FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Tuesday, March 14, 2017

10:07 a.m. to 4:17 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

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AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
Almut Winterstein, RPh, PhD, FISPE	16
Conflict of Interest Statement	
Stephanie Begansky, PharmD	23
FDA Introductory Remarks	
Judy Staffa, PhD, RPh	28
Open Public Hearing	30
Charge to the Committee	119
Questions to the Committee and Discussion	122
Adjournment	265

P R O C E E D I N G S

(10:07 a.m.)

Call to Order

Introduction of Committee

DR. WINTERSTEIN: Good morning, everyone. Thank you for staying here or making your way here through the weather, and we'll get started. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so.

I would also like to identify the FDA press contact, Sarah Peddicord, who is not here, but is available online, via phone, or e-mail.

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

We'll start by going around the table and introduce ourselves. Let's start down on my right.

DR. MENDELSON: Hello. I'm Dr. John Mendelson, who's barely awake, California time. I'm a senior research scientist, Friends Research Institute, specializing in opiates and addictive drugs.

DR. GHANY: Hi. I'm Marc Ghany. I'm an investigator at the Liver Diseases Branch, National Institutes of Diabetes, Digestive, and Kidney Diseases at the National Institutes of Health here in Bethesda, Maryland.

DR. WISH: Good morning. I'm Eric Wish. I'm from down about 15 minutes away from here, from the University of Maryland College Park. I direct the Center for Substance Abuse Research known as CESAR. And we run the coordinating center for NIDA and the National Drug Early Warning System.

DR. WOODS: I'm a grantee of NIDA. I'm at the University of Texas San Antonio, pharmacology. My name is Jim Woods.

DR. SCHISTERMAN: Good morning. My name is Enrique Schisterman. I'm the branch chief of the epidemiology branch at NICHD, NIH, and I'm glad to

be here this morning

MS. ROBOTTI: I'm Suzanne Robotti, and I am the consumer rep on DSaRM. I'm the founder of MedShadow Foundation and the executive director of DES Action USA.

DR. PORTER: Hi. I'm Laura Porter, and I'm a stage 4 colon cancer survivor and the patient representative.

DR. HIGGINS: Jennifer Higgins, the AADPAC consumer representative.

DR. CRAIG: David Craig. I'm a clinical pharmacist specialist at Moffitt Cancer Center and a member of AADPAC.

DR. McCANN: My name is Mary Ellen McCann. I'm an associate professor at Boston Children's Hospital and Harvard Medical School.

DR. RUHA: Hi. I'm Michelle Ruha. I'm a medical toxicology physician at the University of Arizona College of Medicine in Phoenix.

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

DR. ZACHAROFF: Hi. Good morning. My name

is Kevin Zacharoff. My expertise is anesthesiology and pain medicine, and I am faculty and clinical instructor at State University of New York Stony Brook School of Medicine.

DR. BROWN: I'm Rae Brown. I am a pediatric anesthesiologist at the University of Kentucky and professor of anesthesiology and pediatrics at the university.

DR. WINTERSTEIN: Almut Winterstein. I'm professor and chair of pharmaceutical outcomes and policy at the University of Florida.

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

DR. BATEMAN: Brian Bateman. I'm an associate professor of anesthesia at the Massachusetts General Hospital, Harvard Medical School.

DR. WARHOLAK: Good morning. I'm Terri Warholak, and I am an associate professor at the University of Arizona College of Pharmacy in the Department of Health and Pharmaceutical Outcomes.

DR. GERHARD: Tobias Gerhard,

pharmacoepidemiologist at Rutgers University.

DR. GUPTA: Dr. Anita Gupta, vice chair, associate professor of anesthesiology and pain medicine at Drexel University College of Medicine in Philadelphia.

DR. TYLER: I'm Linda Tyler. I'm the chief pharmacy officer for the University of Utah Hospitals and Clinics. I serve as associate dean of the College of Pharmacy.

DR. EMALA: Charles Emala. I'm professor of anesthesiology, vice chair for research, Department of Anesthesiology, Columbia University.

DR. LITMAN: Ron Litman, anesthesiologist at Children's Hospital, Philadelphia and the University of Pennsylvania. And I'm the medical director of the Institute for Safe Medication Practice.

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

DR. BILKER: Warren Bilker. I'm professor of biostatistics at the University of Pennsylvania.

DR. CICCARONE: Good morning. Dan Ciccarone, professor of family community medicine, University of California San Francisco.

DR. LO RE: Hi. Vincent Lo Re, Division of Infectious Diseases, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania.

DR. CALDERON: Good morning. I'm Silvia Calderon, controlled substance staff, CDER.

DR. MCANINCH: Jana McAninch, medical officer and epidemiologist, Office of Surveillance and Epidemiology.

DR. STAFFA: Good morning. Judy Staffa, associate director for public health initiatives in the Office of Surveillance and Epidemiology.

DR. FIELDS: Hi. I'm Ellen Fields, deputy director, Division of Anesthesia, Analgesia, and Addiction Products.

DR. HERTZ: Sharon Hertz, director of the same division as Dr. Fields. And I just want to thank you all, particularly those along the I-95 corridor, for sticking it out with us today. We

really appreciate your being here. Thank you.

DR. WINTERSTEIN: We have two more panel members on the phone. Dr. Acri, would you like to introduce yourself?

DR. ACRI: Can you hear me?

DR. WINTERSTEIN: Yes, we hear you.

DR. ACRI: Okay. This is Jane Acri, Medication Discovery and Toxicology Branch, [indiscernible - interference].

DR. WINTERSTEIN: Thank you. And then we have Dr. Herring.

DR. HERRING: Good morning. I'm Joe Herring. I'm executive director of clinical neuroscience at Merck and industry representative to the AADPAC.

DR. WINTERSTEIN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the 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 Lieutenant Commander Stephanie Begansky, who will read the conflict of interest statement.

Conflict of Interest Statement

LCDR BEGANSKY: Good morning. The Food and

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

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

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

FDA has determined that members and temporary voting members of the committees are in compliance with the federal ethics and conflict of interest laws.

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

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

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of safety issues for new drug application 201655, Opana ER tablets by Endo Pharmaceuticals, with the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The product is an approved extended-release formulation, intended to have abuse-deterrent properties based on its physiochemical properties. However, this information is not currently reflected in product labeling.

The committees will be asked to discuss pre- and postmarketing data about the abuse of Opana ER and the overall risk-benefit of this product. The committees will also discuss abuse of generic oxymorphone ER and oxymorphone immediate-release products.

This is a particular matters meeting during which specific matters related to Opana ER, oxymorphone hydrochloride ER, and oxymorphone hydrochloride IR products 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 topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Joseph Herring is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. His 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 discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the

participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

DR. WINTERSTEIN: Thank you.

We will now proceed with the FDA's opening remarks from Dr. Judy Staffa.

FDA Introductory Remarks - Judy Staffa

DR. STAFFA: Good morning. Welcome back to those of you who were able to return to the second day, to this very important advisory committee, whether in person or by phone.

I'd like to echo Dr. Hertz's gratitude. We are very, very appreciative that, in these difficult circumstances, you were all able to hang in there with us. This is a very important issue and we're really pleased that we were able to have this meeting, despite the challenges.

You were presented with a lot of information

yesterday pertaining to what we know and don't know about the abuse and safety of reformulated Opana ER, other oxymorphone products and comparators. And you will hear more valuable information this morning in the open public hearing portion of this meeting.

The rest of the day will be devoted to discussing the strengths and limitations of all the data you have learned about and to consider the impact of different courses of regulatory action to improve the public health in relation to the abuse of Opana ER. We will then be asking you to provide your recommendation with regard to the benefit-risk balance of reformulated Opana ER specifically.

After the open public hearing, I will try to frame those questions for you, and then I'll be turning it over to Dr. Winterstein to begin the discussions.

I know you're all anxious about the weather situation and your ability to travel back home as planned this evening. Despite our later start time this morning, we will be finishing no later than

5:00 p.m. as planned. We will keep our discussions as focused and concise as possible while still thoroughly discussing the issue.

Thank you again for your participation and your continued support of our mission.

Open Public Hearing

DR. WINTERSTEIN: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee, 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 relationships that you may have with any industry group, its products, and if known, its direct competitors.

For example, this financial information may include industry payments 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 in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

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

MS. WALDEN: Emily Walden. I have no conflicts of interest. Thank you for allowing me to speak. My son, T.J. Walden, achieved the rank of private first class while serving in the Kentucky National Guard. It was his lifelong dream to serve in the military, and he joined as fast as he could.

Knowing the difficult journey he took to get there, I was proud of him. Life seemed blessed by his growth into not just a good adult, but as a wonderful citizen serving his community and his country. His potential was as boundless as his energy, and it was all cut short in July 2012, when he lost his final battle in his war of addiction to the drug Opana.

I was not aware of the prescription drug epidemic until it appeared on my front door and entered my house. I was forced to wake up and confront this assault on my family head on.

I began researching Opana and learned very quickly that not all opioids are created equal. Oxymorphone is more potent, more addictive, and more dangerous than most opioids on the market. I have spoken with doctors, police departments, scientists, anyone and everyone that I could to find out as much information about this drug, and what I have found is alarming.

In 1979, oxymorphone was removed from the market for safety reasons. Endo understood the dangers of this drug, but nevertheless, beginning in 2002, they started attending FDA impact pay-for-play invitation-only meetings where they and other pharmaceutical companies could discuss clinical trial designs with the FDA.

Then in 2003, they brought oxymorphone, Opana, before the FDA for approval, and it was denied due to overdoses in the clinical trial. This drug was not safe.

Endo continued to participate in impact meetings, which ultimately led to a new clinical trial called Enriched Enrollment. In 2006, the FDA

approved Opana using this new clinical trial, bypassing an advisory committee, and suddenly oxymorphone was considered safe. The drug did not change from 2003 to 2006, and it was suddenly considered safe.

There were a total of 49 deaths combined in the trials. 27 participants needed naloxone, two instances of diversion. Up to 50 percent of the participants could not complete the trials due to side effects, and yet, it was considered safe.

That same year, RegenceRX, which is a pharmacy benefit company and provides its members with preferred medication lists, released a review of Opana. On page 2, it reads, "Opana and Opana ER are non-preferred because these products have an unacceptable safety profile." This drug is not safe.

As the marketing of this drug increased and more prescriptions were written, in 2011, the U.S. Department of Justice issued a drug alert that oxymorphone was a growing threat nationwide. And by the end of that year, in my city, 33 people died

in Louisville, Kentucky, two golf pros, a jockey in his car outside of historic Churchill Downs, a 15-year-old girl in La Grange, who took one pill and never woke up.

On August 10, 2012, 1 month and 10 days after my son died, Endo submitted a citizen petition to the FDA saying their drug was unsafe and they did not want the FDA to approve any generics. But even though the first goal of the REMS suggested by the FDA was to inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction associated with Opana, Endo did not seem concerned about safety.

Per a lawsuit settled in the State of New York, they inappropriately marketed this drug that further contributed to addiction, death, and destruction of families.

My son's life was worth more than Endo's profits. He loved his country, and his country failed him. He should not have had access to this very dangerous and highly addictive drug. Too many

mothers have gotten a knock on their door saying their child will never come home again. Too many children have had their lives cut short, families destroyed, communities left in ruins.

I do not understand how a drug that does not cure anything can have this much death and destruction and still be available for use. The truth is, oxymorphone was not safe in 1979, it was not safe in 2003, and it is not safe now. You can put a coating around it and pretend it is safer, and people will still become addicted and people are still going to die.

My hope toady is that the FDA will correct the mistake that was made in 2006 and make sure that not one more life is destroyed by this drug. Thank you.

DR. WINTERSTEIN: The statement for speaker number 2 is read by Dr. Begansky.

LCDR BEGANSKY: Good morning. I'll be reading several statements on behalf of open public hearing speakers that were not able to make it due to the weather today. The first one is the

testimony of Shruti Kulkarni on behalf of the Center for Lawful Access and Abuse-Deterrence.

"Good morning. I am Shruti Kulkarni, and I am an outside counsel for the not-for-profit Center for Lawful Access and Abuse-Deterrence, CLAAD. Our organization works to reduce prescription drug fraud, diversion, misuse, and abuse while advancing consumer access to high-quality healthcare.

"CLAAD's funders include treatment centers, laboratories, and pharmaceutical companies, and are disclosed on our website, CLAAD.org. Thank you for the opportunity to provide CLAAD's input on the risk-benefit of oxymorphone products.

"The U.S. Food and Drug Administration should require a product-specific risk evaluation and mitigation strategy, REMS program, for oxymorphone products so that the benefit of the medication continues to outweigh the risks.

"As you know, opioid overdose is a public health epidemic in the United States. An estimated 4.3 million Americans abuse opioids each year. At the same time, an estimated 25.3 million Americans

experience persistent pain and have a legitimate need for treatment.

"Opioids have been demonstrated to help manage pain when other treatments have not provided enough pain relief. For some individuals, opioids are the best treatment for their pain. In addition, oxymorphone is characterized by specific pharmacokinetic and pharmacodynamic characteristics that make oxymorphone an important option for chronic pain treatment.

"Given the unique needs of each patient, physicians need an array of treatment options at their discretion to individualize treatment, including access to FDA-approved medications, each of which has its own strengths, weaknesses, and risks. CLAAD supports FDA's use of REMS to manage the risks associated with medications and advance prescriber education.

"As you know, a REMS program mandates that manufacturers utilize tools to manage known or potential serious risks associated with certain drugs while also making these medications available

to patients with unmet medical needs.

"REMS include, among other things, medication safety guides, patient package inserts, communication plans, elements to assure safe use, and implementation systems used to monitor, evaluate, and improve application of ETASU.

"ETASU is the strictest category of REMS and may include restrictive distribution systems, which ensure only specifically approved parties have access to a drug under strictly controlled conditions.

"According to the Food and Drug Administration Amendments Act of 2007, medicines carrying serious risks would be removed from the market altogether without ETASU, leaving certain patient populations without treatment.

"A class-wide REMS with ETASU already exists for extended-release and long-acting opioids, ER/LA. And if the FDA deems that oxymorphone products have greater risks than other ER/LA opioids, then we encourage the FDA to require a product-specific REMS with ETASU for these

products. This will allow FDA to mandate that manufacturers manage known or potential serious risks associated with these products while also maintaining access to these products for patients who need them.

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

DR. WINTERSTEIN: Would speaker number 3 please step to the podium? Please introduce yourself.

DR. TWILLMAN: Good morning. My name is Bob Twillman. I'm the executive director of the Academy of Integrative Pain Management, formerly the American Academy of Pain Management. I have no conflicts of interest.

The AIPM, for its entire 29-year-history, has advocated for a multi-modal, multi-disciplinary model of pain management, one that uses all available evidence-supported treatments to create a personalized pain care plan for each individual.

While this model emphasizes maximizing the

use of non-pharmacological treatments, it also recognizes that medications, including opioid analgesics, are critical tools that we need to provide the best care possible. For that reason, we advocate for unfettered access to all opioid analgesics that have been proven safe and effective.

Yesterday, we heard a lot of information about oxymorphone products, especially about Opana ER. The available data were sliced and diced in just about every possible way imaginable. And at the end of the day, I was left with these impressions.

Oxymorphone is a unique medication among opioid analgesics by virtue of its metabolic pathway. Because of that unique metabolic pathway, Opana may be a crucial option for some patients, whether due to their own unique physical make-up or due to their concomitant medications.

As is true with all opioid analgesics, Opana is abused by a subset of people. That, I'm afraid, is a fact of life that isn't going to change for

any opioid in my lifetime. When PEO was added to the original formulation of Opana ER to create an abuse-deterrent opioid product, its predominant method of abuse changed from inhalation to injection.

A certain subset of individuals injecting a highly altered version of Opana ER suffered outcomes, including thrombotic microangiopathy, HIV infection, and overdose death. Unfortunately, only one of these, the thrombotic microangiopathy, is nearly unique to Opana ER. The others can and do occur regularly in people injecting other prescription and illicit opioids.

So where does all that leave us? It leaves us with a product that was proven effective enough to be allowed on to the market, and it leaves us with a product that was proven safe enough to be allowed onto the market, albeit without the requested label indication for abuse-deterrent properties.

But the reason we're here is that the questions have now arisen about whether further

regulatory steps, including the potential withdrawal of marketing approval, should be taken based on these reports of adverse events. And I find myself concerned about the direction we seem to be headed here, concerned that not only might we lose a unique opioid analgesic that could help some patients who weren't helped by other opioids but that a trend might develop that could threaten other products currently on the market.

I want to advise the committee to tread lightly because there's very real potential that your vote later today could establish a precedent that none of us will, in the end, be happy with.

I'm fond of saying that if you want to get the right answer, you first have to ask the right question. And I don't mind so much if after a question is posed and answer, sometimes later the answer changes.

That is an example of a post hoc change in an answer to a question, and it's perfectly acceptable because that's the nature of discovery, of learning, of the result of exploration. What

bothers me, though, is when the question changes after we have an answer. A post hoc change in the question is unsettling, and I think that's what's going on here.

When Opana ER and every other medication approved by FDA was approved, the real question asked was, do the data indicate that this medication is safe when used as directed. That's the question underlying clinical trial design, and it's the question every marketed drug has answered successfully.

Now, however, I perceive that the question is changing after the fact. The new question seems to be, do the data indicate this medication is safe even when it's used other than as directed?

I often search for analogies to try to help people understand what's going on when we encounter complicated situations like this one, and I think I may have one that exemplifies the challenge here.

My take on the issue is that because some set of our population has chosen to intentionally defeat the safety mechanism built into Opana ER,

those individuals have been able to inject its ingredients and some have suffered harm as a result. Because that's happened, there's at least the possibility that Opana ER could be withdrawn from the market, making it unavailable to those who use it appropriately, safely, and with positive outcomes.

It's almost as if a subset of our population chooses not to wear seat belts while driving pick-up trucks and then suffers harm when involved in a crash, leading authorities to consider removing all pick-ups from the market.

But the analogy goes even farther than that. We heard yesterday that half or more people abusing Opana ER don't even have pain, and it seems reasonable to assume that an even greater percentage doesn't have the prescription for it when they do abuse it. They shouldn't even be using the medication.

In our pick-up truck analogy, I suppose this equates to an unqualified driver who decides not to use a seat belt, then is injured in a crash,

threatening the existence of pick-up trucks.

At the risk of stretching the analogy beyond the breaking point, let me suggest a solution that automobile manufacturers already have shown us. When it became apparent that even passing mandatory seat belt laws wasn't sufficient to protect drivers, they began putting airbags into their vehicles, first in the steering wheel, then at the door, and then all over the car.

They design their cars with crumple zones that absorb the energy of head-on and rear-end collisions. They found additional ways to protect drivers, even those who choose not to wear a seat belt.

It seems to me that, in the case of Opana ER, rather than withdrawing it from the market, the better to solution is to figure out why people abuse it in the first place and to address that behavior.

Maybe there should be incentives for innovation so that new technologies are developed to enhance the abuse deterrence already built into

the product. Maybe we need increased access to treatments for substance use disorders, something the federal government seems to be falling all over itself to provide these days.

And maybe we need some help with improving access to pain treatments that don't involve opioids, those pesky non-pharmacological treatments that every guideline touts but no one seems to know exactly how to provide to patients who need them.

I don't envy the members of this committee, because they have a challenging discussion and vote coming up later today, but I urge committee members to engage in some meta-cognition before they start their discussion. Think for a minute or two about what's really going on here about the true meaning of the questions posed and about the potential consequences.

Should you decide that the answer to the overly broad question you'll be asked is that the benefits of Opana ER for people using it for a legitimate medical purpose no longer outweigh the risks to people using it for other reasons because

based on the evidence presented to you, that most assuredly is the question you're being asked, and your answer can have serious consequences for millions of people with chronic pain.

DR. WINTERSTEIN: Thank you. Will speaker number 4 please step up to the podium and introduce yourself?

MR. DELK: Good morning. I'm Wade Delk with the American Society for Pain Management Nursing, and I'd like to introduce our speaker and our president, Dr. Melanie Simpson, also magnet nurse of the year, who will be giving our testimony.

DR. SIMPSON: Thank you.

As he mentioned, I'm the president of the American Society for Pain Management Nursing. I'm also the pain management team coordinator at the University of Kansas Health System in Kansas City, Kansas and a clinician that works with patients every day.

I would like to disclose that I am on a consultant for Mallinckrodt and Pacira, which are not opioids, and I receive no industry support for

the attendance today.

The American Society for Pain Management Nursing's mission is to advance and promote optimal nursing care for people affected by pain by promoting best nursing practices, access to quality care, public awareness, and education.

Nurses have historically been the coordinator between the patient, family, caregiver, and physician and are therefore in a position to play a pivotal role in all aspects of pain management.

Nurses basically function as the glue of the healthcare system. In many cases, nurses are the front-line providers of the care in diverse geographical areas not covered by physicians.

Effective pain management is an important aspect of quality healthcare, and it is widely accepted internationally that patients have a right to professional pain assessment and appropriate treatment, yet many healthcare providers who manage pain daily may lack education in pain assessment, multi-modal analgesic regimens, opioid risk

assessment, and safe prescribing.

For this reason, comprehensive prescriber's education on pain assessment and management, as well as opioid pharmacology and management, including risks, benefits, and alternatives, should be required.

The use of multi-modal analgesia is supported by high-quality evidence and strongly recommended by organizations such as the American Pain Society, the American Society of Anesthesiologists, and of course ASPMN.

The CDC guidelines for the management of chronic pain recommend the use of a multi-modal, analgesic regimen with the use of non-opioids first, but still consider opioids to be a part of the treatment plan when non-opioid modalities fail.

While there is published research demonstrating the benefits and risk of opioids, most of the research extends over several months, but not over years. These shorter time frames limit the generalizability of scientific evidence in addressing the balancing of pain relief and

possible harmful effects of long-term opioid therapy.

An often overlooked factor is that many opioid-related deaths involved more than one drug, including alcohol. The most frequent drug type used in combination with methadone and other opioids are benzodiazepines. This is a combination with an opioid that can significantly add to the risk of overdose.

