote, "Paradoxically, the efficiency of carve outs," referring to approaches to paying for pain management therapy -- "paradoxically produce the effect of steering patients away from multidisciplinary treatments that demonstrably reduce healthcare utilization toward more extensive unimodal therapies associated with poor outcomes."

So getting back to the subject of today's advisory committee and moving away from the question of whether this drug's approval or non-approval is a specific answer to the opioid crisis, you've heard the presentations from the company, from us, about clinical data and about these different assessments of abuse-deterrent properties. You've heard about some of the

differences in our findings based on lab work.

During the discussion of the questions, you're free to comment on anything that has come up during the meeting, any of the data provided as it influences your decision and your approach to answering the questions including anything that we may not have ever. So I say let's go on and get directly to the questions, and go from there.

Questions to the Committee and Discussion

DR. McCANN: Thank you. We will now proceed with the questions to the committee and 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 I'll read the first question. Please discuss whether the applicant has demonstrated that REMOXY extended-release, oxycodone extended-release capsules, has properties that can be expected to deter abuse, commenting on each of the following routes of abuse: A, oral; B, nasal; C,

intravenous.

If there are no questions or comments concerning the wording or the question, we will now open the question to discussion. Dr. Meisel?

DR. MEISEL: Steve Meisel with Fairview. Yes. I think one of the challenges for today, and frankly for all of the drugs that are in the pipeline and have been in the pipeline and that are in this class, is the definition of the phrase "expected to deter abuse."

I think it's been well stated at the beginning of today that abuse deterrence is not abuse. It's not 100 percent. It's not a black or white. And what does the term "deter" mean? Is it 1 percent less likely to be abused than the reference product. And what is the reference product? Is the reference product OxyContin? I don't think that's always clear. Or is it the rapid-release products?

"Can be expected" is a term that is, in my view, softer than the term "proven to deter abuse." There's been evidence from the applicant that for

all three of these, that there is a reasonable expectation that compared to some of the reference products, it might be less likely to be abused. Is it hard evidence that it will be less likely to be abused, by what quantity? I have no idea. That hasn't been proven for this. It hasn't been proven for, to my knowledge, any of the products out there.

So it seems to me that if we say no to this and then deny this application, then it's incumbent upon the agency to go back and perhaps rethink its approach to this entire topic, because the guidance document that's been put together about abuse deterrence and so forth is really geared to encourage manufacturers to create products like we have seen today. And if we don't believe that that's enough, then maybe nothing is enough. And then maybe the whole concept of abuse deterrence is a concept that's inherently flawed, and we should move on to something else.

But in terms of this specific question, has it been expected to deter -- do the

properties -- are those properties that can be expected to deter abuse for oral, nasal, and intravenous? Yes, there is evidence for that. There's some contravening evidence that the agency has as well, but there is some reasonable evidence that it can deter abuse. Whether it will, I have no idea. And my guess is, if it does, it'd be very little.

DR. McCANN: Dr. Nelson?

DR. NELSON: Well, I would say that they've not demonstrated the ability to prevent abuse in any of these three realms, and I'll go through each one real quickly.

The oral data is the most clear because chewing the tablet or the pill produces blood levels that are close to that from the immediate-release formulation. And while they're lower than they would be from an intact pill, they're still substantially elevated, which to me means that it hasn't done anything to deter abuse.

What the blood level is that's required to make something abusable is unclear. But if you

assume that the intact pill is the ceiling, this one is substantially higher than that, and it's almost as high as the immediate release, which we think is abuse prone. So to me, oral is a non-starter. There's no evidence to show that.

The intranasal use I think is a little bit more questionably beneficial, but I don't think it actually supports a benefit because you can still get a substantial amount of drug out of the pill. And we see that by the blood levels in the patients -- or not the patients, but the subjects who were getting the medication administered to them intranasally. They were getting blood levels somewhere about 20 nanograms per milliliter, which is about the same level you get them a 10-milligram oral oxycodone tablet, immediate release.

So while it does reduce the amount of drug you can get into your body through that route, it's still very well absorbed and administered. And since there's no limit to the number of pills you can abuse, taking one pill gets you to 20; taking 5 pills gets you a 100. It doesn't really seem

like it would deter abuse unless we limited the amount of pills anybody could have to 1, which we're not going to be able to do.

So I think while it might slow down the ability to abuse it, which is why I say that there might be some argument that there is some benefit relative to the levels that you'd otherwise get, I think it's pretty clear that it will not deter abuse because people can use more than a single pill.

The intravenous data I think is very confusing given the different findings of the two groups. I don't know what to make of it. I'm very concerned about -- as has been mentioned in several places -- the historical problems with injecting incipients [sic - excipients] that we don't understand. So while it might maybe deter abuse, the consequences might be much more far-reaching than even that.

So short answer to a long question or a long answer to a short question, I would say we've not seen any evidence for any of these.

DR. McCANN: Dr. Brent?

DR. BRENT: Thank you. Jeffrey Brent. There's a there's a narrow question and there's a broad question here, implicit within this discussion a question. And I'm not sure we're going to be able to address the broad one today, but I think it's one that we really need to take into consideration when we look at abuse-deterrent formulations.

Abuse-deterrent formulations is a great idea. They have lots of sort of intuitive benefit, and I know FDA feels strongly about them. But like every great idea, there can always be the unintended consequences. And certainly what we have learned from the OxyContin story is that abuse-deterrent formulations can accelerate transition to intravenous illicit opioids, specifically heroin.

There's very good data that a significant amount of this explosion that we are experiencing right now in heroin use and heroin contaminated with synthetics like fentanyl and fentanyl

derivatives, really derives directly from OxyContin becoming a so-called abuse deterrent formulation, so people could no longer use it intravenously and then had to turn to these other routes.

So there is this sort of broad issue about the wisdom of moving forward with yet another abuse-deterrent formulation, realizing that while it might be a good idea, it is also likely to contribute to the growth of intravenous heroin abuse.

In terms of the more narrow question of the demonstration of the abuse deterrence of this particular preparation, I'd have to agree with Dr. Nelson that it's probably not very abuse deterrent via the oral route. And I realize they're not asking for a label, that as it is, so that's not a concern. And there may be some abuse deterrent from nasal use, and we're not really going to concern ourselves with smoking. And then, of course, we do have the problem of the insufficiently characterized excipients that may play a role in intravenous use.

So I do have some concerns about approval with regard to these considerations.

DR. McCANN: Thank you. Dr. Brown I believe is on the line.

