FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUG PRODUCTS

ADVISORY COMMITTEE

FRIDAY, DECEMBER 7, 2012

8:00 a.m. to 4:50 p.m.

FDA White Oak Campus

Building 31, The Great Room (Room 1503)

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
Randall Flick, MD, MPH	12
Conflict of Interest Statement	
Philip Bautista, PharmD	16
FDA Introductory Remarks	
Bob Rappaport, MD	20
Sponsor Presentations – Zogenix, Inc.	
Introduction	
Stephen Farr, PhD	30
Medical Need for Zohydro ER	
Richard Rauck, MD	39
Zohydro ER Clinical Program Overview	
James Breitmeyer, MD, PhD	55
Zohydro ER Risk Evaluation and Mitigation Strategies (REMS) and Safe Use Initiatives	
Stephen Farr, PhD	76
Benefits Risk Conclusions	
James Breitmeyer, MD, PhD	100
Clarifying Questions to the Sponsor	104

C O N T E N T S (continued)

AGENDA ITEM	PAGE
FDA Presentation	
Outpatient Drug Utilization Patterns for Selected Opioid Analgesics in the U.S. Years 2007-2011	
Rajdeep Gill, PharmD	137
Speaker Presentation	
Abuse Potential of Hydrocodone in Human Studies	
Sharon Walsh, PhD	150
FDA Presentations	
Misuse/Abuse of Hydrocodone and Oxycodone Products by Composition and Formulation: Findings from the Drug Abuse Warning Network (DAWN)	
Catherine Dormitzer, PhD, MPH	167
Extended-Release/Long-Acting Opioid Analgesics REMS: An Overview	
Robert Levin, MD	174

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Clarifying Questions to the FDA and Speaker	181
Open Public Hearing Session	214
Charge to the Committee	
Bob Rappaport, MD	270
Questions to the Committee and Discussion	273
Adjournment	388

P R O C E E D I N G S

(8:01 a.m.)

Call to Order

DR. FLICK: Good morning, everyone. It is time to bring this meeting to order. The press contact, do we have -- thank you.

I'd first like to remind everyone to please silence your cell phones, smart phones, and any other devices if you have not already done so. I'd also like to identify the press contact, Morgan Liscinsky. And then I'd like to go around and ask the members of the committee to please introduce themselves. If we can start with Richard?

DR. LEFF: Yes. I am Richard Leff. I'm an independent consultant in rheumatology, and the industry representative.

DR. ROSENBERG: I'm Jack Rosenberg. I'm an addictionist and a pain specialist at the Ann Arbor VA and the University of Michigan.

DR. KAYE: Hi. I'm Alan Kaye. I'm the professor and chairman of anesthesia at LSU Med School in New Orleans, and director of the pain

services as well.

MS. GRAVOIS: Hi. I'm Angela Gravois. I'm the patient representative.

DR. WARE: Jim Ware. I'm professor of biostatistics and associate dean for clinical translational science at the Harvard School of Public Health.

DR. WESSELMAN: I'm Ursula Wesselman. I'm a neurologist and pain specialist at the University of Alabama at Birmingham.

DR. JEVTOVIC-TODOROVIC: Good morning. I'm Vesna Todorovic, professor of anesthesiology and neuroscience at the University of Virginia, Charlottesville.

DR. BAUTISTA: My name is Phillip Bautista. I'm the designated federal officer for this committee.

DR. FLICK: Randall Flick, chair of the committee and the chief of pediatric anesthesia at the Mayo Clinic.

DR. RAMSAY: James Ramsay, professor of anesthesia, Emory University School of Medicine,

director of critical care services in anesthesiology.

DR. KRAMER: Judith Kramer, professor of medicine at Duke University Medical Center at the Clinical Research Institute. And I'm a former member of the Drug Safety and Risk Management Advisory Committee.

DR. PERRONE: Good morning. I'm Jeanmarie Perrone. I'm the director of the Division of Medical Toxicology and an emergency physician at the University of Pennsylvania.

DR. ZITO: Julie Zito, University of Maryland Baltimore, pharmacoepidemiology professor.

DR. MAXWELL: Jane Maxwell, senior research scientist, University of Texas at Austin.

DR. FIELDS: I'm Ellen Fields. I'm clinical team leader with the Division of Anesthesia, Analgesia, and Addiction Products.

DR. HERTZ: Sharon Hertz, deputy director, same division, at FDA.

DR. RAPPAPORT: I'm Bob Rappaport, director of that division.

DR. FLICK: First of all, let me apologize. I'm getting over a cold, so I'm going to be clearing my throat frequently.

For topics such as those being discussed today 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 discussions 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 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 during lunch. Thank you.

Now I'll pass it to Phil Bautista, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. BAUTISTA: The Food and Drug Administration is convening today's meeting of 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 the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is

being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions at today's meeting, members and temporary voting members of this committee 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 the purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing,

patents and royalties, and primary employment.

Today's agenda involves new drug application 202880, hydrocodone bitartrate extended-release capsules, proposed trade name Zohydro ER, sponsored by Zogenix, Incorporated, for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The committee will be asked to determine whether the benefit/risk assessment of this product favors its approval for marketing.

This is a particular matters meeting, during which specific matters related to Zogenix's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee's members and temporary voting members, no conflict of interest waivers have been issued in connection with the meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the

product at issue.

With respect to FDA'S invited industry representative, we would like to disclose that Dr. Richard Leff is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Leff's role at this meeting is to represent industry in general and not any particular company. Dr. Leff is an independent pharmaceutical consultant.

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

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

Thank you.

DR. FLICK: We will now proceed with

Dr. Rappaport's introductory remarks.

FDA Introductory Remarks – Bob Rappaport

DR. RAPPAPORT: Good morning, Dr. Flick, members of the committee, and invited guests. Let me apologize in advance for my somewhat lengthy opening comments. I think I need to set the stage here. There are some issues that are somewhat complex, so I'm sorry about that, but it's going to take a couple of minutes, at least.

During today's meeting of this committee, we'll be discussing this new drug application for Zohydro ER, or extended-release, which is hydrocodone bitartrate extended-release capsules. As noted before, it's indicated for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. And that's our standard indication for this class of drugs.

In their application, Zogenix has submitted data that are intended to provide sufficient evidence that their product is safe and effective when used according to the proposed product

labeling, which includes a risk evaluation and mitigation strategy, or REMS.

As our review of these data did not raise any different conclusion from that of the sponsor regarding the efficacy and the general safety findings, the applicant will present both the efficacy findings from their phase 3 study and the overall safety profile from the Zohydro ER development program.

However, there is one extremely important issue that must be addressed in regard to the possible marketing of this product. That is, the product's potential for abuse and misuse and their consequences -- addiction, overdose, and death -- and how this potential may compare to the already-approved products in the class.

If approved, Zohydro ER will be the first FDA-approved and marketed single-entity hydrocodone analgesic product and will be available in an extended-release formulation. Hydrocodone is currently only available as a low dose in combination drug product that also include

acetaminophen, aspirin, or an NSAID.

These products, because of the low dose of hydrocodone and because they are combined with other drugs that limit the amount of the overall product that can be used daily, have been deemed Schedule III controlled substances under the Controlled Substances Act. This new single-entity product, if approved, would be deemed as Schedule II controlled substance, such as Avinza, Oxycontin, Duragesic, or Opana ER.

These products, as would Zohydro ER, have tighter restrictions on prescribing and dispensing than non-extended-release narcotic products and fall under the extended-release and long-acting opioid REMS, what we call the ER/LA REMS, that was approved for all high-potency, single-entity opioid products in July of this year.

The ER/LA REMS requires that manufacturers provide unrestricted grants to independent CME providers to create CME courses, based on a blueprint developed by FDA, to educate prescribers of these products about the proper choice of

patients, the abuse-related potential of the products, and the importance of careful control of the products by patients in order to prevent diversion.

Regardless of the existing REMS, it can be anticipated that a single-entity hydrocodone product, in this case Zohydro ER, will contribute to the already critical public health problem of prescription opioid abuse and misuse.

It's also important to recognize, however, that this new product may be a useful addition to the armamentarium of analgesic drug products, considering the other major health problem we're facing, the widespread, inadequate treatment of pain.

In regards to its abuse potential, hydrocodone is similar in potency to oxycodone, has been demonstrated to be highly reinforcing in abuse liability studies at the doses proposed for Zohydro. Additionally, lower-dose combination hydrocodone products, much like oxycodone lower-dose products, are widely abused in the U.S.

Although it is important to note that while there are a higher number of abuse-related reported events for the combination hydrocodone and oxycodone products compared to the single-entity opioid products, the events that occur with the single-entity products due to potency differences are far more likely to have serious outcomes; as you will see in an analysis that we will present later today.

We will be asking you to discuss this product's potential for abuse and misuse, and to comment on how we might incorporate that risk into our decision on whether to approve or not approve the application. In order to assist you in this discussion, FDA staff from CDER's Office of Surveillance and Epidemiology will present current usage data and epidemiological abuse data for the hydrocodone combination products compared to other opioid drug products.

They will also present epidemiological data comparing the levels of abuse of the combination oxycodone products to the levels of abuse of the

oxycodone single-entity products as a possible example of what may occur with the introduction of Zohydro into the market.

This particular analysis should also be considered in light of the fact that the combination and single-entity oxycodone products are all Schedule II products, whereas Zohydro will be a Schedule II product and the combination hydrocodone products are in Schedule III.

This could result in lesser or greater differentiation in the levels of abuse between the hydrocodone combination products and Zohydro based on the differences in restrictions imposed on the accessibility of Schedule II and III products and on the different impressions of risk that many patients and prescribers have about the drugs that fall under these different schedules.

FDA will also present information about the ER/LA REMS. In addition, our guest speaker, Dr. Sharon Walsh, professor of behavioral science, psychiatry, and director of the Center on Drug and Alcohol Research at the University of Kentucky,

will present data from abuse liability studies of single-entity hydrocodone that have been performed by academic investigators.

We hope that these presentations will provide you with a general understanding of the risks associated with this new single-entity product compared to the approved single-entity potent opioid products, and of the components and limitations of the currently available risk management tools.

In addition to considering the potential contribution of Zohydro ER to the problem of prescription opioid abuse, it will also be important for you to keep in mind the regulatory framework that FDA must consider in our decisions regarding drug approval.

The agency as a regulatory body has a responsibility to the public health, which we accomplish by operating within a framework of regulations that have been defined by statutory law. When faced with a safety concern for a new product that falls within a class of already

approved drugs, we must consider the new product and the drug class in our regulatory decisions.

If there is an entirely new signal, we can implement appropriate regulatory actions to address that concern at the time of approval, or simply not approve the application if the risk/ benefit balance is unacceptable. If the new drug has a signal for a problem that exists throughout the class, but the problem is more frequent or more severe than the other drugs in the class, we can also apply appropriate risk mitigation strategies specifically to that product or not approve it.

However, if the new drug has a signal for a problem that exists throughout the class, and if that problem appears to be occurring at a similar frequency and with a similar level of clinical significance, any regulatory action would have to be imposed on the entire class.

For example, while the ER/LA REMS does not require any type of registration by prescribers or patients in order to have those products prescribed, the REMS that we recently implemented

for the transmucosal immediate-release fentanyl opioid products requires registration by the prescriber, the pharmacist, and the patient before the patient can have his or her prescription filled.

These different levels of restriction were imposed based on postmarketing data that clearly demonstrated that there was a greater risk of overdose and death when the transmucosal fentanyl were prescribed to opioid-non-tolerant patients compared to similar inappropriate prescribing of the ER/LA products.

We hope that you will have an open and frank discussion of these issues today, and that you will consider the implications and potential unintended consequences of any recommendations you may provide in response to the questions we will be asking you.

Our decisions regarding whether or not to approve Zohydro for marketing will be neither simple nor easy. The complexity due to this interface of public health concerns and regulatory requirements will make this a challenging

application. Your expertise and thoughtful participation in this committee's deliberations today will assist us in making the most appropriate decision. Thank you.

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

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will proceed now with Zogenix's presentations.

One moment. Mr. Mullins, can you please introduce yourself for the record?

MR. MULLINS: Yes. Good morning. I apologize; there were about 10,000 other people heading in the same direction as I was heading this morning. So I'm happy to be here. I am national director of Public Health Advocates, and look forward to this hearing today. Thank you.

Sponsor Presentation – Stephen Farr

DR. FARR: Thank you, Mr. Chairman, and good morning, ladies and gentlemen. I am Stephen Farr, a co-founder, president, and chief operating officer of Zogenix.

We at Zogenix are pleased to present today a new extended-release opioid, one that we believe moves us a step further in our efforts to help

those with chronic pain. But we also come here today, as I know you do, with a real appreciation for the challenging history that surrounds this class of drug. We have taken these challenges into consideration as we develop Zohydro ER and our safe use program. We look forward to an open and candid dialogue today.

Zohydro ER is an oral extended-release formulation of hydrocodone without acetaminophen. In our presentation, we will discuss the medical benefits of introducing this new extended-release opioid for the treatment of chronic moderate to severe pain, and, importantly, the activities Zogenix is committed to directing towards a safe use of Zohydro and maximizing the benefit/risk balance.

First, I'd like to give you some brief background on Zogenix and the development of the Zohydro product candidate. Zogenix was founded in 2006 with the objective of developing and commercializing medicines for the treatment of CNS disorders and pain. Since our founding, we have

developed and launched our first proprietary product. It's called Sumavel DosePro. It's a drug for the treatment of acute migraine and cluster headache. Today we have in place an experienced management group and a team of just under a hundred sales professionals.

Since 2007, we have conducted the development program for Zohydro ER, which we submitted an NDA earlier this year. We will also be responsible for commercializing the product in the United States under what we believe will be an innovative and comprehensive risk mitigation program.

Why Zohydro ER? All of you know, I'm sure, that hydrocodone/acetaminophen combination analgesics is the most prescribed analgesic in the United States. It's extensively used for treatment of all types of pain, including around-the-clock administration for chronic non-cancer pain conditions, such as back and joint pain.

It was highlighted at an FDA Advisory Committee meeting convened in June of 2009 to

discuss the safety of acetaminophen-containing medications. These products are the leading cause of hepatotoxicity and liver failure associated with unintentional acetaminophen overdose.

Indeed, one of the outcomes arising from that committee was the recognition of the clinical need for a single-entity hydrocodone product indicated for moderate to severe pain, and we believe that Zohydro fulfills that need.

We see the medical benefit for an extended-release formulation of hydrocodone in these important clinical situations in the treatment of chronic pain. First, the patients on immediate-release hydrocodone/acetaminophen who need an extended-release product, would it makes sense for that patient to stay with the same opioid molecule; secondly, for patients who have hepatic compromise and are at risk for further hepatic injury from acetaminophen if their dose of the combination tablet needs to be escalated.

In both these cases, a switch to Zohydro ER would also obviate the need for conversion to

another opioid; and, thirdly, for patients on other extended-release opioids in whom another option for opioid rotation would be of value.

The extended-release technology in Zohydro ER is called SODAS. It's Spheroidal Oral Drug Absorption System. And it's comprised of multi-particulates, or beads as we call them, containing the drug in a capsule dosage form.

In the case of Zohydro, the beads contain hydrocodone bitartrate with and without the addition of polymers that control drug release by diffusion in the gastrointestinal tract. The technology is mature, it's well-established, and present in several FDA-approved products on the market today.

Three of those are Schedule II products -- Avinza, which is a long-acting morphine; Ritalin LA, which is a long-acting methylphenidate product; and Focalin XR, which is a long-acting dexmethylphenidate product.

I'll use this schematic just to give you a brief run-through of the regulatory history of

Zohydro ER. Zogenix acquired the rights to Zohydro in 2007 and transferred the IND in January of 2008. We held an end-of-phase 2 meeting with FDA later that year, where it was agreed that a single placebo-controlled trial in chronic lower back pain would be adequate to demonstrate efficacy in the intended patient population.

In November last year, we held a presubmission meeting with the agency to agree on the contents of the NDA. The application was submitted on May the 1st and is now under active review, which brings us to this meeting today.

The results from our studies met the NDA requirements. In terms of clinical pharmacology, the single-dose and multi-dose studies have demonstrated a pharmacokinetic profile that supports every-12-hour, twice-daily administration for chronic pain treatment.

The pivotal clinical efficacy trial in moderate to severe chronic low back pain met the primary and key secondary endpoints. To our knowledge, this is the first reported study to

evaluate the efficacy and safety of single-entity hydrocodone in the treatment of chronic pain.

The clinical safety database incorporates exposure to Zohydro ER in over 1,500 subjects, of which 1,148 are patients with chronic pain, with 285 of those patients remaining on therapy for at least one year. Collectively, these data have shown Zohydro ER safe and well-tolerated.

I'd like to briefly review with you the proposed prescribing information that we included in the NDA. We are seeking approval of Zohydro ER in the treatment of moderate to severe chronic pain in patients requiring around-the-clock therapy for an extended period of time.

In the clinical development program, we studied dosage strengths of 10 through 50 milligrams of hydrocodone, and we are proposing to introduce those capsules to the market if the NDA is approved.

The lower strengths cover hydrocodone doses typically administered chronically in the form of the hydrocodone/acetaminophen combination

analgesic. In the case of the 40- and 50-milligram capsules, they are well within, on a morphine equivalent basis, the marketed doses of other extended-release opioids for moderate to severe chronic pain.

Similar to other extended-release formulations of opioids, Zohydro is not indicated for acute pain or for intermittent pain requiring PRN dosing.

We recognize and understand the public health concerns regarding potent extended-release opioid products and our responsibility as the sponsor to balance patient access against the risk of misuse, abuse, and unintentional overdose of single-entity hydrocodone.

Zohydro will be a DEA Schedule II product, not Schedule III like all other hydrocodone marketed products today. We will be implementing the recently-established classwide REMS for extended-release opioids. Since submitting the NDA, we have joined the consortium of REMS program companies, and our membership will bring additional

resources for education on opioids, including hydrocodone for the first time. And you'll hear later in the presentation the additional risk mitigation activities we are introducing to complement the FDA-approved REMS to further support the safe use of Zohydro ER. When all these elements are combined, we believe the benefits of Zohydro ER outweigh the risks.

This is the agenda for the rest of our presentation. Next, Dr. Richard Rauck, an expert in the practice and research of pain medicines, will discuss the medical need for a single-entity extended-release hydrocodone.

Dr. Breitmeyer will present an overview of the clinical development program, which will include the clinical pharmacology results and the results from the safety and efficacy studies. Then we will discuss our proposed risk mitigation approaches for safe use of Zohydro ER, before we conclude with a discussion of benefit/risk.

After our presentation, we look forward to hearing your input and taking your questions. In

addition to the presenters, you can see from this slide we have several experts here to help address your questions. And with that, I'd like to invite Dr. Rauck to the podium.

Sponsor Presentation – Richard Rauck

DR. RAUCK: Thank you, Dr. Farr. My name is Richard Rauck. I'm a consultant to Zogenix. I have no other financial interests in the company, and I have no interests in the outcome of this meeting in that respect.