Prescribing opioids safely has limitations. A limitation to the development of abuse-deterrent opioids intended to minimize risk has been hampered by the ability of abusers to overcome the technology. Another limitation to their use is excessive cost or co-pays and the requirement of time-consuming prior authorizations in order for patients to get the pain medication they need to function.

The exclusion of methadone and buprenorphine when prescribed for opioid treatment programs from state prescription drug monitoring programs also limits prescribers' ability to fully evaluate

patients' controlled substance use in order to prescribed opioids safely.

Healthcare practitioners must continually balance legitimate need for opioid analgesics with the serious problems of abuse, diversion, and potential overdoses. While prescribers of opioids have an obligation to ensure patient safety and prevent societal harm, they must also ensure that vulnerable and disempowered populations such as the poor and those with substance abuse disorder are not undertreated or don't subject to undertreated pain.

To promote the responsible use of opioids and to avoid the needless suffering of millions living with persistent pain, we must reject oversimplified solutions to a very complex problem. Because each person's pain experience is unique and requires an individualized treatment plan, we need to have choices in types of treatment, including different types of opioids.

Opioids also have unique qualities. If one pill worked for everyone, we would not need

choices. Please don't eliminate any long-acting opioids that can help those suffering from chronic daily pain. Instead, judicious implementation of evidence-based recommendations must be adopted.

Unfortunately, integrative pain techniques are not reimbursed by the majority of insurance carriers, despite increased use in popularity. Current payment models are focused on conventional medicine, not integrative or preventative care.

ASPMN believes that there is a need for greater reimbursement for integrative pain interventions and greater access to in-network providers skilled in integrative care. ASPMN promotes the need for further research of integrative pain interventions.

Finally, as concern and controversy over opioids has arisen in professional, governmental, and public arenas, it is important to recognize the complex problems embedded within the debate.

The American Society for Pain Management Nursing promotes the pursuit of evidence-based responses to sustain effective pain management for

millions of Americans living with chronic pain and public safety in delivering this care. This includes options for long-acting opioids.

Thank you for the opportunity to provide comments. We stand by to assist in any way we can. Thank you.

DR. WINTERSTEIN: Thank you. Will speaker number 5 step up to the podium and please introduce yourself?

MR. THOMPSON: Hello and good morning. My name is Edwin Thompson. I'm the president of Pharmaceutical Manufacturing Research Services, located in Horsham, Pennsylvania. Pharmaceutical Manufacturing Research Services, PMRS, has extensive experience in the formulation, testing, process development, and manufacturing of abuse-deterrent formulations. We are also a manufacturer of reformulated Opana ER.

The FDA guidance for the evaluation and labeling of abuse-deterrent opioids specifies three key criteria for the preparation and testing of abuse-deterrent properties. These criteria require

category 1 studies identify the method of manipulation, including both physical and chemical, which provides the smallest particle size, yields the greatest release, and causes the highest release and highest plasma levels of the studied opioid.

These goals of category 1 studies must be achieved before subsequent category 2 and category studies are conducted. Manipulation through extraction provides the best material to meet these goals and achieves all three key criteria.

The FDA's review of the in vitro Opana ER, studies as summarized yesterday by Dr. Englund, failed to realize this significant fact. To meet the guidance requirements, extracted material should also be manipulated to produce particles.

Using commercially-supplied material, PRMS has examined the ability to extract Opana ER according to the FDA guidance. An unskilled person can easily extract Opana ER to high purity level, hide label claim using commonly available solvents and tools.

After extraction by PMRS, 97 percent of the resulting manipulated material was found to consist of particles measuring below 500 microns. Furthermore, 52 percent of the particles were below 180 microns, and 16 percent were below 75 microns.

In comparison, human abuse-potential study EN3288114, described on page 94 of the background material provided for this meeting, produced manipulated material where only 41 percent of the particles were below 500 microns.

Study 114 did not produce the smallest particle size, the greatest release, or highest plasma levels, and thus fails to meet all three key criteria required by the FDA guideline. To adhere to the guidance, Opana ER must be manipulated through extraction to produce particles.

Not only did this study fail to use manipulated material of the smallest particle size, this study also failed to use API that meets the manufacturer's particle-size specification. As stated in the background material, oxymorphone hydrochloride used in this study was comprised of

72 percent particles below 500 microns. In other words, 28 percent of the particles in the study of the API were larger than 500 microns.

According to the manufacturer's specification, less than 10 percent of this API is to measure above 180 microns. The API used in this study, with 28 percent above, not even 180 microns, but rather above 500 microns, grossly violates the manufacturer's specification. The API used in this study is adulterated and the study is invalid.

Study 114 is clearly invalid and should not be used to make any decisions regarding Opana ER. The FDA guidance must be fully applied to the design of human abuse-potential studies, including the key criteria of smallest particle size, greatest release, and highest release, and highest plasma level of the studied opioid.

As proven by the presented PMRS extraction data, Opana ER, which has been manipulated in accordance with the FDA guidance, consists of 97 percent particles measuring below 500 microns. Knowing the results of the extracted material,

there is no reason, none, to have conducted this study.

Furthermore, the design of human abuse-potential studies is invalid and should not be required in the approval of any drug product. There is no reason to conduct any study using extracted material of high purity, high label claim, and equivalent particle size to API.

Needlessly administering manipulated opioid products to human patients is immoral, unethical, and should be illegal. Human abuse-potential studies provide no scientific benefit and must be prohibited. Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 6 please step to the podium and introduce yourself?

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

These are data from the recently released annual report from the United Nations International Narcotics Council Narcotics Control Board, and

these are the projected use data, use requirements, for oxymorphone for 2016.

Now, with all due respect to the ideas put forth before, that there is some unique characteristic of oxymorphone -- and I agree with those entirely, but most of the world has rejected this.

So what we have here is that, in 2016, it's estimated based on earlier data that 20.9 million grams of oxymorphone will be used in the world. Of this, 12 or 57.4 percent are the U.S. and other smaller amounts in other countries.

So the four countries listed here, U.S., Italy, Switzerland, and Hungary, are using 96 percent of the entire world use. Most countries use almost none, or in many cases, they don't use any.

So the question as to how critical it is has been answered, it isn't that critical for most of the world. It isn't as though the difference in cancer or other legitimate reasons for using opioids for severe pain are different in this

country. It's that the promotion is different and, to some extent, the approval process is at least somewhat different.

This next slide asks the question, why did the FDA approve reformulated Opana ER in 2011 since it later concluded that the older version, then possibly to be made generic, was not removed for safety reasons?

This is not just a post hoc look because the basis for not approving it was the information based on the tamper activity that was described by Mr. Thompson and by the pharmacokinetic data. This all came up because in order to suppress FDA approval of generic oxymorphone, Endo petitioned the FDA in 2012 to conclude that the original Opana ER was removed for safety reasons.

The FDA rejected the petition in 2013, concluding that the available data do not support Endo's conclusion regarding purported safety advantages of OP ER relative to OP. Again, the rejection was based just on those first two of the three categories that are looked at in terms of

what should you do prior to marketing. The third the human abuse studies, have not been done yet and were not part of their discussion.

Then the next slide shows -- and this is from your briefing package -- the basis for FDA's conclusions. We disagree with the conclusion that it had that OP ER has safety advantages. And they talked about the fact that it does resist crushing somewhat, but they then went on to say that the extended-release features can be compromised, causing the product to dose dump -- this is the reformulated one -- when subjected to other forms of manipulation such as cutting, grinding, or chewing followed by swallowing.

They continue to say how OP ER can be readily prepared for injection despite Endo's claim that OP ER tablets have resistance to aqueous extraction. In addition, certain data suggests that OP ER can more easily be prepared for injection than OP, the older form.

So at the time that FDA approved it, at the end of 2011, all these data were available and

certainly were sufficient for FDA to say that the new product is not any safer. But they could have said the new product is actually more dangerous because this is what Canadians and many in this country called the precautionary principle; you don't have to go through all these tiers if at the first couple, the pharmacokinetic and the tampering studies, you've already raised some serious question about its safety.

So moving on, after this time, when it could have been rejected, I was on the FDA Drug Safety and Risk Management Advisory Committee, and this drug was never brought to the committee for reasons which I don't understand.

Certainly, in retrospect, FDA probably regrets it. But the point is that they had made enough findings to at least be looked at and listened to by the advisory committee.

So as you've heard in the last couple days, newer human abuse studies show that there may be some lower intranasal abuse, but on the other hand, you can dump the dose out, as pointed out in the

other ones, make it almost like an IR as opposed to an ER.

Again, in FDA's briefing documents, an additional factor contributing to intravenous abuse upon manipulation is the feasibility of obtaining suitable solutions for injection upon manipulation of the reformulated tablets, often in small volumes.

Then we get to the postmarketing epi studies, which again you've heard a lot of, and I'll just read a couple sentences of it.

"The totality of the evidence is compelling that, amongst those abusing reformulation caused a shift from non-oral routes from predominantly nasal to predominantly injection.

"The NAVIPPRO study data provided evidence that such shift occurred during abusers being assessed for substance abuse treatment and so forth." And the RADARS data also suggests a shift from inhalation to injection route through poison center calls.

Then just reiterating something, again, in

the FDA briefing document, why is oral oxymorphone not as preferable as by injection? And it has to do with orally 10 percent, only 10 percent is available, compared to 60 to 70 percent of oxycodone.

So as a result, oral administration of oxymorphone will result in lower plasma drug levels than the oral administration of an equivalent amount of oxycodone and could contribute to the oral route being less preferred by individuals and obviously going to the injection route.

So we get to the discussion questions, and I guess we're allowed to at least opine on these. I think that, aside from just the general dangers of switching from intranasal to injection, intravenous, we do have well-documented, confirmed in animal studies, that TTP-like illness and certainly HIV transmission, you do not get these obviously with intranasal use of this or anything else. However, the data inform our understanding of the risk-benefit balance.

In the last discussion question, what are

the consequences of taking regulatory action relating to reformulated Opana ER such as effects on prescribing or abuse patterns for other products?

I think the answer to that goes back to this first slide, where most of the world doesn't really use this drug very much, if at all. And it isn't as though they have drugs that we don't have here. We are the world leader overall.

As most people know from these same data, on any typical day, 1 out of 20 people in the United States, including all ages, is taking a defined daily dose of some opioid. And you see for this particular drug, this country sort of stands out like a sore thumb. If you adjust for population, it may be slightly higher in Italy and Switzerland, but in the rest of the world, no.

So I think on the question of, do the benefits of reformulated Opana ER continue to outweigh the risks, I think it's clearly no. And the no is because there's no unique benefit in terms of pain reduction from this drug, and there

are unique risks such as significantly increased injection use by people because they get high or serve their unfortunate addiction more quickly with this.

What are the consequences to this? Given the small amount of use, certainly the consequence of taking the reformulated Opana ER off the market would not be significant because other people have other dosage forms. Instead of creating something, or hoping to create something, the intention again, as FDA stated, the intention -- and they're absolutely right -- was to try and do something that deterred abuse. They did not believe, although they did have data back in 2011, that actually increased intravenous abuse.

So I think the committee should recommend taking this drug off the market. It is certainly no safer than, and it is arguably, I think very strongly arguably, more dangerous than the other dosage forms. Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 7 please come to the podium and introduce

yourself?

DR. POLANIN: Good morning. Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a licensed clinical psychologist in Washington, D.C. and a senior fellow at the National Center for Health Research. I previously trained at Johns Hopkins University School of Medicine.

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

The development of opioids formulated to prevent abuse is a high public health priority. Although the reformulated Opana ER was designed to prevent abuse by making it more difficult to abuse via intranasal or injection routes, the reality is very different.

Compared with other opioids, reformulated Opana ER, along with its generic counterpart, had

the highest injection abuse rates following reformulation. The FDA states that a product that has abuse-deterrent properties means that the risk of abuse is lower than it would be without such properties. Instead of lowering the risk of abuse, however, the reformulation of Opana ER seems to have resulted in significantly increased rates of abuse via injection.

The term "abuse-deterrent" is not accurate for reformulated Opana ER because the drug is widely abused. The FDA's guidelines state that a drug's label should reflect and describe a product's specific abuse-deterrent properties, such as an abuser's ability to crush a tablet and extract the opioid.

Despite the drug's incorporation of physiochemical properties aimed at making it more difficult to abuse by intranasal or injection routes, it is misleading to doctors, patients, and family members to say or imply that the drug is more difficult to abuse. In fact, the drug's black box warning should be amended to more clearly

specify the risks of injection abuse.

Compared to other types of opioid abuse, the injection of opioids is associated with increased infection risk. This risk is even greater because of Opana ER's high potency and short duration, which results in more injections per day. In addition, the high cost of this drug can lead to equipment sharing.

Individuals who injected the reformulated version have been especially likely to develop thrombotic microangiopathy. Abuse by injecting melted tablets resulted in an HIV outbreak in Scott County, Indiana. This drug is not only failing to deter abuse, but it is generating additional public health problems.

Opioid addiction is an epidemic in the U.S., and labeling a drug as abuse-deterrent, which is actually widely abused, would greatly contribute to the problem by misleading doctors, patients, and family members.

To be part of the solution rather than part of the problem, the FDA should be more specific and

accurate when claiming that a drug is abuse deterrent. Research indicates that many physicians believe that a drug labeled abuse deterrent is less addictive.

If a drug is crush resistant or difficult to crush in a specific way, it should be labeled as crush resistant, not as abuse deterrent. Only those drugs that significantly reduce the chances of abuse should be labeled as abuse deterrent, and the reasons for that label should be clearly explained.

We strongly agree with the FDA's 2013 denial of Endo Pharmaceuticals's citizen petition to label Opana ER as abuse deterrent, and we strongly urge the advisory committee to recommend that the FDA continue to deny this company's requests to include abuse-deterrent labeling. To reduce the epidemic, the FDA must hold pharmaceutical companies to a truthful standard. Only abuse-deterrent drugs should have that label.

We also agree with the FDA's 2013 denial of Endo Pharmaceuticals's request to take the original

Opana ER off the market. This company has not proven that the original Opana ER poses an increased potential for abuse compared with reformulated Opana ER. We urge the FDA to continue to deny Endo's request to withdraw the original Opana ER from the market for safety and effectiveness reasons.

We urge this advisory committee to advocate for patient safety by rejecting the company's requests and instead demanding that reformulated Opana ER have a stronger, more specific black-box warning. Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 8 please step to the podium and introduce yourself?

MR. COHEN: Thank you, Madam Chairman. My name is Dan Cohen. I'm an officer of KemPharm, a pro-drug discovery and development company that works on therapies in the ADHD, CNS, and pain discovery; the chairman of the Abuse-Deterrent Coalition, where I have been involved in the public policy development of abuse-deterrent technologies

since 1999. And most importantly, I'm here as a parent who one month from today would have celebrated my son's 30th birthday but for nine months ago, with a self-administered polypharma cocktail of benzodiazepine, therapeutic fentanyl, and whip-its, lost his battle to schizophrenia.

The Abuse-Deterrent Coalition was formed as a talk group of abuse-deterrent formulation innovators, patients, and issue advocacy organizations, and research groups to educate the public, policymakers, and the FDA on the importance of widespread use of abuse-deterrent technologies for Schedule II products.

The challenge before this committee today is well characterized by the following from an article written by Dr. Scott Gottlieb, commissioner designee of the FDA.

"Data from clinical trials and real-world use show that these tamper-resistant drugs make illicit use much more difficult. Rates of abuse from these reformulated drugs have started declining as a result, but a regulatory action that

FDA may be poised to take could inadvertently undermine those public health gains." His comments serve as a cautionary note today.

The mission of the FDA includes the analysis of whether a drug or device can be reasonably believed to be safe and effective for its appropriate intended use in an appropriate population. This mission can be divided into three generalized categories.

The primary public health benefit in this case is Opana with ADF formulation, reasonably believed to be safe and effective for its intended use. That's not at issue today.

The secondary concern is, does a product have a foreseeable and mitigatable efficacy or safety risk from misuse caused by well-meaning patients, including situations where patients or healthcare providers, for example, try and crush a tablet to make them easier to swallow and inadvertently defeat the slow-release coatings. That is also not before the committee today.

The tertiary public health concern, what is

at issue today, is whether the product, otherwise safe or effective for an intended use, should be restricted or removed from the treatment armamentarium when non-patients purposely misuse the product in a manner not intended for medicinal benefit.

The question of whether the benefits of the ADF outweigh the risks depends on whether the committee is looking at the metaphorical tree of Opana ER abuse with a broader forest of prescription drug abuse.

In addition, how does the forest change if the tree is removed? Do the small numbers of very significant SSEs discussed in the panel presentation outweigh the increased abuse potential and increased occurrence of intranasal abuse and the potential overdose SSEs in the absence of oxymorphone with ADF technologies?

It's important to ensure that we're using appropriate and similar terms for this discussion. Failing to agree or having unrealistic expectations will yield a faulty decision and will not

appropriately address the problem at issue. Those terms include abuse deterrence and who is the customer or the target of ADF.

What is not under consideration today is Opana ER oxymorphone as an abuse prevention technology or APF. There is no APF. Products with abuse-deterrent technology do not and are not expected to prevent abuse of scheduled products, only to lower through deterrence the abuse potential of these products.

Innovators in ADF technology want to do more, but the question on the table involves what science is possible today and not to wait for what we hope will be a technology tomorrow.

The development of abuse-deterrent formulations is part of a multi-factorial effort to reduce the risk of abuse and diversion. APF is not currently technically feasible, even though it remains the lodestar of innovators. But every step we take in technology development is a move closer with current technologies to making effective therapies available for patients while making

abuse, misuse, and diversion of important medications as difficult as possible. But to give full meaning to that statement, it's important to agree on another set of standards. Who is the customer for ADF?

Most of the discussion, data, and the heartbreaking anecdotal stories reviewed yesterday have focused primarily on the addicted or criminal abuses of drugs, but not misusers. Abuse deterrence technologies, ADF, is best understood as a technology that reduces the risk of misuse and diversion, focused primarily on the opiate naïve and the early stage recreational abusers.

Current ADF is not a technology that is capable of effectively deterring an addict or a highly experienced professional abuser. However, ADF's success is that it will ultimately reduce those numbers of addicts and highly experienced abusers by making abuse progression at its early stages more difficult.

Abusers that are deterred from progressing or even starting to ever progress to more

aggressive forms of abuse is the goal of ADF, and Opana has met that standard.

In this hearing, two clusters of significant SSEs were examined, one related to the HIV cluster in Indiana and the other of the TTP-type illness. These are serious SSEs, but based on the observed changes and the abusive behavior as noted in the RADARS data presented yesterday following the introduction of the ADF technologies into Opana ER, this panel must ask itself, what is the unintended consequence of increasing the abuse potential should only the most abusable forms of extended-release oxymorphone be available for patient treatment?

On the issue of the ADF technology, it is again important to step back from the tree and look at the forest. The effort that is required to manipulate ADF and Opana ER is purposeful. It is not a risk of the patient treatment paradigm, nor is it a risk of misuse by the well-meaning patient or healthcare provider. It is a risk of purposeful and illegal manipulation, misuse, and abuse and

needs to be called out as such.

Clear warnings to the abuser community, however, about this potential additional danger for misuse of this product would have benefits, but I urge you not to penalize patients for the risky behavior of the abuser, especially for this moiety, as it is typically prescribed only after patients have failed other therapy. ER oxymorphone is more a treatment of last resort, and it is very rarely a first-line therapy.

By holding this hearing and asking these questions, the ADCOM creates the potential for substantial benefits. The division has held in other ADCOMs that, for example, because of the awareness of liver toxicity by the use of excessive acetaminophen and hydrocodone APAP combination IR products, abusers will seek to mitigate or avoid those risks that cause bodily harm by washing out the acetaminophen. The risk they want to avoid is the liver damage, but not the risk of supertherapeutic doses of the opioid itself.

The same benefit of calling out the risk of

TTP arises here. And of course, needle sharing HIV risk is already well known and unfortunately ignored by abusers.

My last quote, "Policymakers press the drug makers to come up with these tamper-resistance formulations as one way to combat diversion and abuse. It was rightly hoped that these new formulations could become one tool in combating illicit diversion and abuse. It has worked." That's also Dr. Gottlieb. Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 9 come to the podium and introduce yourself?

(No response.)

DR. WINTERSTEIN: Would speaker number 10 come to the podium and please introduce yourself?

(No response.)

DR. WINTERSTEIN: Speaker number 11, Dr. Begansky will read.

LCDR BEGANSKY: Thank you. I'll be reading a statement from Brooks Bono.

"My name is Brooks Bono. I am 38 years old and have been suffering from chronic pain since I

was a teenager. The pain started to get worse in college, eventually resulting in a life that made regular work and a totally fulfilling life impossible.

"I tried almost every medication that was available, but they either did not provide adequate pain relief or the dispersal mechanisms were not even, causing my pain to spike up and down. At one point, the pain had become so intense that I had to use a wheelchair to get around, severely limiting my already limited life.

"All of that changed when I was switched to Opana ER. After being tapered up to my current dosage, I was able to reclaim the life that had been on hold for so many years. I've been taking Opana ER for about a decade now., and while I still do suffer from chronic pain, I have a great job and an exceptional life. This medication has given me the ability to do what most people take for granted, working, being able to have a normal social life, taking out the garbage.

"Before I was prescribed Opana ER, these

things were either difficult or impossible. I hope you take in consideration the thousands of people who have been able to take back control of their lives with this medicine.

"Those of us who tried other medications but only found relief in Opana rely on it, and without this medication, we would be forced back to unfulfilled lives that are dictated by our pain. That would not only be reckless, but cruel. Thank you for your time."

DR. WINTERSTEIN: Speaker number 12, this statement will also be read by Dr. Begansky.

LCDR BEGANSKY: This is the testimony of Orvalene Prewitt.

"I appreciate the time the committee has allowed me to present testimony on behalf of myself and other chronic pain patients I know who could not attend today. Living with chronic pain was never on my radar as something I expected to become part of my life, yet within months, after a traumatic event in our family in 2006, chronic pain became my constant companion.

"One day, I was fine. The next, I couldn't stand up straight. Walking was painful due to inflammation and stiffness in my knees. My hands swelled to the point I could no longer write, and I couldn't raise my arms to reach without intense pain.