DR. BROWN: Thanks, Mary Ellen. I have some significant concerns. and I in general agree completely with the last two speakers. And I disagree with much that has been said. The problems that we come up against as we evaluate these ADFs, and have evaluated them in the past, has been that prescribing is very easy, and comprehensive care is not very easy, and it's expensive.

Why are we worse than the people in Europe? Well, opioids are marketed much more aggressively in the United States than in Europe. There's a problem with the method that we have used to suggest that oxycodone is efficacious, and that's been demonstrated today.

So the issue that we can't answer, that Dr. Hertz suggested was a non-starter, is whether or not chronic administration of opioids is a

reasonable thing to do in a broad population of patients. It could be and is a reasonable thing to do in very carefully selected patients, but we have to be judged against protecting the entire population, and that is one of the problems that we see as we try to understand these drugs.

We've been down this road before. We know from the last 10 ADFs that we've evaluated that they can all be manipulated. In many cases they are being manipulated while we're having advisory committee meetings. The importance of this discussion is the consideration of the entire group. What are we doing here? How did we get here? And as the gentleman before me said, whether we should rethink the concept before we move [indiscernible].

DR. McCANN: Thank you. Ms. Spotila?

MS. SPOTILA: Jennifer Spotila. I don't think we took time to thank everyone for their comments, both here in person and in the docket. There were some personal stories in the docket that I hope everyone had a chance to read. And I want

to thank you. As a fellow person with chronic pain, it's hard to talk about your personal situation in public, so I appreciate everyone who spoke up.

I think something that we've missed today is the voices of people affected on both sides of this issue. There are really two simultaneous public health crises, the opioid abuse crisis and the pain management crisis. And I was actually really disturbed that PTI confined their information collection from abusers to internet forums.

Why don't you bring people in who have used these drugs recreationally? Why don't you talk to them? Why doesn't FDA talked to them? Ask them, how you use this drug? Have them look at it. Especially when you have a novel formulation like we have here with a novel abuse deterrent property, how would you hack this? What would you try? If you lost 20 to 30 percent of the gel when you split it open, are you going to split open another one, and then what dose are you going to get? We didn't even get PK on that to see what that would do.

So I think that we really have to look at defeating abuse-deterrent properties as a puzzle that humans will solve if they are motivated enough to do so. We need to better understand that, so you can design your studies to really answer that question.

Then there's the flip side of people with chronic pain. Again, I was surprised that PTI said there were no other comparator groups, no other control groups or pain models besides osteoarthritis and back pain. I have neither, but I've been a chronic pain patient for 20 years. There are abundant models.

There are many kinds of pain. And we need to take that into consideration when we evaluate these studies as well, because this isn't going to be labeled, like others have said, for osteoarthritis. It's going to be labeled for severe pain from all sources.

What are the barriers to care? How do people who are on opioids use or misuse their drugs, and all of the access issues that come with

that? Outcomes. You asked a great question, Dr. Brent, about the outcomes. You should be taking outcomes throughout the study, after the study, after termination of the drug. I also was not persuaded by the statement that these subjects did not have withdrawal. They would have. That should have been detected in the studies as one of the signals.

Then there's the access to care issue. I've had chronic pain for 20 years. I've been in pain management for 15. I've been on opioids for 10, safely, and my healthcare has been criminalized to a certain extent, the barriers that I have to overcome simply to function with proper medication. And I'm lucky that I still have access to that.

So all of these factors have to play into the question of safety, efficacy, an abuse-deterrent potential labeling requirements, et cetera. It all matters.

DR. McCANN: Thank you. I think we're sort of bleeding into question 3, which we really haven't discussed yet, which is important to

discuss. But we'll just keep that in mind when we finish up with discussing question number 1.

Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF. So a couple of things, quickly. One, kudos to the FDA for pursuing a scientific evidence base to answer a very complex set of questions, both clinical, all the way to public health, and for including public health into the opioid dilemma.

Kudos to the sponsor for coming up with a clever product. I do have to say, though, just to bring in some discussion point around question 1, my research is in the real world. I spend a lot of time with folks that like to use opioids for pleasure as part of what I might clinically describe as opioid-use disorder. They use heroin, they use fentanyl, they use a whole variety of products.

I watch them prepare products. So when I see FDA data, category 1 study data, that says that this product is -- the oxycodone is extractable, it's very disappointing. And I know there's a

dilemma between what sponsor's data has brought in and your third-party studies, and what the FDA lab shows, but decoding, without saying anything about industry secrets, decoding what the solvents are, what the time is, what the temperature is, it's not outside of real world. It's not outside of what is possible in the real world to extract what will turn out to be 83 percent of the label claim or 29 milligrams of injectable oxycodone, which is a big dose if you inject it IV.

So those are my concerns, which in my mind starts to topple a claim of abuse deterrence in the intravenous category. Thank you.

DR. McCANN: Great. Awesome. Could we have a Dr. Nelson again, please?

DR. NELSON: Thanks. I had a quick question -- Lewis Nelson -- maybe for Dr. Hertz. Apropos to my comment before that less drug release doesn't necessarily equal less abuse, when the sponsor gets a label that states that they're going for a claim of less intranasal and intravenous abuse, but they're not asking for a label that

connotes less oral abuse, what does that actually mean when we put the drug out there? Because people are going to know that it's orally abusable. Right?

So I'm not sure I understand the implication of asking or not asking about label claim when we know that it's got oral abuse potential. Does that make sense?

DR. HERTZ: I don't know if we've prepared a section 9.2 to project for this meeting, but the conclusion for all products, regardless of the number of routes in which studies support relative deterrent effects, it still says the product remains abusable by the oral, nasal, and intravenous route. So does that complicate the question?

These are not abuse proof. Nobody has figured that out yet. And because they deliver an opioid as an analgesic, if you can't manipulate it at all, you can still just swallow one. So it's about providing information about the product's performance, and hopefully someday we'll have

sufficient information to see if they are worthwhile.

DR. NELSON: Yes. That answers my question. I guess what I'm sort of getting at is, in a way, by only giving two out of these three routes a label of, quote/unquote "safety," is that a wink and a nod to the fact that it's actually orally abusable if people kind of learn how to read through that? And if we believe the data, which I think is the most clear, that oral doesn't really have any abuse prevention -- the others might maybe, depending on how you want to look at it -- would we be comfortable releasing this with any sort of suggestion that it's abuse deterrent when we know that there's a big hole in that?

DR. HERTZ: These are the questions we'd like you to answer.