I am pain fellowship director, and have been the continuous director and a clinical associate professor, at Wake Forest University for the past 26 years. I'm also president of Carolina's Pain Institute and president-elect of the World Institute of Pain. I have been tasked today to examine the medical need for an extended-release hydrocodone.

I thought I would frame this and start the discussion with just one slide about chronic pain, opioids, and what I term the dichotomy that we see today in clinical medicine.

Chronic pain in the U.S., I think we could all say in this room, is recognized as an enormous public health problem. We might argue whether it's a third of the adults in the U.S. or whether it's 5- to $600 billion annually that's spent on chronic pain. But I think suffice it to say that it's a large number, and certainly one that by most of us is recognized as a serious problem that we face.

The second observation is that opioids remain the prime pharmacotherapy class of drugs that we use to treat chronic pain. They are the drugs we have as clinicians. They're not the only class, but certainly they have been the class that has been written extensively. And I would suggest, at least, that the perception among many chronic pain physicians as the reason we write these is the effectiveness that they exhibit in many of our patients.

However, the dichotomy that I would say to you is that opioids, we all know, are abused, misused, and diverted by what might be a small but certainly not insignificant number of people. And

that dichotomy then is how we as clinicians use this class of drugs effectively and minimize the abuse that we see in some of our patients who use these for reasons other than their chronic pain.

Invariably, when a discussion like this comes up, we talk a lot and discuss effectiveness, and are these drugs effective. Are they effective long-term, or are they simply effective short-term? How should we look at them?

I think there good evidence to support the efficacy of extended-release opioids. There was a meta-analysis done recently that looked at 28 placebo-controlled studies, and showed that opioids outperformed placebo for pain and function in all types of chronic non-cancer pain.

There have also been several long-term studies. These are difficult to do and perform, but there have been long-term studies that also support the effectiveness of chronic opioids.

I'm going to highlight just one of those studies, the study of tapentadol versus OxyContin. And I choose that study because it is the only

randomized, controlled trial that was double-blind and for a longer period of time in that regard. If we look at that study, you can see, out to 52 weeks, benefit of both opioids compared to entry, and again, sustained out to one year of effectiveness.

If I look a little bit at prescribing practices for opioids, I'd make several observations. Again, practitioners write a combination of extended-release and immediate-release opioids for patients suffering from chronic pain. And again, while there certainly may be some pill mills and other nefarious clinics out there, I would hope and suggest that most of my colleagues and others who write these medicines do so with the firm conviction that these drugs are helping the patients that we treat.

If we look at what drugs we have available to us in extended-release or long-acting drugs, it's not that long of a list. Methadone on that list is the only one that's truly a long-acting medication. The rest of them are in extended-

release formulations.

For us as clinicians, it's not unusual to have several drugs in a class. We have the idea that I'll bring to you about opioid rotation later. And these drugs certainly help us when one drug may not be effective and another proves effective.

We have other classes, such as for migraine headaches and triptans. We have it with antidepressants, where rotation of drugs is often useful for us in the clinical practice. And I think we see that in the class with opioids.

How do we as clinicians either start or maintain or how do we look at opioids? It has a lot to do with assessment and reassessment. I don't want to leave here today thinking that all patients on chronic pain need to be on opioids. It's part of a bigger treatment program.

For us, we look at non-pharmacologic activities such as physical therapy. We certainly look at activities and different things such as imagery, psychotherapy. We perform interventional procedures as well. But there are a reasonable

percentage of patients who end up with opioids, and we constantly assess and reassess their effectiveness.

There are some of these patients where they are on immediate-release opioids, and we simply continue those. I have patients in my practice for many, many years who take one or two Vicodin a day. They do well. There's no reason to change them. They need something to help them with some incidental pain that they may have through the day.

There's other patients, clearly, who just don't do well with opioids, and they need to be tapered. So we do have patients who, for one reason or the other -- they either aren't effective, they have side effects, they misuse; in those patients, we just need to taper off the opioid therapy. They're not the right class of drugs.

There are other patients that we convert from immediate-release to extended-release opioids. And finally, there are patients where we do rotate opioids, where one's effective but over time it

loses the effectiveness or the patients develop adverse events, and we need to switch.

For the purposes of today's discussion, I think what we're talking about and what candidates might be for hydrocodone extended-release, we're looking at these last two boxes, patients who we might convert to an extended-release opioid or rotate the opioid to hydrocodone extended-release.

Who might be the candidates for extended-release hydrocodone? In my opinion, it's a small but it is a defined group of patients who are on, currently, immediate-release hydrocodone. So one population of patients are those who are using this drug chronically, but have increasing milligram requirements, and would do well from the pharmacology of an extended-release opioid to switch to an extended-release hydrocodone. They will benefit by staying with the same molecule and not having to switch to a different molecule, as we have to do today.

There are also patients who get into problems with excess acetaminophen dosing and the

toxicity associated with that. And finally, there's patients, again, who would benefit from rotating from one ER opioid to another.

How big is this group? Well, we know, and we've heard already, and I think we'll hear several times today, that the pie is very large for immediate-release hydrocodone. There's quite a few patients, upwards of 47 million patients, who receive immediate-release hydrocodone.

What's the population that might look at chronic extended-release hydrocodone? It's a small sliver of that pie, if you will. I think at the biggest you would say it's 5 percent, even if you take the definition that these are chronic users over 90 days and getting over 20 milligrams of hydrocodone per day.

Actually, that pie narrows quite a bit more, since many of those at 20 milligrams are still getting effective analgesia. So in some ways, I think it is a sliver of a sliver, if you will, of the immediate-release population who we would think are candidates for extended-release hydrocodone.

I wanted to spend a minute on acetaminophen toxicity. I think it's important to us and to the discussion here. We know that these combination products contain up to 750 milligrams of acetaminophen. In 2014, that will change such that the maximum content is 325 milligrams. But acetaminophen will continue in the product for quite some time.

Acetaminophen is the leading cause of acute liver failure when there's overdose situations. And you can see, 63 percent of unintentional overdoses are associated with the ingestion of these combination products. If approved, hydrocodone ER, as we've stated, would be the first single-entity acetaminophen-sparing product in that class.

If you look also at acetaminophen-related emergency department visits, these are the patients I have had in my practice over time. These are patients who certainly don't intend to harm themselves; they either don't understand the other products they have that have acetaminophen in it,

or they just are trying to take more product to get analgesic efficacy.

So you can see over 18,000 of these -- and this does not include a larger group that are intentionally trying to harm themselves -- but 18,000 ED visits, and over half of them are secondary to combination products with hydrocodone. It's not an insignificant number, and certainly one that I have seen in my own practice over the years.

I'll change, then, and speak about two patients in my practice to sort of highlight these patients, this small group of folks who I think would benefit in my practice from an extended-release hydrocodone.

The first patient is a 46-year-old male who had chronic back and leg pain after a work injury. He'd had two surgeries, including a fusion. He tried physical therapy, nerve blocks, non-opioids. He was still working in construction. He was taking about four tabs per day of hydrocodone, 10 milligrams, for the past three years.

He told me that hydrocodone still worked for

him; but as if often the case with immediate-release drugs, the duration of action is shortened. He was only getting one to two hours of benefit from the drug, and needed more per day for maintaining that efficacy.

This is the kind of patient, again, for me it would be nice if we had an extended-release drug that we could switch to in that situation, not have to change molecules, not get into some of the dosing problems that happens with conversion from one molecule to the other.

A second case, a little bit different, is looking at the acetaminophen issue. So this woman was a 32-year-old woman who had had a motor vehicle accident. She'd had multiple orthopedic fractures and abdominal trauma. Her pain was actually from a compound tibia/fibular fracture that had extended into the joint and was producing progressive osteoarthritis.

She'd had only modest relief with NSAIDs. She'd been treated for four years with increasing doses of hydrocodone, was currently, again, on four

tablets with higher acetaminophen-containing APAP and hydrocodone in it.

So she was having problems again with increased pain and insomnia. It's my opinion she would have switched -- or would have benefitted greatly if we'd been able to switch her to an extended-release hydrocodone. Increasing her dose was not an option because of the acetaminophen there. And certainly, had we had this product, it would have been helpful for us in our practice.

Finally, I'll speak to one other topic, and that's the clinical usefulness of opioid rotation. We're not always sure what determines the response to any given opioid with our patients. It's probably somewhat genetic. It's metabolism. And different opioid receptor subtypes are also felt to play a role in why patients may respond to one opioid, why they get side effects to one opioid, and that's certainly still being worked out at the scientific level.

There's also other reasons to rotate opioids. It can be loss of effectiveness. There

can be side effects, as we talked about; tolerance that develops within one opioid such that switching, we don't always see the same degree of tolerance with the second opioid; and issues with, sometimes, the enzyme system, such as the P450 system.

How does this play out in clinical practice? There has been some look at this in the past, where you see, if the first opioid is introduced to a patient, a little over a third of those patients achieve effectiveness, and almost two-thirds, it's ineffective or they develop side effects during their therapy such that rotation to a second opioid reestablishes effectiveness in about a third of the patients.

This continues down, as you see, through third, fourth, fifth, sixth opioids. It extends, actually, past how I have it on this chart. And so rotating opioids in these patients actually, again, reestablishes the effectiveness, allows us to continue with this class of therapy in these patients.

There has been and there continues to be some scientific understanding of this. A lot of this is worked out in animals. The work of Gavril Pasternak has been instrumental in this. And again, a lot of this right now is still evolving, and certainly better understandings are to come.

But what we understand is there's differences, it appears to be, in receptor activation of these different subtypes of opioids. And so while one patient may have a certain activation with one drug, a second new, active drug of similar potency may activate subtype receptors differently.

That may explain some of the effectiveness or side effects that we see with one opioid versus another opioid, and may also help explain some of the incomplete cross-tolerance we see with opioids from one patient to the next.

To highlight that in a third patient, this is a woman who was in my practice who was 52 years old. She had metastatic breast cancer and diffuse, constant pain. She was still functioning at home.

She had developed adverse events with other extended-release opioids. She had nausea and vomiting, sedation. And she came to me and said, "You know, hydrocodone in the past worked very well for me, but I know we switched to these extended-release drugs because of issues with how much I could take. Can I not have an extended-release hydrocodone back? That molecule seemed to work well." I don't think she used the word "molecule," but in essence was saying that to me. I had also expressed to her the thought of using an intrathecal pump. That wasn't of interest to her.

I think an extended-release hydrocodone would have been a good choice. It certainly would have been something that I would have looked at and thought could have been a good drug for her. But it wasn't an option for us. So I think, again, if we had that drug, it's something we would look at in a small subset of our patients in that regard.

So I'm going to summarize with one slide for you and also have one conclusion slide for you.

I think, until we have another class of

drugs that are better, I think opioids will maintain a pivotal role in alleviating and managing chronic pain. There's baggage associated with them, unquestionably. But I think until something like anti-nerve growth factors or some other class comes about that really can displace them, that's where we are today in managing many of our patients.

Hydrocodone, if we had it as a single-entity, extended-release preparation, I think it would be an advancement for us in the management of our chronic pain patients in a small but clearly defined set of patients in that regard.

Again, why that is, I think it would allow us as practitioners to convert patients from IR drug to a more appropriate ER alternative without having to switch to a different molecule. We would be able to diminish the associated toxicities of acetaminophen in chronic use; it is a problem in the United States today. It would give us an effective alternative to other extended-release or long-acting opioids, as we discussed earlier, such

as methadone, oxycodone, oxymorphone, hydromorphone, morphine, or fentanyl when we think opioid rotation would be beneficial.

So I leave you with a last thought in conclusion. As a clinician, I did ask myself this question: Is there currently an unmet need for extended-release hydrocodone? And my answer to you is yes. It's for a small subset of the chronic pain patients, I think I've described to you, but I think it would be of benefit in our practice.

I thank you for your attention.

Sponsor Presentation – James Breitmeyer

DR. BREITMEYER: Thank you for your attention today. My name is Jim Breitmeyer. I'm the chief medical officer of Zogenix. I'm also an oncologist, and I'm experienced in pain therapeutics.

I'm going to present the hydrocodone extended-release clinical program, starting with clinical pharmacology, and then the chronic pain program, which includes pivotal study 801, safety study 802, and an integrated analysis of safety by

dose. We'll first review clinical pharmacology.

Here is first dose pharmacokinetics comparing immediate- and extended-release forms of hydrocodone. Immediate-release hydrocodone in the form of Vicodin tablets containing 10 milligrams of hydrocodone were administered twice, six hours apart, and the hydrocodone blood levels are shown in the green line.

If you look at the blue line, the new hydrocodone extended-release 20-milligram, given once, you can see that the peak blood level of hydrocodone is lower, the initial rise in blood levels is more gradual, and the effective half-life is longer. These are all desired features for an extended-release hydrocodone. The exposure was bioequivalent.

The next slide shows the blood levels of hydrocodone at steady state. Blood samples were collected from patients with osteoarthritis who had been treated with hydrocodone for three weeks at various doses, and a dose was given at time zero. The results show that hydrocodone ER

pharmacokinetics are dose-proportional, and the sustained trough levels support an every-12-hour dosing regimen.

We also did a standard battery of special pharmacology studies. As summarized in your briefing document, patients with renal or hepatic impairment can be treated with hydrocodone extended-release, but they should be monitored closely.

Food study and alcohol studies are summarized on this slide. There was a modest effect on peak blood levels, or Cmax, in a food study, but no effect on overall absorption or AUC. There was a moderate effect on peak blood levels when hydrocodone was ingested with 40 percent alcohol, conditions equivalent to taking it with six shots of vodka on an empty stomach.

Most of the Schedule II extended-release opioids show some degree of alcohol effect. Their maximum reported Cmax from ingesting at 40 percent alcohol, an important indicator of individual patient risk, is shown here. As you can see,

hydrocodone ER is in the middle of the pack, and like the rest, hydrocodone ER should not be taken with alcohol. One extended-release opioid called Palladone showed a much more pronounced alcohol effect, and it was subsequently taken off the market for this reason.

In summary, clinical pharmacology studies demonstrated gradual absorption of hydrocodone, supporting every-12-hour dosing; dose-proportional pharmacokinetics, supporting the intended dosage strengths of 10 through 50 milligrams; a modest or moderate alcohol effect that is similar to other approved extended-release opioid products; and a minimal food effect, which is less than some other extended-release opioids.

I'll now move on to the clinical program, which consisted of six phase 1 studies, two phase 2 studies, and two large phase 3 studies, the latter of which we'll describe here. First, pivotal study 801.

I'm going to walk you through the trial design for pivotal study 801, which may be of an

unfamiliar type to some of you. Opioid trials present unique challenges because people vary dramatically in the dose of medication they require or tolerate. So no single starting dose can be prespecified.

The current standardized approach to this issue is to treat everyone in an initial open label phase, where the opioid dosage is titrated individually. Study subjects are then randomized to continue active treatment or to placebo. This enriched enrollment randomized withdrawal design was agreed between Zogenix and FDA, and it was also the pivotal design used for other recently approved extended-release opioids shown on the slide.

An important aspect of this trial design is that the treatment effect that is the difference between active and placebo groups is usually on the small side in numerical terms during the placebo-controlled period because subjects on placebo tend to leave the study as soon as small increases in pain are experienced. This study was powered to detect a one-point difference in pain scores.

Eligibility criteria targeted subjects with moderate to severe chronic low back pain requiring continuous, around-the-clock therapy with any opioid for at least four weeks, at least five days a week, and at least 30 milligrams per day of hydrocodone equivalence.

Everyone received individualized open-label hydrocodone ER for every 12 hours, but to be randomized, they needed to experience during titration at least a two-point decrease in pain, have stable average daily pain less than 4 out of 10, and be compliant with all of the study procedures. If they met these criteria, they were then randomized to either their titrated dose of hydrocodone ER or a matching placebo for 12 weeks.

The study was conducted at 57 sites across the United States. The enrolled pain sufferers were an opioid-experienced population with advanced back pain, as indicated by an initial pain score of 7 out of 10 and a disability score of 62 out of 100, both in the severe range, despite the fact that they were taking over 55 milligrams per day of

hydrocodone equivalents.

At the time of randomization, and this was after six weeks of open label hydrocodone ER, there was a substantial reduction in pain of 4 points on the pain scale and of 12 points on the disability scale. At the time of randomization, key features were similar between the two groups; that is, the one randomized to hydrocodone ER and the group that was to receive placebo.

Fifty-five percent -- I'm sorry -- 59 percent of the enrolled subjects completed open-label conversion and titration to hydrocodone ER. The enriched enrollment feature of the study did what it was supposed to, as 13 percent of the subjects discontinued because they did not achieve protocol-specified criteria, primarily for response; 9 percent because they could not be compliant with study procedures; and 9 percent because they did not tolerate treatment.

During blinded maintenance treatment, 82 percent of the subjects randomized to hydrocodone ER completed the 12 weeks, compared

to only 39 percent on placebo. The most common reason for discontinuing was lack of efficacy for both groups.

The discontinuations from study 801 were compared to other approved Schedule II extended-release opioids. This slide shows discontinuations for adverse events in the titration phase of similar enriched enrollment studies. The 9 percent discontinuation rate from study 801 is shown in the hatched bar, and it's on the low end of the range for this type of study.

Several other comparisons of discontinuations are presented in your briefing document, and they show in the aggregate that the rates of discontinuation due to adverse events or lack of efficacy from hydrocodone ER study 801 were similar or lower than many of those reported for the other Schedule II extended-release opioids.

The primary endpoint of pivotal study 801 was changed from baseline to day 85 or early termination in the average daily pain score for the intent-to-treat population. Hydrocodone ER was

superior to placebo, with a treatment effect of 0.5 points on the pain scale and a p-value of 0.008.

The efficacy results for this study were robust and clinically significant and were confirmed across multiple domains of response from multiple secondary endpoints. In order to place these results in context, a meta-analysis of Schedule II extended-release opioids studied in similarly-designed clinical trials was performed using methods described in Appendix 2 of your briefing document.

Standard effect sizes are considered an appropriate means of comparing studies because they incorporate both treatment effect and variability. An effect size of zero represents no effect, with an increasingly negative number, or further to the left on this graph, representing a greater effect.

Hydrocodone is shown in blue near the bottom of the slide for viewing convenience only. The overlapping confidence intervals indicate that the results are not different between the various

opioids studied, including HCER.

There were two prespecified key secondary endpoints in the study. This is the first one, a standard responder rate display, with the cumulative percentage of subjects experiencing various levels of pain reduction from study entry to the end of study. Considering the 30 percent response, 68 percent of the subjects randomized to hydrocodone had pain scores reduced by 30 percent compared to only 31 percent in the placebo group, with a p-value of less than 0.001.

A 30 percent response is considered clinically meaningful, and the more stringent 50 percent response, which was also significant in favor of hydrocodone ER, is considered substantial or major.