"Activities of daily living like dressing, personal hygiene, et cetera, were dreaded because of the associated pain. Cutting my food became impossible at times, even to the point of having to allow someone else to cut my food. Chronic pain robbed me of my ability to work full time. Simple things like diapering my infant granddaughter became impossible, and I could no longer pick her up because of the associated pain.

"Each day became a challenge to get through, and I felt I was existing rather than living. Diagnosis for the origin of my chronic pain wasn't easy, but after several visits and tests, my medical team diagnosed me with rheumatoid arthritis.

"This was just the beginning of my journey

with this lifelong condition. I wanted to be part of life and not just watch it go by due to the crippling effects of chronic pain. Thus, I embarked on my new job, to regain a quality of life to accomplish that goal.

"I've worked in the health education non-profit world for 29 years with many of those years helping others through Stanford University's evidence-based self-management programs.

"I know that the majority of time spent managing a chronic condition is done outside the medical setting. Thus, self-management had to be an integral part in achieving my goal. Healthcare is very personal and must be coordinated between physician and patient based on complete knowledge of a patient's medical history.

"We started first by trying to reduce my inflammation and pain so I could function well enough to add other comprehensive treatments. Medications gave temporary relief during the daytime, but nighttime was the worst with the chronic pain reaching its peak.

"After trying steroids and NSAIDs, without success, to get the pain in control, opioids were added. During times of relief from chronic pain, I did chair exercises for arthritis, stretching, hand exercises, muscle relaxation, biofeedback, distraction techniques, coping skills, occasional massage, et cetera. Simultaneously, we used disease-modifying anti-rheumatic drugs, which gave me short periods of relief, but soon became ineffective.

"I then moved to biologics. I was fully informed of the potential side effects, including higher risk of infections, of which I ultimately had many, but made my decision hoping that the benefits would outweigh the risks.

"I was willing to take the chance for a better quality of life. The first IV biologic, a TNF inhibitor, gave me 4 to 6 weeks of some relief followed by two miserable weeks until I could get another IV.

"After two years, I finally moved to an IV biologic that affects IL 6. I set goals for

myself. I was able to taper and get off the opioids within the first two years with steroids and NSAIDs being continued for chronic pain management. My desire was to improve enough to taper off the steroids and the NSAIDs.

"Today, almost 11 years later, I am better. I no longer take biologic steroids or NSAIDs. My chronic pain is now manageable because of the comprehensive approach we took, including the self-management tools I used from the Stanford programs. Because my pain is no longer front and center, I'm participating in life by working full time, enjoying family, socializing, et cetera.

"You might wonder why I wanted to share my story. It is because I am not unique, but rather, like so many other people I work with who experience chronic pain, we all have an unexpected journey when chronic pain arrives. Lives are disrupted. Dreams seem out to reach.

"Relationships are challenged when no one knows how to help, and we are often judged if we complain of chronic pain and seek treatment for it.

After all, it cannot be measured by a blood test. It cannot be seen by the human eye.

"We all have a backstory, yet many will judge us without ever knowing how chronic pain entered our lives or how it impacts us. We all long to be able to participate in life by managing our chronic pain rather than having it control us, but we need the tools to do that.

"So what are some of these tools? Comprehensive medical treatment that is readily available and affordable. Few comprehensive care clinics exist and sure as often do not cover many of the services like I used that are offered.

"Number two, treatment decisions should be made only between the patient and the physician with the goal being improving the quality of life for the patient. Physicians should have the latitude to prescribe what is medically necessary for the health and well-being of the patient.

"Number three, for chronic pain management, opioids should not be the first choice for pain management nor the only treatment offered.

However, sometimes they are essential for chronic pain patients for temporary use to get pain under control.

"Getting pain under control can be a gateway for other comprehensive treatment options to be initiated and hopefully eliminate the need for opioids Physicians should not be afraid to use opioids if chronic pain management cannot be successful with other options.

"Lastly, as a nation, we need to realize the impact chronic pain can have on our economy and society if not controlled. Jobs can be lost, finances impacted, healthcare burdened. Chronic pain patients want to have fulfilling lives in spite of our chronic pain. We are not the cause of the opioid epidemic, but rather find when our chronic pain cannot be managed, opioids may be necessary for pain control.

"When pain is more manageable, it allows us to try other comprehensive treatment modalities like the ones I used. Our goal as people living with chronic pain is to manage our pain in order to

have a quality of life that allows us to participate in life and society, provide for ourselves, and contribute to the economy rather than drain it.

"I hope this committee can be part of the solution to this problem. Thank you for your time in listening to my comments."

DR. WINTERSTEIN: Would speaker number 13 please step to the podium and introduce yourself?

MS. CAWKWELL: Hi. Good morning. My name is Gail Cawkwell, and I'm chief medical officer of Purdue Pharma and a full-time employee of Purdue Pharma. I appreciate the opportunity to speak today about Purdue's approach to the important national health challenges related to opioid abuse and its consequences, including addiction and overdose.

I personally, and Purdue by extension, do not want a single opioid prescription written or filled other than, to wit, by a fully informed and fully trained healthcare professional for carefully selected patients and at the dose and for the

duration needed to achieve treatment goals.

One of the ways we at Purdue are working hard to reduce abuse and diversion is through the development of opioid analgesics with abuse-deterrent properties. Last year, former FDA commissioner Cailiff said, "We recognize that abuse-deterrent technology is still evolving and only one piece of a much broader strategy to combat the problem of prescription opioid abuse."

At Purdue, we believe that the FDA has set appropriately rigorous standards to achieve abuse-deterrent labeling, and it is critical that the pharmaceutical industry continue to evolve and develop meaningful abuse-deterrent technologies.

I want to emphasize that the potential societal benefits of abuse-deterrent technologies will not see their maximum impact until most or all opioids have achieved FDA standards and have approved abuse-deterrent labeling and until patients have access to medicines that have met these standards.

At present, we are far from achieving these

objectives. In fact, just over 2 percent of all opioid prescriptions filled are for an opioid that includes abuse-deterrent labeling.

Last year, Dr. Cailiff also urged opioid manufacturers to "step beyond the requirements from the FDA and display corporate responsibility to contribute in tangible ways to dealing with the societal consequences of these products."

We at Purdue are striving to meet that challenge. Although our products represent 2 percent of the prescriptions for opioid analgesics, we believe we are taking important actions to help.

In addition to our work on abuse deterrence, we are taking other steps including developing novel, non-opioid treatments for pain through our research and development efforts. We have also sought out research proposals on tapering and discontinuation of chronic opioid therapies, since unfortunately little data exists to help doctors do this important task.

The CDC's guidelines for prescribing opioids

for chronic pain were distributed by Purdue to more than 140,000 prescribers and pharmacists shortly after they were issued, and we've also provided important materials to physicians and pharmacists that we call on. This includes one that the surgeon general created as part of his Turn the Tide campaign, and it talks about appropriate patient selection as well as treatment risks. And of course, we provide materials designed to raise awareness about the extended-release long-acting opioid REMS.

With respect to prescription drug monitoring programs, we support their universal and effective use and have done so for many years. Recently, we announced a collaboration with the Commonwealth of Virginia to integrate information from its prescription drug monitoring program into the doctor's work file and to encourage more prescribers to access the prescription drug monitoring program. These are just some of the steps we're taking.

Before I conclude, I thought I would take

the last minute to provide some facts about OxyContin's PEO-containing formulation since questions were raised by the committee about this topic yesterday.

While both Opana ER and OxyContin do use a PEO basis in their formulations, they use different processes around PEO, and as an FDA speaker noted, there are many different types of PEO. OxyContin's final formulation is convection cured while Opana ER uses a hot melt PEO extrusion process.

These are distinct processes, and they confer distinct properties on the final formulation. The distinct properties require separate evaluation of their potential for abuse-deterrent properties. And, in fact, differences were found, and these led to differences in labeling.

In conclusion, I just want to reiterate, of course we all know prescription opioid abuse and addiction are serious problems and they are very complex problems. By far, the best opportunity at improving this problem depends on all stakeholders

partnering for solutions.

We look forward to participating in additional collaborations with both the public and private sector, including perhaps with some of you in the room here today. I want to thank you for your attention and for the important work you are doing as part of this advisory committee meeting. Thank you.

DR. WINTERSTEIN: Thank you. The statement by speaker number 14 will be also read by Dr. Begansky.

DR. BEGANSKY: All right. This is the statement of Andrew Kolodny, executive director of Physicians for Responsible Opioid Prescribing.

"My name is Dr. Andrew Kolodny. I have no financial relationships to disclose. I am the executive director of PROP, Physicians for Responsible Opioid Prescribing, an organization with a mission to reduce morbidity and mortality caused by overprescribing of opioid analgesics. My comments today are on behalf of PROP.

"There are important issues specific to

oxymorphone and abuse-deterrent labeling that I will mention, but there are also general concerns about the approval process for opioids and opioid labeling that I would like to take this opportunity to raise.

"With regard to oxymorphone, I urge the advisory committees to consider that the molecule has a unique risk. I am referring to its low oral bioavailability. When injected, oxymorphone becomes 10 times more potent compared to morphine, which is 3 times more potent than hydromorphone, which is 5 times more potent when injected.

"This characteristic makes the drug especially desirable and especially dangerous to opioid-addicted injection drug users, and they also explain why Endo pooled oral Numorphan off the market in the 1970s after widespread reports of abuse and overdose deaths.

"With regard to abuse-deterrent labeling, I would like the advisory committees to understand PROP's position. We believe the term 'abuse deterrent' is misleading because making opioids

hard to crush does not deter abuse. Furthermore, because the term 'abuse' is often used interchangeably with addiction, the term abuse deterrent may mislead many prescribers.

"A survey of primary care physicians by Dr. Caleb Alexander found that 46 percent of doctors mistakenly believe that abuse-deterrent formulations are less addictive. PROP is fearful that opioid manufacturers will exploit this misunderstanding. If prescribers underestimate the risk of addiction, they may continue to overprescribe, which will worsen the opioid addiction epidemic. PROP's position is that a pill that has been made difficult to crush for injection use or snorting should be labeled crush resistant, not abuse deterrent.

"With regard to PROP's general concerns about opioid approvals, I would like to point out that Opana was approved in 2006 using a new efficacy trial methodology called Enriched Enrollment, and this methodology has been used for all subsequent opioid applications.

"Enriched Enrollment means that only patients who tolerated oxymorphone and found it helpful were randomized to participate in the trial. Patients randomized to the placebo arm were tapered off oxymorphone and onto the placebo. Setting up a trial in this manner results in a loss of the double blind because patients' switched from an opioid to a placebo are sure to know it.

"Perhaps the most serious problem with Enriched Enrollment trials is that the results are not generalizable because the drug is studied in a unique population. This is why some researchers liken Enriched Enrollment trials to cooking the books.

"Another serious concern about approval of Opana in all other opioid formulations is that the efficacy trials are done on patients with back pain. This is inappropriate because there is an expert consensus that opioids should not be used for back pain.

"Just last month, the American College of Physicians issued a guideline on treatment of

acute, subacute, and chronic back pain, which recommended that physicians avoid opioids. Exposing study subjects to weeks of treatment with a highly addictive drug that is not recommended for the condition they suffer from raises serious ethical questions.

"PROP has serious concerns about opioid labeling. According to the Food, Drug, and Cosmetic Act, drug makers are only permitted to promote products for conditions where benefits abuse outweigh risks. These conditions become the on-label indication. If FDA was properly enforcing this law, opioid manufacturers would not be permitted to promoted opioids for chronic pain.

"To quote Dr. Thomas Frieden, the former CDC director, in a New England Journal of Medicine editorial, he wrote, 'The science of opioids for chronic pain is clear. For the vast majority of patients, the known, serious, and too often fatal risks far outweigh the unproven and transient benefits.'

"Lastly, PROP is concerned that opioid

labels do not include a suggested upper dose limit. Opioid overdoses are one of the leading causes of accidental death in the U.S., yet they are one of the only medications that do not include a suggested upper dose. Even over-the-counter medications include a suggested maximum dose.

"The CDC has asked prescribers to avoid increasing opioids to 90-milligram morphine equivalence. The CDC has made clear that this is a dangerously high dose, yet opioid formulations come in dosage units that are so high, just one pill twice a day can exceed 90 milligrams of morphine.

"For example, a patient taking Opana ER, 40 milligrams, twice a day, is taking the equivalent of 240 milligrams of morphine. That is more than 2 and a half times the CDC's upper dose limit, yet the patient and prescriber may be unaware that this is a dangerously high dose because it is only one pill taken twice a day.

"In addition to the questions FDA will be asking you, the advisory committee members, I hope you will consider the following additional

questions.

"One, should oxymorphone be pulled from the market in light of its unique risks?

"Two, should FDA abandon use of the term abuse deterrent?

"Three, should Enriched Enrollment methodology be used for efficacy trials involving opioids?

"Four, should efficacy trials for opioids be done on back pain patients?

"Five, should opioid makers be permitted to promote use for chronic pain?

"Six, should opioid labels include a suggested maximum dose?

"Thank you for your careful consideration of my testimony."

DR. WINTERSTEIN: Would speaker number 15 please step up to the podium and introduce yourself?

DR. ADAMS: My name is Joseph Adams, M.D. I'm a board-certified addiction medicine specialist, and I'm the medical director of an

addiction treatment program in Baltimore. I'm testifying on behalf of the National Physicians Alliance, which represents physicians across medical specialties with a commitment to professional integrity and which accepts no funding from pharmaceutical companies. And I have no conflicts of interest to report.

I'm here to testify that Opana ER should not be considered as an abuse-deterrent formulation and that the approved indication for opioids in general for long-term use in chronic non-cancer pain should be reevaluated.

The determination that benefits outweigh risks should be mandatory for labeling and promotion of any medicine for any particular indication, of course, but when it comes to opioids used long term for chronic non-cancer pain, this has never been established. Opioids have never been shown to be either safe or effective for long-term use.

In this cost-benefit analysis, the benefits are unknown and the costs are catastrophic since

one of the side effects of opioids is death and over 180,000 Americans have experienced that side effect. That's the number that have died of overdose from prescription opioids over a 15-year period. That's more than the number of Americans who died in the entire Vietnam War.

With these massive numbers of deaths from prescription opioids and unknown benefits from long-term use, opioids clearly should no longer be approved or promoted for long-term use for chronic non-palliative pain.

At the opioid treatment program where I work, some patients come to us because they have developed an addiction problem from swallowing prescription pills, and others have developed a problem by shooting heroin. And either way, it's exactly the same problem.

Most patients we see have heroin addiction, and I ask every patient how their problem began. In the great majority, their addiction began by taking opioid pain medicine as described by mouth, typically after surgery or an injury, and

typically, they have never tried to snort or inject the medicine.

A smaller number of patients have snorted their pain pills, but the addiction problem had developed while taking the pills by mouth. Only after they had developed problem use did they ever attempt to try snorting the pills.

Today, we're considering Opana ER, but I'm going to use as a more familiar example reformulated OxyContin, which is also crush resistant, and what I say will apply equally to Opana ER.

It is true that OxyContin as an example deters snorting and shooting OxyContin, but it does not deter opioid use generally in any way. The literature is clear that people tend to develop opioid abuse and addiction by the oral route. Generally, people who attempt to put oxycodone in their nose already have an abuse problem.

OxyContin deters people from snorting or shooting OxyContin, but since the people it deters already have an abuse problem, if they're inclined

to snort an opioid, they just use another brand or they use heroin. At that point, they'll snort or shoot one opioid or another if they are inclined to do so.

The literature is clear on this point, that the reformulation of OxyContin in 2010, making it harder to snort or inject, was immediately followed by a surge in abuse of oxycodone IR and generic oxymorphone ER. The patients just used a different opioid. Snorting did not cause their abuse. The sequence was the other way around.

OxyContin represents 10 percent of prescribed oxycodone and only 3 percent of prescribed Schedule II opioids generally. So deterring the snorting of the brand OxyContin in no way deters people who are inclined to snort an opioid from doing so. This applies equally to Opana ER, so the term 'abuse deterrent' is not accurate.

The other problem is the unintended consequence that the term abuse deterrent will give prescribers a false sense of security so that they

won't worry so much about causing abuse or addiction. Abuse deterrent will more than anything be a marketing term that will lower the threshold for prescribing. It will clearly lead to more prescriptions. And it's likely that that is an intended consequence by the manufacturer. But more prescriptions will predictably lead to more abuse and addiction and more deaths.

When I practiced internal medicine, I was influenced by Purdue Pharma's infamous marketing campaign because I learned not to worry too much about causing addiction. In retrospect, I prescribed opiates for chronic pain in more patients than I should have. Now, only years later, am I able to recognize the consequences of that kind of prescribing, and for the great majority, opioid addiction is iatrogenic.

Abuse and addiction develop in a certain proportion of patients as an inevitable consequence of large numbers of patients taking chronic opioid pain medicine as prescribed by the oral route. Formulations that deter crushing of one particular

brand of opioid do not deter abuse of opioids generally. Thank you.

DR. WINTERSTEIN: Thank you. Would speaker number 16 please step up to the podium, introduce yourself?

DR. TWILLMAN: I'm Bob Twillman. I'm standing in for Dr. Charles Argoff. Dr. Argoff has submitted videotaped testimony.

(Video played.)

DR. ARGOFF: My name is Dr. Charles Argoff, and I'm professor of neurology at Albany Medical College and director of a comprehensive pain management center at Albany Medical Center in Albany, New York. The comments that I'm about to make reflect my own personal opinion regarding this subject matter.

Appropriate, meaningful, and compassionate treatment options for tens of millions of Americans with persistent chronic pain have come under significant scrutiny in the past few years in the face of our nation's deepening concerns with rising opioid abuse rates.

As a physician who's American Board of Medical Specialties certified in neurology and in pain management, I focus on prescribing safe, responsible, and effective treatments for people who are experiencing severe chronic pain. In that context, I am increasingly concerned that policymakers and prescribers are conflating two different and critically important issues.

Addressing the treatment needs of people experiencing severe chronic pain and addressing real concerns regarding the abuse and misuse of various controlled substances, including opioids, are being conflated to such an extent that as a result, undue harm to people in pain is becoming the new standard of care due to sudden cessation of treatment that had previously been efficacious. This is clinically unacceptable.

The foundation of the accepted standards of medical practice is based upon offering appropriate treatment in as safe and effective manner as possible. When clinicians are able to choose among multiple treatment options for any medical

condition, the safest options are meant to be prioritized over those that are less safe. This principle of medical practice is extremely relevant to pain management.

Tens of millions of people experiencing severe chronic pain do not experience sufficient relief from multiple non-opioid therapies. These include complementary approaches, rehabilitation approaches, non-opioid-pharmacological approaches, as well as interventional therapies, including injections, spinal stimulation or even intraspinal analgesic approaches.

For these tens of millions of people experiencing severe chronic pain who have not benefitted from non-opioid therapies, chronic opioid therapy may be a safe and effective treatment approach. Thus, appropriate access to such is necessary.

Recognizing that all prescribed and over-the-counter medications carry risks, we need to focus on the availability of all types of medications that are as safe as possible.

Therefore, patients prescribed opioid analgesics, both immediate release or IR and extended-release, also known as ER, should only be prescribed as safest available agents.

What is the state of available opioid analgesics? Currently, multiple opioid analgesic preparations, including multiple distinct opioid chemical entities, can be prescribed. This is vital to optimizing patient care, as is true with various non-steroidal anti-inflammatory agents, statins, and certainly with medications used to treat diabetes, while one compound may be effective for some patients, a different compound may be best for others.

This underlies with respect to opioid therapy the concept of opioid rotation and highlights the need to have multiple opioid analgesics, including oxymorphone, available to most effectively utilize this class of analgesics to treat chronic pain.

Yet, currently available opioid analgesics, even if the same chemical ingredient, are not

equal. Safety enhancements have been made to certain but not to all preparations. The FDA has designated specific opioid formulations as having abuse-deterrent properties.

Other formulations have been developed to provide greater safety, but the FDA has not designated them as meeting the standards for receiving an abuse-deterrent label. However, what cannot be overlooked is that there are multiple additional IR and ER opioid formulations that have not been manufactured to enhance safety in any specific way. Again, we cannot overlook that there are multiple IR and ER formulations that have not been manufactured to enhance safety in any specific way.

Shockingly, the prescriber too often does not have full control of what preparation his or her patient picks up at the pharmacy. We need to find a path to ensure that all opioids, both immediate-release and extended-release, are armed with abuse-deterrent properties.

Equally important, we need to ensure that

physicians as well as other prescribers understand these benefits.

The reality is that for millions of people with chronic pain, opioid therapy is effective and safe in helping them to live more comfortable and productive lives. Let me say that again. The reality is that for millions of people with chronic pain, opioid therapy on a chronic basis is effective and safe in helping them to live more comfortable and productive lives.

This is true, even in the absence of abuse-deterrent formulations for all opioids and for all prescriptions, but we can and must do even better on three fronts.

First, we must maintain the availability of multiple specific opioid analgesics to meet the specific and personalized needs of the people we treat, who without such availability would suffer unnecessarily.

Second, we must take actions that meaningfully incentivize the development of the next generation of abuse-deterrent formulations.

Third, we must ensure that those experiencing severe chronic pain for whom chronic opioid therapy is an appropriate treatment option have access to the safest medication options currently available.

In summary, conflating appropriate and effective opioid use with opioid abuse and harm will neither help those who benefit from chronic opioid therapy to be optimally treated, nor will it sufficiently address the disease of addiction, as well as the harms associated with opioid abuse and appropriate treatment for such. Thank you.

DR. WINTERSTEIN: Will speaker number 17 please step up to the podium, introduce yourself?

(No response.)

DR. WINTERSTEIN: The statement of speaker 18, Dr. Begansky will read.

LCDR BEGANSKY: Thank you. This is a statement from Michael and Barbara Lissner. I'll start with Michael.

"Members of the committee, I would like to present my personal history and success with Opana

ER. I am 60 years old, a child of Holocaust survivors, a husband, a father of two children, and a practicing attorney who together with my wife and law partner manages a relatively small law and accounting firm with a staff of 20 people.