(Laughter.)

DR. McCANN: Dr. Shoben:

DR. SHOBEN: Yes. I just wanted to make two quick comments, I think. One is to say that I would agree with the comments that have been made

about the oral, that I don't think there's -- there's maybe a suggestion that it's possibly in the right direction, but it's certainly not anything that would rise to the level of abuse-deterrent properties via the oral route, based on the chewing studies.

I do want to make a pitch, I guess, on behalf of the sponsor, that I do think that their nasal data is convincing, that it is actually abuse deterrent from the nasal route, given sort of what we've done previously and the data that they have from the abuse potential studies showing lower drug liking, and take drug again, and things like that.

Intravenous data is much harder for me. The conflicting data between the sponsor's third party and the FDA makes it hard to know in the real world how quickly would abusers be able to defeat the properties, and then how much additional risk is there from the types of things we saw with Opana in terms of getting larger volumes of injectable solutions, and the kinds of things that might follow from that. But it is certainly not as easy

to abuse intravenously; that's just sort of a standard, like the old school, crush it up with a spoon and dissolve it in a little bit of water, and inject. So I'm sort of torn about the intravenous route.

DR. McCANN: Thank you. Thank you for getting back to the original question also. And we're going to go with Dr. Goudra.

DR. GOUDRA: Basavana Goudra, pain medicine, anesthesiologist. I think the questions are kind of twofold here, and many of you have kind of addressed it. One is kind of both philosophical and practical, but having worked in both Europe -- I worked in England and Ireland both and here -- it's kind of incorrect to compare the two.

Just to give an example, if you explain to a patient what I'm going to do in terms of anesthesia, patients will tell you, you are the doctor; do what's right. Such a thing doesn't happen here.

So in terms of patients' tolerance, and in terms of the whole issue of how they tolerate the

pain, how they approach the pain and the patient's expectations -- and even the physicians' approach is different, so I don't think we should be comparing both of them.

The second thing is, we're looking at I guess three things here. And the efficacy was to deter oral abuse, both nasal and intravenous. I don't think anybody's asking us to quantify the amount of data in terms of abuse. I am willing to accept that oral abuse may not be that much different, but in terms of nasal and intravenous, it is. And just going by that, I was looking over, and in at least one study, almost 19 persons, their admissions to the ER were because of nasal abuse of OxyContin. Even if it 15 person [indiscernible] detriment, for example, it is still very significant.

As it is, I think it's kind of mixed, but overall, I'm kind of willing to accept definitely it's a deterrent in terms of nasal and intravenous, and probably, to a certain extent, oral. In fact, the bigger concern is regarding its clinical

efficacy, whether we should be extrapolating the results coming from one study in patients with chronic pain in knee and hip to patients who have much more intense pain, common being the back ache. But I guess we cannot expect a company to do studies in every possible condition, every possible group.

As a result, I'm willing to go by whatever that's presented to me to make up my mind, as I stated. Thank you.

DR. McCANN: Dr. Arfken?

DR. ARFKEN: [Inaudible - off mic].

DR. McCANN: Oh, okay. Dr. Terman?

DR. TERMAN: Sure. My two cents is I think that they have shown that there is a deterrence of nasal abuse and intravenous abuse. Now, how much deterrence is always a question. It depends how hard people are willing to try. The oral is, clearly, they have not, in my opinion, shown deterrence. And I guarantee that there will never be a drug where there is complete deterrence since my patients need to extract that drug in their gut.

The phase 3 showed that there was so much extraction in some of the patients that they quit taking the drug because no one likes taking opiates because of all the side effects; that is, the vast majority of people don't like taking opiates because of the side effects.

I guess I would the FDA, this is not the first time that this drug has come before the FDA. According to the sponsor, at least once before, I think maybe twice, the concerns, deficiencies, were around commercial manufacturing, which I won't understand anyway, and nonclinical support, which it seems like I should understand, but I don't.

Can you tell me what nonclinical support means?

DR. HERTZ: The studies that Dr. Mellon described are the nonclinical support, in part, and then the additional work on the excipients, so all of that material.

DR. McCANN: Ms. Robotti?

MS. ROBOTTI: I'm going to hold most of my

comment for question 3, but I do want to just ask rhetorically, of what use is there to the doctor when told that the drug is abuse deterrent for nasal only? I'm not sure that that's useful information, unless you've got a patient who has a history of drug abuse, nasally only; then, here, try this drug. I don't quite get the usefulness of that.

DR. McCANN: Thank you. Dr. Zibbell?

DR. ZIBBELL: Hi. Jon Zibbell, RTI International. I'm going to save most of my comments for question 3 as well, but I did just want to express -- something like Dan, I actually do community-based research, and I work with a population of people who abuse these medications. And it's hard to conceptualize and separate one route of administration from the rest.

One of the things that we learn is that abuse happens on a continuum, and I would say 90 percent of the people I've spoken with over the course of 20 years, they start out orally abusing them and orally taking a medication, not chewing

it, just orally taking it.

The thing about opioids is you get an increase in tolerance, the more you use. People realize when you break that extended release, it's going to release more drug, and so people orally take it. And then they learned chewing it is going to release more of the medication, and then you're getting more of the rush so to speak. Then you get up a tolerance to that, and a lot of people transition to insufflation, smoking or sniffing, and then injecting.

My concern with the oral is the chewing, really, because it's going to release those opioids. We do know that higher doses are at higher risk for folks for addiction opioid use disorder, which can also lend itself then to trying nasal. If you're going to chew a drug, you're trying to get more of it. And kind of separating out different routes of abuse, if it doesn't tackle all those, I think it's just problematic for the real world.

It just brings me back the field work I did

in Scott county, Indiana, where people reported there that the OxyContin formulation, the reformulation, they were sniffers before that, and they could no longer sniff OxyContin anymore. And they found Opana, and they couldn't sniff Opana either, but they could inject it. And there were a lot of people that reported to me in the field that they were sniffers, and then with the OxyContin reformulation, they started to inject. So they transitioned through different routes of abuse due to the abuse deterrence.

So it's just hard for me. I just want to express that it's hard to parse out and take away one form of abuse when opioid-use disorder and addiction is along a continuum. People traverse these routes back and forth. I just wanted to make that comment.

DR. McCANN: And we're going to wrap up with Dr. Meisel, and then I'm going to try to summarize this discussion.