Responder rates were also subjected to meta-analysis. There were five other studies of Schedule II mu opioid agonists available for comparison. And odds ratio of 1.0 indicates no response, and a higher odds ratio, or further to the right in this case, indicates a greater

response. Hydrocodone ER is shown in blue on this slide, and the results compare favorably to the combined results, as well as to those from tramadol and buprenorphine.

The second of two prespecified key secondary endpoints was a subject global assessment of medication. There was greater satisfaction with hydrocodone ER than placebo, with a p-value of less than 0.001, and a higher proportion of subjects very much are completely satisfied with their pain medication at the end of the study.

Time to exit was one of several other secondary endpoints that provided supportive evidence of the efficacy of this product. Subjects in the hydrocodone ER group had a significantly lower probability of discontinuing from treatment for lack of efficacy than those in the placebo group. This was readily apparent within the first seven days of the randomized maintenance treatment phase in this Kaplan-Meier plot.

The substantial difference between the two groups remained to the end of the study. Data on

time to exit for adverse events and for all causes are shown in your briefing document, and indicate that hydrocodone ER was well tolerated.

Opioids are often viewed as a class of medications that confer pain relief but do so at a cost of diminished physical functioning. Subject disability was measured in this study with the validated and widely used Oswestry Disability Index.

Disability decreased in both groups during the open label treatment period, and there remained a clinically significant difference for hydrocodone compared to placebo at the end of the study, with a p-value of 0.026. Results of other supportive secondary endpoints are presented in your briefing document.

I'm now going to move on to the safety results of pivotal study 801. In the initial open label titration phase, which was a maximum of six weeks in duration, 510 subjects were treated with hydrocodone ER for an average of 28 days at an average daily dose of 79 milligrams. In the

blinded maintenance phase, subjects randomized to hydrocodone ER were treated for an average of 77 days at an average daily dose of 119 milligrams of hydrocodone ER.

There were no deaths in study 801. During randomized treatment, only two subjects receiving hydrocodone ER discontinued due to adverse events, while nine went off study in the placebo group. There were five serious adverse events, all for subjects in the hydrocodone ER group, that were adventitious concurrent medical events that were not considered related to hydrocodone.

This figure shows the treatment-emergent adverse events during randomized treatment for the hydrocodone group in blue and for the placebo group in grey. Adverse events were generally those expected for an opioid, and were seen at rates that are not different from those in other Schedule II extended-release opioids.

I'll now move on to phase 3 safety study 802. 802 was a long-term safety study with a study design that was similar to that of study 801; that

is, enriched enrollment followed by 48 weeks, in this case of open label hydrocodone ER. Enrolled subjects were similar to the previous study except they represented a broader spectrum of chronic pain conditions, with osteoarthritis the most common, and had a lower disability score at study entry.

We'll discuss the safety results of study 802 first. Sixty-six percent of the subjects who enrolled in the study completed the run-in period. Similarly to 801, 11 percent of the subjects discontinued because they did not achieve protocol-specified criteria, 8 percent because they could not be compliant with study procedures, and 9 percent because they did not tolerate treatment.

Sixty-seven percent of those selected for long-term treatment completed the 48-week open label treatment, a high retention rate for a long-term study such as this. Eleven percent were discontinued due to noncompliance, and 9 percent discontinued due to an adverse event.

The study was conducted at 56 sites across the United States. 638 subjects were exposed to

hydrocodone ER for an average of 300 days, with 336 subjects exposed for more than six months and 285 exposed for more than one year.

The mean dose of hydrocodone, shown as the crosses in this plot, was about 150 milligrams per day, and increased only modestly over the 48-week maintenance phase. Thirty-eight percent of the subjects had no dose increase. As with all opioids, some individuals required substantially higher doses of hydrocodone ER for pain relief; but only outliers, who are shown as the small boxes, used more than 350 milligrams per day.

As expected, there were more treatment-emergent adverse events observed in the long-term maintenance treatment phase of the study, shown here in the blue bars, compared to the shorter titration phase, shown in yellow or orange.

The side effects were not different from other extended-release opioids, and no new or unexpected adverse events related to hydrocodone, compared to other Schedule II extended-release opioids, were observed.

There were four deaths during study 802, which did not appear to be directly related to hydrocodone ER, and one suicide 13 months after the study that probably involved hoarded study drug plus other prescription medications. Other serious adverse events are listed in your briefing document and were observed in 67 subjects over this year-long study.

They were a heterogeneous collection, usually one of each, mainly representing concurrent medical events considered unrelated to hydrocodone ER use, plus some that are known consequences of opioid therapy, primarily in the gastrointestinal and nervous systems. There were no new or unexpected serious adverse events compared to other Schedule II extended-release opioids.

Although this was primarily a safety study, effectiveness data were also collected, and they support the results of study 801. As you can see, average daily pain scores were reduced from 6.4 to 3.1 out of 10 during the initial run-in, or conversion and titration treatment phase, and this

benefit was largely sustained over the entire 48 weeks of maintenance treatment. Supporting evidence of sustained effectiveness was also found for individual response rates and physical function.

I'll now turn to an analysis of adverse events by dose of hydrocodone ER. For this purpose, the safety results of 801 and 802 were pooled as the largest available experience, with hydrocodone ER in subjects with chronic pain.

Safety results from the two phase 3 studies were pooled, and the combined database was studied for any evidence of a dose response for safety. In this slide, the most common adverse events are shown for the subjects receiving less than 100 milligrams per day of hydrocodone ER in the light blue bars, and those receiving greater than or equal to 100 milligrams per day in dark blue.

Some adverse event rates appeared slightly higher, above 100 milligrams hydrocodone per day, but not dramatically so. In fact, some events such as nausea, headache, and somnolence were slightly

lower at the higher doses.

Subjects were also divided into five groups according to their modal dose of hydrocodone; that is, the dose of study medication they took most often over the course of the study. A list of typical opioid side effects was created, shown on the bottom of the slide, and the percentage of subjects with any one or more of these was tabulated and examined by modal dose.

Typical opioid side effects were slightly less common at daily doses of 40 to 80 milligrams hydrocodone ER per day. They increased modestly at doses up to 160 milligrams hydrocodone per day, but did not continue to increase at doses above that. And this is in subjects that required higher doses of medication to achieve their pain relief. And there was no further increase in these typical side effects over 160 milligrams per day. This result suggests that hydrocodone side effects do not continue to rise with increasing dose, and are not worsened at the highest doses tested.

It was also important to examine the

effective dose on serious adverse events. As shown in this figure, there was no apparent dose response for serious adverse events in the integrated safety data from studies 801 and 802. The types of serious adverse events were also examined, and were not different in the highest dose group compared to the lowest dose groups of hydrocodone ER.

Zogenix was aware of concerns about high levels of suspected study drug diversion in clinical trials of other Schedule II extended-release opioids, and so took particular case to minimize and quantify abuse-related events in these studies.

Compliance was measured as the number of pills taken compared to prescribed. Any missing drug was investigated. Missing medication counts were derived from case report form drug accountability data. Finally, all adverse event terms were examined for events of misuse, abuse, or overdose.

Compliance was good in study 801, with no instances of the prespecified cutoff of

130 percent or -- sorry, in the titration phase -- and only one case of more than 110 percent diversion from compliance in the treatment phase; 0.19 percent of the hydrocodone ER, and less than 0.53 percent of the hydrocodone/acetaminophen, could be considered missing from case report form data.

Of 27 -- I'm sorry -- of 24 subjects with drug accountability discrepancies, all of which were investigated as possible diversion, seven had plausible explanations, and the other 17 did not, and they were discontinued from the study. Adverse event data contained one case of abuse, four cases of misuse, and one overdose.

Study 802 results were similar to 801. Compliance was good, with no indication of medication used above the prespecified cutoffs. Around 0.5 percent of both hydrocodone ER and hydrocodone/acetaminophen could be considered missing from case report form data.

Of 66 subjects with drug accountability discrepancies, all of which were investigated as

possible diversion, 30 had plausible explanations, and the other 36 were discontinued from the study. Adverse event data contained one case of abuse, eight cases of misuse, and two overdoses, one occurring 13 months after the end of the study.

In summary, misuse, abuse, and diversion were assessed rigorously and acted on quickly in these two phase 2 studies. There were few cases of misuse, abuse, or overdose, around 1 percent, and low numbers of missing study medications, around 0.5 percent for the two studies taken together.

These results compare favorably to a 36 percent rate of potential missing study drug that was presented by the CSS staff at a 2009 advisory committee meeting for another extended-release opioid.

In summary, the efficacy of hydrocodone ER compared to placebo was robust across the standard methods used in clinical pain trials. Hydrocodone ER was superior in controlling pain in the primary endpoint and on measures of clinically meaningful individual improvement in pain intensity, as well

as a longer time to exit due to loss of efficacy. There was also evidence of efficacy in global participant rating of satisfaction and in physical functioning.

Hydrocodone was generally safe and well-tolerated, with no new or unexpected safety issues; and its safety profile is qualitatively similar to that of the other Schedule II extended-release opioid products.

I'll now turn over the presentation to Dr. Farr to discuss Zohydro ER safe use program.

Sponsor Presentation – Stephen Farr

DR. FARR: Thank you, Dr. Breitmeyer.

Before I begin, I want to emphasize that we at Zogenix acknowledge prescription opioid misuse and abuse is a critical issue. In bringing Zohydro ER to patients, we'll be able to leverage the good progress made in establishing the new classwide REMS for extended-release, long-acting opioids under now-heightened awareness about the safe use of opioids for the treatment of chronic pain.

We also believe we can do more to improve

the effectiveness of the REMS, and we are proposing to implement and evaluate some innovative voluntary activities. We certainly welcome your input into these areas today.

We are here because of the significant public health issue of prescription opioid misuse and abuse, leading to the terrible consequences of addiction, unintentional overdose, and death. Immediate-release hydrocodone combination analgesics are part of this problem, no doubt because they are very commonly prescribed, the only Schedule III opioid product, and therefore widely accessible to be misused and abused.

Therefore, the overriding question today is will the introduction of Zohydro ER exacerbate this public health issue? And related to this question, does the product have greater abuse risk compared to other approved Schedule II extended-release opioids?

In order to answer the FDA's question about whether the abuse of Zohydro ER will be different than that of any other extended-release opioid, we

should begin with how one assesses abuse liability of any product. This is typically done by reviewing a mixture of different types of data on the product, or closely related products, as in these five categories you can see on the slide: in vitro, pre-clinical, human abuse liability, experience in clinical trials, and epidemiological information.

Regarding our product, Zohydro ER, and like the majority of approved and currently marketed extended-release opioids, it was not designed with the physicochemical characteristics that would deter tampering, and there is no dispute that hydrocodone pharmacology is typical of a full mu agonist.

The third element on the grid is human abuse liability studies, where opioid-experienced individuals are administered drugs in an inpatient setting, and their subjective responses are collected. A recently published Cochrane review of these studies concluded that hydrocodone had no worse abuse liability than other opioids, and maybe

better than oxycodone.

In case some of you are not familiar with how this type of data looks, this graph shows an example of a study from Dr. Walsh comparing drug high of different doses of hydromorphone, oxycodone, and hydrocodone. Hydrocodone, which is depicted by the solid squares in this graph, is not worse than the others. You'll be hearing more on this and similar studies, I'm sure, from Dr. Walsh later this morning.

The fourth element on the grid was clinical trials. In terms of our clinical experience with Zohydro ER, these are the summary of the data of abuse-related events, which were just provided earlier by Dr. Breitmeyer. There were few cases of misuse, abuse, or overdose, around 1 percent, and low numbers of missing study medications, around half a percent for the two studies.

Let's move to epidemiology, the fifth element of the grid. And before we get to specific opioids, the first point to note is that abuse is directly related to availability. This graph from

a study by Dasgupta, et al., shows the relationship between kilograms of opioid in the marketplace on the X axis, and DAWN emergency department mentions by year on the Y axis. You can clearly see that emergency department mentions are directly proportional to the availability of opioids.

A key event of interest in evaluating abuse liability is emergency department visits, which are often associated with overdose. FDA has exhaustively evaluated DAWN data for the upcoming advisory committee meeting on the rescheduling of hydrocodone.

Without attempting to review all their extensive work today, here is a sampling of the emergency mentions associated with either oxycodone or hydrocodone from 2004 through to 2009. And these have been adjusted for prescription volume.

The graph indicates that oxycodone combination products are consistently associated with more emergency department mentions than hydrocodone combination products. Perhaps the most important opioid-related event is fatal overdose,

which is a major public health problem in the United States.

Here we see a recently published study from Dr. Paulozzi at the CDC. This is a case control study from the state of New Mexico, examining the risk factors of fatal opioid overdose. This analysis indicates that the odds ratios of death on the Y axis are based on the prescribed drug on the X axis.

Hydrocodone, highlighted by the blue bar, is amongst the opioids least associated with mortality in this study, with a substantially lower odds ratio than buprenorphine, methadone, morphine, and other opioids.

So the completed grid looks like this, and indicates that based on existing, available data, there is no evidence for increased abuse liability or relative abuse rates of hydrocodone versus other extended-release opioids.

So let's address what all this means for Zohydro ER. As I just mentioned, the abuse liability of the hydrocodone molecule is clearly no

higher than other mu agonist opioids. Despite this conclusion, we recognize that higher strength in an ER formulation is likely to be more attractive to abusers than a lower strength in an IR formulation, and that any opioid will be abused in proportion to its availability.

Therefore, our focus for safe use of this product should be on responsible commercialization, controlling availability, and effective risk mitigation approaches.

Before discussing how we intend addressing this safe and appropriate use of Zohydro ER, I want to put into perspective the use of extended-release opioids in the United States by looking at opioid prescription trends since 2008 all the way through to July of 2012.

What you can see from this graph is that the number of prescriptions per month of IR opioids -- that's the red line on this graph -- continues to slowly increase. In contrast, prescriptions for extended-release opioids, the blue line, shows no appreciable rise,

even during a period when three new branded products have been introduced. In other words, the total use of extended-release opioids appears to remain constant and independent of new products entering the market.

We also do not expect the introduction of Zohydro ER to appreciably increase the use of extended-release opioids. As discussed by Dr. Rauck, the target patient population for Zohydro ER is a small fraction of chronic pain patients.

To put all this into perspective, we have requested, and the DEA has approved, our hydrocodone quota for Zohydro ER in 2013. That's the amount of active pharmaceutical ingredient available to us to be able to manufacture Zohydro ER.

The amount available is a fraction of 1 percent of the aggregate total of hydrocodone available for pharmaceutical sale, which is verifiable evidence of our commitment to limit Zohydro's availability to only those patients we

know will benefit from it. With that said, however, we fully embrace our responsibilities in ensuring safe and appropriate use of Zohydro ER.

So this is what we will do. Zohydro ER will be supported by all the newly introduced, FDA-required, risk mitigation efforts. We are committed to commercializing Zohydro ER in a responsible manner, with the goal of achieving safe and appropriate use in patients with chronic moderate to severe pain.

We want to augment the required risk mitigation elements because we think it could be helpful to assure safe use and unlikely to cause unintended consequences. We're calling this our Zohydro ER safe use initiative, with the following objectives you can see on the slide: Improving training across the entire health care chain; upholding safe use amongst patients; instituting regular surveillance systems and promptly applying corrective actions to suspicious signals as they arise. We will monitor the effectiveness of these programs, and if they appear to be successful, they

would be expanded.

Now let's go through these components in more detail, starting with the required risk mitigation elements.

Unlike all other hydrocodone products, Zohydro ER will be regulated as Schedule II, and therefore subject to tighter prescribing restrictions. The product label for Zohydro ER will be consistent with what is being used for all other extended-release, long-acting opioid analgesics in terms of the same indication, the same contraindications, the same warnings, the same precautions.

This will be the first time a hydrocodone product is part of the classwide REMS just recently approved by the FDA. These requirements alone would make Zohydro ER the most stringently controlled hydrocodone product available.

Our commercialization plan is based upon introducing Zohydro ER with a specific sale focus on practitioners who are familiar with prescribing extended-release opioids for the management of

chronic pain. This represents a relatively small percentage of DEA registrants, all of whom will receive the REMS educational materials.

This list of clinicians will be formally reviewed and approved by senior management at Zogenix. That will occur at launch and on an ongoing basis as the product is marketed.

Our sales professionals will be compensated on specific goals in support of the Zohydro ER Safe Use Initiative, including the successful completion of the REMS training by their prescriber audience. In the first year after launch, 100 percent of their incentive compensation will be directed towards this objective.

On recognizing that Zohydro ER could be the first single-entity formulation of hydrocodone introduced into clinical practice, we have decided to proceed with a limited top dosage strength compared to currently approved extended-release opioid products.

This diagram compares the upper dosage unit of currently marketed extended-release opioid

analgesics. All dosage strengths have been converted to morphine equivalence, as depicted on the Y axis, to allow product-to-product comparisons. You can see from the dotted horizontal line that the highest intended dosage unit of Zohydro ER is less than the highest dose of all other extended-release opioid products.

So to conclude, the upper strength of Zohydro ER is not atypically higher relative to other ER opioids; and recall that all these strengths were evaluated in our phase 3 clinical program.

I mentioned earlier that the current formulary of Zohydro ER is not tamper-resistant. We view tamper-resistant formulations as just one spoke in the wheel of abuse deterrents. We know today that most of the abuse of prescription opioid products is ingestion of unaltered product by the oral route, something that no formulation can prevent, although tampering of prescription opioid products for the purpose of abuse remains a real public health problem.

Current evidence of the beneficial impact of tamper-resistant formulations is mixed. Some studies show a positive impact, while others show none, which could be related to the fact that the observation period is still too early.

However, we are actively developing tamper-resistant formulations of Zohydro ER that provide meaningful risk mitigation while maintaining the established safety and efficacy in the patient population. But most importantly, we are planning today a comprehensive approach to other elements of safe use, especially education and surveillance initiatives that I'll discuss during this presentation.

Now let me turn to the recently established shared REMS for extended-release, long-acting opioids. I'm not going to go into the details of the REMS program because the upcoming presentation from FDA will do it. But I'm using this fairly simple graphic to highlight the principal components that are focused on prescriber training, on all opioid products in this class, and a

medication guide for patients for each of the extended-release, long-acting opioid analgesic drug products. If approved, Zohydro ER would of course be part of this same REMS program.

In assessing our overall approach to risk mitigation for Zohydro ER, we have evaluated where we could supplement the shared REMS with additional elements to assure safe use. Probably the most controversial part of the REMS is the voluntary nature of the education and whether it can be implemented widely enough so that prescribers use the drug in a knowledgeable way, and the patients also play their part in the safe use.

For prescribers, we are focusing on innovative, non-promotional training tools and programs we can offer in a comprehensive way, and also monitor whether they impact prescriber participation in education and improve outcomes in the use of extended-release opioids.

We also believe it's important to include pharmacists in our safe use initiative, as they can play an important role in counseling patients as

well as detecting suspicious behaviors. There is currently a lack of training resources for pharmacists who dispense opioids, highlighted by the fact they were not part of the target group in the recently-approved REMS.