"Our firm focuses on the needs of Holocaust survivors, and for many years, we have worked closely with the Social Security Administration to ensure that Holocaust reparations are properly exempted from federally funded programs. I have always led an active lifestyle and competitively participated in many sports and activities.

"In 1993, my life changed. I suffered a severe disc herniation with terrible neurological symptoms. After almost a year of untold pain and misery, I underwent a laminectomy. My symptoms abated and, for several years, I was able to participate again in my family life, my law practice, and even managed to win a 1995 Bergen County, New Jersey tennis championship.

"Then in 1997, I suffered post-surgical failure and was re-admitted to the hospital for a

discectomy. From 1997 to 2009, I was generally able to function. But in 2009, I again suffered from post-surgery failure and my pain and accompanying neurological components were worse than ever, to the point that my life was severely restricted.

"I tried every possible therapy. And then, after sequential opioid and adjuvant medication trials, which I was unable to tolerate, my physician placed me on Opana. The results were almost immediate. My dose is stable, cognitive effects are minimal, and I have relied on the same dose for many years.

"Opana has efficacy without untoward side effects and allows me to function successfully. Without Opana, I would not be able to maintain my law practice, exercise which I do regularly, or participate in family functions such as my daughter's upcoming wedding. Opana provides pain control for people who suffer from cancer and other chronic pain where other medications were not successful.

"In conclusion, I respectfully request that the committee not compromise the health of people that are using Opana correctly. Respectfully submitted, Michael Lissner."

DR. BEGANSKY: This is from Barbara.

"My name is Barbara Urbach Lissner. I have been married to Michael Lissner since 1984, and we have two children. Our daughter is 28 years old, and our son is 31 years old. We have also been partners in our law firm since 1988 and our accounting practice since we established it in 2008. Together, we employ approximately 20 people and provide support for most of our employees' immediate families.

"Michael has already presented to your committee his history of several serious back episodes, which left him with severe and chronic pain. His pain was so debilitating at times, prior to his treatment with Opana ER, that he could not leave our home, get in and out of a car, work, and even lift his leg from the floor to bed without assistance.

"He could not even imagine a time in his life without excruciating pain and could not think about returning to his regular activities of work, coaching our children in their sports, playing tennis and golf, dancing, bike riding, and even simply enjoying a simple walk.

"My husband loved life, but was so debilitated by pain that it really felt to the both of us that we would never again enjoy life as we had previously enjoyed it.

"Through the years, doctors recommended numerous physical and medication treatments. It was only as a result of his determination to again enjoy life that he continued to work with a pain doctor to find a drug that would control his pain without side effects such as loss of memory, energy, et cetera.

"He and his doctor persevered to develop a regimen which included a regimen of physical therapy, exercise, and Opana ER that allowed him to return to his active, professional, and personal life.

"Michael is responsible with his medication. He does, however, depend on this medication to manage his pain and continue living a healthy and meaningful life.

"I write to the committee in the hope of demonstrating that Opana ER is not a danger that should be taken off the market or made unavailable to those who could benefit from its controlled use. Instead, I write to show the committee the important value of Opana ER to patients, their families, colleagues, and friends.

"Abused by some should not prevent patients who benefit from Opana ER from refilling their prescription and properly using this medication to live life as close to the life they once knew prior to falling victim to severe chronic pain.

"Thank you for your consideration and kindly allow my husband and others also suffering from chronic pain to have access to this life-maintaining medication."

DR. WINTERSTEIN: The open public hearing portion of this meeting has now concluded, and we

will no longer take comments from the audience. The committee will now turn its attention to address the tasks at hand, the careful consideration of the data before the committee as well as the public comments.

So given that we have less time -- okay. Since we have a little bit more time, first question I'm supposed to ask now is, are there any other clarifying questions in regards to the presentations from yesterday?

(No response.)

DR. WINTERSTEIN: So we will now break for lunch, and then return with the start of our discussion. We will get our charge from Dr. Staffa right after lunch.

Are we going to have a one-hour lunch break or shorter? One hour? So we will break for lunch, and we'll reconvene here at 1:00. Please be on time, so that we can get out on time. I think that's in everybody's interest.

I'm trying to see what I have to read over lunch. Yes. The big thing that you need to know

is don't discuss anything over lunch. Reserve your discussion for when you return, and we'll see you soon.

(Whereupon, at 11:59 a.m., a lunch recess was taken.)

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

(1:03 p.m.)

[Audio gap - technical difficulty].

Charge to the Committee - Judy Staffa

DR. STAFFA: [In progress] -- that complicate drawing inferences from the available epidemiologic studies, based largely on convenient samples that change over time.

The anecdotal data, however, are compelling and appear to paint the picture of a perfect storm in which a highly potent opioid that's short acting can best be extracted from its original formulation and abused in a specific manner that both enables and encourages the kinds of behaviors that can result in sharing solutions and needles, and thereby heightening the risk for transmission of bloodborne pathogens.

We also have animal data to demonstrate a likely mechanism by which the particular high molecular weight PEO used in the formulation of Opana ER may cause a TTP-like illness when injected.

Finally, but quite importantly, all of this may be occurring in an environment where other oxymorphone products, both extended release and immediate release, are also increasingly abused by both snorting and injecting, and the injecting seems to be occurring at similar rates to Opana ER.

Based on the information you've heard, we're asking for you to address the following three questions. The first question is a discussion question. Please discuss the strengths and limitations of the experimental and epidemiologic data regarding the safety concerns with reformulated Opana ER, including the observed shift in abuse patterns from nasal to injection route of abuse and reports of a TTP-like illness and HIV transmission associated with intravenous abuse of this product.

How do the data inform our understanding of the risk-benefit balance for Opana ER relative to other oxymorphone products?

The second question is also a discussion question. Please discuss any potential

consequences of FDA taking regulatory action relating to reformulated Opana ER such as effects on prescribing or abuse patterns for other products, including other oxymorphone products.

Then third, the third question is a voting question where we're asking specifically, do the benefits of reformulated Opana ER continue to outweigh its risks?

Just to provide a little clarification, when we talk about regulatory actions, we're talking in general about the kinds of actions that are within FDA's authority to take. FDA can take many kinds of regulatory actions. Labels can be changed. REMS, the risk evaluation and mitigation strategies, can be invoked, and products can be withdrawn from the market.

Each level of regulatory action clearly has with it a different hurdle of data or justification that are needed. But our goal right now is to be asking for your recommendations in the broadest possible sense. So don't feel limited to any particular kind of action. We're not being coy.

We're not secretly thinking that we're going to do something. We're actually looking for your recommendations as to if and whether regulatory actions should be taken on this particular product. Thank you very much.

Questions to the Committee and Discussion

DR. WINTERSTEIN: Thank you, Dr. Staffa.

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

There are a few new panel members, and some of you may not have watched those discussions. There are two things that are important. One is, we have always information from the last day in our heads, but the discussion questions are actually structured. And it is very helpful with such a large committee to stick to the question at hand

and try to focus the discussion on that particular question.

There are two reasons for this. One, we will have a much more effective and efficient way of exchanging opinions, and, two, you make my life much easier because I'm the one who has to summarize all of this at the end.

So please stay on topic. And the very first thing that we're going to discuss is A. So our question is, please discuss the strength and limitation of the experimental and epidemiologic data that was presented to us regarding the safety concerns with reformulated Opana. And we will focus the first portion of this discussion to the observed shift in abuse pattern from the nasal to injection route of abuse.

So the question focuses on the data that we have been presented and the shift that has been presented to us with respect to abuse pattern. Okay? I saw Ms. Higgins first.

DR. HIGGINS: My feeling is that, overall, the data do support a shift in abuse from

intranasal to IV route of abuse. And I really look to Tennessee as a case study of that experience. And that's really what hit home for me yesterday.

DR. WINTERSTEIN: Dr. Ciccarone?

DR. CICCARONE: Hi. So again, my perspective is that of a three-headed person. I'm a clinician, I'm an epidemiologist, and I'm also an anthropologist. So my read on the data, both quantitative and qualitative, goes along with my experience. I'm currently NIH funded to do a project called heroin transition. I spend a lot of time in the field with injection drug users.

I think the evidence does support stable and/or increasing IV route of misuse of Opana post-reformulation while clearly decreasing intranasal routes of misuse.

Opana appears to have street cache. It's a valuable drug. The Zibbell paper from New York shows that IV users are choosing Opana 3x over any other street opioid. Perhaps that relates to availability, but I have a strong anecdotal experience that it relates to desirability, the

same way in which we say all opioids are not equal. Industry knows this. Patients and their advocates know that.

Well, guess what? The street users know this as well. There's something about oxymorphone that's highly desirable. If users are willing to pay $200 for a 40-milligram dose of oxymorphone, that says something.

Oxymorphone is a powerful opioid. For those on the street, it is interchangeable with heroin. I know a number of users that I've followed over the years who go back and forth. It is dose equivalent 4 to 1 over heroin. That's my calculation. And the HIV outbreak in Scott County and the hepatitis C epidemic that's going on through Appalachia is directly related to the reformulated PEO product.

I'm going to walk through that. You've noticed I've been asking questions yesterday about volume and extractability, so I'm just going to quickly walk through that.

ADF products such as Opana ER, particularly

Opana ER, here is the mechanism. The ADF of this particular formulation requires high volumes for syringeability and extractability. Users have figured this out. It took a little time. It took a lot of experimentation on the street. The method out there now is not difficult. It's not hard, but it does require high volumes.

How do high volumes fit into this? Each 40-milligram Opana requires 5 to 10 milliliters to go into solution. Now, I know we heard yesterday from the CDC expert that he was talking about 150 to 200 units. That's 1.5 to 2 mLs of liquid. That was for a quarter, a 10-milligram dose of a 40-milligram divided up. If you want to inject a whole 40 or split it equally among colleagues, it requires going into a solution with 5 to 10 mLs of water.

Here's what makes the drug more social. The fact that it requires high volumes invites other people in. Nobody injects 10 milliliters of drug solution anymore, but it does allow a group, a quartet, to divide it four ways and each do 1 and a

half to 2 mLs. This requires multiple injections per person. It's still 3 to 4 injections in a typical 1-mL syringe to get 1 and a half to 2 mLs per dose.

So now, here's the social milieu. You have an increased number of pokes. You've got 3 to 4 people at an injection scene. The users, anybody who uses pills regularly loses their veins. Venosclerosis is very common. They're poking, they're poking, they're looking, they're trying to find. You've got a bloody mess. So you've got a large number of people, you've got a large number of poking per episode and per day, and you have blood spilling around. Okay?

This is the hypothesized mechanism for the social outbreaks of hepatitis C that we're seeing in Tennessee, Kentucky, West Virginia, and New York due to high-volume extraction of Opana.

The use of high-volume syringes is an alternative. However, Zule and Bobashev have shown in their models this is worse because there's dead space in high-volume syringes. If blood gets in

there and those syringes are shared, you've increased HIV and hepatitis C transmission.

Finally, I'd like to argue that Tennessee is not an outlier. Kentucky and West Virginia have high rates of opioid pill misuse, and some of those states are not making it into the NAVIPPRO data. Tennessee is not an outlier. Tennessee can have the high rates of misuse and the problems that they're having, then other states are also involved and missing the data or can be replicated.

With that, I'll end my comment.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: What have we learned over the last couple days? Well, one, we've learned that Opana ER is a very potent opioid medication that appears to be being overused based on the current recommendations for treatment of chronic pain. The effect of the relatively short half-life and the potency of the drug seems to have created a high-addiction liability.

There are problems associated with the analysis of the data, especially the NAVIPPRO data,

that we were shown. I think that careful analysis, such as was done by the FDA staff, and which I appreciate demonstrates pretty well, that the reformulation to reduce the prevalence of intranasal abuse likely increased the prevalence of intravenous abuse. I think that's a firm observation we can make from this data.

Now, in the course of changing from intranasal to intravenous abuse with the potency of the drug and the number of injections that were caused to be used, as was just observed, this raised the risk of a number of other circuitous healthcare public health issues, which make the safety of this drug doubly questioned in my mind.

DR. WINTERSTEIN: Dr. Woods?

DR. WOODS: I'd like to make some comments on some of the comments already. I was very impressed by both the TTP data as well as the HIV episode that were described nicely yesterday. This is something that probably has some common elements with other things that we might expect in the future if abuse continues in the way that it is

with the class of narcotics that we're talking about, at least with respect to the HIV when it's made up in the same way that Opana is.

So I would say, from that, that we have a significant disadvantage that Opana happens to be the first example perhaps. On the other hand, I would like to worry a little bit about some of the generalizations that Dr. Ciccarone made with respect to how addicts do their arithmetic with respect to injections and things of that sort. I'm not sure that we can use those as generalities.

On the other hand, I don't see any significant advantage, from a therapeutic point of view, of Opana relative to other kinds of drugs that are available. And so I see a significant disadvantage by their problems.

To emphasize a point, the TTP episode that they've gone through looks as though it has waned, but we have a mechanism, but we don't have anything to really treat problems should they exist with other agents that present the same problems.

So I don't see any significant advantages

with respect to those particular problems, and I'll save some of my comments for later.

DR. WINTERSTEIN: Dr. Gupta?

DR. GUPTA: So I have five points that I want to make. First of all, I think everyone did a really excellent job. There's a lot of information that was presented, very overwhelming amount of information both from the FDA and also from Endo, so I'm going to try to make this very concise.

Number one, regarding the TTP, I am very overwhelmed with the amount of information that was presented. There was about 60 patient cases or more, and I cannot figure out from the information that was presented why it's happening. It seems to me that there are still ongoing studies that are being conducted, and that is still yet to be determined.

I mean, from what we have heard from CDC, there's still no clarity on why those cases occurred, and to me, that's concerning. The physiological mechanism, I can't really understand. I mean, if it's the burning of the product that's

causing it, we need to know why that's happening. I need to be able to counsel my patients. If they're going to abuse this drug, what am I supposed to tell them?

I mean, there's no clarity on that risk. If they're going to abuse these products, we need to know why those things are happening. And I think those studies need to be understood clearly what the mechanism is, whether there are different methods of preparation of how the drug is formulated, if there's an increase or decrease on how's it's to be injected or how people are abusing it, why this is occurring; again, why the macroangiopathic disorder is occurring, the missing clarity, the physiological mechanism. That's point number one.

Number two, what we heard from the CDC and the commissioner about the frequent desire to inject, some of the patient comments that we heard from the abusers, a short duration of action, the escalating use of Opana even with the risk of TTP is very concerning. We saw some numbers from the

commissioner. Those numbers that I saw were very concerning to me.

Number three, the fact that there's no definitive human studies evaluating the risk of the injectable product -- I know that it's an oral product, but there's been no definitive human studies. I know that's not part of the industry responsibility, but the fact that it's being injected and that TTP is occurring in humans, we don't have any evidence. Why are we looking at postmarketing and deaths in these patients, and now looking back, and saying why is this happening? I would like to see what's happening in humans, not in animals.

On number four, the FDA noted that there's easy syringeability. It's filterable. That made me concerned. They stated there's low abuse-deterrent properties. There's potential for suitable -- there's other suitable solutions for IV route of abuse for this product.

There's higher rates of TMA associated with IV Opana ER. I mean, all the statements that were

presented from the FDA regarding the PEO and whether PEO is activated by the heating sources, this was directly from the FDA presentation yesterday. That also made me a little concerned.

Lastly, some of the public comments that we heard today, obviously, the many overdoses that we've heard about regarding Opana was concerning. Many of the Department of Justice proceedings that we've heard regarding Opana were very concerning.

So that was my last absolutely not the least of concern, but obviously that brings to concern why we're all here. And that's why it makes it a very hard decision on what to do. But being a pain physician, I understand the importance of having alternatives. I understand the importance of having very potent opioids on the market and having alternates for patients who are having severe, severe pain. But at the same time, I need to know that products that are out there are safe for my patients, too.

So this is not an easy decision here today that I have to make and all the advisors, but at

the same time, there are a lot of questions that need to be answered, and I don't seem to have them. There's really a lot of information that has not been answered clearly.

DR. WINTERSTEIN: Could we please, in the next comments, focus on 1A so that we can confine our discussion to a specific topic and not go all over the place? I mean, question 2 is going to be that discussion, what are we going to do and what is the biggest thing. Just let's make sure we try to stay a little bit on topic.

Dr. Gerhard?

DR. GERHARD: In light of what you just said, I'll keep most of what I wanted to say for question 2 and just directly answer this question by saying, although the epidemiologic data certainly isn't as strong as we would like and there is a lot of room for interpretation, I think in its totality, the data tells the story of a shift from the intranasal route to the intravenous route.

So I think the evidence for that, while not

as strong as we would want it and not necessarily based on any one of these data points, altogether, I think that the case for that is pretty strong.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: With just limiting my comments to item 1A, I was satisfied that there was a demonstration about a shift in abuse patterns from the nasal to injected route of abuse. However, when the CDC made their presentation yesterday, there was something that made me question the accuracy and possible confusion about what abusers are identifying as the substance they're abusing.

It was the anecdotal comment that said that if you buy these pills, a whole pill is like $200, and sometimes we just have enough money for a quarter of one. Sometimes two or three of us would do a quarter of a pill.

I believe that with the reformulated Opana ER, it would be difficult to reliably quarter the pill. I think that it could be crushed. I think it still might be difficult to nasally snort,

but I don't think it could be reliably quartered. So that made me think about the fact that maybe there was some confusion, and they were referring to other Opana ER preparations, the generic formulations, not the reformulated Opana ER.

DR. WINTERSTEIN: Dr. Emala?

DR. EMALA: Charles Emala. Again, confining my comments to question 1A, I do agree that the sum total of the data was supportive, that there has been a movement from nasal to intravenous abuse. I think it's a function of the unintended consequences that the reformulated Opana did succeed in decreasing intranasal abuse, but coupled with its relatively remarkably easy extraction using very common solvents and modifications created the opportunity to divert this to intravenous use, which in turn I think leads to the part B questions.

I'm actually quite satisfied that the part B question, particularly with the PEO, was conveyed by Drs. Adams and Brooks yesterday when they talked about the real-world experience with frequent

dosing. And I think we're looking at a dose effect of PEO that's causing the toxicity that is not yet appreciated with other formulations simply perhaps because the dose effect is not achieved with those other formulations.

So I think the totality of the evidence is a diversion to intravenous use and nicely explains why we have these problems with both the HIV and the TTP-like syndrome.

DR. WINTERSTEIN: Dr. Lo Re?

DR. LO RE: I felt like the consistency of the data really indicated that there was a shift to the injection route, but I was struck really overall by the limitations of the postmarketing epidemiological data.

The bulk of the data were really based on cross-sectional data analyses of secular trends among really limited groups. I mean, the NAVIPPRO study were individuals who were being assessed for substance use disorders. The RADARS poison center study was merely limited to calls to poison control centers.

I think, really, this highlights the need, certainly, going down into the future, for developing new epidemiological methods to evaluate abuse of these types of products. And certainly, I think population-based cohort studies of new users potentially following with qualitative analyses about real-world use, desire for use, injection, I think would be valuable for the future.

DR. WINTERSTEIN: Dr. Ghany?

DR. GHANY: Yes. Thank you. So again, I will limit my comments just to the question A that's being posed to us. And I think I would agree with some of the other comments that were stated here, that the epidemiologic evidence actually is quite weak. But in sum, it certainly suggests that the abuse-deterrent preparation of this extended opioid has certainly led to an increase in injection use and certainly a decrease in nasal abuse.

So this is, I think, an unintended consequence. It was well intended, but this is an unintended consequence of this action. And I would

also echo that we clearly need stronger epidemiologic data.

DR. WINTERSTEIN: Dr. Schisterman?

DR. SCHISTERMAN: I want to also echo the concerns about the quality of the epidemiological data. The magnitude of the question of the epidemiological data should have been matched much better to answer some of the concerns that are associated with this question.

Moreover, I think there was waste quantified unknown. There are methods available without collecting data that you could have done, a sensitivity analysis on non-measure confounders, all kinds of ways to try to verify how robust the results are, and that's lacking on the presentation.

So I strongly suggest better data collection, including CoRD studies and like that.

DR. WINTERSTEIN: Dr. Shoben?

DR. SHOBEN: Yes. So I just wanted to say I agree that the epidemiological evidence in total suggests this shift from nasal abuse to injection.

I just want to caution sort of the inference that that was caused directly by the change in formulation, because we certainly see the increase in injection rates amongst the generic as well.

If you look at the injection rates, they're pretty comparable between the two, so this showed an overall shift toward injection patterns, and there's also a problem thinking about true longitudinal trends from this NAVIPPRO data especially.

DR. WINTERSTEIN: Dr. Wish?

DR. WISH: Thank you. This is the first time I've served on an FDA panel, and I'm humbled by the fact that our deliberations can really affect people. Most of the research we do might or don't. My research goes back to the setting of the Vietnam veterans in the '70s and showing that those who used heroin, of which many did, used everything else. And I think it's still true, and I think it has applications to our discussion today.

So I'd probably take a look at this a little bit differently than you do. I think that the FDA

did an exquisite job at articulating the quality of data that we need to make decisions. And after listening to the conversations, basically what we did is, we said you need all these things, and we don't have it, but we're still going to use the data. We're still going to make decisions based on it.

I'm not a perfectionist about this, but I think, for me, the data that were presented had enough problems that raised in my mind, I wouldn't make decisions based on them.

It's sort of like I think of this in terms of what we are doing is taking pictures from a satellite and then trying to decide what's going on inside the houses, that what's missing from all of our deliberations is asking people out on the street, sort of like the type of research Dan does, asking about whether or not this reformulation changed things, rather than trying to find correlations in these big datasets and trying to infer that it was caused by that.

I mean, in NDEWS, which is National Drug

Early Warning System that we run for NIDA, when we see a problem emerging in the country, we send researchers out there. We talk to people. We talk to users, we take biologic tests, and we try and find out what's really going on.

Now, the Indiana study did that, but the Indiana study was the study of people who are big HIV and injection problem. Of course you're going to find people who move from non-injecting to injecting. If you want to know what the probability is of moving on, you look at people who are using these drugs, and then you find out how many of them did go on and why did they go on when the drug was reformulated. That's totally missing from our deliberations.