DR. MEISEL: I'll be brief. I just decided to do a little Google search on the definition of

the word "to deter". "Discourage someone from doing something typically by instilling doubt or fear of the consequences, and prevent the occurrence of." And I think it can be pretty clear that nothing we could do with a oxycodone product would deter abuse. If somebody's intent is to abuse it, they'll find a way.

DR. McCANN: All right. I'm going to try to attempt to summarize this. It strikes me that people answered this question both broadly and specifically. The broad concern was about the whole entire concept of abuse deterrence, which may refer back to question 3 to a certain extent.

People were concerned that successful abuse deterrence can possibly accelerate the transition to illicit drugs; that it's important to remember the voices of the affected people, both those that have the propensity for abuse and those who are suffering from chronic pain, and what the implications are of labeling a drug as non-oral abuse potential, whether that means that people would realize, well, this you can't inject this

drug maybe easily, you can't intranasally use it, but you sure can abuse it orally.

Dr. Meisel in particular has been our word parser, and he has expressed difficulties with the phrase "expected to deter abuse," what that exactly meant. He helped us out with the definition of abuse and pointed out that the reference materials used by the sponsor varied quite a bit. So to some degree, it was difficult to make adequate comparisons.

Then specifically, I think the consensus was that oral abuse potential was the greatest. There was the least evidence for deterrence in that route. Most people felt that this drug, the sponsor did demonstrate some nasal deterrence. And the discussion I think was fairly mixed about whether there's IV drug abuse potential. The FDA data was quite compelling for several of the people on the panel.

So that's how I summarize it, and I think if that's all right, we can go on maybe to our second question.

The second question as I read, or read it before, is fairly specific, and I think we may want to deal with the specifics of it. So question 2, please discuss whether there are sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label of REMOXY ER, commenting on support for abuse-deterrent effects for each of the following routes of abuse: A oral, B, nasal; C, intravenous.

DR. GRIFFIN: Marie Griffin. I'd say no, yes, no.

DR. McCANN: That was a very specific answer. That's what I asked for.

(Laughter.)

DR. McCANN: You get what you ask. Dr. Nelson?

DR. NELSON: My specific answer is no, no, no. It really is what I enunciated before, just clearly oral doesn't have that. Nasal, I'm still very concerned that the multiple dose issue, again, less drug released doesn't necessarily equal less abuse. And intravenous, they just don't have data

to show that. It's too conflicting.

DR. McCANN: Ms. Spotila?

MS. SPOTILA: Jennifer Spotila. At first a question -- if it was more appropriate to have asked this morning in closed session, then that's fine. Can we have any additional information about the effects of chewing in terms of the experience of chewing, not pharmacokinetics but the property of the gel itself? So that's my question, and then I have an answer to the stated question.

DR. McCANN: I don't think we have an answer to that. We probably should have asked that. It's a great question. FDA may know more data about these excipients used in other chewable products.

DR. HERTZ: I don't think we can comment on the experience of chewing.

MS. SPOTILA: That's fine. Then for the question under discussion, apart from labeling that there are abuse-deterrent properties, we got one label, I believe, Apadaz, where it was specifically stated in the label that the studies did not show abuse-deterrent properties. So can we have some

discussion on the flip side of a specific negative label for abuse deterrent?

DR. McCANN: Sharon? Dr. Hertz?

DR. HERTZ: Sharon's fine.

(Laughter.)

DR. HERTZ: Sharon Hertz. What we have decided, with Apadaz as an example, is that when a product is designed intended to be abuse deterrent, and we don't believe there are data to support those features, but it would otherwise be reasonable for someone who perhaps followed development or read our reviews, whatever, to have thought that this was, we will put in studies so that people can be fully informed.

Does that provide what you were questioning?

(Ms. Spotila gestures in the affirmative.)

DR. McCANN: Dr. Brent?

DR. BRENT: Jeff Brent. Just a fast point. Oral, clearly not; nasal, somewhat equivocal. I think there's reasonable data that if we don't look at deterrence as being absolute, we do see it as something that sort of makes it a little harder. I

would have a huge objection to nasal, although I agree with Lewis that it's not a huge deterrent.

The comment I wanted to make, though, is more regarding the intravenous. We have to realize that there are two components to the concerns about the intravenous; one, which is the relevant one here, which is the likelihood of releasing drug; but the second component is also the potential infusion relatively uncharacterized excipient, which probably we should discuss under 3. But I just wanted to be sure we were pretty clear that they were two separate components to the concerns about the intravenous.

DR. McCANN: Dr. Terman?

DR. TERMAN: So again, I am a little bit more positive about the intravenous just because of all the information that we saw in the closed session about all the different parameters that were done. But even if people did decide that even just the nasal was worth talking about in the indication, that the nasal did deter abuse, I think this a situation where you really would need to

point out that the oral route has kind of demonstrated that it's not abuse deterrent because -- and not just stay silent on that issue.

I am concerned about how little I heard -- and part of that's my fault for not asking, but why it is that you can do all those things without releasing all of the drug, and yet you can chew it, and you get a very rapid -- I mean, essentially, it's no longer ER/LA. They didn't show the figure out past 4 hours, but my assumption is that it is no longer long acting. And the question is how long you have to chew it, which, again, we didn't hear anything about, not just the chewing is a problem, but what if, as someone else said, someone just decides to chew it once or twice, not for five minutes.

That is a big concern, particularly if it's on top of a standard dose several days into -- and again, I'm not talking about abuse here. I'm talking about just use, and someone mistakenly, perhaps for the last time, chews their drug?

DR. McCANN: Dr. Hertig?

DR. HERTIG: John Hertig, Purdue University. So to answer this specific question at hand, I'm a no, yes, and then incredibly complicated, because there's almost this incremental deterrence that's happening where it may be incredibly difficult the first time, but because of things like social media and websites and the internet, that subsequent deterrence actually lessens because the way to get around that is shared. So that's why this becomes incredibly complex for me.

DR. McCANN: So with that, I think will briefly summarize this question, and then maybe take a short break. So I asked for specifics. Of the 1, 2, 3, 4, 5, 6 people that gave specifics, 6 out of 6 said that there's no oral deterrence. 5 out of 6 said there was nasal deterrence. 4 out of the 6 expressed IV deterrence -- actually, it was 3 out of the 6, and 3 expressed concern about the IV data, which is probably more like they did not really think there was enough data to support IV deterrence.

There were also specific concerns expressed

about the dangers of injections of excipients that was not adequately explored by the sponsor. And a number of people wanted the label to state explicitly that this drug had no oral deterrence. And it was also expressed by several people that they were a lack of chewing studies, that we don't know what the effects are of chewing for a long time as opposed to just chomping down once on the tablet.