Finally, patients also need to play their part in safe use. Since it is well known that the vast majority of recreation abusers of prescription opioids get their product from friends and family members, we will be focusing on both reinforcing patients' responsibility and providing practical steps to help them maintain safekeeping of their drugs at home.

In seeking a partner to enhance our education initiative beyond the REMS, we are delighted to be collaborating with Inflexxion, who we believe have the best in class intervention and prevention educational tools for effective pain management.

We will be utilizing their NAVIPPRO programs with the objective of achieving an educational relationship directed towards all stakeholders.

The programs are described in detail in your briefing package, and Dr. Zacharoff, who is the vice president of medical affairs at Inflexxion, is here with us today to help address any specific questions.

Briefly, we'll be providing this suite of web-based interactive programs that start with an entry portal called painCAS. This provides clinicians with web-based standardized assessments and evidence-based guidelines and recommendations to improve quality of care.

PainCAS will further direct clinicians to painEDU, an established and recognized non-promotional pain management resource, with a host of print and online materials available to the clinician. Prescribers will also be able to direct their patient to painACTION, an education resource for caregivers and people with chronic pain. These programs work synergistically to provide health care education for all stakeholders.

Although often disputed, education of stakeholders may indeed make a difference, and here

are some examples I want to share with you. In 2008, the Utah Department of Health created a program to decrease deaths and other harm from prescription pain products, which included components of painEDU and painACTION. After one year, unintentional overdose deaths from prescription opioids dropped 14 percent from the previous year and remained stable the following year. This study at least points to the idea that education may have contributed towards mitigating risk.

In a recent clinical trial, painCAS was shown to improve utilization of opioid risk assessment tools compared to baseline, almost 80 percent compared to 41 percent. PainACTION has also been shown to be efficacious in chronic back pain and migraine patients, along with other NIH-funded trials demonstrating efficacy in cancer pain, neuropathic pain, and arthritis pain patients as well. We believe this suite of tools and programs can enhance the risk/benefit profile of Zohydro ER as well.

For prescribers, we will provides access to the NAVIPPRO suite of resources. This will be enabled by both Inflexxion and Zogenix, and will give prescribers access to online and printed non-promotional materials for proper patient selection, risk assessment, treatment plans, and monitoring tools.

A unique component that we are piloting is virtual simulation-based training that we believe will increase physician engagement and provide practical knowledge through interesting case study evaluations.

In addition, we are providing a prescriber toolkit to help physicians understand what they need to discuss with their patients prior to initiation of Zohydro ER therapy. This toolkit will include all of the REMS materials plus additional resources in a single package.

Another program we will offer is assistance with the setup of urine drug screening services. We will use the opportunity of training physicians on the metabolism of hydrocodone and what to

measure in urine as a means of advocating the importance of conducting regular urine drug screening for new and existing patients to monitor for signs of abuse as well as signs of diversion of the product.

We also believe it's important to include pharmacists in our safe use initiatives. We will be directing pharmacists towards utilization of the educational resources available to them via painEDU. Because Zohydro ER will be different to current hydrocodone combination analgesics, we will issue information alerts and make pharmacists aware of the fact that it is an ER form of hydrocodone. It comes available in different doses/strengths, it has a different indication, and it has a different DEA scheduling.

As part of the dialogue we hope to encourage between pharmacists and patients. We'll also provide a pharmacy brochure, which reviews safe storage and disposal tips pharmacists can communicate directly to the patient.

In addition, we'll be providing patients

with free locking pill caps and discounted access to storage units. Recently, the locking cap, a combination bottle cap to prevent unauthorized access to prescription medications, was recognized as one of the leading technologies to reduce prescription drug abuse. We agree. These products can limit the ability of the drug getting in the hands of the unintended users.

Also for patients, we want to supplement the REMS medication guide with the trusted non-promotional resource being offered by painACTION, which they will receive via their clinician, and a comprehensive patient treatment kit containing easy-to-read information regarding how to safely use Zohydro ER and information about how to connect with patient advocacy groups, online pain management resources, and addiction prevention information.

Now I will switch to our surveillance activities. We will be implementing a comprehensive approach to surveillance to monitor the occurrence of intentional and unintentional

overdose and abuse of Zohydro ER as well as diversion activities.

We'll also be forming an independent safe use board of experts who will provide feedback and recommendations regarding the safe use and benefit/risk of Zohydro ER. You can think of this group as analogous to a data safety monitoring board for a clinical study, except their function will be directed towards decisions on Zohydro ER in the postmarketing environment. They will have direct access to the Zogenix CEO and our board of directors, and will have the authority to report findings directly to FDA and/or the DEA.

The areas of expertise of the standing members of the board are shown in the table. The board will convene monthly during the first six months after Zohydro ER, and then at least quarterly, or as needed, thereafter.

The ISUB is responsible for reviewing available data and analytics on the prescribing and use of Zohydro and providing input regarding the activities you can see on the slide: Zogenix's

interpretation of signal identification from the data; assessment of the Zohydro ER risk/benefit profile; effectiveness of the current surveillance tools; effectiveness of the current safe use education program; opportunities to enhance signal detection or risk mitigation activities. How all this works together is shown on the next slide.

The surveillance system will use a variety of information resources, and these are beyond the requirements of the REMS program today. Many of them will be familiar to you, however, because they represent state-of-the-art tools used in other risk mitigation plans.

The surveillance activities will focus on two major constituent groups. First, for health care related surveillance, our existing pharmacovigilance activities will monitor adverse events of interest, such as drug dependence, overdose, drug abuser, suicides, and deaths.

Proprietary prescription databases will be monitored for prescriber patterns, and the supply chain will be audited for suspicious or unusual

orders, and the incidence of dispensed prescriptions paid for with cash. Second, under our partnership with Inflexxion, we will obtain a regular data stream from the validated suite of NAVIPPRO tools to monitor for substance abuse amongst the general population.

Information from all these surveillance systems will be fed back to Zogenix and the independent Safe Use Board. As I mentioned earlier, this board is here to evaluate signals and their context, and report back to Zogenix with recommended actions. They will also provide oversight to ensure the responses to corrective actions are monitored, and that changes are made to the surveillance activities or safe use components as needed. The ISUB will have the authority to report their findings directly to FDA, as I mentioned earlier.

I want to stress a few important points. Our surveillance -- sorry. Information from all these -- no. Our surveillance system examines several sentinel populations of stakeholders, as

you can see on the slide. All potential signals of interest will be carefully evaluated, and we are committed to taking action starting with notification letters all the way through to stopping product shipments and informing law enforcement authorities.

What I wanted to achieve today is demonstrate that our strategy for safe use of Zohydro ER is based on two key elements. First is limiting the availability of Zohydro ER in the marketplace. This starts with the DEA quota, which determines the manufacture of the product through to identifying the patient population who would benefit from the product and, in turn, working with the appropriate prescribers to make it available for their patients.

Secondly, we are implementing a broad and vigorous surveillance plan to detect signals of abuse, misuse, and diversion, and take immediate corrective actions.

It is our hope that the advisory committee will appreciate and endorse the strategy and design

we have put into the risk mitigation efforts for Zohydro ER. As president of Zogenix, I can assure that it is my intent, as well as the intent of all employees, to be responsible stewards of this potential new product. We all share the same concerns of abuse of prescription pain medications.

I would now like to ask Dr. Breitmeyer to return to the podium to conclude our presentation.

Sponsor Presentation – James Breitmeyer

DR. BREITMEYER: Thank you again for your attention and considered review of this material. I will now summarize our presentation.

We showed you today that the efficacy of Zohydro ER was robust across the standard measures of efficacy for a chronic pain treatment. It was superior in controlling pain, for clinically meaningful improvements in pain, and for time to exit. Patients who used Zohydro reported higher degrees of satisfaction with their pain medication and achieved improved physical and emotional function stores.

You've also heard about the medical need for

this product. First, because hydrocodone is so well-known to prescribers, it is often prescribed in combination with acetaminophen for treating chronic pain. Patients may be tempted to take too much acetaminophen when their hydrocodone needs increase, causing accidental acetaminophen overdose and liver damage.

Second, physicians prefer to use the same opioid when transitioning from an immediate-release opioid to extended-release, and hydrocodone is the only opioid that is not available for this transition.

Finally, prescribers need choices when a chronic pain patient must rotate from one extended-release opioid to another, particularly if that patient did well on hydrocodone in the past. Given these and other factors, we believe the availability of a single-agent extended-release hydrocodone will offer important clinical benefits.

We hope you heard clearly that Zogenix grasps the magnitude and the importance of prescription opioid misuse, abuse, and diversion.

We understand that hydrocodone is a powerful drug that is dangerous when used improperly.

Our part in mitigating this public health issue is the Zogenix Safe Use Initiative, a serious and comprehensive program of training, tools, surveillance, and effective response, which includes important and innovative features that go above and beyond the opioid REMS:

First, an independent safe use board that is empowered to communicate directly to FDA;

Second, web-based patient and provider educational programs with proven success in early quantitative studies;

Third, a compensation program that incentivizes our field representatives for success in education over sales;

Fourth, training in a device to help patients keep their medication out of the wrong hands;

Fifth, a realtime surveillance program to actively monitor information from the health care system, distribution channels, and end users;

Finally, and perhaps most importantly, a company-wide commitment to take immediate and meaningful action when faced with abuse, up to and including cutting off product distribution and reporting such abuse to the appropriate law enforcement authorities.

The data presented today demonstrate that this extended-release formulation of hydrocodone meets and unmet medical need and is effective in treating chronic moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed.

Zohydro ER has been shown to be safe in the intended population. It is not different from the class of other approved extended-release opioids in safety or abuse liability. We have described a comprehensive and innovative voluntary risk mitigation program that goes above and beyond the ER/LA opioid REMS. Zohydro ER will be the only form of hydrocodone that is covered by such a risk mitigation program.

In conclusion, the data indicate that

Zohydro has a favorable risk/benefit profile that supports its approval. We look forward to your deliberations, and are happy to answer any questions that you may have for us.

Clarifying Questions to the Sponsor

DR. FLICK: Thank you, Dr. Breitmeyer.

We'll proceed with clarifying questions to the Zogenix folks. Please remember that you must state your name before you speak, and direct your questions to a specific presenter from the sponsor.

Before we begin, Dr. Denisco, could you please introduce yourself for the record?

DR. DENISCO: Yes. I apologize for being late. Richard Denisco, medical officer at NIDA, at the NIH.

DR. FLICK: Questions from the panel? Dr. Kramer?

DR. KRAMER: I have two clarifying questions about the efficacy study. I just want to make sure -- and this would be for, I guess, Dr. Breitmeyer. I just want to make sure I understood the actual results completely.

So I know that you frequently refer to the p-value in your summary of benefit and risk, but I'd like to understand better what happened in that study. And if I understand correctly, since you're using a mean numerical rating scale, the fact that the placebo group was positive 1 from baseline to the end of study, meaning they got worse by that amount. So their pain scale was higher at the end. Is that correct?

DR. BREITMEYER: That is correct.

DR. KRAMER: So that is also the case that the pain scale for the treated group got worse from baseline to the end. Is that correct? Just not as -- not as -- it was a difference of .5. But they both got worse. Is that correct?

DR. BREITMEYER: Yes. Both -- is the microphone working?

DR. KRAMER: Okay. I just wanted to make sure the positive -- that my interpretation was correct, that it was --

DR. BREITMEYER: Your interpretation is correct.

DR. KRAMER: Okay. And the other question I have is, could you explain why you did not include cancer pain patients in the study?

DR. BREITMEYER: Dr. Robinson will answer that question.

DR. ROBINSON: Cynthia Robinson, chief development officer, Zogenix. We sought to look at a very uniform group within our pivotal efficacy study, a group that's been studied several times with other extended-release opioid products. So for that study, we focused on a chronic lower back pain population as a population where doses and so forth in these studies were well understood.

Within our open label 802 study, we did allow subjects with any pain etiology to enter into that trial to understand the safety of that population with treatment of the drug.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Yes. My question is for Dr. Rauck. We know that opioid use varies from subject to subject. So my question is, so that this panel can measure effectiveness, do we have a

profile, both postmarketing and in study 801 and 802, to determine which subjects had a better response rate based on metabolism, genetics, and mu opioid receptors?

DR. BREITMEYER: If I could clarify, are you asking for that information from these Zogenix studies?

MR. MULLINS: Yes, I am.

DR. BREITMEYER: I don't think Dr. Rauck needs to stand up. The genetics that -- Dr. Pasternak's interesting generics having to do with splice variance of the mu opioid receptors were not studied in these Zogenix pain trials.

MR. MULLINS: That's what I'm concerned, because we are looking at -- the statement that Dr. Rauck made was that this opioid, hydrocodone ER, was effective -- was not effective for -- or recommended for all subjects. So I'm trying to understand, in order to determine effectiveness, which population or which patient profile has a better response rate for hydrocodone ER.

DR. BREITMEYER: Yes. Dr. Rauck will answer your question.

DR. RAUCK: Thanks. It is an appropriate question. I don't think clinically yet we know how to determine responders to opioids in general. So I don't think we have that relative to that. The Pasternak work is what's evolving and helps to possibly explain what will happen in the future, the ability to look at responders and how we might look at one patient versus the other.

Clinically, when we look at the patient profiles and who might go into this product, it's driven more by that group of immediate-release folks who have done well with the drug who might do better with the pharmacology of an extended-release drug in that regard.

MR. MULLINS: My follow-up question to that, Dr. Rauck, how do we make a more accurate assessment and prescription of the proper subject for this suggested therapy if we're not sure exactly who it should be prescribed to?

DR. RAUCK: Right. So I think, again, we

look at patients in several ways. One, they are using the drug appropriately, in an immediate-release form, but they're now needing more drug or the duration of action of the immediate-release drug isn't long enough for them. And so they would benefit from an extended-release product.

As I said, I really think it's a smaller group. It's not a large group of those patients who would be needing to switch in that bucket. The other small bucket are those who are receiving problems with acetaminophen; too much acetaminophen, but the molecule otherwise is providing effective analgesia. That would be another small group that probably would benefit, I think, by staying with this.

The benefits, we think -- at least I think as a clinician -- is if we can stay with the same molecule, we don't have to, as we do now, go from an immediate-release hydrocodone to an extended-release oxycodone or an extended-release oxymorphone. So it is of benefit to us clinically to stay with the same molecule when we make that

switch.

Given that a whole bunch of this IR drug in hydrocodone is used for things like acute strains or sprains, they wouldn't switch. They're used for postoperative considerations. So we're talking, again, a small, small piece of the pie that way.

DR. BREITMEYER: If I could, Dr. Katz has a follow-on comment.

DR. KATZ: Just a quick addition. It's a wonderful question. My name is Nathaniel Katz. I'm a pain researcher, and I've been doing clinical research on the opioids for about 20 years now.

I think the heart of your question is why can't we have some diagnostic test where we could just test people up front and then figure out who's going to respond and who's not going to respond, or who's going to have side effects, and then do a clinical trial that way.

That's a very active area of research. We're doing work in that area. But at this point, we don't really have any such diagnostic tests that have been shown to provide us that information.

Maybe sometime soon.

DR. FLICK: Dr. Rosenberg?

DR. ROSENBERG: Yes. Given that hydrocodone is the most commonly abused opioid, and it even is used in the pediatric population, or misused in the pediatric population, do you have any estimates as to the AE profile, or the adverse event profile, of this 40- or 50-milligram drug taken in a single dose by a opioid-naïve individual?

DR. BREITMEYER: We have not studied this medication at that dose range in opioid-naïve individuals. All of the patients in 801 and 802 were required to be opioid-experienced. There is some experience with the product in an acute bunionectomy study that was performed in individuals who were largely opioid-naïve. And the adverse event profile in that case was similar to a comparative group that was hydrocodone/ acetaminophen.

DR. ROSENBERG: But were they taking the larger doses in that bunionectomy study?

DR. BREITMEYER: The highest dose that was

taken in the bunionectomy -- and this was a single-dose study, immediate post-bunionectomy pain management -- they took doses up to 40 milligrams.

So, for example, nausea occurred at -- and I know your question's about overall safety. But we have comparative data for typical opioid side effects. So nausea occurred at a rate of 39 percent with a 10-milligram Vicodin tablet, and was seen at about the same rate with a 20-milligram hydrocodone extended-release, and at a 55 percent rate for the 40-milligram hydrocodone ER capsule.

DR. FLICK: Dr. Denisco?

DR. DENISCO: Thank you. My question is about the abuse resistance. And I'll leave this open to any of the sponsor's representatives. When will those tablets be available?

DR. BREITMEYER: I'm sorry. I couldn't hear the question.

DR. DENISCO: I'm sorry. I'm asking about abuse resistance. There was a mention that there would be abuse resistance tablets developed in the

future. When would that be?

DR. BREITMEYER: Thank you. Dr. Farr will address your question.

DR. FARR: Well, first and foremost, we'd like to really establish first that these are truly meaningful out in the real world. As I mentioned earlier, some data suggests that they are, and others say they're not.

We are, however, actively working on abuse- or tamper-resistant formulations, and we have, in fact, even discussed that with the FDA. Our view is that we would like to try and find an approach that is not going to run into some of the issues that some of the tamper-resistant formulations have seen. Slide up, please.

Slide up, please. This is just an example from some of the issues that have been run into when sponsors are trying to look for ways to have been able to provide tamper-resistant formulations -- choking, intestinal obstruction, acute withdrawal syndrome, manufacturing issues, as well as diminished efficacy as being seen in

development studies.

So our view is we're taking it very seriously. We have several candidates, formulations, in development, the most promising of which, from our side, is actually the earliest. So it's in pre-clinical development now. So that would be, really, several years away from the market.

DR. FLICK: Dr. Wesselman?

DR. WESSELMAN: I have two questions. The first relates to cancer patients, as Dr. Kramer had already asked. I understand that you were not instructed to study cancer patients. But my question is, would this be a safe drug for them if this drug would be on the market?

I was worried about the deaths that you reported on the patient with lung cancer. I don't know exactly what the incidence is in the general population, but there was a recent study from the University of Chicago where lung cancer tumor cells were growing significantly in an opioid environment. And therefore, it caught my

attention.

What is your comment on this?

DR. BREITMEYER: That particular case was an individual, a 68-year-old, with a long history of smoking, who was diagnosed with unresectable stage IV cancer early in her participation in study 802. So the cancer was already well-established -- you have to presume it was well-established -- before she entered the study. It was extensive local/regional disease.

She elected to stay on the study. Stayed on the same dosage of medication. And in fact, what we heard from the clinician was that it was an effective cancer pain regimen for her as well as providing pain relief for her osteoarthritis, which was the original reason that she entered the study.

In this particular case, she had a typical lung cancer course from there forward. And I don't think that it's -- I don't think we can -- I take your point, but I don't think we can pull anything about this particular case to indicate whether or not there was an interaction between the use of

hydrocodone and the progress of her disease.

Dr. Rauck has a comment as well.

DR. RAUCK: I'll address the first part of your question, which was, would this drug be beneficial in a cancer population? I think, actually, it would be a good drug in some of our cancer pain patients. As you know, the disease, when it is progressive, many of those patients' pain problems start not as severe as it is later in their disease process. So a lot of them do get exposure to immediate-release hydrocodone early in their disease.