In terms of the data that were presented, I'm really concerned that, over time, you're potentially measuring different groups of patients in terms of their primary drugs of abuse and their primary route of administration.

I know that we tried to do some studies where we picked a similar group of sites, but you

know what? I don't know if that controlled for the different types of patients in those populations. Why not show in the similar sites the percentages of the people being studied who were methadone patients versus residential or whatever.

This is very important because it looked like to me that the biggest changes occurred among the residential patients. And in addition, even if controlling for the sites and picking a standard group of sites didn't control for the different client mix, why in the world aren't we using modeling to control for that or at least take that out of the factor when we see if it had an effect in terms of the change in use. We didn't do any of that.

In addition, when I'm looking over these tables, if I were reviewing this for publication, I would never approve it. I've got tables showing percent, people who injected and whatever. There's no Ns in there. I can't even judge how many cases these are based on. Furthermore, there's no statistical tests, and you've got people

presenting, saying this changed or that changed. There's absolutely no way that I can assess that.

Finally, in terms of the NAVIPPRO, I was doing a study once of people who would come into treatment. Do you know what the treatment people said? Don't ask them about drugs when they first come in admission. Ask them after they've been in treatment a couple of weeks because then they'll really tell you what's going on.

All of this is based on what newly admitted people said about drug use in the last 30 days. And I did some research that said, among people in treatment -- this was a study -- we said, of those who tested positive, how many admitted to using that drug that we found in the last 30 days, it was very low. But if you asked them about use in the past year or past six months, you got much better estimates.

So we're only picking up the tip of the iceberg here. So to me, the data aren't sufficient to making any decisions. And I just want to tell you that I've got some data here that we're doing.

We're studying people -- remember, these are people who overdosed on fentanyl in New Hampshire, 136 of them, and I got their urines.

The number of drugs they had in them was amazing, including oxymorphone, including cocaine, including marijuana. And yet, in our deliberations, we talk like it's the drug that makes the difference. It is not the drug. It is the person. And if the person is misusing these drugs, they are using a variety of drugs, and we need to focus on that. You take away Opana, they'll go to heroin, they'll go to another drug. That's what happens with people who are misusing these opioids.

So I guess what I'm saying is, instead of taking a drug away -- and I'm finishing by the way -- I wouldn't focus on that. Focus on making sure that the physicians do urine testing of everyone given these prescriptions and do that over time, so you can weed out -- not weed out, but you can identify the persons who are most likely to be abusing the drug and get them into some other type

of monitoring and treatment.

The material that you gave for the physicians or for the patients just said these people should be monitored. You cannot monitor people who are abusing these drugs by self-reports and just asking them what they are using. You need a biological test like a urine test in order to do that.

So I would recommend that the committee, when we talk about these things, focus on the person, and focus on identifying the person who is totally dedicated to misusing these drugs, and then get them into the appropriate treatment that focuses on the total repertoire of drugs they're using and not just on one drug.

DR. WINTERSTEIN: Dr. Mendelson?

DR. MENDELSON: I think the data do show that the abuse-deterrent formulation resulted in a transition from nasal abuse, which was prevented, to IV abuse, which was unintended and unexpected. And I think, actually, there's enough data to say that at this point. And that would be the answer

to question A. There is a shift in pattern, and the pattern is reasonable to infer from the data.

DR. WINTERSTEIN: To summarize, I think the majority of the committee members agree that the data supports a shift from nasal to injectable administration of Opana, that the syringeability is suddenly still there and therefore can be abused in that fashion.

The panel pointed out that Opana also may be a drug that has an increased desirability compared to some other opioids, which is evident by the high street value that is placed on it, that it's very powerful.

The committee noted that it's not completely clear whether the question related to Opana abuse is really confined to the brand, that there clearly is an increasing trend in abuse of the generic products as well, but for the brand, because the nasal administration seems to be complicated, there clearly has been a shift to the injection.

Then finally, the committee pointed out that they need to be more -- and I think I say this in

every advisory committee. They need to be more, better epidemiologic studies that would not only look at the patient pool that we have right now. That is my own addition to this.

The main sampling frame for all the studies, that we have seen patients who have agreed to be treated for substance use disorder or patients who had an overdose, which of course is a different pool than the universe of people who are abusing opioids.

So we need that other larger part of the iceberg and not only the tip to really get a better idea of what's happening. There were suggestions that cohort studies of new users and looking at trajectories of their development of this opioid use disorder might be important.

There could be more advanced analytical methods, even with the data sources that were available and that have been presented, that might have helped to interpret the data in a little bit better way than had been presented.

Does that summarize pretty much everything?

DR. ZACHAROFF: Yes, very nice.

DR. WINTERSTEIN: Thank you. Moving on to TTP, the question there is, what are the strengths and the limitations of the evidence that was presented to us, that there is a causal association between IV or injection of Opana and TTP? That would be the next question.

Dr. Zacharoff?

DR. ZACHAROFF: With respect to item B, I agree with some of the comments that Dr. Gupta made earlier. There is no data in humans that we're aware of to show what the effects of PEO that is injected are. I think we don't judge the safety of other medications that are intended to be ingested orally based on their injection because we have no reason to, but it's not clear to me that this is necessarily different. I don't know, if somebody was to melt a statin, and try, and inject it, what the effect would be, for example.

I think that there is also a lack of satisfaction on my part that for the cases of the TTP-like illness that people did experience, as to

whether there was a consistency in terms of the way that the medication was prepared. Also, in line with what Dr. Gupta said, I don't know that browning is necessarily a strict consistent approach, or maybe there are other approaches that people took.

With respect to HIV transmission, my inference is that this is a behavioral scenario, and it's a result of needle sharing and some of the other things that people have mentioned. I don't specifically consider that the data has shown me that there's an immunologic effect of injected Opana ER to infer some kind of HIV-related phenomenon.

DR. WINTERSTEIN: Dr. Tyler?

DR. TYLER: Thank you. So speaking about the TTP, I agree with Dr. Emala's comments in terms of I think there's some issues perhaps in the quantity of the PEO. As I was reading the briefing materials prior to coming here, I felt like is there something in the PEO, does it change in how it's being handled, or the manipulations that

happened to make it syringeable. I think those are possibilities. Obviously, PEO is not just one compound, and the polymers can vary.

One of the difficulties, which I think was presented very honestly, is we're dealing with rare events. We're having to study the issues using epidemiologic methods. They're not perfect, but the question is, in all the data, do we have a signal that there's something different about Opana with a PEO in this formulation that can potentially contribute to TTP. And I believe there is a signal in that data, given all the limitations of both the epidemiologic studies and the data that were presented.

DR. WINTERSTEIN: Dr. Emala?

DR. EMALA: Thanks. Charles Emala. I just wanted to draw the committee's attention to the publication that Dr. Hunt presented yesterday. We were all given this paper in our packets that was published in Blood last month that looked at the three index patients that initially brought up the issue of PEO and the TTP-like illness presenting

primarily with renal failure and myocardial dysfunction, as well as retinal changes.

Within the context of that paper, the one of the three index patients who required dialysis, it was noted that, during dialysis, gelatinous material within the patient's plasma was found to occlude the dialysis catheter apheresis tubing and bedside data.

The group then went on to try to recreate this in an animal model, and I thought were very careful in predicting what the concentration would be achieved in a human patient with an injection.

That coupled with the presentation that because this volume of extraction requires a slightly higher volume, and therefore has led to repetitive dosing at frequent intervals because of the short duration, I think it's completely plausible that these patients are seeing an increase injection volume of PEO that is a very plausible explanation for the TTP-like relationship.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: I'm still a little bothered by the TTP. I definitely agree that it was associated with injection of Opana in Tennessee. But it bothers me that despite looking for it in Indiana with the HIV outbreak, they weren't finding it. And it really seems to be isolated, so I feel like it's not just injection, but there was something else going on with the injection at that time that we don't understand.

It also bothers me -- I mean, evidently, it's been reported with OxyContin, but I'm not clear that there was surveillance for it with anything other than the Opana.

So I don't really know if it's really isolated to just the Opana containing the PEO or if it's all PEO meds. I feel like we're looking for it with just this one drug, and yet we're still not finding everywhere that that drug is being injected. So I'm a little still unsettled with that data.

As far as that HIV transmission goes, I tend to agree, it's hard to blame the actual drug. I

understand what's been presented about the frequent injections, but that is more related to injection drug abuse and behaviors to me than the actual Opana.

Lastly, I guess, although TTP clearly occurs and it's a concern, it's still with unintended use of the product. So I have a hard time saying if you use Opana ER, you have the risk of TTP. It's if you're using it not as directed by injecting it, that you potentially have the risk of TTP.

DR. WINTERSTEIN: Dr. Bateman?

DR. BATEMAN: So along those same lines, I think perhaps the strongest evidence that we would have that Opana is the sole drug that's associated with this is the case control study from the CDC. But there are some methodological concerns with that study.

If you look at the way the cases were identified, they were TTP cases associated with IV drug use collected from across Tennessee, and controls in contrast were recruited from methadone clinic patients at a single location in eastern

Tennessee.

So it's not at all clear to me that the controls are representative of the sort of population from which the cases are drawn, so I think we have to be a little bit cautious in our interpretation that the relative risk of Opana, of TTP, is 35 with Opana compared to other drug abuse of prescription opioids injected IV.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: From what I can discern, the combination of the epidemiologic data and the laboratory data, which was very nicely presented, gives pretty strong evidence of a strong correlation, if not causation, for TTP being caused by the adulterants in Opana ER. I'm perfectly satisfied, especially given the fact that we had two or three types of evidence, that there's a very strong possibility of causation there.

Now, one thing that I don't understand is why this seems -- in terms of seeing, a lot of other people have mentioned this. But given the data that we have observed over the last two days

and the fact that there are many areas where opioid abuse is endemic that are not covered very well by any sort of data gathering, I guess I am not shocked that we find something like that.

Going on to HIV, I think the observations for Dr. Adams were very instructive because it gave us a picture of why Opana ER might be associated with HIV. Someone suggests that you can't indict Opana ER, but if you have a formulation, a medication that has a high addiction potential, then that drug will be more likely to be used, and that use will be more likely to cause passage of HIV, especially as it was described by Dr. Adams.

The question to ask ourselves, if Opana ER was not available, would we have seen this outbreak of HIV. I think the only way we can know that is that we need to have more granularity of data.

We need to have nationwide surveillance, and I would ask the FDA to involve the CDC in looking at both of these issues over the course of time throughout the country, especially in West Virginia, Indiana, southern Ohio, and Kentucky, to

assure all of us that we haven't missed a whole group of patients who have had the same problems but have not been observed.

DR. WINTERSTEIN: Dr. Ciccarone?

DR. CICCARONE: Hi. So a couple of comments to add to the discussion. One is I appreciate from the epidemiologist who had spoken about the quality of the epidemiological data. I do want to remind the committee of something that Dr. Rick Dart mentioned yesterday, and that is this is a hidden population. All right?

It is unfeasible to do a national cohort study. It will not happen. It's been tried; it doesn't work. And yes, we can collect biologics on a lot of people, as Dr. Wish did in the Adams project, and create good inferences from there, but we have problems with epidemiological.

The best way to do it is local regional studies, as Dr. Brown just recommended. I would certainly support that. It's a lot of work into making a cohort study in this population work, and it may not work.

The reason I bring up anecdotal anthropological stuff is to suggest mechanisms. Right? It's not because my data is somehow the right answer here. It might be terribly wrong. But in anthropology and in multi-disciplinary public health, you try to triangulate between answers.

So I want to revisit the idea of why HIV with this product? Yes. There are a lot of products that can be injected. They get injected with normal dose levels of volume. Okay? If I want to inject an IR product that's out there, I need 50 units; I don't need 5 to 10 milliliters.

So it's the high volume that's required for extraction. We talked about individual risk factors. Yes, there's individual choices and there's risk factors depending on my dependency needs, my physiology, my genetics. And then we talk about structural risk factors. Opana represents a structural risk factor, the way in which the drug needs to be used if you're going to abuse it, if you're that sort of individual who has

a need to misuse this drug, the structural risk factor requires high volume. It enables, not requires, but enables sociability.

The paradox that we're having now is that the drug availability is going down. That's a good thing. That's because of prescribing restrictions. That's because we're learning that we overprescribed for a while. That's raising the street price.

So there's a syndemic, a structural force here that while the price is going down and with the high-volume extraction, it's requiring an increased sociability, increased number of injections. It fits -- it doesn't necessarily make it the right mechanism, but it fits the hepatitis C and the HIV data, epidemiological data that we're looking at.

DR. WINTERSTEIN: Ms. Robotti?

MS. ROBOTTI: Thank you. It seems clear to me, based on the information and the comments around the table, that there is a definite shift in abuse to IV drugs, to IV use. Sorry. And I do

believe that the two clusters that we've heard about are signals, that this is a hidden population. And as Dr. Brown said, they can quite well exist and not yet be observed. This worries me.

It also concerns me that there are victims here. Addiction is a disease. This is a problem. As one of our speakers said earlier today, there will always be abusers among us.

While that may or may not be true and that's very hard to hear, there are abusers here today -- or not here today, here within our society today, meaning no illusion, and we need to consider the entire effect of this drug on the entire society, not just on the patients, not just on the abusers, but on everybody in a drug that encourages multiple puncture wounds, that encourages multiple use, leads to other confounding medical issues such as HIV and potentially this TTP.

Families that have addicts in the family, their goal is to keep that addict alive long enough until some rehab takes, until they can reach

healthy again. And with these confounding factors, God help me, let them use it nasally, but keep them away from the IV.

DR. WINTERSTEIN: Dr. Setoguchi?

DR. SETOGUCHI: Sticking to discussion 1B, regarding TTP-like illness, I think acknowledging that the data are limited, the cases that arose from Tennessee, based on the epidemiological data showing this switch from nasal to intranasal injection, and then I guess Dr. Hunt's data kind of is supporting the pathophysiology, I think we can safely say that cases reported in Tennessee are probably from Opana use.

However, I'm still not clear, like Dr. Ruha said, if this is a class effect, the PEO or is this specific to Opana? And I was hoping that, actually, Dr. Hunt's data, like the data that Dr. Hunt showed, would show something like compared to Opana to other agents with PEO so that at least, at an animal level, we know if this is really specific to Opana or more of a class effect.

Regarding the HIV transmission, I agree this

is more of a behavioral that's caused by the structure of the medication drug that requires high volume and then sharing

DR. WINTERSTEIN: Dr. Warholak?

DR. WARHOLAK: This has been a lot of information, and a lot of it has been, as many people have pointed out, a lot less rigorous, perhaps, than we had wanted. I do think, though, that it was really admirable of Endo to try to reformulate the drug.

Considering B, I think there is a correlation with HIV, and that's obviously with unintended use and then with TTP as well. And I think that we haven't seen that in the other situations just because it's a pretty rare event. And if you're looking at a very, very small number of people in Indiana, it's going to be really hard to see a rare event.

I agree that it's difficult to fault the drug for unintended use because that's not what it was created for, and I'm glad that the supply is decreasing. But if we know there's such an abuse

potential for it -- one of the things I was so struck by yesterday was the evidence from Indiana and the CDC about the widespread distribution. That is one of the things that, at the very least, I would hope to see settled by this meeting.

DR. WINTERSTEIN: So the committee points out that there is a biological plausible pathway that would explain a causal association between Opana use specifically, a PEO component of Opana and TTP, that in particular, the fact that there needs to be repetitive dosing or large injection volume repeatedly may accumulate that much of that agent, that there could be a plausible causal association.

The committee points out that there is no data in humans and that probably won't really be available in studies, I would imagine, any time soon. The committee also points out the case controlled study that was presented, which is the only controlled study that we have available, may have selection-bias issues that we really weren't able to explore to the fullest because we don't

really have that much information available.

There was also some concern that there were no cases evolving from Indiana, but it was pointed out that Indiana was a very small population. I actually looked it up. It was 24,000 patients who are in this particular population.

We are looking about a million Opana prescriptions in a given year, and we are looking at a very rare side effect, so that there were no cases in Indiana is probably not really particularly concerning in terms of looking at a causal association.

From my own end, I'd like to point actually to the case studies and the FAERS reports that are available. I thought they were actually quite compelling. And the reason for this is, if we are looking at case reports, obviously we all are trained that we should not consider that there is a causal association nor that they can point to a causal association.

However, number one, this is the only drug that has FAERS reports on TTP, except that one case

we saw in OxyContin. Number two, if there were an overreporting that was sparked by a particular press release on this issue, we would see that sporadic. But the reality is that the FAERS reports have come in over the entire six years fairly consistently, so that seems to be an issue that is consistently going on.

Then third, if we are looking at the causal association of MI in patients who are using statins, there clearly is another alternative cause in this population. Here, we're looking at a very severe, rare, and unexpected side effect that has nothing to do with the underlying indication of those medications, neither pain nor substance use disorder.

So I cannot really see in those case reports alternative explanations because they are so much confined to one specific ingredient, don't show up to one specific drug, don't show up anywhere else, and don't really seem to have the classic selection bias or confounding issues that we would typically be concerned about.

Does that summarize everything on TTP? Okay.

HIV, we started to discuss, but are there any other comments on the HIV portion of question B?

(No response.)

DR. WINTERSTEIN: Okay. With respect to my notes, I think that the committee understands and supports the idea that there is a clear mechanism to transmission specific to Opana because of the need for a higher volume and the high price for this medication, which invites sharing to make the administration more efficient, if you will. It was pointed out that that certainly is not confined to Opana alone, that syringe sharing has been happening for decades before Opana came on the market.

Does that summarize the committee's opinion? All right. Good. Moving on to question 2 --

DR. MENDELSON: I think you may want to discuss a little bit of the very last point there. I'd like to make some comments on how the data

inform our understanding of risk-benefit relative to other products, because I think that's the real question here.

The real question here is -- and it's kind of an embarrassing question -- do abuse-deterrent products make life better or make life worse? Here, we have an innovator who came forward and responded to the requirements to make a drug less nasal, to decrease intranasal abuse risk and to decrease intravenous abuse risk. They demonstrated decreased intranasal abuse, but increased intravenous abuse risk, but only as a consequence in part of decreasing the intranasal risk.

This leaves us with inferior products that neither discourage intranasal or intravenous abuse. That's sort of the end-game here, that if we say no to this particular technology, then we end up with a technology that we know is easily diverted and abused.

So it's an embarrassing choice. And having been in the opiate abuse-deterrent world for 20 years now and thought about this, this is just

the kind of scenario we don't want to have.

I think what the agency can take away from this is that the emotionally charged nasal abuse, intranasal abuse of a drug, is rarely fatal and rarely leads to other diseases. But intravenous abuse, parenteral abuse, whether it actually gets in a vein or not, leads to all kinds of other complications.

Rewriting the rule some to emphasize parenteral abuse would be useful and not giving an innovator -- like Endo spent a lot of money worrying about whether they could crush this with tool W or item X, or which coffee grinder worked better over another one. And that was all a waste of effort, a huge waste of effort for their company and time because the real abuse portion that's biologically and medically important wasn't really addressed well.

So I think, in some ways, for those people who have actually been working in abuse-deterrent and resistant technologies, this is a failure, a failure of the FDA and of the scientists' advice,

which could include me, to come up with a better, more meaningful set of definitions.

That's something I think should be taken away from here, where the innovator is going to be penalized for having done what they were supposed to do, and it didn't end up with exactly the right consequences; they ended up with something worse, with a new iatrogenic illness. It's great, like how could you screw up more? You ended up with a new iatrogenic illness, plus it doesn't deter the IV abuse, even though it looked like it might.

So that I think is the real lesson here, and I'm not sure, again, how that translates to this particular drug, but I am sure how it should translate to how the agency thinks about and regulates abuse-deterrent products.

If the net result of this meeting is that we leave with an eventual removal of this particular product, but leaving products that are completely abuseable still available, and inexpensive and abuseable, so they can be more widely abused, that's not the outcome I think we want. And that's

my point.

DR. WINTERSTEIN: Do we have a few more advisory committee members who want to speak as still to question 1, or can we move on to question 2? Yes?

DR. BROWN: Can I just make a comment?

DR. WINTERSTEIN: Sure.

DR. BROWN: I think it's unfortunate -- and this addresses the last comments that were made. It's an unfortunate circumstance, but I don't think it's embarrassing, nor do I think that it's a failure.

The problem of creating abuse-deterrent formulations for opioids is something that we've been working on, you've been working on for many years, we've been working on for the last 18 months to two or three years, and we've learned something every month about that. We can't expect that the agency nor any of us on the advisory committee are going to know the right thing to do.

That being said, I certainly agree with you in the strongest possible way that one of the best

things that might be able to come out of this is some recognition that acceptance of intranasal abuse in an attempt to get rid of intravenous abuse might be the most useful thing that we can do.

DR. MENDELSON: Get the priorities, get the priorities.

DR. WINTERSTEIN: Dr. Gerhard?

DR. GERHARD: Yes. I agree that this is the important discussion here. So I think, just conceptually, it's important to realize that, obviously, many of the risks that we've been talking about -- and that certainly came out in the public testimony -- are common to all opiates, or certainly to all ER opiates used for chronic pain, a big part of the overall opioid epidemic.

There are some issues that relate to the molecule oxymorphone, so the high potency, low bioavailability, maybe the resulting high street desirability of the drug, maybe an increased likelihood of developing addiction to oxymorphone compared to other opiates. We didn't really see a lot of data, but that's kind of the underlying

question there.

Then there are the specific questions that relate to the reformulation of Opana ER. And here I think we've discussed specifically the shift from the intranasal to the IV dosage form, the abuse route, the resulting high volume that's needed for injection that has these -- basically leads to shared frequent multiple injections, which increase risk for infectious diseases potentially because of the higher volume for PEO-caused TTP risk, just as we discussed.

But I think this issue that we have these risks at multiple levels and the specific question only relates to one level makes it important. But keep in mind that the bigger question obviously is the role of opioids in the treatment of chronic pain and the overall approach to dealing with abuse-deterrent labeling.

Then I think two points that came from the public meeting, from the public comments, that were very important are that abuse is not necessarily the developed addiction, and abuse-deterrent

labeling might increase the perception of safety and therefore maybe have unintended consequences.