So with that, I would like to adjourn for 10 minutes for a quick break, and then we'll go to the third question.

(Whereupon, at 3:24 p.m., a recess was taken.)

DR. McCANN: Hello. I'm going to ask everybody to take their seat now for question number 3.k

Question number 3. The applicant is requesting approval of REMOXY ER as an analgesic with properties expected to deter abuse by the intravenous and intranasal routes. Discuss whether you have any concerns regarding the impact of

REMOXY ER on public health. Take into consideration its potential effect on the abuse of extended-release oxycodone, as well as potential consequences of administration of this product by unintended routes.

If there are no questions or comments concerning the wording of this question, we will now open the question to discussion. Dr. Arfken?

DR. ARFKEN: Cynthia Arfken. These three different routes of administration are not just three different colors. They recognize different consequences and severity of use. So I have concerns about the most severe route of administration not being shown to be a deterrent. So even though there might be discussion on whether nasal route is deterred, the whole idea that the IV route is of great concern to me. So that makes me very uncomfortable with supporting any indicator for this.

DR. McCANN: Thank you. Dr. Zibbell?

DR. ZIBBELL: Jon Zibbell, RTI International. First of all, I want to say thank

you to FDA for having this question. It's a really important question, and also hard to see into the future without some postmarket studies as well. In public health, we often think of primary versus secondary prevention. And when we think about people with addictions and opiod-use disorders, primary prevention is stopping someone from ever starting, ever taking a medication that might cause them harm, whether it's orally taking it, whether it's chewing it, but someone who is a neophyte, is opiate naive.

Secondary prevention is people that already have an opioid-use disorder, already have an addiction beyond recreational use, problematic use, chaotic use; the things that they'll do to manipulate pharmaceutical medications in order to abuse them are great.

So if we look at both of those, this absolutely for me doesn't deal with primary prevention because of its oral aspect. The people can still take it. And it's not just about the oral aspect. It's the dose dumping, it's the

chewing, it's the interruption of the extended-release mechanism. I'm guessing swallowing this, at least from the data, it seems like that you're going to get your, whatever, 5 milligrams every hour for a period of time, but chewing it breaks that mechanism, getting some type of dose dumping, and getting that euphoria, and getting the trigger in the brain.

So the primary prevention thing, I don't think this deals with that, but the secondary prevention is another big concern. And one of the things I've learned from my field work over the years has been that people that are already physically dependent and addicted to opioids will go through great lengths to manipulate products in order to extract the drug from them in order to use. And I just brought up Scott County because that's the most acute in my mind, that I got to see that really firsthand, the lengths that someone would go to do that.

So I just table the nasal thing because I'm a little confused about the nasal. The data seems

like it could go either way, and there's not a lot of it. But the injection aspect does give me great cause for concern. It's hard to make sense of FDA's position in terms of the data and the sponsor's, but nevertheless, the chance that it can be manipulated, and looking actually at the process, which was 20 to 30 minutes -- a little bit longer than the patience of most people, but not too, too long, like a couple hours, the ability to manipulate that -- in Scott County, what we found -- and this has been research that we've been trying to figure out for a long time, what is the disease risk associated with injecting pills, manipulating pills?

What we found from Scott County was the volume of solution in liquid that is needed in order to do that. Give you an example. So the Opana medication had excipients in it to resist crushing. Well, people in Scott County found that if you put that in an oven, and you burn it, you can interrupt that excipient, and then you're able to make it malleable, and crush it with your finger

or whatever. And then you add water to it, and you start mixing it up. But you can't just use regular water like 1 mL in a syringe like you would with heroin. You need copious amounts of water to override mostly the hydroxyethyl cellulose.

So you put a lot of water in there, and what that does is it makes a big solution. But the people in Scott County only have these 1-milliliter needles, so they had a 5-milliliter solution, a 3-milliliter solution. In order to turn that pill into an injectable solution that wasn't goopy, add enough water; it gets liquid enough, and they would do multiple injections.

Really, that's what we believe led to the spread of disease, because right now you had a solution that was 3 to 5 mLs, and you had 3 to 5 shots. So you could do all three of those yourself or you could share them.

Those of us on the ground really even couldn't come up with this. We didn't even foresee this. And I think what this showed to me is that if these substances can be manipulated with -- I

won't say household products, but citrate is a pretty easy product to get, or ascorbic acid. And in California, they already use that to deal with tar heroin because tar heroin is hard water soluble, and so you already use the citric or ascorbic acid.

If that can be done in 20 to 30 minutes, that raises concerns for me, and it raises concerns like I almost see this as an Opana like product. You could eat it, you couldn't sniff it, but you might be able to inject it. So I do have concerns that this will be manipulated, and it's able to be extracted, and that we could see similar HIV and HCV transmissions because we know that if it can be extracted, people are going to do that. Now, that's not a huge part of the population, 20, 30 percent of the population, but a large enough number to raise concern. Thanks.

DR. McCANN: Thank you. Ms. Spotila?

MS. SPOTILA: Jennifer Spotila. I want to echo the concern about an Opana-like situation and tertiary and down-flow effects in terms of spread

of disease and other issues. I have a question about the nasal mode of abuse. We didn't get pharmacodynamics in the nasal human abuse potential study for oxy ER, and PTI said that was based on FDA's advice.

Can you comment at all on would that have made a difference to the signal that we saw relative to intact REMOXY manipulated and then the oxy IR?

DR. HERTZ: We can't speculate on that.

MS. SPOTILA: So you can't speculate. Was there a reason for telling them to use IR instead of ER?

DR. HERTZ: As we learn about whether or not a product -- as we learn about the features of these different products, abuse deterrence is a relative concept. It's something more difficult than something else. So the first question is how does it compare to IR because that's what people would seek out if they had a choice. Then the question is, where relevant, according to the guidance, other active comparators should be

included.

So if someone had taken only an extended release, maybe another ADF, and showed it was a little better, or a little worse, somehow different, do we know if in that particular population, in that particular study, there was any effect? We can show two products or two sets of data are similar, but we can't necessarily assume that they are showing an absolute effect.

So you need to have the IR for essay sensitivity to show that it's actually better than the IR because they might both be the same, and they might both look as bad as something without product. And as you have gotten a sense, there are so many variables in a lot of these studies, that it's hard to know how to recreate one company versus another's conditions.