There's a reasonable number of those patients who do do well with that molecule. As their disease progresses, their dose requirements increase over time. And again, as a clinician, it's always nice if you have a patient who tolerates a molecule well or tolerates a drug well that if they have increasing dosing requirements, that you'd be able to stay with the same drug.

So I think in the cancer population, it would be a very appropriate use of this drug in

some of the patients.

DR. WESSELMAN: Yes. I was just -- I agree with that, that in patients with advanced cancer, it would be really good to have more options, including opioid treatments. But I was still puzzled that the patient was able to enroll into the study, and then just a very short time afterwards was diagnosed, not with early stage lung cancer but with stage IV.

DR. BREITMEYER: And if I could address Dr. Kramer's earlier question, there were a total of five patients enrolled with cancer in these trials. Our study sites were ones whose primary practices were around non-cancer pain, and so the enrollment of the cancer patients was on the light side.

DR. FLICK: Dr. Jevtovic?

DR. JEVTOVIC-TODOROVIC: Thank you, Mr. Chairman. I have two questions for you. One is for Dr. Rauck and the other one is for Dr. Farr.

Now, first question for Dr. Rauck is in regards to the number of patients that you think

could benefit from this, which in some ways is a continuation of choosing the proper subject that is responsive because we know that chronic patients are notoriously unresponsive to chronic opiate treatment.

Could you give us an estimate that could help your cause as to how many patients, or the percent of patients, that you think would really benefit from introducing yet another very dangerous drug that could be abused by ones who are not really in that category? Can you give us a sense of how many patients are we talking that you truly think would benefit from this particular formulation?

DR. BREITMEYER: I think I might be able to address that question initially, and then Dr. Rauck can address it from a clinical perspective.

We've examined the number of patients who end up being prescribed each of the three most recently launched extended-release opioids, which we think gives some indication of what the first year or so of introduction of this product might

look like.

If I could have the slide up. What we're showing here -- could I have the built version, please? What we're showing here is monthly prescriptions. And the blue line is for all extended-release and long-acting opioids. The first thing you'll notice is that, by far, the majority of usage here is fentanyl, morphine, oxycodone, and methadone.

When Exalgo, Embeda, and Nucynta were introduced to the market, the utilization by patients was in a very small fraction of the overall usage. We expect the initial uptake of Zohydro ER to look like these three products.

You can see that in terms of monthly prescriptions, they're barely above the baseline. They're in the tens of thousands of ranges, where there's about 4 million patients who receive an extended-release or long-acting opioid over the course of a year.

Does that address your first question? Would you like to hear more from Dr. Rauck on the

clinical aspects?

DR. JEVTOVIC-TODOROVIC: It really doesn't. So you think that this is 4 million patients that could potentially benefit from this formulation? No?

DR. BREITMEYER: No. No, that's not what -- no, not at all what we're trying to say.

DR. JEVTOVIC-TODOROVIC: No? Okay. So how many are we talking in terms of raw numbers and in terms of percentage? You know what I'm actually, as a clinician, asking you, basically.

DR. RAUCK: Yes. It's a fair question. I apologize if I presented it all sort of erroneously that way.

I think the point is, it is a large pie as far as immediate-release hydrocodone. Right? We know that from the number of prescriptions out there. I guess what I was trying to bring home was that the vast majority of immediate-release hydrocodone are clearly patients who one would never think to go to extended-release.

So again, whether there's postoperative

patients, which is a big percentage, trauma out of the ER, patients with minor injuries that way, I think that constitutes the overwhelming number of those.

But within chronic pain patients, we certainly have a small percentage of patients who are on IR drug who either are getting into issues of acetaminophen problems or patients who get into other problems of not having good efficacy.

I mean, right now those patients do go into that extended-release market already. So they go into the extended-release market that has its own abuse issues that we'll hear more about, and we know that that's there when they go there.

I think the advantage here is being able to stay in the same opioid class. Some of the overdose problems we have is when we switch molecules from immediate-release, possibly hydrocodone, to a different extended-release product that way.

If you talk about exact numbers, I think you're right. Some of the best numbers we have are

coming out of our clinics, and my clinics would be in the tens of thousands if you look at those numbers. So I don't think the number is a huge number at all or referenced when you look at the big pie versus the small number who would get it.

DR. BREITMEYER: And I'll add one other, I think, important fact for the committee to have in hand to consider this question about the numbers of patients, and you're also asking about amount of hydrocodone extended-release.

This has to do with the DEA quota. And so the way this works is that a manufacturer makes some estimation of the amount of raw material, of opioid, that they expect to need. And on a yearly basis, they make an application to the DEA in which they request DEA permission to process a certain amount of material. We've done that. We have requested our amount of material for 2013, and DEA agreed with and granted that amount.

If I could have the slide up. This is not a build slide. The amount that we requested is shown here in the left space, compared to the total

amount of hydrocodone and the total amount of oxycodone that has been granted authorization by the DEA to other manufacturers.

The amount that we intend to distribute -- and this is a maximum -- you always estimate up a little bit -- is 0.3 percent, as you can see, of the amount of hydrocodone that is available for distribution in 2013. That, of course, will be entirely combination products because those are the only ones that are available.

These quotas rise slowly once they're established, and we anticipate a rise in subsequent years in the range 20 percent or so. DEA tries to keep these things contained, for all of the reasons that you're deliberating today.

DR. JEVTOVIC-TODOROVIC: Thank you. I had second issue that I thought maybe Dr. Farr could address or maybe you, sir, can address.

As I was getting ready for this meeting, I looked at some of the statistics that are available in regards to the epidemic of prescribing opioids for various types of pain, including

pulling your teeth -- you know, at the end of your dental visit where you get a whole box of Vicodin.

The question for me was, looking at some of the statistics, it turns out that -- and you're probably aware of that -- that in 2008 we had an obvious switch from number of deaths from motor vehicle accidents actually going below the incidence of deaths due to the overdose of opioids. And a couple of days before this meeting, we got an extra package where Dr. Hamburg actually refers to that. And we could provide you with the -- I could provide you with the slide.

DR. BREITMEYER: Okay.

DR. JEVTOVIC-TODOROVIC: So when I look at a relatively small population of patients that would really be benefitting from this formulation and the huge risk that is involved -- we are basically doubling the amount of hydrocodone, from 10 to 20 milligrams, really, in your formulation -- the question is, how is the safety measure that Dr. Farr was talking about going to help remedy the problem that we already have? How is that any

different than what other companies are asked to do who produce the same type of products or the same family?

DR. BREITMEYER: Yes. Dr. Farr will address your question.

DR. JEVTOVIC-TODOROVIC: Thank you.

DR. FARR: Before I address the question just asked, I can add a little bit more color to your first question in terms of, I think, the number of patients you were looking for. So there are a number of issues that we looked at and tried to estimate the number of patients that would be on this product. And we're seeing it in the 100,000 level, at peak.

So there's clearly a medical need. There are patients who would benefit from the product. But because we're entering the market -- the products go into a mature market -- there is a managed care market, and we see that as being an appropriate number of patients who would benefit from it.

In terms of your second question regarding

the concern or bringing forward hydrocodone -- because everyone knows Vicodin is so widely abused -- I think it goes back to what I said in my presentation, and that is that I think we feel that abuse equates to availability. So by ensuring that we are limiting the availability and focusing on the patients who need it, we feel that we can control the abuse issue there.

Also, I think the other elements that we put in place here -- particularly, I think, the locking cap in this sort of situation, where one of the big issues with Vicodin is that teens are taking it from medicine cabinets -- by having a locking cap available, that's going to be much more difficult. And we'll be able to essentially use the educational materials we provide to patients to really enforce their responsibilities.

DR. JEVTOVIC-TODOROVIC: Thank you.

DR. FLICK: Dr. Ware?

DR. WARE: Thank you. Dr. Breitmeyer, I think I'll start with you, but you might want to call upon some of your colleagues.

So I think there are contextual reasons to believe that this formulation is effective in management of pain. But when I actually look at 801, study 801, I find it a little challenging to evaluate the efficacy data there because, as you pointed out, there's an enormous amount of attrition. And there are a variety of data decisions made about how to deal with the patients who aren't continued.

You used some baseline carried forward. You used last observation carried forward. And the actual effect sizes are small. It's 1 point versus .5 points. And even though the p-value is .007, I was trying to assess how robust the findings are from this study 801 regarding efficacy.

DR. BREITMEYER: Sure. Yes. And I agree that there's a colleague that is well placed to address your questions, Dr. Ware. If I could call Dr. Davis forward.

DR. DAVIS: My name is Chuck Davis. I'm a statistical consultant to Zogenix, and I have no financial interest in the company or the outcome of

this meeting. I'll review the approach that was specified.

If we can have slide up, please. At the end of phase 2 meeting, the plan for the prespecified analysis of the data was discussed with the FDA, and the reasons Professor Ware mentioned were specified for the various types of discontinuations: last observation carried forward for discontinuations due to lack of efficacy, baseline observation carried forward for discontinuation due to opioid withdrawal, and a screening observation carried forward for discontinuation due to an AE. So these reasons were prespecified in the protocol and in the prespecified statistical analysis plan.

There are other approaches that can be used to analyze the data. The key secondary endpoint of the responder rate is important. I actually think that's probably more -- something that's more easy to interpret clinically.

We also carried out some sensitivity analyses that used a different approach. This was

not part of the prespecified analysis but, as discussed at the pre-NDA meeting, there's been a lot of work in this area, recommendations from the National Academy of Sciences report on missing data. And we used a linear mixed model. This was a post hoc analysis. It was not prespecified.

Can we have the slide up, please? This was a very general linear mixed model that included fixed effects for treatment time, the treatment by time interaction. It used an unstructured covariance matrix. No specific imputation was done, just the available data was used for each subject. And this slide displays the treatment difference estimates at each of the five time points at which data were collected.

The treatment difference is increasing over time. And actually, by the results of this analysis, the treatment difference at the final time point is larger and more statistically significant than from the prespecified primary analysis.

DR. FLICK: Dr. Maxwell? This will be the

last question before break.

DR. MAXWELL: Okay. I have a couple of quick questions that you can respond to later.

One, you put up a slide on the tamper-resistant problems. I'd like to see the citations on that. How many different studies have found those problems with tamper-resistant pills?

DR. BREITMEYER: We'll provide you one with citations on it after the break.

DR. MAXWELL: Okay. Secondly, you're going to monitor the signals. Now, I spent a lot of my life doing this. Exactly which signals are you going to monitor?

DR. BREITMEYER: Yes. So I'll ask Dr. Smith to address this, our head of drug safety at Zogenix.

DR. SMITH: Edward Smith, vice president of drug safety and regulatory affairs for Zogenix.

We have a number of different surveillance tools -- slide up -- which we'll be utilizing to monitor a number of different events. We will be monitoring patients' adverse events through our

pharmacovigilance system. We have a current pharmacovigilance system for our current approved product. We will be getting that information on a virtually daily basis.

Also, in regards to prescribers, we have a surveillance tool which will identify new prescribers for Zohydro. And we'll be getting those reports on a weekly basis. Pharmacies would actually have two different sources for surveillance information, coming directly from the wholesalers and an independent source. We'll also be getting that information on a weekly basis. That also includes our distributors.

Then for substance abuse, those are the Inflexxion tools, and we'll be getting those reports on a regular basis.

DR. MAXWELL: Okay. Let me follow up a little bit closer. This is looking at indicators within the industry. I really don't see anything on what's on the street. Are you using NFLIS? Are you using DAWN? Any of the indicators? You don't have to go into detail, but this is just within

your system. This is not looking at what's on the street. And this concerns me.

DR. BREITMEYER: Yes. We are looking at what's on the street. And Dr. Butler will describe that to you.

DR. BUTLER: I'm Dr. Steve Butler. I'm chief science officer at Inflexxion, and Inflexxion is a consultant to Zogenix.

Our substance abuse data involved three data streams. One is adults in substance abuse treatment. The other is adolescents in substance abuse treatment. And the third is internet monitoring of recreational drug forums online.

DR. MAXWELL: Okay. Quickly, what's the data sources on the treatment? Where are you getting that from?

DR. BUTLER: The data sources for the treatment for adults is an assessment that we have called the Addiction Severity Index, Multimedia Version.

DR. MAXWELL: Yes. But who's going to submit it? Who's going to see the client and send

it in to you?

DR. BUTLER: We have a network of sites around the country that are treatment sites. They do evaluations using our software, and the patients interact with the software.

DR. MAXWELL: Okay. I'm aware of the ASI.

DR. BUTLER: Yes, ma'am.

DR. MAXWELL: But the treatment -- how do you find the treatment programs that are going to see the clients who have misused it?

DR. BUTLER: These treatment sites purchase the software from Inflexxion and use the software clinically.

DR. MAXWELL: Okay. Then we could have a number of sites that are seeing abusing patients who are not part of the system. Poison control data? We don't hear that mentioned. I don't hear anything about the NFLIS data.

I'm very concerned because I've spent a lot of time listening to other similar alleged systems that need a lot of work. Now, then, you've answered enough for me to indicate what you don't

know.

Now let me ask another question. You're going to have a board, and you showed the slide of the people that are going to be on the board. Now, I've sat through some meetings with other abused drugs sponsored by other pharmaceutical companies. And how do you ensure the board isn't going to weigh the data to your benefit? I mean, I've heard the presentations about the glories of some of these drugs that have the problems.

DR. BREITMEYER: Yes. No, I understand exactly what you're asking. We're using the DSMB model for the Safe Use Board. And all of you who do clinical trials, and you, of course, Dr. Maxwell, are familiar with that, is that the board will be -- like the ER/LA REMS, it will be funded by an unrestricted, hands-off grant. And the board members will be empaneled and empowered to work independently from the company. We expect them to work independently from the company. The commission comes from the company; it has to.

But in handoff -- in a hands-free fashion

like a DSMB, where they have -- and if I could have the slide about information flow -- the board will not only be empaneled to process, evaluate, and determine the significance of information that comes in, but they will also have independent access to all of the raw data as it comes in.

So if I could have the slide up. For their convenience, like at DSMB, they'll get digests of material that the company is processing in any case. However, they will have a staff and have the tools and ability to hear, take raw information that they get from patients, pharmacists, distributors, and the street to look for signals and process independently.

We expect that they will inform the company when a signal is detected or a concern is uncovered. But they are fully empowered to take their concerns directly to the FDA or directly to the DEA by charter.

DR. MAXWELL: Okay. Because I know we need to take a break, but I'm not real comfortable with this. I've seen it happen before, and it ends up

being self-serving. But anyhow, we need to take a break.

DR. BREITMEYER: We're trying to ensure that it won't be. We understand your concerns about past practices and are determined to have this product brought forth in the most responsible way possible.

Dr. Katz had a follow-on comment.

DR. KATZ: Super-quick. I just want to make sure that Dr. Maxwell's primary question doesn't go unanswered. Of course the standard epidemiologic surveillance systems will be looked at -- DAWN, NFLIS, National Household Survey, et cetera.

All of those epidemiologic sources for the surveillance of specific drugs have very serious methodological deficiencies, but nonetheless paint a picture when taken in their totality about the abuse of a specific drug. And of course those standard data sources will not be overlooked. It just was not on the slide.

DR. FLICK: Thank you.

We'll now take a 15-minute break. We will

return at 10:35. Please remember that there should be no discussion of the meeting topic during the break among the panel members.

(Whereupon, a brief recess was taken.)

DR. FLICK: Please take your seats. We will now proceed with the FDA presentation from Dr. Gill.

FDA Presentation – Rajdeep Gill

DR. GILL: Good morning. My name is Rajdeep Gill, and I'm a drug utilization analyst in the Division of Epidemiology, Office of Surveillance and Epidemiology. Today I will be presenting outpatient drug utilization patterns for selected opioid analgesics in the U.S. from year 2007 through year 2011.

Currently hydrocodone is not available as extended-release, single ingredient, but is only available as immediate-release hydrocodone in combination with a non-opioid such as acetaminophen. The goal of my presentation is to provide a snapshot of the current marketplace into which Zohydro extended-release, if approved, will

be introduced.

We focused on describing the extent of use of the currently available formulations of hydrocodone-containing analgesics as well as combination oxycodone-containing analgesics because these are among the most widely used opioid analgesics.

We also thought it might be helpful to describe the extent of use of selected single-ingredient, extended-release or long-acting products such as oxycodone, oxymorphone, morphine, and hydromorphone ER.

My presentation will be in the following order. First, I will present the sales distribution analysis of the selected opioid analgesics. Then I will present the dispensed prescription- and patient-level analysis. Following that, I will present prescriber specialty, duration of use, and diagnoses data. Finally, I will present the limitations of my analysis, and conclude with a summary of my presentation.

Now I will present the sales data for the selected opioid analgesics for this analysis.

The IMS Health, IMS National Sales Perspectives database, was used to obtain the sales of selected opioids included in this analysis. This database measures the volume of products, in units and dollars, moving from the manufacturer to retail and non-retail channels of distribution.

This graph displays sales distribution of selected opioid analgesics towards U.S. outpatient retail pharmacies for year 2011. The U.S. outpatient retail pharmacy settings accounted for a majority of the sales distribution for all the selected opioid analgesics. Therefore, the drug utilization analysis in my presentation is focused on U.S. outpatient retail pharmacy settings.

Next I will be presenting prescription and patient-level data.

IMS's Vector One National and Total Patient Tracker were used to analyze U.S. outpatient retail pharmacy utilization patterns. VONA and TPT are national-level projected prescription and patient-

centric tracking services. They measure dispensing of prescriptions out of retail pharmacies into the hands of consumers. Data are obtained from 59,000 pharmacies throughout the U.S., which accounts for nearly all retail pharmacies in the country and nearly half of all retail prescriptions dispensed nationwide. From this database, we can also obtain data on prescribing specialties.

This graph displays the number of prescriptions dispensed through U.S. outpatient retail pharmacies from year 2007 through year 2011 for combination hydrocodone-containing analgesics, combination oxycodone-containing analgesics, oxycodone extended-release, morphine extended-release, oxymorphone extended-release, and hydromorphone extended-release.

During year 2011, approximately 131 million combination hydrocodone-containing analgesic prescriptions were dispensed, followed by 35 million combination oxycodone-containing analgesic prescriptions. The number of combination

hydrocodone-containing analgesic prescriptions exceeded the number of prescriptions for any other individual opioid selected by at least threefold.

In this graph we focus on the number of prescriptions dispensed for selected extended-release or long-acting opioid analgesics. In year 2011, approximately 5.7 million prescriptions were dispensed for oxycodone extended-release; 6.1 million prescriptions were dispensed for morphine extended-release; 1.2 million prescriptions were dispensed for oxymorphone extended-release; and approximately 95,000 prescriptions were dispensed for hydromorphone extended-release.

In general, as you can see, the number of prescriptions dispensed increased for all of the agents analyzed, with the exception of oxycodone extended-release, which decreased during the time period examined. Of note, the number of prescriptions dispensed for morphine extended-release exceeds that for oxycodone extended-release in year 2011.