So generally, the issue of here for one specific example, but raising the broader question of unintended consequences of abuse-deterrent labeling in general, I think is something that not at this meeting, but eventually the agency has to address more directly. And the problem with that discussion is obviously that the groups that tend to benefit and that are at risk are different groups.

So the groups that abuse-deterrent formulations are affecting are abusers. They don't necessarily keep somebody who initiates treatment from chronic pain from becoming addicted.

So I think those are the issues that will come up when we discuss question 2 of what will be the consequences of taking a particular action that relates to one product.

DR. WINTERSTEIN: Dr. Woods?

DR. WOODS: I have just one specific suggestion that falls into this theme that we're

talking about, the more general consideration of extended-release formulations and their abuse liability.

We have not discussed a major player at all in our deliberations, and that's extended-release morphine. And we've drawn all of our extraordinary considerations toward you-know-what, OxyContin of course. A more balanced view would include morphine.

DR. WINTERSTEIN: Dr. Porter?

DR. PORTER: I'm sorry. I think that one of the things that is clear to me is that the intravenous use increased, like everybody has said. But to say that by changing the formula or removing it from the market will make people go back to snorting I think is a misconception. So I just wanted to point that out.

DR. WINTERSTEIN: Dr. McCann?

DR. McCANN: I also wanted to make her point, and I wanted to reiterate what Abby said earlier, is that if you look at the generics, the incidents of IV drug abuse is almost the same as

with Opana ER. So I'm not sure that there wasn't going to be a huge uptick in IV abuse regardless of whether it was unpleasant or not effective to inhale the drug, is one.

One thing that's not been discussed is that by preventing people from inhaling the drug, there may be a subset of at-risk people that are not willing to go the full step or the additional step of IV drug abuse. So you may actually end up deterring a small percentage or even a moderate percentage of people that otherwise might abuse drugs.

DR. WINTERSTEIN: Moving on to question 2 -- I think that's a good lead-in to question 2. Sorry.

DR. SETOGUCHI: I just wanted to point out -- because we've been focusing on TTP and HIV transmission in terms of the risks, but we really did not have enough data and we did not discuss overall sort of deaths or serious consequences resulting from Opana use or overall opioid use.

I would care, with a new formulated Opana,

if the overall deaths increased after deterring people to injection from nasal or this deterrence didn't really change the overall result in terms of the deaths and then serious consequences, including TTP-like syndrome and HIV transmission.

DR. WINTERSTEIN: Moving on to question 2, this brings us to the discussion that we have already started. So this is about the potential consequences of taking regulatory actions. And we were reminded that those actions could be as simple as a labeling change and as drastic as withdrawal of Opana, such as effects on prescribing or abuse patterns for other products, including other oxymorphone products. Dr. Mendelson?

DR. MENDELSON: There will be.

(Laughter.)

DR. MENDELSON: Do you want more?

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: Just to reiterate a couple of things with respect to potential consequences of taking regulatory actions, I would like to restate that there is a significant role of oxymorphone in

the strategy of rotating to opioids.

The CDC guidelines have been mentioned a couple times during the course of this meeting. And one of the things that's always confounded me with respect to abuse-deterrent formulations is the CDC guidelines are directed really towards people in a primary care setting that are prescribing opioids for a chronic non-cancer pain problem on a long-term basis.

One of my personal conflicts has been, is it the role of somebody in primary care who doesn't have a higher level of expertise to prescribe a medication that is intended for people who are at a higher risk of an aberrant drug-related behavior, i.e., an abuse-deterrent formulation. That being said, that has to assume that there are no other non-abuse-deterrent formulations available.

So for me, it's created the conflict of, if the primary care provider is the one making these decisions, the likelihood of them deciding to prescribe an abuse-deterrent formulation is probably lower, or if I were reviewing a medical

record where they did, I would say, "Why didn't you get someone with a higher level of expertise to help you manage?"

With respect to relative potency, I've heard it mentioned a number of times, and from a clinical perspective, I actually don't consider that to be a negative attribute. I think the potency in terms of morphine milligram equivalence for oxymorphone has been well established, and in many cases, even in line with the CDC guidelines, the goal is to create a ceiling for your dosing. And sometimes what you need to do, if somebody exhibits therapeutic fatigue, is you have to switch to a different opioid.

The metabolic differences are more numerous than just the cytochrome P450. But on the flip side, the fact that -- as somebody mentioned earlier there, stability of dosing is important. And one of the reasons that there could be a stability of dosing beyond just the concern about drug-drug interactions is the fact that the enzymes aren't induced.

So one of the things that may make it more attractive to abusers is the fact that they don't need more to get the same high over time because to see why P450 enzyme system isn't involved in this whole story.

So that's sort of a positive or a negative. But as a first-line medication, I don't think most of us clinically would think that oxymorphone is the first-line drug of choice. Generally, it's a drug that we go to when we find we have therapeutic failure, lack of efficacy, so on and so forth.

So I think the potential consequences of taking away a reformulated Opana ER, which at least we all seem to be in agreement dissuades crushing and snorting, would have a negative impact on patients at the end of the day, and that's my real concern.

I think if we talk about risk-benefit balance for patients and we talk about risk-benefit balance for abusers, they're really two totally separate discussions. And I tend to focus on the risk-benefit balance for patients, and clearly,

oxymorphone has a role. And actually, the abuse-deterrent formulation in a primary care setting is really just an extenuating circumstance as far as I'm concerned. Thank you.

DR. WINTERSTEIN: Dr. Bateman?

DR. BATEMAN: So I think one consequence that we can anticipate if there was some regulatory action with respect to Opana is that there be more widespread prescribing of generic oxymorphone. And I don't know if it's possible to put up the slide from yesterday.

If we look at the -- this is from the FDA's presentation -- NAVIPPRO data that shows the abuse reports on a per-tablet-dispensed basis, generic oxymorphone ER was by quite some margin the most frequently reported abused opioid by any route, by snorting and even by injecting.

So to me, it's quite worrisome if we take away this medication. Despite all the problems that we've discussed, those red bars, the generic oxymorphone ER, is what we would in many instances be shifting to, and that could come with real

consequences.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: I agree. I think the opioid epidemic is a huge problem. There's a lot of different approaches right now to tackling it. I think that if Opana ER was taken off the market, it wouldn't make a difference at all. It would just be -- the people who are abusing it would just replace it with generic. And if generic wasn't available, then another opioid. I'm even getting Imodium overdoses now in my practice and people who can't get prescribed opioids.

I do think that there should not be any type of abuse-deterrent labeling. I am convinced by the discussion that that may actually be detrimental in the mistaken impression that it's actually safer when it probably isn't. But I am sort of attracted to some of the suggestions of labeling, that perhaps it's not first-line, or really emphasizing in the label that it shouldn't be the go-to, which would perhaps make prescribers think twice about just easily handing it out for some back pain.

So I like the ideas of coming up with new ideas for limiting the prescriptions.

DR. WINTERSTEIN: Dr. Gerhard?

DR. GERHARD: I think we all agree that there will be consequences, and I think if there is anything -- from reducing the supply in any way, from the most dramatic of taking the drug from the market to having some kind of labeling change that reduces prescribing, any type of reduction in supply of Opana ER will have consequences of abusers replacing that product with other means.

How they will exactly play out, I think is impossible to predict given what we've learned over this meeting. I mean, there are just a lot of factors playing a role there, many of them local. And it's, I think, in a way almost futile to try to predict the exact consequences.

Now, obviously, the one thing that's directly addressed by taking away the specific product or limiting it drastically to Opana ER would be the issues specifically associated with that product, so the issues related to the

large-volume extraction.

To what extent how that relates to the larger issue of adverse effects of the abuse, obviously we don't really have the numbers. But I think that's clear that's the one thing that would be specifically addressed.

The other issue I think that, again plays in here is to what extent do we hold products accountable for risks that are exclusively limited to its illicit use. And I think we've certainly heard the argument that I think is pretty strong to say that we don't do this for other drugs. Most drugs, if ground up and dissolved and injected, would probably lead to all kinds of problems.

However, I think that other drugs, I haven't heard of anybody injecting a statin because people don't do this for most of the drugs. Here, they do. So I think from a public health perspective, if this is what happens with the drug once it is available, it is on the market, it has to be taken into account in the regulatory decision-making. And that is just inherently very different for

opiates than for the vast majority of other drugs that the agency regulates.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thank you. So what consequences to whatever regulatory actions we take? I mean, that's a pretty broad statement, and I'll just take the most extreme one. I'll just say taking it off the market.

There are two types of patients or people that this would affect. There are the chronic pain patients or any pain patient, and there are people that are addicted. Fortunately, I've been on sabbatical, and I've had the time, before this meeting, to immerse myself in the material. And I've talked to a lot of my friends who are pain experts from across the country, and not one of them uses oxymorphone. And we discussed this whole issue of opioid rotations, and there's no evidence for that at all.

We are really in the midst of a seismic shift in this country in the way we approach pain patients and the way we prescribe opioids. And

there's no question that there are safer methods that are constantly being discovered, and new technologies, and ways to get around treating patients with opioids.

Believe me, I mean, I have complete empathy for patients with pain. I suffered through several painful operations where I took lots of opioids, and I even had experiences with chronic pain, and I know how useful they can be, but oxymorphone is a special drug.

Let's take a hypothetical example. So I'll address the pain physicians and patients that we heard from. Say that some pain physicians and patients came to the FDA, to this committee, and said, "Listen, you guys have got to approve heroin because heroin makes me -- it's the only thing that takes away my pain. It makes me feel great. It makes me have a functional lifestyle." I mean, that would be a non-starter. We would laugh at that, and I don't really see any difference here.

So as far as the other side of the coin, the people that are actually truly addicted, what would

the consequences be? Well, addiction is such an indescribably powerful brain phenomenon that, of course, they would find other ways to satisfy the addiction. But that's just not a good enough excuse for me. We have to start somewhere.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: So let's have a little discussion about what some of the options for the agency are before we begin to talk about what we would like to have done.

So the agency can change the labeling. The labeling on this classification of drugs is already relatively stringent, some of the most stringent of all pharmaceutical compounds that are marketed and licensed.

Providing Opana ER with a black-box warning would offer an increase in the strength of the labeling, but I'm not at all certain that in patients that have chronic pain, that that would actually be workable.

Last May, the advisory committee had a two-day examination of the risk evaluation and

mitigation strategy program designated by the FDA. We heard from experts from around the country, educators. We heard a lot of epidemiologic data about the use of REMS.

I want to inform you, for those of you that are not aware, that when REMS were first discussed, the advisory committee -- and I think it was in 2014 or 2015 -- strongly suggested that REMS programs be a requirement of folks that were going to be licensed to dispense and utilize opioid compounds. The FDA chose not to do that.

Subsequently, late last year, we examined the number of prescribers that were actually involved in the REMS program and found that there were many fewer people that were actual prescribers that had involved themselves in any REMS program. And therefore, the educational objectives of this very well thought-out program were useless to a large majority of the people that were actually prescribing it.

So REMS is a possibility that the agency could lay out for Endo and other people that are

manufacturing oxymorphone. If that occurs, then there would be a strong signal, based on what we saw last year, to make it a requirement. Whether you make it a requirement for this individual compound or whether you make it a requirement for the entire class of compounds, unclear to me. It's a very complex, political, and social issue to make any of these things required.

But the only other thing that can be done would be to recommend that Opana ER be taken off the market. If one believes that there is an increased addiction liability for Opana ER, then requiring licensed prescribers to have a separate educational program would be called for if the agency decides not to take this off the market. Labeling changes, black-box warnings, I don't think are going to be useful.

DR. WINTERSTEIN: Dr. Tyler?

DR. TYLER: Thank you. This is Linda Tyler. I want to build on Dr. Brown's comments and Dr. Litman's comments. There's no question that in the landscape of the opioid crisis right now, this

makes this a very, very challenging discussion. I would have phrased it as, we are not going to be able to black-box our way out of this nor are we going to label our way out of this.

The classic dilemma is what we've been discussing is consequences when used in an abuse situation. And labeling may help with some warnings around that, but labeling helps us with how we use it in the therapeutic sense. And I think that's part of why those are options that are not going to help as well.

I agree there's lots we can talk about in terms of how we structure REMS programs, but we also need to think about, in general, is this a drug that we want on the market at all. That's not a discussion for what we're talking about today. We're talking about this very specific dosage form, and that's our next discussion point.

But it's clear that we prescribe this particular compound at a rate greater than other countries, so the discussion needs to be around what constitutes appropriate use of this, where

should it be slotted, and how can we address what I think most of us after the discussions would view a high use, and probably in many cases inappropriate use.

I think the other thing that I would add is the landscape of abuse-deterrent formulations over the last 6 to 10 years has changed significantly. So something the FDA can address is updating what those guidelines look like and what we really should be looking at today based on everything we've learned over the last few years about what those guidelines should be and what really constitutes abuse-deterrent formulations.

I think the bar has been raised over the last few years, and I think this is where this particular product has gotten caught in all of that, that the landscape is changing, what constitutes abuse deterrent. And in this particular case, the abuse-deterrent formulation probably had some unintended consequences that again ups the ante of what should we consider when we talk about those formulations.

DR. WINTERSTEIN: Dr. Mendelson?

DR. MENDELSON: Yes. I had a few points to make. First, I think, again, we've said if the result of our discussions is that we leave more abuseable formulations on the market, that would be a mistake. And I hope that comes out clearly to the agencies writing the rule.

The second is, people have said a couple of times that we're not going to solve this by either pharmacologic means or other means. And I would point out the precedent is pediatric medications, where we put bittering agents in and other adulterants to make sure they did not abuse them, is something that's widely accepted now, but 50 years ago was not accepted at all.

So we're very good at making medications unattractive to children, and it's not much of a stretch to say we can make medications unattractive to people who want to inject them or want to misuse them in some other way.

So I think there is a compelling logic you can work through and develop medications that

achieve your goal. The problem is that the goals have shifted a little. As you pointed out, we've learned a lot over the past few years, and just preventing intranasal administration is not an adequate endpoint. Right?

So I think they could write a label for this, that this particular product is resistant to abuse by the intranasal route but not by the intravenous route. That'd be a perfectly reasonable label to come out at the end of this meeting and would suggest that there's a pathway for them to get full abuse deterrence or abuse resistance. Those are my points.

DR. WINTERSTEIN: Dr. Ghany?

DR. GHANY: Yes. Thanks. So if we focus just on the actual question being posed to us, that is how do the data inform our understanding of the risk-benefit balance, I would say actually we don't have enough data to answer this question.

In listening to all the testimony that's been presented here yesterday and today, I'm still uncertain what the role of Opana is in the

management of patients with chronic pain. I've heard many different indications for its use, but I don't know what the actual indication is. And I would say it's probably being overused in this country outside of its intended purpose.

So I think what we need to do is really have more research on how to manage chronic pain that doesn't include opioids, not just Opana. I think we probably overprescribe opioids. As you can see in the data that was presented by one of the speakers this morning that here in the United States, we prescribe almost 60 percent of opioids in the world.

I mean, I don't think we as people experience pain any differently from anybody else in the world, and I don't hear that other countries in the world, that their population is suffering pain more than we are.

So I think there needs to be education about how pain management should be properly done and to find a way to remove opioids unless it's the absolute last line. And I'm not talking about

post-surgical pain or people with terminal cancer. I think that's a different subset. But certainly, for the rest of the population, we're probably overabusing opioids for management of pain.

So that's the one side of the coin. Okay? If you remove this medication, maybe a small percentage of individuals may not have adequate pain relief, but maybe the labeling could indicate that it's only indicated for a certain subset of individuals and no one else.

I do agree with other speakers here that trying to change the label is not going to have any effect. People who want to abuse this drug don't read the product label. They don't care what it says. They're still going to abuse the drug because of how it makes them feel.

The other side is the public health implications of removing this drug from the market. After yesterday, as I was beginning to formulate my opinion, I really thought that this drug should be removed from the market because it was dangerous. But in listening to other testimony here today, I

think it's really the opioid class as a whole. And removing this drug really is just going to be replaced by something else. So I think the broader question is how to limit opioid access and how to deal with addiction in society.

I think these are bigger, more general questions that need to be addressed. Otherwise, we are not going to make any inroads into the public health issue that we have right now.

DR. WINTERSTEIN: Ms. Porter?

DR. PORTER: Yes. I want to continue with that. I'm not sure what the role of Opana is, either, so I don't know how many people are prescribed it and what they're prescribed it for.

From the information that was provided yesterday, it was looked at in clinical trials or the trials that they did in back pain. Is that correct? And the back pain, it's not supposed to be prescribed for that.

Along that, also I think that replacing the Opana, is removing it from the market forcing drug addicts or abusers to use something else, is that

necessarily a bad thing If we know that Opana is linked to the TTP and the HIV? So I feel like there's a trade-off there. And no, we're not going to solve the problem today. And no, we're not going to prevent people from becoming addicts. But if this medication is so strong that it has people doing what they're doing, I don't know.

I'm sorry. One other thing I wanted to say is that some people do become addicts from being treated therapeutically. I mean, it happens. I will just say that, in my case, when I had met [ph] to my pancreas, I was in excruciating pain. I was on OxyContin, and I went through withdrawals when I came off of it.

I mean, even people that are treated correctly can go through withdrawals, and not all of us make it to the other side of that. And I feel like if the Opana is causing these problems, there are other pain medications out there, and that it should be removed from the market. And I think the consequences would be on the positive side and not on the negative.

DR. WINTERSTEIN: Dr. Warholak?

DR. WARHOLAK: I was going to bring up REMS and wanted to talk more about that, but I think that's been done.

DR. WINTERSTEIN: Dr. Setoguchi?

DR. SETOGUCHI: Thank you. So like the other panel members, I'm thinking about two situations or two different populations. Sometimes the populations overlap. But I think the benefit lies in population or the situations that Opana is used appropriately. And then the risks that we're discussing is in the situation or population that would misuse.

Then thinking about the consequences of the most extreme sort of action, which is withdrawal, I wanted to make the best educated guess. So if we take the drug from out of the market, we lose the benefit in the population who is appropriately treated and benefitting from the drug. Then the gain that we might have in the population or situations that drugs are misused intravenously, what's going to happen?

So based on the discussion, we agree that most likely these people are seeking for different drugs. Right? And then based on the discussion, we think that the drug was most likely causing TTP and HIV. So in the consequence, we would probably see new or less TTP and HIV. But like the point I made, we didn't really talk about overall sort of risk of serious outcomes and deaths.

So I wanted to refer you to the FDA presentation yesterday in the packet at page 15, that they were comparing the events before and after. And then before the Opana was reformulated, event was coming from the original Opana. And then the events after the reformulation was most likely coming from the reformulated Opana. Then knowing that this data is really limited, the RADARS data, on the major medical dozen consequences, there's really not much difference there.

The other thing is, if people were to shift to other sort of formula, like morphine ER or something, again, comparing at the population level, the major deaths and then outcomes are not

so much different between the two sort of formularies. So based on the data, it looks like pulling Opana from the market would probably not make sense if you assume that the people would go to a different formulary or medication.

This doesn't hold, however, if Opana use is spread throughout the countries, like it's happening in Tennessee and Indiana. So I cannot really make an educated guess based on the old data. That's where I am.

DR. WINTERSTEIN: Dr. Wish

DR. WISH: Yes. I often tell people I have the easy job, that all I do is uncover the problem and describe it, and other people, especially around this room, have to decide what to do about it. And I don't have the answers.

But I do want you to keep in mind as we deliberate on this that if the data I've been collecting are accurate -- and I've been collecting more than in New Hampshire. I've been collecting around the country various urine specimens from high-risk populations.

When I find one of these pharmaceutical opioids, I find it in the presence of heroin, a lot of other drugs. And keep in mind, that means they used it within a recent few hours. It's not like they switched from heroin to oxymorphone, and back and forth, and everything. They had it all in their urine at the time.

So if you would assume that what I've been finding -- and I have reason to think that it is accurate. If what I'm finding is true and what we have is, among the people who are misusing oxymorphone, they're also misusing heroin, they're also misusing cocaine, they're also using a number of other drugs, benzodiazepines and anti-depressants, how does that affect what we say about what we need to do about Opana? Because, at least to me, that's only talking about a little piece. From the way I think, we need to think of the bigger picture of what this person is presenting who's misusing the Opana, because they're using just a whole lot of other opioids and a lot of other drugs.

DR. WINTERSTEIN: Dr. Ciccarone?

DR. CICCARONE: I'm so glad I get to go after Eric, given what you've just said. So we have to recognize that the opioid epidemic is broad, it's intertwined. There are so many moving parts. My team and I have written a number of papers on the intertwining between prescription pills and heroin misuse.

Also, just to state the obvious -- that's obvious point one -- obvious point number two is that the population is intertwined. I'm hearing a lot of language, which raises some of my hairs a little bit, about this population versus that population. The population is overlapping. The deserving patients and the undeserving illicit abusers are the same population.

I don't mean to overinflate it. I'm not saying that every patient is also a potential abuser or every abuser started as a patient. All I'm saying is that there is a continuum here. Let's just please be careful about blaming the population at risk.

People have tested their genetics and found a drug that they liked, just like those of us who have tried X, Y, or Z drug, and maybe we like a certain type of gin or a certain kind of whiskey. We're just testing our genetics.

So there is a lot of mixed effects here. So it's easy to say that if we take out one opiate, there will be some balloon effect, guaranteed. Guaranteed. What balloon effect that is? No idea and no data.

So just while I wrote four years ago an intertwining between the prescription drug use epidemic and heroin, I have clear stories of people who went from industrial accidents, to being patients, to getting on high-dose opioids, to finding the way to heroin when their prescriber cut them off, I'm now finding the opposite.

I'm finding new people, the young people that are coming their way, finding their way to heroin all by itself. Heroin is a big deal in certain parts of the country right now. So I don't know what happens if one pill that has 1 percent or

2 percent of market share goes away, whether that's going to lead to heroin or not.

I will tell you that much of Appalachia is heroin poor, which is why the pills were big all along, and it's still relatively heroin poor compared to mid-Atlantic and the northeast, into the northern industrial, post-industrial areas, where heroin is big.