So you would say, well, but product x is already abuse deterrent, so if it's the same, it's as good, and therefore, my product's abuse deterrent; except unless you didn't study it properly, unless you found a different way to

defeat it. I mean, there are so many ifs. To eliminate the ifs, we say use IR.

We are always asking for active comparators. We asked for active competitors in these studies. We asked for active comparators in efficacy studies. We push as hard as we can, but people don't listen. They don't say, okay; they just do what they feel is best for their individual development programs. So we need to have some understanding of the low-side assay sensitivity even though we'd also like that other side.

DR. McCANN: Dr. Goudra?

DR. GOUDRA: Basavana Goudra from pain medicine, anesthesiologist. The question, as an analgesic, has it got properties that are expected to deter abuse? I think the answer is absolutely yes for intravenous and intranasal. How much? That's probably debatable.

The next question is can it worsen IV drug abuse? Yes, in certain individuals. Maybe they can probably exploit it for intravenous abuse, but these two have to be looked at differently,

deterrence of intravenous use versus a specific group of people trying to manipulate it for intravenous series.

The next thing is do we have alternatives to this. Not many, so we certainly need analgesics. Opioid analgesics are definitely needed for certain types of pain, and I certainly think this drug is -- it's not the holy grail. It's not going to address everything. It's certainly a step in the right direction.

DR. McCANN: Thank you. Dr. Brown, now.

DR. BROWN: Thank you, Dr. McCann.

I'd first like to commend the agency for the good work that they've done over the course of the last 10 years to try to get this issue right. This is an incredibly complicated problem, and it's easy to ask these hard questions that we're asking. But it shouldn't be thought of as reflecting on the desire or the hard work that's been put in by every member of the agency to try to rectify what is a global population problem.

That said, when the agency states that

something is abuse deterrent, what they actually included in the label is a statement that it would be expected to be abuse deterrent. The question becomes, is that equivalent to say it is abuse deterrent? I have a personal belief that most prescribers, if they look at the labeling at home, believe that when it says would be expected to be abuse deterrent, count on it to be abuse deterrent. Now, the agency doesn't believe that it is abuse deterrent until we get all of the postmarketing data, which we cannot derive from our friends in industry.

The sponsor of this, -- or the agency wonders if we have concerns regarding the impact of REMOXY ER on the public health, and I have substantial problems with the impact on the public health. And ,any of the folks that have spoken before me have very eloquently considered those. But one potential effect is putting another one of the ADFs or another opioid compound on the market has the potential effect of making a statement that the agency does not believe that there is a

problem. And I think that is a problem or an issue that the agency has consider very closely in their overall discussions of what to do about this particular opioid formulation and what to do about the further formulations.

The potential effect on abuse of extended-release oxycodone, as well as the potential consequences of administering these products, are being played out now and have been demonstrated well. The report by the National Academy of Medicine asked very eloquently for the agency to determine whether or not there needs to be reconsideration of the global mechanism for defining what is safe and what is not, specifically with opioids, using the word "exceptionally" [indiscernible] when describing these drugs. I happen to concur with them.

So I guess that's the end to my diatribe, but I would think the agency, and I would also like to thank Dr. Mary Ellen McCann for being so eloquent today in herding rabbits.

DR. McCANN: Thank you, Dr. Brown.

Dr. Meisel?

DR. MEISEL: Steve Meisel. Two points, on this question anyway. To sort of echo what Dr. Brown was talking about or maybe elaborate it or say it a different way, when these things are labeled as abuse deterrent, there could be a false sense of security on the part of the prescribing and consuming population, that these really are abuse preventing, and that they're safer to use than they might otherwise be.

I don't know what the marketing or the experience with labeling is like in Europe or other countries for products like this, but it may well be that one of public health impacts of this product, as well as OxyContin for that matter and the others, is that it provides a false sense of security, and we end up prescribing more of these to more people than we might otherwise if they weren't labeled as abuse deterrent. I think we just have to keep that in mind. I don't think there's an answer to that, but I think we have to recognize that potential.

Several people have mentioned this before, and we can't lose sight of the fact a potentially -- well, the uninvestigated risks of the excipients when given intravenously or elsewhere. The agency did comment that their toxicology studies were pretty okay with this stuff, but I was less than satisfied with the data that was presented to us, that these items when given either safely by intent or unsafely by intravenous or other kinds of routes, wouldn't cause unintended consequences. And I think that's an area that needs to be further explored before we could fully understand the public health impact.

DR. McCANN: Thank you. Dr. Ciccarone?

DR. CICCARONE: Thank you. Dan Ciccarone, UCSF. Given the question around public health implications, I have two disease categories that I'm worried about with this drug. One is blood-borne virus transmission, hepatitis C and HIV, and the other is vein loss leading to a whole variety of conditions. I want to echo what Ms. Spotila and Dr. Zibbell have brought up, and

that is the Opana-like potential characteristics here that this drug, if extracted using the FDA category 1 study results, will result in a -- I know the FDA wants to call this low volume, but in the real world, a moderate to high volume injection solution.

Dr. Zibbell and colleagues' study in Scott County, Indiana showed that multiple injections per dose, per desired dose of a drug, led to a sharing situation, led to a high-risk blood-borne virus transmission situation, and we all know the outcome of that. That work has been published.

If these volumes -- again, going to the FDA data, I'm concerned about multiple injections per episode, HIV. I'm also concerned about -- without divulging what the solvent is, I am concerned about the acidity of the compound as it exists, but also as it's dissolved, according to the FDA study. There are places in the world that use acid to dissolve heroin. They use acid to dissolve pills. In those places that use acid to dissolve heroin and/or pills, they have a tremendous problem.,

public health problem, with vein loss among the users who inject.

Vein loss leads to skin and soft tissue infections. It also leads to more dangerous routes of injection. You go from peripheral veins to central venous to leg veins and neck veins, which have -- I can leave it to your imagination -- very potentially disastrous clinical implications, one of which is happening in the UK right now, which is about to hit press. And that is a renal disease due to immunological burden from skin and soft-tissue infections due to vein loss. They're seeing a rise in amyloidosis and other renal failure problems.

I would hate to see us five years down the road, with postmarketing surveillance, saying, hmm, I wonder where all the renal disease came among the injection drug users, what caused that. We don't know, and we don't know with this drug. I'm just raising it as a hypothetical, given the discussion question about public health consequences.

DR. McCANN: Are there any more comments?

Dr. Terman?