Here we look at the unique patient data. During year 2011, approximately 47 million patients received combination hydrocodone-containing analgesic prescriptions, followed by 15 million patients receiving combination oxycodone-containing analgesic prescriptions.

Similar to the prescription data, the number of unique patients receiving combination hydrocodone-containing analgesic prescriptions exceeded the number of unique patients receiving any other individual opioid analgesic by at least threefold.

In this graph we focus on the number of unique patients receiving selected extended-release or long-acting opioid analgesics. In year 2011, approximately 1.1 million unique patients received oxycodone extended-release prescriptions, and approximately the same number of unique patients received morphine extended-release prescriptions.

Approximately 237,000 unique patients received oxymorphone extended-release prescriptions, and approximately 29,000 unique

patients received hydromorphone extended-release prescriptions.

Similar to the prescription data, the number of unique patients increased for all of the agents analyzed, with the exception of oxycodone extended-release, which decreased during the time period examined. Of note, the number of unique patients receiving prescriptions for oxycodone ER and for morphine ER were approximately the same in year 2011.

Now I will be presenting prescriber specialty data.

This table provides percentage of prescriptions for selected opioid analgesics by prescribing specialty. Each column sums to 100 percent. The greatest proportion of immediate-release combination products, as well as oxycodone ER and morphine ER, were prescribed by general practice, family medicine, osteopathy, and internal medicine.

As compared to immediate-release combination opioid analgesics, extended-release or long-acting

opioid analgesics were more commonly written by anesthesiologists and physical medicine and rehab. As compared to extended-release or long-acting opioid analgesics, immediate-release combination products were more commonly prescribed by dentists and orthopedic surgeons.

These prescribing patterns suggest that the extended-release or long-acting opioids may be used to treat chronic pain conditions treated by anesthesiologists, and immediate-release combination products may be used to treat acute pain conditions treated by primary care practitioners, dentists, and orthopedic surgeons.

But it is worth mentioning that even though combination hydrocodone-containing analgesics may be used more often to treat acute pain, even a small percentage of use for chronic pain conditions can translate into a vast number of prescriptions and patients simply because of the widespread use of hydrocodone-containing analgesics.

Next we will look at duration of use. This graph shows the average number of days of therapy

dispensed per prescription for year 2011. The average days of therapy per prescription was approximately 27 days for oxycodone extended-release, and approximately 28 days for morphine extended-release, oxymorphone extended-release, and hydromorphone extended-release.

Comparatively, the average days of therapy for both combination hydrocodone- and oxycodone-containing analgesics was approximately 14 days per prescription. These findings also support the idea that extended-release opioid analgesics may be used more often to treat chronic pain conditions.

However, the data are limited because they do not account for the fact that multiple prescriptions can be dispensed to the same patient over time, and thus do not measure actual duration of use at the patient level. The data also rely on the average, or mean, which can be easily skewed by outliers.

To address some of these limitations with average days of therapy analysis, we conducted a crude analysis of total days of therapy on a sample

of patients. We used Source Healthcare Analytics ProMetis Lx database to conduct a crude duration of use analysis. It measures longitudinal product use based on medical and prescription claims from commercial plans, Medicare Part D plans, Medicaid claims, and cash prescription claims.

In this analysis, the duration of individual patients' prescriptions was added together over a two-year period from January 2010 through December 2011, ignoring gaps in treatment. The range of therapy days for all selected opioid analgesics was similar, from two days up to full two years.

For combination hydrocodone- and oxycodone-containing analgesics, the median days of therapy was eight days and six days, respectively, and the mean or average for each was skewed to 45 and 30 days respectively. The median days of therapy for oxycodone extended-release was 31 days.

This analysis provides additional support to our theory that single-ingredient, extended-release opioid analgesics may be used more often to treat chronic pain conditions, while the combination

immediate-release opioid analgesics may be used more often to treat acute pain conditions.

Next we analyzed the diagnoses data.

Encuity Research treatment/answers is a monthly survey that monitors disease states and physician intended prescribing habits at a national level. The database contains data from 3200 prescribers in the panel that report on all patient activity during one typical workday per month, which is then projected nationally.

This slide shows the most commonly associated diagnoses with the use of selected opioid analgesics, as reported by office-based physician surveys in the U.S. Diagnoses, coded to ICD-9, are linked to each drug product mentioned during a patient encounter and then grouped into diagnostic categories, collapsed to three-digit ICD-9 codes.

The most common diagnoses associated with the use of combination hydrocodone-containing analgesics included: diseases of the musculoskeletal system and connective tissue,

accounting for 25 percent of total drug use mentions; diseases of the respiratory system, accounting for 21 percent of the total drug use mentions, which includes diagnoses related to chronic tonsillitis and adenoiditis; and fractures, sprains, contusion, injuries, accounting for 19 percent of total drug use mentions.

The extended-release opioid analgesics were mentioned more often in relation to diseases of the musculoskeletal system and connective tissue, ranging from 59 to 68 percent of total drug use mentions, and with headaches and nerve pains.

These data also appear to support the idea that combination hydrocodone- and oxycodone-containing analgesics appear to be used more often to treat acute pain, whereas the single-ingredient, extended-release or long-acting opioid analgesics appear to be used more often for the treatment of chronic pain conditions.

As we mentioned earlier, even though it appears that combination hydrocodone-containing analgesics are more often used to treat acute pain

conditions, even a small percentage of use in chronic pain conditions can translate into a large number of patients using it for chronic pain conditions as well.

Before I conclude, I would like to disclose the limitations of this analysis. This analysis was representative of national outpatient retail pharmacy usage patterns. Inpatient use was not captured in the analysis. No statistical tests were performed to determine any statistically significant changes over time.

In summary, the number of prescriptions and unique patients receiving combination hydrocodone-containing analgesics far exceeded any other self opioid analgesic in this analysis. Primary care practitioners prescribed about 40 percent of total immediate-release combination opioid analgesic prescriptions, and they appear to have shorter mean days of therapy and appear to be used more often to treat acute pain conditions.

As compared to immediate-release combination opioid analgesics, extended-release opioid

analgesics were prescribed more often by anesthesiologists and physical medicine and rehab, and they appear to have longer mean days of therapy and appear to be used more often to treat chronic pain conditions.

Thank you.

DR. FLICK: Thank you, Dr. Gill.

Now we'll have a presentation from Dr. Walsh.

Speaker Presentation – Sharon Walsh

DR. WALSH: Good morning, everyone. My name is Sharon Walsh, and I'm from the University of Kentucky. And it's a pleasure to be here this morning to have an opportunity to share the results of some studies that are published in the literature that I hope will be helpful in informing your deliberations today.

So this slide describes the outline of my talk. I'm going to begin with a background, with some definitions for abuse liability and abuse potential. I'm going to describe the approach that's used in the human laboratory to study abuse

potential, including populations and methods.

I'm going to then share results from some published studies that have been conducted in both normal volunteers and opioid-abusing individuals. And finally, I'll summarize the results of these studies and hopefully provide a few succinct take-home messages.

So just by way of background with regard to abuse potential, when we speak of abuse potential as a construct, we're talking about characterizing the ability of a drug with central nervous system activity to produce positive psychoactive effects. And these positive psychoactive effects may include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes.

Based upon past experience, we know that, identifying these effects in the laboratory, these are viewed as correlated with or predictive of the risk of abuse and/or addiction of an agent when it gets into the marketplace.

With respect to abuse liability, these two terms are sometimes used interchangeably. But in

fact, abuse potential is just one small component of abuse liability because abuse liability captures other factors such as the ease of synthesis of an agent, prior drug abuse diversion history of similar drugs or drugs with structural similarities. So abuse liability actually describes abuse potential in a larger social and public health context.

How are each of these measured? Abuse potential is measured in the laboratory, and this can be done in nonhumans, and animal studies typically include self-administration procedures and physical dependence testing. Abuse potential can also be evaluated in human subjects, and this typically involves direct drug administration under supervision.

Abuse liability is also measured in the community, and this includes surveillance data from various reporting sources such as hospitals, treatment centers, national surveys, and medical examiner deaths.

So the next two slides are just going to

describe some general methods that are used in the laboratory to study abuse potential with humans.

Typically, you'll enroll adult volunteers who have appropriate drug use histories, and you'll enroll them preferably as inpatients so that they can be maintained in a secure environment and other drug use can be precluded. In the case of hydrocodone, one would want to enroll individuals who had prior opioid abuse histories, but who were without physical dependence on opioids at the time of their participation in the study.

These studies include tests of appropriate control agents for comparison with the test drug of interest, and the control conditions can be both positive and negative if available. For test of hydrocodone, the appropriate control condition would be another full new opioid agonist, which has already shown some signal for abuse. In all these studies double-blind testing is employed, and doses are given in randomized order.

These studies collect a very comprehensive array of outcomes. They include physiological

measures, some for safety such as respiratory and cardiovascular measures. In opioid studies we typically include pupil diameter because it's an excellent and sensitive physiological sign of opiate agonist activity in the CNS.

A broad array of subjective measures are collected, in which the subjects are being asked questions about their internal drug experience during the period after dosing. And these can include visual analog questionnaires, adjective scales, and street value estimates.

Typically, observers are in the same room who are blind to the study conditions, and they are simultaneously rating what they see in the volunteer during the drug experience. And finally, an array of cognitive and psychomotor tasks can be incorporated in order to assess impairment.

In the studies that I'm going to share with you this morning, I'm not going to have the time to show this broad array of measures, although each of the studies did collect those. I'm going to limit it to just a couple of representative measures.

So with respect to contemporary studies of hydrocodone, I'm going to describe four human abuse potential studies that were published between 2005 and 2010. Three of these studies examined the effects of oral hydrocodone, two of which examined hydrocodone in combination with acetaminophen and one which examined the effects of hydrocodone alone. The fourth study examined the effects of intravenous hydrocodone alone. And all of these studies employed within-subject crossover designs.

The asterisk on the combination studies indicates that these were conducted in healthy, non-drug-abusing volunteers rather than in opioid-abusing individuals.

So these data are from a study by Dr. Jim Zacny and his colleagues at the University of Chicago in which they examined a range of doses of hydrocodone in combination with acetaminophen and compared those doses to a single dose of morphine, a single dose of acetaminophen, and placebo. And I'll take a moment and walk through this slide because the subsequent slides are formatted

similarly.

So the outcome that you're looking at is shown in the title, and then the response is shown along the Y axis. For pupil diameter, it's the trough level over the course of the whole session, so we're really looking at the peak minimum effect. And then the doses are shown along the X axis, and in this case, the doses in yellow are for the acetaminophen doses for reference.

So the figure on the left-hand side for pupil diameter, you can see that hydrocodone over this range of doses produces significant and dose-dependent decreases in pupil size. At the highest dose of 20 milligrams, it produces myosis that's equivalent to that produced by 40 milligrams of morphine given orally.

The data shown in the last point here are for acetaminophen alone, and that just demonstrates that the effects of the active drug here are attributable to the hydrocodone, and that the acetaminophen is not contributing to this.

On the right-hand side, you're looking at

data for a visual analog questionnaire that poses the question to the volunteers, "How much do you like the drug?" And this is commonly accepted as a good index for abuse potential prediction.

In the case of Dr. Zacny's lab, he uses a bipolar scale from zero to 100, and 50 is neutral. Anything above 50 indicates liking, and anything below 50 indicates disliking. And you can see from these data that hydrocodone produced dose-dependent increases above placebo that were significant on ratings of liking, and that the highest dose -- again, 20 milligrams -- was comparable to 40 milligrams of morphine.

This is another study that was done by Dr. Zacny and colleagues. In this study they compared doses of oxycodone and hydrocodone to one another in the same group of volunteers. In this case both of the formulations included acetaminophen, and the range of doses is shown along the X axis. For oxycodone the doses were 10 and 20 milligrams, and for hydrocodone they were 15 and 30 milligrams, given acutely.

You can see that in the left-hand panel, looking at the outcome for pupil diameter, the drugs look comparable with respect to potency over this range of doses. In the right-hand panel, when examining the subjective effects of, "Do you like the drug?", you can see that oxycodone produces endorsements of liking in this slide, but there's no dose-related effect; and hydrocodone produced dose-related increases, but these did not reach statistical significance in this study.

These are other outcome measures from that same study, compare oxycodone and hydrocodone combination products. In the left-hand panel you're looking at an outcome of coasting that the subjects are scoring. Coasting is a relaxed, calm feeling that is recognizable by opiate abusers.

You can see that both oxycodone and hydrocodone produced significant and dose-related increases in coasting. And in these normal volunteers, we also see endorsement of "nauseated" that reaches significance at the higher doses.

These are data from a study conducted in our

laboratory, in which we looked at the effects of oxycodone, hydrocodone, and hydromorphone in a cohort of prescription opiate abusers. And in this case you're looking at the time/action curve for each of the three drugs rather than peak response.

So the data are shown for the first six hours after drug administration. And you can see that in each case, for oxycodone we see dose-related increases over the range of doses tested. Here the doses are 10, 20, and 40 milligrams. For hydrocodone, again, you see the effects are dose-related at 15, 30, and 45 milligrams. And for hydromorphone, the doses were 10, 17.5, and 25, and the effects are somewhat dose-related, although they're more compressed at the higher end of the scale.

I should say that in this study, we actually did some pilot evaluation with subjects who were not included in the final analysis because one of our aims of the study was to identify dose ranges for these drugs, that are not equivalent in their potency, that would produce effects of the same

magnitudes because we were interested in actually conducting formal relative potency estimates.

So these are data from the same study. These are trough data, peak reductions. And they're plotted similarly to the earlier studies that I showed, except that the axis looks a little bit different because it's on a log scale. And that's because the same range of doses were not tested among the three drugs.

But you can see that in the case of pupil diameter for all three, oxycodone, hydromorphone, and hydrocodone, that you see significant reductions in pupil diameter compared to placebo, and that the shape of the dose response curves are generally similar, and that the maximum doses of each produce about equivalent effects.

In the right-hand panel you're looking at respiratory rate, and we see for all three drugs modest reductions, significant but modest reductions, with a maximum decrease in respiratory rate of only about three breaths per minute under these test conditions.

This is the final outcome measure that I'll show you from that study. They're plotted similarly to the last slide. These data depict scores from a composite scale known as the Opioid Agonist Scale. And this scale consists of a number of single items that the subjects are asked to rate on a scale from zero to 4 that, in total, are representative of the opiate agonist experience. And they include things like nodding, energized, coasting, a sick feeling in your stomach, things like that. The observers also rated the same scale while they were blind to the study condition.

What you can see is that, overall, we see dose-related increases in ratings on the Agonist Scale that are reported by both the subjects and the observers, who are blind to the study conditions, and that the range of effects that we're seeing are generally equivalent across the dose ranges that we chose to study.

So what we do with those data is once we've analyzed them and we've identified the effects for which we've found significant main effects of dose,

then we can take those and test them according to a procedure defined by Finney to determine that they are useful for a valid bioassay. And we can compare those dose response curves to one another in order to generate a relative potency estimate.

The bottom line of this analysis was that once we analyzed the relative potency, what we found for the potency of oxycodone to hydrocodone was that hydrocodone was only slightly less potent, not by very much, than oxycodone. And it's expressed in milligrams at the end of that equation.

So if the drugs were equivalent, you would expect it to be 1 milligram would be equivalent to 1 milligram; in this case, 1 milligram of hydrocodone is required to produce the effect achieved by .93 milligrams of oxycodone. So there's only a slight difference.

This is somewhat different than what you would see in relative potency tables for analgesia. And I think that that was one of the primary findings for the study because it was also the same

case with hydromorphone, where you would expect to see a much greater difference in potency, given their analgesic potencies. But these data suggest that the abuse liability potencies may actually not be on the same scale as that for analgesia.

These are data from the final study that I'm going to present. This was also done in our laboratory. And in this study, we examined infusion of acute doses of morphine, oxycodone, and hydrocodone in a cohort of prescription opioid abusers. And again, what you're looking at is the time course curve following administration of each of the ten study conditions.

The doses in this case we used were identical, so we tested 5, 10, and 20 milligrams of each of the three test agents. And I just want to point out that along the Y axis, or the X axis here, for the time course, that the early part of this time course, there's a break in the curve if you're not able to see that. And that's because in the early part, it's showing minute-by-minute data that are collected after the infusion because we

expect the effects to come on very rapidly after intravenous administration. And in the later part, the intervals between numbers actually represents a longer time period.

But what you can see from these data is that all three drugs produced robust and rapid increases in ratings of liking that were evident within minutes after infusion. The effects peaked fairly early on after intravenous infusion. And all three of the drugs produced dose-related effects, although the lower doses, 5 and 10, of morphine were closer together with the effects that they produced on this outcome measure.

These are data for pupil diameter, and in the right panel, expired end-tidal CO2, which we were using in this study rather than respiratory rate as our measure of respiratory depression. These data illustrate that all three drugs are active at each of the test doses given intravenously, that they all produce dose-dependent decreases in pupil diameter.

From these data you can see that the

oxycodone doses are slightly more potent than the two comparators. And in the right-hand panel, the data for end-tidal CO2; in this case an increase in CO2 is a reflection of a decrease in respiratory function.

So end-tidal CO2 increases in the presence of morphine, oxycodone, and hydrocodone, all dose-dependently, and morphine and hydrocodone look more similar, with oxycodone producing a slightly more potent effect at the same doses.

This is another outcome that we like to ask with our substance abusers that participate in the studies, is what would they pay for this on the street, because this is a real currency, that they are spending their money on the street for drugs, especially when you're testing a new entity that they may not have used. It puts it into some perspective about street use.

You can see that all three drugs produced increases in ratings of street value ranging from about $10 up to $40 for a single injection, with the highest amount being offered for the highest

dose of oxycodone.

I'm going to summarize these findings. So the studies that were done in healthy volunteers who were not opioid abusers, hydrocodone combined with acetaminophen produces dose-dependent euphorigenic effects. These effects are similar to those produced by morphine and oxycodone in the normal volunteers. A dose of hydrocodone at 20 milligrams was like 40 milligrams of morphine. And a dose of 30 milligrams of hydrocodone was like 20 milligrams of oxycodone.

Acetaminophen in those studies produced no discernible effects by itself, and unpleasant effects -- nausea and dizziness -- occurred at the upper range of the hydrocodone dose range. And this is very common with opioids in normal volunteers.

To summarize the studies in prescription opioid abusers, hydrocodone produces dose-dependent increases on ratings of positive subjective reports, including ratings of liking, good effects, and endorsements of street value. There's little

to no evidence that hydrocodone produces reports of negative or unpleasant effects in this population.

Hydrocodone is only slightly less potent than oxycodone on subjective effects that are related to abuse potential, and this was true regardless of whether the drug was given orally or intravenously. And the profile of hydrocodone is similar to comparator opioids, including morphine, hydromorphone, and oxycodone.

With that, I thank you.

DR. FLICK: We will continue with our FDA presentations.