But this is a cohort. It's not a cohort study, but it's a cohort or period effect that we need to move through. Okay? And there's other mixed effects that are coming in now, too. Right? The dialogue has changed. We've got a bipartisan dialogue about how to address this mixed epidemic, treatment, opiate substitution. I've never heard so many people talk about opiate substitution. Right?

Remind me, John, I mean, how many years do we have to go back where opiate substitution therapy was a dirty word?

DR. MENDELSON: From the '60s forward, it's been that way.

DR. CICCARONE: And now, it's all of a sudden like we need buprenorphine programs, we need methadone programs. So there's mixed effects going on, on the positive side as well. So I don't think we should be completely worried that we downregulate one drug, that somehow it's going to lead to a heroin epidemic or something like that.

I have been moved over the last few years. I was resistant to this at first from my DEA and ONDCP colleagues that we need to turn down the tap. We simply overprescribe in this country. Right? We overprescribe opiates, and turning down the tap in the short term might have some painful effects.

Again, we have to move this population wave through the natural cycle of opioid dependency. Just like an enzyme system in the body or cellular system in the body, we need to downregulate. At this point, I don't think the evidence supporting oxymorphone, particularly this formulation, as I've stated before about its particular ADF-like or weak ADF formulation is a good one. I think it should be taken off the market.

DR. WINTERSTEIN: Dr. Schisterman?

DR. SCHISTERMAN: Thank you. One other thought I have is that the problem with the situation we are facing is that the company was successful in one mode of delivery prevention, but not the other. And we would have been having a different discussion if they would have been successful at both modes of delivery, meaning the preventive route of delivery would work.

So there is a failure here that we have to recognize that needs to be encouraged. This is not a bad venue to continue to do research, but we can't on the other hand charge this company with solving the opium epidemic of it all. So that's it.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: I'm just trying to get my own thoughts in order. So it seems to me that, of the data that was presented, we did not hear any data to support that there's an increased risk of overdose or addiction in people who are appropriately using their prescribed Opana ER in

comparison to other opioids.

We have heard that there's rare complications with the injection use, and it was even pointed out to me that we didn't see any TTP cases in Indiana because it's such a rare complication.

I haven't heard that with misuse, there's disproportionately a high number of overdose deaths. I know that hasn't been the focus, but I just want to caution speculation as to, if we take away the Opana, they might, you know -- I think, to echo something that was said, we don't know what will happen. We don't know what people will use instead, and we're commonly hearing about epidemics or clusters of deaths from people who had heroin laced with fentanyl.

So maybe people will inject something safer. Maybe people will inject something more dangerous. Maybe there will be more deaths. I don't think we have any data. We can't speculate on that.

I agree that with a change in labeling, that targets, what happens with misuse through the IV

route, that's not going to make any difference. But I would favor labeling that is focused towards the physician and limiting the prescriptions.

So if I pulled up my Lexicomp or whatever drug reference, and I saw should not be used first line, should be like third line if the other opioids have failed, then I think that would limit prescribing. And some of the data that we have heard is that there is a subpopulation of patients who have tried other things and feel that they were helped only with this.

So I hate to take the drug away from people who need it. There's been strong arguments that it's a useful drug with different pharmacodynamic properties that's helpful to some people. But I fully agree that it's not something that should be casually prescribed, and I agree that we're not going to be able to prevent people from injecting it with labeling changes.

DR. WINTERSTEIN: Dr. Gupta?

DR. GUPTA: I just wanted to raise another issue that we haven't talked much about, insurance

coverage of more affordable opioids. As this product is going to become more affordable as time goes on, if it remains on the market -- I deal with patients in Philadelphia that don't have insurance, that have chronic pain, and most of the patients I see can't afford controlled opioids, but they need opioids. And I envision if this product was available over the next 10 years, this would be affordable for them, and it would be an option that I would probably consider.

But the issue is, there are safety issues that I'm very, very concerned about, that I've heard about that have been presented that are not convincing to me, that I've already discussed in detail.

So that's where I'm at. And I really feel that those things have not been answered clearly to my satisfaction. The patients that I see want answers to those things, and they demand that. And even though they don't have the availability to pay for their prescriptions, if I'm going to give them an extended-release opioid, they really want to

know what I'm giving them is safe enough for them to take at home alone and that they'll be okay with it.

I don't feel confident that I can give those prescriptions to them and that they can go home with that. And knowing that the cost will drop with the insurances, they will be affordable and the payers will probably allow me to prescribe this easily, I don't know if I will feel comfortable prescribing it.

So my recommendation would be to remove it from the market and allow other companies that are more innovative, that are creating abuse-deterrent products that we have already recommended for approval, allow them to be put forward that have abuse-deterrent properties to be used in patients who really need it and get insurance payers to cover those products.

It would force them to use those products, to be added to formulary, and to remove some of the products that don't have the safety metrics that we look for. That's what I want to give to my

patients, because we've reviewed those, and we know that they offer some of those safety metrics that I'm confident that really would allow them to be safe when they're home alone.

DR. WINTERSTEIN: Thank you. Quick question to the panel. We are approaching 3:00. That would be the classic time to break. We have right now two more people who have raised their hands to speak. I'm sensing that we are getting close to the discussion, which would bring us to the vote, and then we would be done.

So the question is, is anybody in favor of breaking and then returning, or should we just finish this and try to get everybody a little bit earlier out? I'm imagining that many people are worried about their flights and would probably appreciate if they arrived a little earlier at the airport.

Who is for breaking?

(No audible response.)

DR. WINTERSTEIN: Okay. All right. Then shall we? Let's finish the discussion. There are

two more, and then we have a quick break, and then we reconvene. Ms. Robotti?

MS. ROBOTTI: Thank you. I read recently a study that talked about it takes 10 years for doctors to change their prescribing habits, even after being directed with new labels from the FDA or from their associations.

Given that, this is honestly a question. I'm not a doctor. Is there a way that we can keep doctors that -- that, A, we can change with the label, with the REMS, with licensing, special licensing, that we can get them to change their prescribing habits and that we can keep them from prescribing off label?

DR. WINTERSTEIN: Was that a question?

MS. ROBOTTI: Yes. It was a question.

DR. WINTERSTEIN: Would the FDA like to respond to the question?

DR. FIELDS: Hi. Ellen Fields. As you know, prescribing off label is not illegal certainly. It's a practice of medicine. There are ways to prevent it with REMS and things like that.

A very restrictive REMS could prevent off-label prescribing. Whether that's appropriate in this situation, you can continue to discuss.

DR. WINTERSTEIN: Dr. Bateman?

DR. BATEMAN: So I would just want to make the point that I think it's important that we don't lose sight of the fact that this reformulation was associated with quite a significant reduction in abuse by snorting.

The effect on IV abuse, I agree, is less certain and may be associated with some increase in that risk. But if there's going to be oxymorphone on the market, I think it's important that -- and if I had to choose between patients being prescribed generic oxymorphone ER without any abuse-deterrent properties or without any resistance to crushing or syringeability or the Opana product, despite its imperfections, I would want them to be prescribed Opana.

So I think there is real risk if the FDA moved forward with withdrawing this from the market that, as long as oxymorphone is going to be used in

clinical practice, not having an alternative, that is at least in some ways safer.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thank you. I was just going to respond to the off label that that would be great in a perfect world. But I can tell you, as a pediatric anesthesiologist, almost every day, I use drugs off label because it's impractical to ask for studies that the FDA could approve for everything, and we just have to use our judgment as to what's safe for either non-indicated labels or different populations.

MS. ROBOTTI: I don't mean to condemn off label at all, and I understand it's an important aspect. I'm speaking only very specifically about this drug at this time.

DR. WINTERSTEIN: Let me summarize the discussion.

DR. FIELDS: Can I make a quick clarification?

DR. WINTERSTEIN: Sure.

DR. FIELDS: I just want to say the current

REMS for the ER/LA REMS doesn't prevent off-label use. I was just saying that, in theory, a very restrictive REMS could potentially do that.

DR. WINTERSTEIN: I'm not sure how much everybody knows about the current ER/LA REMS. Current ER/LA REMS recommends a voluntary CE program for physicians who prescribe opioids. It's voluntary, so it's the sponsor that offers CE programs for physicians. That's the REMS that we have right now. There is nothing else in terms of restricting use.

Is that correct?

DR. FIELDS: I'm sorry. Could you repeat that?

DR. WINTERSTEIN: Yes. It's a voluntary CE program that's offered.

DR. FIELDS: There's voluntary education --

DR. WINTERSTEIN: Yes.

DR. FIELDS: -- a medication guide.

DR. WINTERSTEIN: Yes, and a medication guide.

So to summarize, I think that the panel

agrees that patients who are abusing opioids will find something else to abuse if Opana was not available. I think that it seemed that many panel members felt that that alternative might however be safer than Opana in its IV application, so that may not necessarily be a negative, to have them shift someplace else. However, there was certainly an uncertainty about in which direction the balloon would indeed expand.

I think that the panel agreed that the generic product has its own problems, in particular since it allows intranasal use quite easily and also because its use as IV application seems to increase as well.

There was a lot of discussion about what place Opana has in the pain management as such. There were several recommendations made that it really is not a first-line therapy, that it might need to get restricted in its indication or to certain physicians who would be allowed to prescribe it because of its use in specialty populations. That might in itself reduce the

availability and the potential for abuse.

There was value recognized, specifically that there are pain regimens that require switching, where oxymorphone might become an important alternative and in regards to drug-drug interaction in patients with poly-pharmacy where oxymorphone may have value.

I think that several panel members talked about whether it is important to regulate a drug with respect to abuse because that's not the intended use.

I like to make another analogy there. I mean, any REMS regulates inappropriate use in some way or the other. Every REMS regulates something that makes a drug safer when it's being used properly. And that might be that there needs to be hepatic levels checked because the drug can increase, or can be hepatotoxic, or there might need to be another laboratory value that needs to be checked. And in reality, many people don't do it, prescribers forget it, patients don't show up, and, therefore, there is a REMS that forces this.

This is not different from thinking about another way of inappropriate use, which is abuse. So considering more restrictive REMS to mitigate the risk of abuse and specifically the risk of IV administration in this particular product seems to make sense to me.

I think, yes, that's the summary of a very long discussion. Anything that I didn't cover? Yes?

DR. BILKER: In terms of REMS, REMS in itself is voluntary, right? Is there an option for a mandatory REMS?

DR. WINTERSTEIN: Yes. So the current REMS -- do you want to, FDA?

DR. FIELDS: Dr. Lehrfeld will answer. She is from the risk management group.

DR. LEHRFELD: Hi. Kim Lehrfeld. I'm a team leader in the Division of Risk Management. There are many levels of risk management through a REMS, everywhere from voluntary to very restrictive. We have all sorts of different programs, lots of different tools available,

including mandatory education of prescribers, mandatory education of pharmacies, having pharmacies having to check that the prescriber has taken education before they can dispense the drug, mandatory patient-prescriber agreement forms, many, many tools.

So yes. There can be restrictive REMS, which can help educate different prescribers, different healthcare providers.

Did that answer the question?

DR. BROWN: But the current REMS for ER/LA that were discussed last May are voluntary.

DR. LEHRFELD: They are voluntary. It involves the drug companies. The consortium of drug companies that make ER/LA products have to fund continuing education that's focused on proper prescribing of opioid analgesics, particularly the ER/LA products.

DR. FIELDS: Hi. It's Ellen Fields. I misspoke earlier. Although the REMS can be restrictive, as Dr. Lehrfeld said, they cannot specifically prevent off-label use.

DR. STAFFA: This is Judy Staffa. I just want to add, Dr. Brown has referenced several times the meeting we had last May to discuss the evaluation of the ER/LA REMS, which you have a copy in your background, which applies to Opana ER just like it does to all the ER/LA products.

We are evaluating the recommendations from that committee and determining how to move forward. So that committee had recommended to us to add IR products into the REMS, to also require the training to be mandatory and to be expanded to other members of the healthcare team beyond prescribers.

Then the third one was to expand the blueprint, which is the basis that the training is based on, to be about pain management in general and not simply about opioids. So those recommendations were made and heard, and we continue to work on those and how we would move ahead with thinking about which of those and how we would possibly implement them.

DR. WINTERSTEIN: Dr. Emala?

DR. EMALA: I was part of the advisory committee when REMS was discussed. And just so those who weren't are aware, one of the central take-home disappointments with that meeting was that there was no assessment of the effectiveness of REMS.

So before we get too comfortable with the idea that a product-specific REMS will have an impact, I'd be curious to know if there's any update from the FDA about really whether all of this effort at REMS has an impact on any kind of prescriber habits or outcomes.

DR. STAFFA: Judy Staffa again. I can speak to that. We are actively working on that, and we heard the committee and share your frustration. It's been very challenging to evaluate the impact of the program for a lot of reasons that I won't go into.

But as we consider how we're going to change the requirements to evaluate the program, we also have to figure out how we're going to change the program because the evaluation has to be tied to

what the elements of the program are. So yes, those discussions are definitely ongoing, and we're hoping that, in the future, we'll have better evaluation of whatever the REMS ends up being.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: Just one quick comment with respect to the extended-release long-acting opioid REMS, and that is that the curriculum includes opioid rotation strategy and the scientific basis for that is well-referenced within the REMS education as it stands today.

DR. WINTERSTEIN: I think we'll break now. It's dragging out longer and longer, if that's okay with everyone.

DR. ROTMAN: I wanted to ask if there was one piece of data that was asked for we have we could present before you make your decision. It's just one slide about the number of deaths pre-reformulation, post-reformulation.

DR. WINTERSTEIN: Let's talk about that during the break real quick.

DR. ROTMAN: Right.

DR. WINTERSTEIN: So it's a quarter past 3:00. Let's reconvene at 3:25 to 3:20.

(Whereupon, at 3:13 p.m., a recess was taken.)

DR. WINTERSTEIN: Let's get started. I received several questions during the break and discussed this with the FDA. And the questions look specifically at risk-benefit evaluations and what they mean.

So with respect to your votes, if you vote that there is not favorable risk-benefit, that does not mean that Opana would have to be withdrawn from the market. It means that something needs to be done to either mitigate the risk or change the risk-benefit into something that would make sense. I think Dr. Staffa can say that better than I do.

DR. STAFFA: You did great. Judy Staffa here. The purpose of asking this question is trying to understand -- obviously, when Opana ER was approved, it was perceived that the benefit outweighed the risk. At this point in time, with the new information we've discussed over the past

few days about the risks, we'd like to get an understanding from the panel whether you believe that that benefit being greater than the risk continues or whether that calculus has changed.

If that's the case, there are a variety of things the FDA can do to try to mitigate risks in relation to benefits. So what we'd like to do is to get a vote on what your thinking is with the benefit-risk calculus, and then we'd like for you to go around and give us an idea. If you have an idea of how you think that problem should be solved, what action should be taken, we'd appreciate hearing that.

DR. WINTERSTEIN: Any more questions, comments before we proceed to the vote? You would like to say something, yes? I gave you too much time, and now you came up with something.

Dr. Ghany, I think I saw you first, then Dr. Woods. Dr. Marc Ghany?

DR. GHANY: Yes. Thank you. So maybe we could ask for some clarification. At this meeting today, all we've heard about, really, are the risks

associated with Opana ER use, but we really haven't heard what the benefits are other than the one study that seems to be not a well-conducted study.

So I'm not clear in my mind how we can answer this question if we don't know what the benefits of the drug are. And we haven't heard any data on what the benefits are. Thank you.

DR. STAFFA: This is Judy Staffa. I believe the sponsor presented yesterday on the trial data prior to approval. I believe that was the basis. I'll turn to my colleagues in DAAAP of what the basis for the approval was, but I believe those were the data. Correct?

DR. FIELDS: Hi. It's Ellen Fields. It's an approved opioid for the treatment of pain as per the indication. It's been demonstrated to have efficacy that supported its approval. So when we look at risk and benefit, we look at the benefits in terms of efficacy and what it does for patients, and then the risks are the adverse effects.

So that's how we approach the benefits. I guess you could include in the benefits anything in

terms of its abuse-deterrent properties if you feel as though any of them are beneficial.

DR. GHANY: If I may just comment, I'm looking at the package insert here, and if I may be allowed to read it, it says, "Opana ER is an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time."

DR. FIELDS: That's not the current indication. You might be looking at an older package insert. That's not the approved label, the most recently approved label. I believe it's in the background package.

Is that where you got that?

DR. GHANY: No. I got this from the FDA site, the access data.

DR. FIELDS: That's not the most recent label. But regardless, all the ER/LAs have the same indication. I'll read it to you. I'm just looking it up. Oh, it was in my notes. I don't have it with me. But it's basically treatment of

pain severe enough to require around-the-clock opioid treatment and for which other treatments are not adequate.

DR. WINTERSTEIN: Any other questions, comments?

(No response.)

DR. WINTERSTEIN: We will be using an electronic voting system for this meeting. Once we begin the vote, the button will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. 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.

Obviously, the FDA wants you to state that reason and also make specific recommendations if you voted that something needs to be changed, how you would see that change evolve.

DR. FIELDS: Just a reminder, this question relates only to Opana ER, not to all oxymorphone formulations.

DR. WINTERSTEIN: I was also reminded I should ask Dr. Acri on the phone whether she has any questions.

DR. ACRI: No. I don't have any questions.

DR. WINTERSTEIN: 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. If there are no questions or comments concerning the wording or the question, we will now open the question to vote.

So there should be now, yes, lights flashing, so there is a yes or no. Please choose

one of those or abstain.

(Vote taken.)

LCDR BEGANSKY: The results of the vote are 8 yes, 18 no, 1 abstain.

DR. WINTERSTEIN: We'll now go around the room and, since we started this morning here, we start now on the left-hand side, Dr. Lo Re.

DR. LO RE: I voted no. I did not believe that the benefits of reformulated Opana ER outweighed its risks. I thought, based on the data from the National Survey on Drug Use and Health in 2015 that showed that oxymorphone use comprised only a small number of those who have used prescription pain relievers as directed by a physician, so a small fraction of overall opioid use -- but misuse among the users was reported in 28.9 percent. I thought that was very notable.

I thought that the reformulation of Opana ER resulted in increased abuse of the drug via the injection route, and I thought that was consistent across multiple analyses.

I thought Opana ER's increased potency and

the short duration of action resulted in what seemed to me an increased intensity, particularly of the withdrawal symptoms, and I thought its short duration of action seemed to contribute to a need to inject frequently.

I thought the reformulation of the drug with the goal of abuse deterrence seemed to have resulted in several unintended consequences. The reformulation increased the likelihood to abuse via the injection route, which contributed to the transmission, as we heard, of two bloodborne infections, both HIV and hepatitis C, which I did not hear necessarily with any of the other opioids. And one of the constituents of the reformulated Opana ER, the PEO, may contribute to a TTP-like illness.

The reformulation in the presence of the gelling capability increased the amount of solvent needed to dilute the diverted Opana ER tablets for injection, allowing for more injections and potentially potentiating abuse and the transmission of bloodborne infections.

So to me, the risks of Opana ER, which included the high potential for abuse and the increased abuse via the injection route that has resulted in serious outbreaks of HIV and chronic hepatitis C, as well as cases of thrombotic microangiopathy, again findings that we haven't necessarily seen with other prescribed pain medications, to me outweighed its benefits, particularly with other available opioids and since this product makes up a relatively small part of the market here in the U.S. And I would have favored removing it from the market.

DR. WINTERSTEIN: Thank you. Dr. Ciccarone?

DR. CICCARONE: Hi. Dan Ciccarone. I also voted no, believing that the risks outweigh the benefits. While I believe that oxymorphone, from listening to my clinical colleagues here and my own clinical experience, has a limited place in the repertoire and a useful place, this particular formulation, this particular weak ADF-like formulation is not good at this point. It needs more innovation.

I believe there's evidence for increasing IV route of misuse following the reformulation of this particular drug, not other high-dose -- or no other ER/LAs, that oxymorphone is a powerful opioid, it has street value, that the HIV outbreak and the hepatitis C outbreaks were seen throughout Appalachia based on particular structurally moved, structurally forced modes of behavior that have related to this weak ADF formulation, and that we need to, in general, downregulate high-dose ER/LA formulations in general, and that a lot that the FDA can do in terms of strengthening REMS, encouraging this as a second- or third-line drug are possible.

But the best thing moving forward is to go back to the lab, that taking this off the market and increasing its ADF properties, whether using a micro-bead encapsulation, using the irritants that can be put into the formula so that it can't be abused to IV, whether it's a better PEO formulation, should be very strongly considered by this company.

DR. BILKER: Warren Bilker. I voted yes. I do believe that the benefit-risk calculus has changed dramatically, but I still believe it's favorable enough that it should remain on the market. I think that there should be a stringent REMS program for this and a mandatory REMS program if possible for Opana.

DR. SHOBEN: Abby Shoben. I voted yes. I do still think it's favorable. There's a favorable benefit-to-risk profile for Opana specifically. I was convinced about the benefit both from the clinical trial data that led to the initial approval and from some of the conversations about a specific sort of subset of the patients that really need this as an option for their chronic pain.

The specific wording of the question about Opana suggested to me that it actually has some benefits relative to the generic version of oxymorphone that may be relevant in terms of at least reducing the abuse by the nasal route. And then it's not at all clear to me that there's an increase in risk from injection from this

particular product.

DR. LITMAN: Ron Litman. I voted yes, but I strongly believe that there's no place for oxymorphone in American society today, but that's not what you asked me.

You asked me if I thought that the risk-benefit ratio of this particular product has changed, and I don't think it has. I agree with what Abby just said. I haven't seen convincing evidence that the IV formulation has made such a difference.

I have two kids in college. And you know what they say? They say, "Dad, we can get any drug at any college campus at any time." And that really scares me. And that scares me not only for kids in college, but anywhere. I think that anything we can possibly do to deter any kind of use of these things, of this particular compound, is the right thing to do.

I strongly believe, again, that there should be some type of restrictions or whatever REMS program, whether it works or not, just more

advances in trying to get people to -- or preventing people from using this illicitly. I think if you consider the general population as a whole, whether or not this abuse-deterrent formulation will benefit them, I think as long as oxymorphone is still on the market, that it will -- because if you just take away Opana ER, then it will clearly be replaced with things that people will figure out how to snort and use intravenously.