DR. TERMAN: Sure. So as a pain doc who also is licensed to do some addiction medicine, this is obviously a bias of mine, to think that we're going to ever have a compound, which is truly abuse deterrent across all routes, it just doesn't strike me as very realistic. So my public health issues are going to be in the world of pain. Can this drug, the impact of this drug on public health, improve pain? And the phase 3 suggested that it can help people with pain, those that don't drop out of the study, about twice as much as placebo. Despite all the talk about withdrawal concerns, in fact, the people that titrated down to placebo actually improved their pain from the time they started titrating down.

So I do think that that can help pain, based on the data that was presented, and it does have pharmacokinetics that wasn't really talked about in detail here, that would, in terms of peak to trough differences, might actually improve things, might actually suggest that the drug, unlike other

long-acting drugs, might actually last the amount of time that it's approved for.

Nonetheless, I am concerned about this chewing and whether that might accidentally take place, accidentally in people trying to take it for the right reasons. So I am concerned about public health in that way that offsets improved pharmacokinetics in my mind.

DR. McCANN: So I guess it's time to try to summarize a very broad question. I think I'll start with the last comment. The belief is that this drug does help with pain. And another member felt it did deter IV and intranasal use; although a number of people commented on the lack of information about the nasal route pharmacodynamics.

There are also concerns about misuse of this drug in patients who are trying to use it correctly with the fact that they may chew the drug and inadvertently get high doses. Of the three routes of administration, people were most concerned about the intravenous route. The concern is that you may get excipients with this route; that it's the root

where the testing between the FDA and the sponsor differed the most; and then there's a belief that people who are abusers are going to go through any number of steps to get the drug if they decide they need it, so we have to worry about that.

Somebody brought up very eloquently the differences between primary prevention and secondary prevention, and pointed out that this would not be a drug that would be useful for primary prevention because you can just chew the drug and get yourself high that way. In terms of secondary prevention, this particular individual is not hopeful that this drug would be deterrent to somebody who was determined to get IV use of this drug.

Then there was also -- which echoes the discussion with question 1 -- the whole concept of abuse deterrence and does it have unintended consequences; the idea of putting in a whole bunch of excipients when you know a certain small percentage of people are going to defeat the drug and therefore get much sicker with the effects of

the excipients; and that we don't really have adequate studies of the excipients for this drug, for use with IV medication, and probably don't have enough information about the effects of chronic use orally of this drug used appropriately in terms of the excipients.

A number of people also brought up the issue that when you use the FDA's -- called it recipe, but extraction method, that you're left with a fairly large volume of fluid. So it is very tempting for abusers to share the drug, and therefore we need to worry about blood-borne pathogens, as well as vein loss, peripheral infections, and possibly leading all the way to renal damage.

Does that cover it for people? Dr. Meisel?

DR. MEISEL: Just one additional point. Steve Meisel. There's been a lot of discussion about the bolus effect upon chewing this product, and that's true. But I just want to remind people that any sustained release product, whether it's an antihypertensive or drug like this, or any other

sort of pharmaceutical, if you start chewing it up, you destroy the sustained-release component of it, and you can end up with a bolus with bad effects, potentially bad effects.

So that is something that's inherent to the fact that it's a sustained-release product and not necessarily a mark against this drug.

DR. McCANN: All right. So now we're on to the voting part of the day. If there's no further discussion on this question, we'll now begin the voting process. Please press your button on your microphone that corresponds to your vote.

I've got to read the question fist. Sorry.

(Laughter.)

DR. McCANN: Question number 4, based on the data presented and the discussions about the data, does the efficacy, safety, and risk-benefit profile of REMOXY ER support the approval of its application?

I haven't told you how to vote, though, yet. You will be using an electronic voting system for the meeting. Once we begin the vote, the buttons

will start flashing and will continue to flash even after you've 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. The DFO 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 vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

So we're ready to vote, right? Are there any questions about that process?

(No response.)

DR. McCANN: So if there is no further discussion on this question, we will now begin the voting process. Please press the button on your

microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. McCANN: Did everybody vote? One person's abstaining. So if you want to abstain, you have to hit the abstain button. So has everybody voted?

Everyone has voted. The vote is now complete. Now that the vote is complete, we will go around the table and have -- sorry.

DR. WANG: For the record, for question 4, we have 3 yeses, 14 noes, and zero abstain.

DR. McCANN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We're going to start on my right,

so that would be Dr. Arfken, I believe.

DR. ARKFEN: Cynthia Arfken. I voted no because I was very concerned about the safety. There were certain questions that were left unanswered, but more importantly about the public health benefit.

DR. CICCARONE: Dan Ciccarone, UCSF> I voted no, given the FDA lab category 1 study results on extractability. If the FDA lab can do it, then it will be extractable in the real world. And I'm concerned about the public health consequences.

DR. ZIBBELL: Jon Zibbell, RTI International. I voted no. I do believe that we need safer opioid medications, but given the data presented, especially around oral and injection data, combined with the public health risks, specifically around primary and secondary prevention, I just couldn't say yes.

DR. GOUDRA: Basavana Goudra from pain medicine. I did vote yes. I think most of the reasons are kind of elaborated during the

discussion. I think the biggest factor is that there are no other real alternatives, and this at least addresses some of the concerns. And for that reason alone, it should be approved. Thank you.

DR. SHOBEN: Abby Shoben. I voted no. For me, it sort of came out to the benefit to risk aspect, that the benefit here is potentially another abuse-deterrent opioid that would have abusable [indiscernible] properties. And that would, in theory, put another barrier to potential abuse on the market. But with these data, compared to other abuse-deterrent drugs that are already out there and the potential risk of creating another type of Opana situation, the unknown risks outweighed any potential incremental benefit of adding another abuse-deterrent opioid.

DR. ZELTZER: Lonnie Zeltzer, UCLA. I voted no because while the only area that had some convincing data in terms of positive benefit was the intranasal route, I think the public health risk of, in particular, the large volume for IV use would create I think more risk than the overall

benefit of approval.

DR. GRIFFIN: Marie Griffin. I voted no mainly based on the data on IV use or the potential for IV use. I also think the standard for some of these efficacy trials really needs to change because our concept of risk of these drugs is different now than when the drugs were originally licensed.

So I think the data that we saw on safety and efficacy was really not up to par for -- it certainly wouldn't be for a new drug. But I think we need to think about this in a different way, in a public health way. And I don't think we saw a lot of evidence for long-term safety.