FDA Presentation – Catherine Dormitzer

DR. DORMITZER: Hi. Good morning. My name is Cathy Dormitzer. I am an epidemiologist in the Division of Epidemiology in the Office of Surveillance and Epidemiology.

Today I will examine one question, which is, how much abuse can we expect to be associated with a single-ingredient extended-release hydrocodone product? To date, there are no such products on the U.S. market.

So for this analysis I will examine abuse patterns for the current formulation of hydrocodone products, which are all combination immediate-release, as well as for oxycodone. I will examine the abuse patterns for both combination immediate-release products, and then separately for single-ingredient extended-release products; and then examine differences in the abuse patterns for these two different formulations of oxycodone.

By examining the abuse patterns of these different formulations of oxycodone, we may learn about abuse patterns that are possible for single-ingredient, extended-release hydrocodone products.

So let's look at using oxycodone as a comparator drug. Both hydrocodone and oxycodone are opioid analgesics, both have a long marketing history, and both have a large market share. But oxycodone products have combination products as well as single-ingredient products on the market, and they're all Schedule II products. Hydrocodone combination products are Schedule III, but single-ingredient hydrocodone products are Schedule II.

I will be presenting data from DAWN. DAWN is the Drug Abuse Warning Network that is administered by SAMHSA, which is the Substance Abuse Mental Health Services Administration. DAWN provides national estimates on all drug-related emergency room visits, and it can provide estimates by substance, by composition, and formulation. There is no other data set that is this granular. And that is why we are using these data to examine abuse patterns between opioids and between the differences in compositions and formulations.

To understand how DAWN ED visits are related to drug misuse and abuse, SAMHSA developed a construct based on type of case. We are going to be using AllMA, which stands for All Misuse and Abuse Cases. These are ED visits where the case type was classified as over-medication -- in other words, exceeded the prescribed dose, seeking detox -- and the case type "Other," which generally has been used to classify drug abuse cases. AllMA cases also include ED visits where illegal drugs or

alcohol were present and contributed to the reason for the ED visit.

DAWN provides national estimates of abuse-related ED visits associated with opioids, but it does not adjust for drug utilization, which can be thought of as exposure opportunity or as drug availability. So drug utilization data is used as a proxy for drug availability, and abuse ratios were calculated. Drug estimates of AllMA ED visits were used for the numerator and drug utilization was used for the denominator to estimate these abuse ratios.

So abuse ratios are the national estimates of AllMA ED visits divided by one million tablets dispensed. It's also called extended units by the vendor. Using tablets dispensed adjusts for the number of tablets per prescription, which can vary if a prescription is for an acute indication rather than for a chronic one.

Presented here are the numerator data, which are the DAWN national estimates of ED visits classified as AllMA, associated with hydrocodone

and oxycodone by composition and formulation. These national estimates are unadjusted for use.

As you can see, there were roughly 41,000 AllMA ED visits in 2004, and that rose to more than 115 (sic) AllMA ED visits for hydrocodone; whereas for oxycodone combination IR products, there were close to 22,000 AllMA ED visits in 2004, and that rose to 66,000 in 2010. For oxycodone ER single-ingredient products, there were almost 29,000 ED visits in 2004, and around 70,000 AllMA ED visits in 2010.

Here are the abuse ratios for hydrocodone and oxycodone IR and ER, which are the national estimates of AllMA ED visits per million tablets dispensed. And as you can see, in 2004, for hydrocodone, there were almost 10 AllMA ED visits per million tablets dispensed, and that rose to 15 AllMA ED visits per million tablets dispensed in 2010. The ratios were somewhat higher for oxycodone IR combination products, ranging from 18 in 2004 and close to 31 in 2010.

But the ratios are remarkably higher for

single-ingredient ER oxycodone products than they are for the combinations. In 2010, there were 120 AllMA ED visits for the single-ingredient ER oxycodone product versus 31 for the combination IR oxycodone products. And that is a three- to fourfold increase in the ratios between the combination IR and the single-ingredient ER products for all years examined.

When examining these ratios, it is important to keep in mind its limitations. These data, emergency room visits and drug utilization, are in no way linked. The sampling methodologies used to derive the national estimates are different, so confidence intervals for these ratios cannot be derived, at least not yet.

The populations are similar, but for DAWN the population is for emergency rooms, and for drug use data the population is retail pharmacies. There's no information collected by DAWN on how many patients had a prescription or if a member of their household had a prescription that resulted in the drug that was the reason for the ED visit,

and that's an important limitation.

Lastly, emergency room data does not adjust for differences in lethality or safety. If someone dies before assistance is obtained or if someone doesn't have an event that's that serious, they won't be taken to the emergency room, and that can vary between products.

But in summary, the abuse ratios for single-ingredient ER oxycodone products is three- to fourfold higher than the combination IR oxycodone products. It may be useful in anticipating the abuse patterns for single-ingredient ER hydrocodone products, if approved.

So although the magnitude of abuse ratios between -- well, the magnitude of abuse ratios is higher for oxycodone products than it is for hydrocodone, but the abuse patterns between formulations might be similar. And it is important to consider whether this same pattern of abuse found for oxycodone will occur with hydrocodone ER single-ingredient products.

Thank you.

DR. FLICK: Dr. Levin?

FDA Presentation – Robert Levin

DR. LEVIN: My name is Robert Levin. I am a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products at the FDA. My presentation will include an overview of what is a REMS; goals of the extended-release long-acting opioid analgesics REMS, also referred to as the ER/LA REMS; and the components of the ER/LA REMS.

The ER/LA REMS would apply to hydrocodone ER, if approved, but the additional voluntary safety strategies Zogenix are proposing are not part of the REMS and will not be covered in this presentation.

What is a REMS? REMS are risk evaluation and mitigation strategies intended for drugs with serious risks that would outweigh the benefits absent some special risk management tools. A REMS is a risk management plan that uses risk minimization strategies beyond approved professional labeling to manage serious risks associated with a drug.

A REMS can be required at the time of drug approval, or post-approval if the FDA becomes aware of new safety information and determines that the strategy is necessary to ensure that the benefits of the drug outweigh the risks.

A REMS for drugs in general can include a medication guide or patient package insert; a communication plan, if the FDA determines a plan may support implementation of an element of the REMS. The plan could include sending letters to health care providers about the risks of a drug.

REMS can also include elements to assure safe use, also referred to as ETASU. ETASU are restrictive elements, and depending on the risk, the elements might include one or more of the following:

Health care providers who have the drug have particular training or experience, or are specially certified;

Pharmacies, practitioners, or health care settings that dispense the drugs are specially certified;

The drug is dispensed to patients only in certain health care settings;

The drug is dispensed to patients with evidence or other documentation of safe use conditions;

The patient is subject to certain monitoring;

The patient is enrolled in a registry.

When an ETASU containing elements described under (b), (c), and (d) is established, an implementation plan may be required. All REMS are required to have a timetable for submission of assessments of the REMS. If the FDA determines that the REMS is not meeting its goals, the agency will reevaluate the program.

The goals of the ER/LA opioid analgesics REMS are to help address the significant increase in inappropriate prescribing, misuse, and abuse of these products over the past decade; and minimize the burden on the health care system of having all these products with a different REMS. Any new member of the ER/LA opioid analgesic class,

including hydrocodone ER, will be required to participate in the REMS as a condition of approval.

This slide lists the ER/LA opioid analgesics included in the REMS. These products are long-acting, either because they are extended-release or transdermal, or for methadone, pharmacologically long-acting.

The following are the elements of the ER/LA opioid analgesics REMS: the medication guide; elements to assure safe use, which include the patient counseling document and training for health care providers who prescribe ER/LA opioid analgesics; and a timetable for submission of REMS assessments. These elements of the ER/LA REMS will be further discussed in the next few slides.

A key element of the ER/LA REMS is the medication guide which will be dispensed with each prescription. The medication guide uses consumer-friendly language to explain essential information to patients. It is not intended to replace patient counseling.

The ER/LA REMS medication guide is a

convenient one-page document to aid patients in the use of medication at home. It has both common content applicable to all ER/LA opioids and product-specific information necessary for safe and effective use of the drug.

An important part of the ER/LA REMS is patient/prescriber communication about the safe use of opioid analgesics. A one-page counseling document has been developed to facilitate patient counseling, and includes important dos and don'ts. This document also allows specific patient information to be included by the prescriber.

It is critical for prescribers to understand the appropriate precautions in prescribing extended-release opioids. Continuing education training will be provided through accredited CE activities supported by independent educational grants from ER/LA opioid analgesic manufacturers.

The FDA developed the core messages, or FDA blueprint, to be communicated to prescribers. This blueprint will be discussed in more detail in the next slide.

The prescriber training program is voluntary, but if the REMS assessment warrants, the program will be modified as needed. The core REMS prescriber education will be about three hours in length. The content is not exhaustive nor a substitute for a more comprehensive pain management course. A list of REMS-compliant CE courses offered by accredited CE providers will be posted on the ER/LA REMS internet website when the list becomes available.

The core messages to be communicated to prescribers in the blueprint for prescriber education covers the risks and appropriate prescribing practices for the safe use of the ER/LA opioid analgesics, and specifically include:

Why prescriber education is important;

Assessing patients for treatment, initiating therapy, modifying dosing, and discontinuing use;

Managing therapy, counseling patients and caregivers about the safe use of ER/LA opioid analgesics;

General drug information about the

toxicities and drug interactions of opioid analgesics; and

Specific drug information, which includes the dosing interval, key instructions, specific drug interactions, use in opioid-tolerant patients, and product-specific safety concerns.

ER/LA REMS assessment are required on a preestablished schedule. The FDA may modify the REMS based on information learned through the REMS assessment. Assessment, among other metrics, includes: health care providers' awareness and understanding of the serious risks associated with these products; patients' understanding of the serious risks of these products; surveillance for adverse events.

Important ER/LA REMS dates include the following. The REMS was approved July 9, 2012. REMS-compliant continuing education courses offered by accredited CE providers should be available no later than March 1, 2013.

In conclusion, the FDA aims to balance ensuring appropriate access to needed medication

with minimizing undue risk. REMS programs enable the FDA to make products available that require additional risk management tools to ensure that the product's benefit outweigh its risks. If approved, Zohydro ER would fall under the ER/LA REMS. Thank you.

Clarifying Questions to FDA and Speaker

DR. FLICK: Are there any clarifying questions for the FDA or Dr. Walsh? Please remember that you must state your name before you speak and direct your questions to a specific presenter from the FDA.

Dr. Zito?

DR. ZITO: Thank you. Julie Zito. I wanted some clarification, if I could, on the impact of the ER/LA REMS, which with this July date, I'm not sure. Did any of the previous ER products come with REMS, or did it all begin this July?

If we have earlier REMS, ER/LA REMS, then I'd like to know their impact on drug utilization. And the way I would characterize that would be that we would be able to see national patterns of

population-based measures of utilization that would include the patients, numbers of patients with and without substance use diagnosis; and not only users, but duration of use, dose, and prior opioid use.

DR. FLICK: Dr. Hertz, can you respond to that, please?

DR. HERTZ: Yes. This is Sharon Hertz with FDA. We can't answer your questions yet because the REMS did just get initiated this past July, and we don't have the assessments yet.

Prior to the ER/LA REMS, we did have risk management plans for some. But one of the reasons why we chose to pursue the REMS was because the risk management programs that were in place -- for instance, with oxycodone -- we did not feel were particularly effective. So we don't think they impacted access, for instance, because we don't really think they did too much of anything.

DR. ZITO: If I might, a follow up, then, to ask, what is the plan for the collection of information such as I'm suggesting?

DR. HERTZ: So the surveillance plan that's associated with the new ER/LA REMS is pretty extensive. It will use data that -- it will acquire data and review data that's being collected from all the national programs, the ones that we've mentioned earlier. And we are also implementing a number of different surveys to address patient experience, provider experience, as well.

So we are going to look to see if this program has any impact on access. We're going to look to see if it has any impact on the important abuse and misuse indicators. In particular, we're looking at DAWN data and NHSDA data, pretty much anything that we can gain access to.

The program is not expected to have an impact on access because it is voluntary. So yes. The way this program is set up is we have required the companies to provide the educational grants. That's a requirement.

But for prescribers to use the training is currently voluntary. We're hoping that the availability of them through CE -- we're expecting

a lot of it to be free CE -- we're hoping to motivate a number of prescribers to take the training.

Part of the assessment for this REMS is to look at the numbers of prescribers who actually do take the training over periods of time. And there have been some estimates of what we hope will happen, or what the companies hope will happen. And if we're failing to meet those estimates, then we're going to need to reconsider the program, whether changes need to be made.

DR. ZITO: The major public health dimension here, though, is really not only education, which is fine, but really about the impact on utilization. What will happen to all those -- for example, what would happen to -- what will happen to hydrocodone with acetaminophen users who now -- and practitioners who now have a new option, which actually carries more liability?

I'm wondering how you grasp that over a couple of years of usage. It'll take time for the drug to get established and so on. But five years

from now, will we know the impact of a higher liability product on prescribing?

DR. RAPPAPORT: This is a novel effort for us, so we're learning as we move forward here. The folks who we work with on this risk management plan are looking at all of the programs, as Dr. Hertz said. DAWN, NHSDA, RADARS, all the programs, and trying to collect as much data. But exactly when we're going to know whether there's a difference and which markers are going to be the most appropriate we don't know yet.

DR. ZITO: There's -- oh, I'm sorry.

DR. FLICK: We'll try and move along. There's quite a few questions to be answered.

Bob, do you have anything else to clarify there?

DR. RAPPAPORT: Well, I was just going to add, I think this is a good topic for the discussion later as to what can we capture at this point and what can't we?

DR. FLICK: Thank you.

Dr. Ramsay for Dr. Levin.

DR. RAMSAY: I'm not sure if Dr. Levin's the right person, but I will -- this is again about the REMS program.

Are there any REMS programs regarding any drug monitored or controlled by the FDA that involve mandatory training, certification, and surveillance programs? Or is that not yet enacted for anything?

DR. LEVIN: Yes. Robert Levin. There's also a TIRF REMS for the transmucosal fentanyl products, and that has certification for prescribers and pharmacies.

DR. RAMSAY: So that's the only one?

DR. HERTZ: There are others within the agency for other drug groups. This is the only other opioid REMS, and it's the only opioid REMS that has mandatory enrollment for prescribers, dispensers, and patients.

DR. RAPPAPORT: I should note, just because I think I know what you're getting at, Jamie. But the reason that we didn't go in that direction with the ER/LA REMS after three years of discussing it

with ever group of stakeholders in the country was that the impact on the public health system would have been immense.

I mean, the numbers of prescriptions of these products in this country and the wide use is so immense that to try to institute a type of registry for everybody who's prescribing, dispensing, and getting these products would have been a huge burden on the health care system. And it's actually in the law regarding REMS that we have to minimize the burden on the health care system with these tools.

So the situations where those types of extensive restrictions have been used are only for REMS where they're addressing a drug that's used by a very small population.

DR. HERTZ: Also, I just want to add that given the number of prescribers for -- this is Sharon Hertz, sorry -- for the ER/LA REMS, setting up a system to enroll all of those individuals alone would be massive and somewhat duplicative since there is already DEA registration.

So in addition to what Dr. Rappaport said, we were also very cognizant of the fact that just the infrastructure that would be involved for something like that would be a very massive undertaking, and we weren't sure that that was the most efficient way to go.

DR. RAPPAPORT: And duplicative of the existing system for registration for prescribing of controlled substances. I can't really get into why it didn't get tied to that, but the agency and the department have been public about thinking that that would be a good way to go with this.

DR. FLICK: I have a question for Dr. Walsh. Dr. Walsh, on slide 20 -- and I just want to make sure that I'm clear -- if I understand you correctly, equal analgesic potent doses of oxycodone versus hydrocodone, the abuse potential of hydrocodone would be, then, greater than oxycodone.

Am I correct in that?

DR. WALSH: You are probably correct. It depends on which equianalgesic dosing table you're

looking at for the two drugs because they vary.

DR. FLICK: Well, based on what you presented -- and I think this is an important point. So if I have an equal potent dose, analgesic potency --

DR. WALSH: Right.

DR. FLICK: -- the abuse potential of hydrocodone would be greater based on the research that you presented.

DR. WALSH: Yes. I mean, that would be presuming that you're using an equianalgesic table that reflects hydrocodone as being less effective in treating pain than oxycodone on a milligram-per-milligram basis, which is what most published --

DR. FLICK: Am I correct in saying that that's what you showed us, and that is the conventional wisdom or expectation?

DR. WALSH: I didn't show data on analgesia. But when you look at analgesic conversion tables, you typically see that hydrocodone is reported as less potent, so that you would be prescribing more to treat the same pain than you would for

oxycodone. And what I showed was that they're more similar when you look at measures of abuse liability.

DR. FLICK: So less potent from an analgesic perspective, but equally potent in terms of abuse potential?

DR. WALSH: Equally potent for abuse potential.

DR. FLICK: Roughly so?

DR. WALSH: Roughly so.

DR. FLICK: Thank you.

Dr. Rosenberg?

DR. ROSENBERG: This is for Dr. Dormitzer. I was wondering, do you have any estimates of deaths for oxycodone versus the controlled-release oxycodone? And do you have estimates for admission to substance abuse treatment programs, comparison between immediate-release and the sustained-release?

DR. DORMITZER: No, I don't. The difficulty with deaths is that they're able to detect hydrocodone or oxycodone. But you don't have data

on whether it was extended-release or immediate-release, or dosage form.

So for death, for medical examiner data, that's just not available. And even with medical examiner data, you can't rely on NCHS data because they don't differentiate between opiates.

Then for the treatment, it again doesn't differentiate between immediate-release and extended-release oxycodone. And right now, all of hydrocodone is immediate-release, so -- I don't have that data.

DR. FLICK: Dr. Kaye?

DR. KAYE: I have a question for Dr. Walsh. Hydrocodone is metabolized to, of all things, hydromorphone. And I was just wondering what your thoughts were vis-a-vis what we're talking about and your presentation in terms of what we're offering that's different, given that there's a subgroup of people who poorly metabolize to hydromorphone. So if anything, it would be a little more difficult to get to the active substrate.

DR. WALSH: Well, I think that hydrocodone is an active substrate. It just happens also to have an active metabolite. There's at least one published study that came from Ed Sellers' group where they inhibited metabolism of hydrocodone to hydromorphone, and found that it didn't make a real appreciable difference in the outcomes that they examined.

So I wouldn't argue that any hydromorphone that's formed would be active. But apparently its inhibition of formation doesn't actually alter the response to hydrocodone significantly.

DR. KAYE: Thank you.

DR. FLICK: Dr. Kramer?

DR. KRAMER: Dr. Rappaport answered my question. It was about the voluntary aspect of the program.

DR. FLICK: I have a question for Dr. Gill. If you go to slide 10 in your presentation, it looks like in 2010, the amount of extended-release long-acting OxyContin, the number of prescriptions declined. Can you speculate as to why that

occurred?

DR. GILL: It could be because of the new formulation, but the analysis is underway. We cannot say for sure.