DR. EMALA: Charles Emala. I voted no, largely because I think this particular formulation of oxymorphone has unintended consequences that deserve its removal from the market. And I believe it should be removed from the market because I don't have any confidence that labeling changes or a REMS program really has an impact on its abuse potential.

The question of oxymorphone remaining on the market as a general class I think is a separate issue, but I think this particular formulation should be removed.

DR. TYLER: Linda Tyler. I voted no as well. As I discussed earlier, I believe there's a signal of increased risk for TTP. I believe, coincidentally, the reformulation of this product has the shift from nasal to IV abuse.

In the discussion, it's clear that there's something about this PEO formulation that is contributing to both of these situations. I too would advocate considering removing it from the market, as I believe other regulatory strategies will be ineffective in addressing this. And this product has no advantages over the other products that are currently on the market.

There's no question that this discussion comes on top of a very complicated landscape right now. We have unprecedented opioid deaths in our communities due to unintended deaths when used in a therapeutic sense and due to abuse. Based on data presented in an earlier advisory committee, it's clear when we decrease the number of opioids in our community, we decrease the number of deaths.

So we must address our prescribing patterns

both in considering this product and considering oxymorphone in general. We need to consider the role of formularies, and rebate incentives, and how these are used. We have different controlled substances, laws, and enforcements at the state and federal level.

We've talked about needle exchange programs. We've also talked about our grave concerns about access to pain specialists and access to treatment addiction programs in our United States.

There's no question we bumped up against that this is a very extremely difficult thing to study. We are left with epidemiology data and, worse, voluntary reports. It's imperfect data. We have imperfect denominators. We have bias, in particular classification bias, but these are the data on which we must make a decision.

So this speaks to our surveillance methods are very poor, so opportunities to improve our surveillance would benefit us from a public health standpoint. There's no question that this formulation caused unintended consequences in our

communities.

DR. GUPTA: Dr. Anita Gupta. I voted no. So there was really an extraordinary effort that I heard over the last two days that was put forward by the FDA, by Endo, by the CDC, the health commissioner, by the various non-profits, the public citizens, which I really appreciated all the efforts to really understand such a broadly complex issue that was put forward.

I really do believe opioids have a place for treating pain, and I do believe that many of the opioids really help thousands of people every day. As an anesthesiologist, I see that, how important it is. But Opana ER has specific unique risks, and it has what we've heard over the last two days, that there is a potential for IV abuse. There is a potential for this microangiopathy. There is formulation inconsistencies. There's low abuse-deterrence properties.

All these inconsistencies are broadly unclear to me, and they're imperfect, and they're yet to be defined. There thankfully is a lot of

research that's still being conducted by many of them, we heard, by the federal agencies, and I hope that this continues in the future.

Moreover and probably most importantly, I believe that it should be removed from the market because many of our patients and my own patients really deserve better alternatives for treating pain that are safer, that are innovative, that are creative. And hopefully, if that is done, it will be an impetus and an opportunity to do better.

DR. GERHARD: Tobias Gerhard. I voted no. And I believe the appropriate action for this specific product should be withdrawal at this point. This doesn't mean that many of the concerns that I have with Opana ER don't also apply more broadly to oxymorphone and even other long-acting opiates in general. But for one that was in the question, Opana ER also has some specific unique risks that are related to its reformulation.

In many ways, that reformulation of Opana ER is a case study that demonstrates that adding abuse deterrence to a product actually can go wrong and

have unintended negative consequences. In this case, the high volume needed for extraction leads to shared frequent multiple injections, which may increase the risk for infection and other problems.

This issue comes up time and time again at advisory committee meetings when it comes to adding abuse-deterrent languages to labels. Some abuse deterrence is better than none, and I think this demonstrates that it actually can go wrong.

So I think in many ways, the most important outcome of this meeting could be a more broad rethinking of the requirements role and labeling for abuse deterrence and maybe getting rid of that term abuse deterrence.

Maybe, in many ways, while implemented, abuse-deterrent features should be a requirement for any long-acting opiate rather than a marketable label addition that might create the, in many ways, false impression that such features add safety and protection from addiction.

DR. WARHOLAK: This is Terri Warholak, and I voted no as well for many of the reasons already

stated, so I won't belabor those points. But what I think should be done is, at the very least, there should be a REMS with an ETASU, which is elements to ensure safe use, that are mandatory, something like what was done with clozapine, so that there were providers who were a limited set. They were educated. There was a limited set of pharmacies. They were educated. And failing that, then I think it's time to withdraw and reformulate.

DR. BATEMAN: Brian Bateman. I voted no. But my vote was not a vote for the withdrawal of Opana, but rather for a need for more clear labeling regarding the risks and perhaps more stringent REMS that would apply to both Opana and generic oxymorphone.

I think we've heard data to suggest that there are properties of oxymorphone that may predispose it to being abused, particularly the low bioavailability of the medication via the oral route.

That said, there are clinical circumstances where oxymorphone may be the preferred opioid,

particularly with respect to drug-drug interactions and meet a distinct clinical need. And if oxymorphone is going to be prescribed, I would prefer practitioners prescribe Opana because I think there are clear advantages of Opana relative to oxymorphone. It's more difficult to crush and snort and at least has some properties that make IV use more difficult, although obviously those are imperfect.

But for both Opana and oxymorphone more generally, I think these drugs need to be used very cautiously, and we need regulatory interventions that will facilitate this.

DR. WINTERSTEIN: Almut Winterstein. I voted no. I based my vote on the risk when abused is higher for Opana compared to other opioids, including the generic version. And that is of course mainly related to the increased risk for TTP and HIV infections, as we discussed earlier.

I agree with Dr. Bateman that the risk doesn't really seem to be confined to Opana. There are certainly concerns about oxymorphone in

general. And given its limited position in pain management that really seems to be confined to very specialized populations, it might be worthwhile to consider a more restrictive REMS that would try to limit use of oxymorphone to specialized physicians who see those types of special populations.

DR. BROWN: This is Rae Brown. I voted no, and I voted no because Opana ER is a very potent opioid medication. I think it's been overused. It's got a relatively short half-life. I think that probably because of that, there's a high addition liability. I think there's a direct relationship between the reformulation and the increased prevalence of intravenous abuse. I think that the ADF formulation of this drug just is not effective.

That said, I think that there's a lot that we can take away from this meeting, and I want to mention a few things that I have learned and that I would suggest to the FDA.

Number one, related to chronic pain, we hear

assertions on both sides of this issue with regularity in the advisory committees. Opioids are effective for chronic pain, opioids are not effective for chronic pain. These are assertions of fact based on little evidence.

I think we need evidence. There have been very good people that have written on one or both sides of this analysis, and I think it's in the best interests of the FDA and the NIH that we formulate an evidence-based response to whether or not chronic pain is treatable over the long haul with opioid compounds and that is more safe than not treating with opioid compounds.

I think that the issues with the abuse-deterrent formulation need to be re-thought. I think that we've heard the secondary consequences of having industry produce abuse-deterrent formulations that I'm certain that nobody in the agency -- I certainly wouldn't have -- could have reflected on in the beginning. And I think that as more and more manufacturers make an attempt to define abuse-deterrent formulation, we have to

think about what other secondary problems that we're going to be seeing.

The fourth thing would be surveillance. I really think we have to expand our ability to surveil some of the problems associated with all of these agents across the country. That, in my mind, is the perfect opportunity between the CDC and the FDA, and I would hope that the agency and the CDC will move forward with that.

The last thing is that there's some recent data out of the University of Michigan that suggests that all opioids are not the same in terms of dopamine output related to administration of an opioid. This change in dopamine outflow likely is a part of the reason that some of the agents that we see are more addictive or less addictive.

I think that the agency probably needs to examine this in some detail. Is this a problem of Opana ER? Is this a problem of oxymorphone? Is this a problem of OxyContin? Because those agents are very different in terms of the outflow of dopamine from the nucleus accumbens than drugs like

morphine.

I think it would be in the best interests of all of us if we could have some understanding of whether or not these drugs, that is oxymorphone, OxyContin, are different, systematically different, than other opioids that are being used.

DR. ZACHAROFF: Kevin Zacharoff. I voted yes, and my yes vote was in light of the fact that, to my understanding, Opana ER did not receive abuse-deterrent formulation labeling, and therefore, I didn't look at it as if it was an abuse-deterrent formulation. I looked at it as if it was a formulation of oxymorphone that dissuades people or prevents, maybe partially successfully, crushing and snorting, although it seems to have certainly failed with respect to intravenous injection.

When I look at the data, especially the older data, I'm concerned about seeing misuse and having people interpret that as the same thing as abuse, having dependence be considered the same thing as addiction. And I consider those to be

very dramatically different situations. So I'm not a hundred percent sure when I see a misuse rate, that I consider that to be an abuse rate.

With respect to the action and education about the dangers of injecting this particular formulation of oxymorphone, I think about the challenges associated with that as when Dr. Litman talks about the fact that his daughters in college say that they can get basically their hands on any medication they want.

The likelihood is, in my mind, that those weren't prescribed by healthcare providers, that there's some other channel by which they are coming into the hands of people in college and other places.

So I'm not a hundred percent sure that education impacts abusers, so I have no choice but to think about the fact that education can potentially impact prescribers and patients. And then unless we want to extrapolate the fact that most of the patients are the ones who are abusing the medication and tampering with the product,

et cetera, which I don't personally believe, I'm not a hundred percent sure that that may be effective, although I would make that recommendation.

I think something that basically conveyed the message that no matter whose hands this medication ends up in, it's not to be injected because it could be severely hazardous and even fatal to someone's health could be a benefit.

My own pharmacist lets me know when something is prescribed for me that doesn't work well with one of the medications that I'm on, on a chronic basis, so it should be implementable. Thank you.

DR. SETOGUCHI: So I voted no for the reasons previously mentioned, that there seems to be strong data suggesting a link between Opana ER and then TTP and HIV outbreaks. However, this vote was not to support withdrawal from the market unless we see -- because there is insufficient data, to me, to make that decision.

One data we didn't see is really the

outcomes in the population that Opana ER was used and if there was any increase in risk of TTP or not in that situation or any worse outcomes other than TTP or HIV that are mentioned in the abuse community.

Another reason is that I didn't see any data on the overall risks of death or serious outcomes in Opana ER. So unless we see that, I thought it a premature withdrawal from the market.

The other question that remained was really TTP was related specifically to Opana ER or to any sort of agent containing PEO. So that has to be I thought answered because it's possible if we withdraw the product from the market and it is shifted to OxyContin, then you might still see the outbreak of TTPs.

Finally, I think there has to be some restrictions in terms of use of Opana, maybe restricted to the provider who specializes in pain management, or restricted to the patients who have, I guess, suspected drug-drug interactions, or if we need rotation of opioids.

DR. RUHA: I voted no based on the instructions that went with the question. I'm sorry. Michelle Ruha. I voted no based on the way we were instructed to answer the question, although I sort of feel more like a yes.

I feel like we need to assess the medication based on the risks and benefits with its intended use, and I don't think the risks outweigh the benefits when it's used as intended.

So I don't support removal of the drug from the market for those reasons. However, I recognize that there are risks associated with the misuse and injecting the drug that may be in excess of other opioids. And for that reason, I do think that we should take steps to limit the prescribing, perhaps with labeling changes to make it a second-line agent or if people -- that has been mentioned -- had drug-drug interactions.

It does have unique properties that may make it more effective for some people who have failed other therapies, and I would support changing the label, focusing on prescribing patterns rather than

warnings against misuse. And I agree abuse-deterrent warnings or labeling will not be helpful.

DR. McCANN: Mary Ellen McCann. I voted no, and I would recommend that the drug be withdrawn from the market. The reasons I voted no were that I didn't see any evidence that was presented that it provided a benefit to chronic pain patients over the generic version, and yet it had significant possible downsides.

I was convinced with both the epidemiologic as well as the animal data that there is an association with TTP. And I think the structural features of reconstituting it do promote needle-sharing and activities such as that, leading to HIV and other bloodborne pathogens.

I would support what Dr. Bateman said, that oxymorphone, generic version, we should take steps to limit the way that that's prescribed. It seems that it has a place for people with chronic pain, but a very limited place, and that should be the focus of the FDA, to encourage limited use of that drug as well.

DR. CRAIG: Dave Craig. I voted yes. I guess from a clinical perspective, I think that that's really kind of where my perspective comes from. I'm thinking about the cancer patients that I have and I see and talk to every day.

The drug interaction thing is really legit, something that I deal with every day. We have patients that come in for chemotherapy that have significant interactions, and we have to get fancy and change stuff around a lot. So having tools like this is really, really important. It's really, really key. You wouldn't want to be in the bed and me talking to you about a drug that you can't have available that could be beneficial to you.

So I think I'm very sensitive to not having treatment options available for patients, specifically cancer patients, which I think are significantly underserved for a number of different reasons.

If you think about the epidemiological studies that we looked at today and thinking about

the other meetings that I've been to recently, we talked about ADF. I mean, hands down, we have way more data today to look at. I mean, just think about in the past two meetings or past several meetings, we have these small studies with, like, 20 patients each, and we have no epidemiological studies. We're looking at ADFs in these small populations, and we're making basically recommendations to the agency that they can be ADFs.

I think that the data here you could argue, actually, is better than some of that data that we're actually making recommendations on those products who are currently abused with ADF labeling, and this does not.

So I think that that's where my mind is in thinking about whether those benefits outweigh the risk. And what's really the genesis of where my vote came from, does it have risk? Clearly, it does. But for the patients that are taking it appropriately, I think that there is a role for Opana ER in those particular patients.

DR. HIGGINS: Jennifer Higgins. I voted yes. I think Opana ER does provide an important treatment option for people in need, and for those who don't use it as prescribed, I am suggesting that there be additional resources made available for substance use treatment.

DR. PORTER: Hi. Laura Porter, and I voted no for many of the reasons that were mentioned already. It appears that this formulation of Opana tends to increase the risk of TTP, and HIV, and hepatitis C. And like others have said, it's used in a lower percentage of people. And there are other drugs available for use, and I recommend it being removed from the market.

MS. ROBOTTI: Hi. I'm Suzanne Robotti, and I voted no. I was persuaded for many of the reasons that were already said, the high percentage of misuse and the low bioavailability is a significant problem. The prevalence of intravenous use with the drug bothers me.

The use of PEO was no advance in protection for the drug. It just wasn't good enough. It

wasn't tested enough before put on. It's not good enough. We're entering an era with dramatic change in pain management. We need new ideas. We need effective answers. We need multi-modal solutions.

I would only support keeping it on the market if there's a way to limit prescribing that required follow-up and testing for other recreational drugs being used simultaneously. A voluntary REMS in this time of opioid overprescribing is absurd. Thank you.

DR. SCHISTERMAN: So most likely what everybody said today, I voted no. And I actually would have want to -- does not reflect that I think it should be removed from the market, although the implications of the risk-benefit is exactly that, that it will maybe be removed from the market. I think it has a place for appropriate use, but the risk-benefit balance is not there yet.

DR. WINTERSTEIN: Could you state your name into the record?

DR. SCHISTERMAN: Sure. Enrique Schisterman.

DR. WINTERSTEIN: Thank you.

DR. WOODS: I voted yes, and I agree with a lot of people that voted no as well. Let me say just a few things that mirror some of the things that have been said.

I think I agree mostly with Dr. Brown from listening to everyone around the table, with a few exceptions. I don't buy dopamine as the explanation for differences in addictiveness very much.

I should say a little bit about my history because I have evaluated pre-clinically abuse liability of narcotics for most of my career, and I think we're splitting hairs to talk about differences among drugs that act through the same receptor to produce pain relief, and mu receptor is what I'm talking about.

So I though appreciate the difference between morphine and a lot of other drugs that work through the same receptor, so those differences are important to me. And I think that there is actually a real difference between extended-release

morphine and extended-release Opana, or whatever we want to call it. So it's with a little bit of a mixed opinion that I vote the way I do.

DR. WISH: I guess there's one in every group, and I'm it. So I abstained. I told the committee earlier that I focus on describing the problem so much, not solving it.

But in preparation for this meeting, I read this. Maybe I didn't read it well enough. But it seemed to me that almost all of it was about the risk of this drug. In order for me to make a decision like you're asking me to do, I would need another binder like this on the scientific evidence for the receptivity of this drug by patients and by physicians and how effective it is.

I assume that the rest of this committee knows all that because I don't. So that's why I voted that way.

The other thing I want to tell you is that, in terms of a solution -- I will deviate for a minute -- when the military saw a rise in drug use, they instituted a drug-testing program that, to all

intents, has been very successful. People just don't use drugs in the military because they know they're going to be randomly tested.

I just want it in the record that if FDA could do anything to make a dent in this problem with this drug and other similar drugs, it would be to require, not recommend, but require physicians to institute some type of random drug testing of their patients to make sure that they are in fact taking the drugs that they're receiving the prescriptions for and that they're not using a panoply of other drugs that would indicate that they might need additional types of treatment that would focus on that.

DR. GHANY: Hi. This is Marc Ghany. I voted no. And I guess what influenced my vote the most was concerns about the risks to public health than with unintended use rather than the effectiveness of the drug for intended use. So that was the reason for the way I voted.

I mean, I am obviously sensitive that this medication probably does have a limited role in

clinical practice and that it likely should be continued to be available for patients, but I think this is a very selected population. And if somehow the FDA can indicate this in their label, I think that would be the only reason to continue to have this drug in our armamentarium; otherwise, it probably should be removed because I think they are alternative agents that probably could do as well. But clearly, it speaks that we need more data for this particular issue.

One other point I'd like to make is that I think, while well intentioned, having drug-deterrent indications in the label actually led to unintended consequences. I think it gave physicians a sense of false security that the drug that they were prescribing had less abuse potential when in fact we saw what the outcome of this was.

Until we have more science and better data to support the use of this practice of anti-deterrent mechanisms in pharmaceutical formulations, we should probably remove it from the label.

The one final comment that I would make is, hopefully, this exercise can stimulate the community now to invest more in understanding the mechanisms of pain, and through better basic science, we can come up with better pharmacotherapies to manage patients with chronic pain.

DR. WINTERSTEIN: Before we move to Dr. Mendelson, we need the virtual Dr. Acri.

DR. MENDELSON: Do you want to do Dr. Acri first?

DR. WINTERSTEIN: Yes.

DR. MENDELSON: I mean, she's sitting right here next to me.

DR. WINTERSTEIN: Right, exactly. Let's give her a chance to talk. Dr. Acri?

DR. ACRI: This is Jane Acri, and I voted no. And the reason I did that is it seems clear that the abuse-deterrent characteristics of the product have resulted in unintended consequences that have clearly influenced the route of administration by which Opana ER is being abused.

Opana ER presents a unique risk because of its increased bioavailability through the injection or IV route relative to the oral or nasal bioavailability and accompanied by the short duration of action it creates, in some respects a perfect storm of abuse-related characteristics.

As has been pointed out, this is one of several opioids that are available for the treatment of chronic pain. If it were the only one available, I would have voted differently, but it's not. And I would encourage the industry to continue to develop abuse-deterrent mechanisms and technologies.

DR. WINTERSTEIN: Now, you may.

DR. MENDELSON: So I'm on. So I have 45 minutes of prepared remarks. No. John Mendelson.

DR. WINTERSTEIN: We look forward to it.

DR. MENDELSON: We look forward to it. So I don't have very much. So I voted yes. And I thought on the narrow issue of the question, the drug actually met the requirement, that it was

actually better. The reformulated was an improvement over prior.

That doesn't mean -- I could have easily voted no with all the other comments. I actually do agree with most of them. And I think, if I were actually scoring this in a more reasonable way, I would have said, "Revise and resubmit." That would have been my actual choice, with major resubmission, because I think the problem here is this is a child-resistant cap.

This is not crushing, not being able to manipulate these pills in your kitchen or your garage is basically just like putting child-resistant caps on for preventing pediatric drug complications. It's a first essential step, but it doesn't get you very far.

I think we need to encourage innovators and manufacturers, after they've learned how to put a cap on that children can't take off, to put something else on the bottle and inside the bottle. And I didn't' want to discourage them completely from that task by simply saying the drug needs to

be taken from the market. If you do that, then you're just going to end up with generic, totally abuseable medications that do nothing.

So if I were an innovator listening to a lot of the comments here, I'd say, "To hell with it, I'm just going to make, like, the most abuseable formulation possible and sell as much as possible until someone dings me, and then get out of the market." It would be a business strategy.

So I want to be encouraging to the agency to develop, to go all the way and really make these drugs more -- they've got a start that needs improvement. Their vehicle for the hardening of the tablet may need improvement, and certainly the issue of what to do once the drug is put in a syringe. And you just have to assume someone's going to figure out how to do that is the next task. A milligram of Narcan would totally change our discussion today in this medication.

So at any rate, that was my yes, that it was a qualified yes. It was really revise and resubmit, and I don't want to tell the authors to

go find another journal. Thank you very much.

DR. WINTERSTEIN: Are there any comments from Dr. Herring?

DR. HERRING: No. Thank you. I have no comment.

DR. WINTERSTEIN: Thank you.

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

DR. STAFFA: Yes. This is Judy Staffa. I just want to thank all of you. I know we normally bring you difficult challenges, difficult issues without enough data. That seems to be our theme. But we don't always accompany it with a snowstorm. So I want to thank the committee, both the members who have been on committees before with us, thank you for your insights.

For those of you who are joining us anew, we are deliberately trying to broaden the expertise of the committee and bring in folks from different disciplines. So thank you for the new insights you've shared.

Thank you to the company, to Endo, to our

public hearing speakers, and to the FDA staff. I think that everybody went above and beyond, and we really appreciate the advice. And we will take it back, and it will be very helpful, so thank you.

Adjournment

DR. WINTERSTEIN: Thank you, everyone. You were a wonderful committee. We made wonderful time. I hope that everybody makes it home safely and hopefully not too delayed.

Panel members, please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge on the registration table on your way out so that they may be recycled.

We will now adjourn the meeting. Thank you very much.

(Whereupon, at 4:17 p.m., the meeting was adjourned.)