MS. ROBOTTI: I'm Suzanne Robotti. I voted no. I've sat on this panel for just over a year, and I've sat on at least five different opioid anti-abuse drug reviews. And I've learned that any drug can be abused by a determined addict, as has been said here before. And therefore, to me, the primary goal is to deter the initiation of abuse. The fact that chewing can release the opioid at a

high level, any abuse to me by a nasal and IV is a secondary concern. That said, I sat on the Opana panel, and that was a terrible, unforeseen outcome that we need to avoid if there's any foreshadowing of it here.

On the public health level, we also need to slow initial use of opioids for pain management in general. We need to emphasize to the opioid-naive patient that the side effects for opioids used appropriately as prescribed, the side effects are significant and uncomfortable. And we need as a society to make access to alternatives affordable and realistic whenever possible.

MS. SPOTILA: Jennifer Spotila, patient representative. I voted no because I think the risk of oral and IV misuse and abuse, both to those individuals and to public health, as well as the risk of creating a false sense of safety, those outweighed the benefits of possible nasal deterrence and also the benefits to patients in pain management.

DR. McCANN: Mary Ellen McCann. I voted

yes. I think there was evidence for nasal and IV deterrence.

DR. McCANN: Dr. Brown, we're ready for your comments.

DR. BROWN: I voted no because of the public health implication. I'd just like to comment that for patients that have chronic pain, we must offer solutions. But we don't improve the lives of patients by offering bad solutions. And in this and other circumstances like it, that is what I fear that we are doing.

DR. McCANN: Thank you.

DR. MEISEL: Steve Meisel. I reluctantly voted no. In some respects, I wanted to vote yes because I think the applicant met its burden of evidence for abuse deterrence for intravenous and intranasal. I think the intravenous, despite the FDA's data, the syringeability, it's a deterrence. It's maybe not the perfect deterrence, but it is a deterrence. But at the end of the day, I don't think any of these products are really a deterrent, and I wonder if OxyContin, with its current

formulation, was submitted today, whether we would approve that labeling as abuse deterrence. And my guess is we'd have the same questions today with OxyContin as we do with this product.

With that in mind, I would challenge the agency to rethink the entire pathway of abuse deterrence, the guidance document, the encouragement of vendors to come up with products like this, because I'm not convinced that we'll ever see a product that meets the criteria that's been articulated here today. And I would also challenge the agency to consider a process to reevaluate the approved labeling for OxyContin as a product with abuse-deterrent properties.

DR. NELSON: Lewis Nelson, and I voted no. I think that's not a surprise based on my previous comments, which I won't repeat. I do have concerns about the credibility of the abuse deterrence that they were able to show, the sponsor was able to show. And of in an unpopular way with the FDA, I don't really support the efficacy studies that are being done to show the benefit, the beneficial

effects, of chronic opioid use to manage pain. I'm not convinced that these enriched enrollment and controlled, randomized withdrawal studies are adequate given the change in what we understand now to be the risks of using opioids and the development of worsening progressive chronic pain due the hyperalgesia and dependence, and other long-term use disorders that we seem to be grappling with in this country.

So I'd be very concerned the messaging around the abuse deterrence and the harm reduction effects of these opioids if they were approved. And I think we have to deal with this with the others that are out there because the message that people are getting with abuse deterrence is safe, and I'm just not really sure that's what we're intending people to hear, whether it's the public or the medical community. So for those reasons and others, I voted no.

DR. PRISINZANO: Tom Prisinzano. I voted yes. I felt that the sponsor had met the criteria, at least for abuse deterrence, in terms of

intravenous as well as that for nasal. I think oral is always going to be a problem in this particular case. And I thought we're in desperate need of things for chronic pain, and I thought they showed, at least the data, that it was effective in treatment of pain.

DR. TERMAN: Greg Terman. I voted no, and I, too, am very concerned about abuse deterrence. And I realize that tamper resistant sounds more like packaging than a drug. But that's really what we're doing here, is talking about tamper resistant product. And to think that we can stop abuse by making it difficult to extract out of 15 different solvents or can inject through a bunch of different needles is not what I know about addiction. And people will pursue their drug of choice. And if they can't get it here, they'll get it from Chin, even sometimes in pill form.

But because we put so much emphasis on abuse deterrence, I think the obvious studies of how much chewing needed to take place to unleash this acute, this immediate-release effect, seemed to be

completely ignored. So I can't really think about risks and benefits because I don't know what that risk is; someone trying to do the right thing and biting into a capsule.

DR. BRENT: Jeffrey Brent here. I voted no, and I did so for some minor reasons and for some major reasons. To keep my remarks very succinct, it's late in the day, to say that, for one thing, I'm not even sure we would need this drug. And even if it was the perfect drug, whether it really would be a great addition to our public health arsenal. Perhaps if it was the perfect drug, as it was intended to be, we can get rid of OxyContin and substitute this, and it might work better. But other than that, I'm not sure it would really be necessary to have.

As I mentioned before, I'm always concerned that if it is truly an abuse-deterrent medication, it's going to enhance our experience of people then turning to other forms of opioids, and particularly intravenous opioids like heroin.

On a more specific level, I did have

concerns about the uncharacterized toxicology of excipients with IV use. I think that's a very easily remedied problem. To characterize something like that is quite easy. It's just standard run-of-the-mill toxicology testing, but at this point, I certainly didn't feel comfortable approving the drug.

Then lastly, it's not a great deterrent orally. It's not a great deterrent intravenously. It's a so-so deterrent nasally. So it really doesn't add that much. I will say I applaud the FDA's efforts in trying to encourage abuse-deterrent medications. I think they do play a role. Maybe this drug will come back into better form at some later point, but at this point I find it not approvable.

DR. HERTIG: John Hertig. I also voted no, and I think ultimately we need to do better, both for our patients with chronic pain, as well as those who struggle with abuse. I do applaud the sponsor for being innovative and taking a step in the right direction and really appreciated those

efforts. But ultimately, when I'm balancing the risk-benefit, and the availability of some similar options that are currently on the market, compared to the possible public health impact for me, it was a no.

DR. McCANN: Before we adjourn, are there last comments for the FDA?

DR. HERTZ: I just want to, one last time for today, thank you all for coming to provide us with advice, taking time from your busy schedules. It's greatly appreciated it.

Adjournment

DR. McCANN: Thank you. We will now adjourn the meeting. Panel members, please leave your name badge here on the table so that it can be recycled. Please also take all your personal belongings with you, as the room is cleaned at the end of the meeting day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 4:22 p.m., the open session was adjourned.)