DR. FLICK: Can you tell me, was a REMS in place at that time?

DR. GILL: No, sir.

DR. FLICK: Thank you.

Dr. Perrone?

DR. PERRONE: Thank you. My first question is maybe to Dr. Levin.

So for the more mandatory TIRF REMS that we have, do we have outcomes information? Nothing? Okay.

DR. HERTZ: We are just getting, I think, our first assessment now. So we hopefully will have some information soon.

In terms of general -- I'm sorry. This is Sharon Hertz. In terms of general reports, we are hearing some concerns about access. The transition was a little rocky in some areas. We've tried to address those issues.

There were some issues with some of the closed pharmacy systems and getting access there, including some of the military systems. But we've been working with the group responsible for this REMS to make these particular instances fit.

When the systems themselves are closed, for instance, we've been developing approaches for accommodating that, and trying to make sure that there are mechanisms in place so that when there have been problems in different areas or local areas -- it seemed more of an issue with some of the pharmacies in some cases. So we've been trying to work on that as those issues have arisen.

DR. PERRONE: But how about safety? Are we seeing better outcomes, less deaths?

DR. HERTZ: We don't have that yet. That's what we're hoping to see. We're hoping to look to see what that means when we get these assessments.

DR. PERRONE: And my last comment, really, is about this idea, this DEA registration and education.

Currently DEA requires you to just pay

money. There's really no education linked to that. So if we're in the midst of a public health crisis, linking those two things is a simpler, more efficient option, I think.

DR. RAPPAPORT: I would note that at the advisory committee meeting we had on the opioid REMS and whether it was appropriate what we were doing, the committee took it upon themselves to vote to recommend that that happen. Again, I can't comment on why it hasn't happened because I don't know.

DR. FLICK: It seems to me I got in trouble for that, didn't I?

(Laughter.)

DR. FLICK: Dr. Kaye?

DR. KAYE: I had a general question. We're talking today about, in part, issues related to acetaminophen and liver toxicity. I was looking at some data on my way here from the Office of Drug Safety that indicated it was a few years ago about 450 or so patients ended up with acetaminophen toxicity. But of the 450, about a hundred were

described as "unintentional." In other words, only 100 of them were unintentional rather than people trying to hurt themselves.

Does anyone in the group have more current or more precise data so that we can weigh or vet this out a little more clearly?

DR. RAPPAPORT: Well, we took an action -- which I'll let Dr. Hertz describe in a little more detail -- recently to reduce the amount of acetaminophen in the combination products, hopefully having some impact. Again, I don't think we have numbers yet. But we hope that that's going to reduce those numbers of inadvertent overexposure to acetaminophen.

There have also been efforts by the safe use group in our center to educate patients about using over-the-counter drugs and what acetaminophen is and to avoid taking multiple products with acetaminophen. But I don't think we have numbers yet.

DR. HERTZ: So it's very complicated. I mean, the short answer -- this is Sharon

Hertz -- the short answer to your question is, no, we didn't prepare more recent data than what we reviewed when we were planning to take the action on the acetaminophen-containing products.

DR. KAYE: And I think that's great. But there's injury and then there's death. And there is associated, as we know from ER preparations -- we saw some data three and four times -- the risk of morbidity and mortality. So I just thought it might be helpful for us to try to balance this very difficult question we're asked to sort out today. Thank you.

DR. FLICK: Dr. Jevtovic?

DR. JEVTOVIC-TODOROVIC: Thank you, Mr. Chairman.

I have a question for Dr. Gill. If I can ask the organizers to show her slide number 9. So in this particular slide, you're actually looking at the number of prescriptions of extended-release products that are available versus immediate release of oxycodone and then immediate release of hydrocodone, of course in combination.

DR. GILL: Correct.

DR. JEVTOVIC-TODOROVIC: So -- oh, now that's better. You can see what's -- sorry. So I am making some extrapolations in my mind that I need to run by you so that I'm fair to the sponsors.

When you look at that graph, what that would tell me is because of the fact that the use of immediate release of hydrocodone is about four times higher than for other immediate-release products, would it be fair to say that the use of extended-release would quadruple if we were to approve this product for use?

DR. GILL: That would be really hard to speculate. But as I mentioned in my other slides, not all the use of hydrocodone combination analgesics is for chronic pain. Most of its use is for acute pain. So I'm not sure how much and what percentage would translate into the chronic pain use.

DR. JEVTOVIC-TODOROVIC: But a combination of oxycodone and other analgesic is also for acute

type pain, perioperative type pain as well. So to a certain degree, that logic would apply, don't you think?

DR. HERTZ: Hi. This is Sharon Hertz again. One thing that makes it difficult to compare the number of prescriptions dispensed for the hydrocodone combinations and the oxycodone combinations is the difference in scheduling. Because it's easier to prescribe and renew the hydrocodone products, that may be one factor for the larger number of prescriptions.

As an ER product, the hydrocodone will be Schedule II, comparable to the oxycodone ER. So it's a little hard to know if the proportion would remain intact, given those differences.

DR. RAPPAPORT: And also because of the difference -- this is what I said in my opening comments -- because of the difference in the scheduling that you'd have for the hydrocodone combinations versus the single entity, as Sharon was saying, there's a difference in accessibility.

There's also a difference in the way that

prescribers and patients think about those two drugs. People think of hydrocodone combination products as less dangerous because they're Schedule III, when we know that really isn't true.

DR. JEVTOVIC-TODOROVIC: Right.

DR. RAPPAPORT: That's just the way it is. So the impression and the combination of the difference in accessibility could have impacts on differentiating where hydrocodone single-entity goes. Maybe it's going to go up because people think it's less abusable, or maybe it's not going to go up, or it's going to go down because it's going to be in Schedule II. It's all speculation at this point.

DR. JEVTOVIC-TODOROVIC: Yes. It is hard to know. It would help me if I could assess whether the approval of this extended-release formula would simply exchange use of oxycodone versus hydrocodone for a similar population of patients, or would that mean yet another drug of abuse that is being added. And when I saw this slide, a very simplistic thought would be, there we go tripling the number

of people that are going to use the extended-release formula just because now it is readily available. Thank you.

DR. FLICK: Dr. Leff?

DR. LEFF: I had a question for Dr. Walsh. I think you presented a nice summary of the oral risk. Could you help summarize the intravenous risk liability?

DR. WALSH: That's a really good question because there are very few data that speak to that.

In the study that we did, where we used an intravenous preparation, you could see that the abuse liability of intravenous hydrocodone looked very much like that of the comparator agents. The absolute relative potency may have been a bit less -- Bob, you want to bring up a slide?

I think that --

DR. BAUTISTA: Can you give me the slide number, please?

DR. WALSH: Not off the top of my head.

DR. BAUTISTA: Dr. Leff, do you have that?

DR. WALSH: Maybe 18 or so. Thank you. So

go back just a couple to the time course data. That's the most instructive, I think.

So you can see here the onset for effects at the doses shown here, zero, 10 -- I'm sorry, 5, 10, and 20 milligrams of hydrocodone in the last figure -- that they're all producing discernible effects, and that the higher dose is close to equivalent to a 20-milligram infusion of morphine.

One of the concerns that I would have about IV administration is that we don't know much about higher dose administration. So in this study, we only went to 20 milligrams, and the formulation that's being discussed goes up to a dose of 50 milligrams.

At least in our region, bringing prescription opioid abusers into studies like these and others, we have -- what was said earlier is that the majority of abuse is done by the oral route. And that is true. But with the earlier problem with OxyContin, it wasn't that people were taking it orally as intended; they were chewing it and bypassing the protection and getting the whole

dose essentially bolus.

In our region, we see a lot of intranasal and intravenous abuse of oxycodone, single-entity products. And we don't see people coming in and misusing by the intravenous route for hydrocodone, even though we see a lot of hydrocodone abuse.

In a recent study where we were enrolling people for detoxification, of more than 100 people that we screened, no one had ever used hydrocodone intravenously. And it's, I think, largely because they know that there's a risk of injecting a combination product.

So I think that having a single-entity hydrocodone product, we don't know what that risk for intravenous injection is. And of course, that kind of risk is associated with substantially more medical consequences. So while we see a lot of emergency room presentations with oral administration, a lot of them, significant consequences come from using routes that have greater bioavailability and greater danger associated with them.

I'm not even aware of control data that have looked at the higher doses that were described here today for the product under discussion. So is that helpful?

DR. FLICK: Dr. Rappaport?

DR. RAPPAPORT: Just a clarification. Dr. Hertz heard me say something in my last comment, which was that hydrocodone is less dangerous than oxycodone. If I said that, I misspoke. What I had intended to say, and what I thought I said, was that hydrocodone, in spite of the impression of people in the community and some prescribers, is no less dangerous than oxycodone.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Yes. This question is for Dr. Levin. I have a number of concerns from a public health standpoint, but I'll just delve into a couple right now, Dr. Levin.

When you look at slide 2 -- excuse me, slide -- yes, page 2 and slide 4, I believe -- and we look at the REMS communication plans and elements to assure safe use, the

questions I have is, how do you measure the effectiveness of training, first of all? Who's monitoring those metrics?

Then secondly, I have another question about what are the standards for the packaging? What did we learn from oxycodone and morphine? What are our standards for packaging, and what is the FDA's position on that?

DR. LEVIN: Well, let me try to address some of the questions you've asked.

In terms of the assessment built into the REMS, there's specified time periods for assessment, six months after, and then a year, and yearly thereafter that the REMS will be assessed. And part of what they're looking for is the understanding on part of whether the education is working for prescribers and patients in terms of knowing the risks in proper prescribing. So that's, I think, part of what you're asking, how they'll assess that.

I don't know if, Sharon, you have additional information?

DR. HERTZ: So part of the assessment for learning will follow some of the standard CME practices in terms of pre- and post-tests to see if the training is -- if the messaging for the training is being adequately conveyed. And then part of the assessments will hopefully -- well, will include surveys which will hopefully show that there are -- will show whether or not there are changes in practice behaviors.

So that's part of how we plan to understand the impact of training on prescribing practices. I'm not sure what your references are for the --

MR. MULLINS: No. I'm saying that how do we know -- first of all, how do we know that training is leading to a behavioral change or behavior modification? And then secondly, who and what body intervenes once we find a lever of diversion or we find abuse with a prescriber? What --

DR. HERTZ: Right. So what I'm trying to say is for the training part, we're going to ask doctors; we're going to actually ask them if they are doing anything differently as a result of the

training. Then we're going to look at what's happening with regard to prescribing practices using the database sources that have provided some of the information here. And we're going to look at the measures that show us when there are bad outcomes that you've seen here in terms of the data that went into the abuse ratios that Dr. Dormitzer presented.

We'll look at the prescribing patterns that you saw from Dr. Gill and other indicators. Data will be collected on surveys for substance abusers who enter treatment programs. There's the National Household Survey. There's the DAWN data.

So we're going to try to piece together from many different sources to see if there is an impact of the training from the REMS, which is the predominate component for the REMS.

In terms of who intervenes if there's abuse and diversion, well, the DEA is responsible for criminal activity resulting from diversion and anything that is in conflict with the laws associated with the Controlled Substances Act.

More locally, in terms of what we can do from FDA with our authority is if we, through looking at the different aspects of the REMS assessments, find that we're not getting positive change, we need to reassess whether there have to be modifications to the REMS program.

So there may need to be changes to the REMS program. There are other federal efforts that may also help in reducing the misuse and abuse. And we work to support those efforts as well.

MR. MULLINS: Well, as I said, what's confusing me is that we know from past history that a lot of the ER visits, visits to the emergency room, are from teenagers that were never prescribed the medicine at all or the therapy. So my question is, has the FDA established some type of standard for packaging? Because typical you can have all the education in the world. But how we mitigate the abuse by non-patients using -- or subjects using this therapy that have not been prescribed the medicine?

DR. HERTZ: We don't have authority over

drugs that get repackaged by pharmacies into amber bottles and sent into the home.

MR. MULLINS: So there's no one monitoring the packaging for this particular --

DR. HERTZ: Well, the packaging is child-resistant, but it's not theft-resistant. Part of the REMS is an attempt to educate prescribers and patients that these products are, in fact, being stolen.

Why is that product in an unprotected space in the home? Because it is a target for potential theft by, among others, especially teenagers. I mean, that's part of the educational program.

If parents and people who have these products in their home understand that this is a target for theft, that they are responsible for trying to secure it better, that is part of what we hope to achieve through the educational programs; that prescribers counsel their patients about this, that patients understand it through their counseling from their physicians, as well as from additional information that's available with the

medication guide and the patient counseling document, and then take appropriate steps to properly secure the medication in the home.

We also think these products should not remain in the cabinet when they're no longer necessary, and they should be disposed of. And that's a whole series of projects. There are difficulties with disposal of scheduled products. We have national take-back programs or regional take-back programs that occur. We recommend that a lot of these products -- in particular these products -- be flushed.

I know, for those of you who have concerns about drugs in the water, that's an issue. But we think that disposal of unused products is also important. That's part of the educational material, again, for prescribers to convey to their patients and for patients to get through understanding of the available information that we're making part of the REMS.

DR. RAPPAPORT: Can I just get some clarity on what you're asking? Because I'm not sure you're

getting the answers you want. Are you asking about identifying the drug when a patient, teenager or whoever, comes into the emergency department having overdosed? Somehow having the packaging allow people to identify the drug?

MR. MULLINS: No. I'm saying that from a public health standpoint, you have a highly toxic, highly addictive drug that is easily accessible from a certain aspect or a certain subpopulation. And particularly young people, youth, they are abusing this drug on an epidemic level.

I'm saying right now we have no standards for packaging for mitigating that risk to that particular subpopulation. And there are on the market now various -- various manufacturers have utilized different approaches to making the packaging more tamper-resistant.

Then on my other issue with the brochure -- excuse me, with the education, that in the past we've had sponsors that would consider education giving someone a brochure or flyer. Now, I think that's more idealistic than practical, and

more idealistic than effective. Giving someone a brochure is not necessarily education, which is why abuse is so rampant, because we're living in one world and then reality is another world.

So I'm trying to see how we have modified our approach to eliminate the abuse, and how we will -- because this is a much more -- this drug has a higher level of toxicity, much more active agent, and highly -- to me, much more addictive attributes than even oxycodone. So I think that -- how will we address those issues?

DR. RAPPAPORT: Let me just clarify that your questions are good ones. But we've told you what risk management tools exist today, and part of what we're asking you to discuss later today is, if you believe that additional risk management tools are necessary for this drug or for the class of ER/LA opioids, then that's what you should be discussing this afternoon and expressing your opinion about it.

These are perfectly appropriate opinions. But this section right now, it's just

clarification. There's nothing more that we can tell you that we haven't told about the risk management tools. Those are the tools that exist at this time, and if you think we need more, let's discuss that this afternoon.

DR. FLICK: I think we'll carry this discussion on this afternoon. It is now 10 minutes after 12:00, time for lunch. The open public hearing will begin promptly at 1:00 p.m.

This room is secured during the lunch period, so whatever you need, please take now with you as you go. We will break, then, till 1:00.

Please be reminded that there is to be no discussion of the meeting topic during lunch amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 12:10 p.m., a luncheon recess was taken.)

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

(1:01 p.m.)

Open Public Hearing Session

DR. FLICK: Good afternoon. I think we're ready to get started.

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

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

Likewise, FDA encourages you at the

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

The FDA and this committee place great importance 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 to the podium and introduce yourself? And please be reminded that

your time is limited to four minutes, and the microphones will be turned off at the end of that four-minute time period.

MS. FOSTER: Good afternoon. As stated, my name is Wendy Berggren Foster. Zogenix has paid for my travels today.

I am the senior advocacy ambassador for U.S. Pain Foundation, a national organization representing the voices of those living with pain. I am here to urge your support for open access to all medications used to safely aid in the treatment of individuals living with pain. I am also a pain patient.

Since 1992, I have suffered from an as-yet-undiagnosed neuromuscular disorder, which seemingly began while swimming with my children while camping. I suffer from progressively weakening, tired, painful limbs, and a lung capacity of 50 to 60 percent if healthy. It was best classified by the Mayo Clinic as bilateral restrictive lung disease secondary to a proximal myopathy.

I have also suffered from severe atypical

migraines for many years, which on at least three occasions have proved to be mild strokes. I now add degenerative arthritis of my lower spine to the list, causing at least three of my vertebrae to press into my spinal column.

While chronic pain is at best difficult to control in its own right, each individual suffering from chronic pain to any degree responds to each medication differently. What may work for one may not work for others, and vice versa. While there are certain drugs that are shown to work well with pain associated with specific disorders, even those patients with the disorder will respond differently to each one.

In my particular case, with no specific diagnosis, there are very few medications for pain which help me. My daily pain level is usually 8 to 9 out of 10, if I'm lucky. I also have a very difficult time remembering to take my midday dose, which allows the pain to build before the next scheduled dose.

I often experience a great deal of nausea 15

to 30 minutes following my dose, which with most current meds means every 4 to 6 hours, making it most difficult to maneuver through my day. I can also count on a roller-coaster effect regarding my pain, as it begins to increase with an hour still to go before my next dose.

Along with the above-stated pitfalls of pain medications comes the realization that the meds can often do more harm than good over the long course of treatment. Both acetaminophen and ibuprofen have been linked to possible liver damage when used to help control moderate to severe chronic pain.

This makes making the decision to take pain medication to improve one's quality of life a more difficult choice than it should be. I often choose to go without treatment rather than take the added chances of additional health issues.

I believe that while I may be a person with pain, my pain does not have to define me as an individual. Unfortunately, with many of the pain medications now available, I sometimes slip back into thinking that my pain has power over me.

I'm not alone on my pain journey. I also speak for the many individuals who reach out to the U.S. Pain Foundation in their search for safer options for chronic pain management.

I strongly urge you, both as a patient and as a representative of U.S. Pain Foundation, to help increase the options for safe pain management. A person with pain who needs the medications to live does not abuse the meds. Addicts abuse the meds. Thank you.

DR. FLICK: Thank you.

Speaker number 2?

DR. NALAMACHU: Good afternoon. My name is Sri Nalamachu. I am a physical medicine/ rehabilitation physician practicing in Kansas City. I'm also a clinical researcher. My disclosure, I am actually a principal investigator for both Zogenix clinical trials and also been a principal investigator for multiple clinical trials in the last ten years. And my travel for today is paid by Zogenix.

I'm not here to convince the efficacy of the

Zohydro. You all have seen the data, and the fact that the hydrocodone is one of the widely prescribed medications in this country for years; obviously, it works. And I'm also not here to convince anybody here that there's no problem with the opiate abuse. But what I'm here is to plead on behalf of my patients. I see patients with chronic pain from osteoarthritis, diabetes, cancer, and multiple other causes.

A lot of these patients, when they see their primary care physicians for the first time, they get a prescription for hydrocodone short-acting combination medication. And the primary reason for that is that it's Schedule III, which was supposed to be a matter of convenience.

But over the years, what has happened is that the convenience has become two public health crises in this country, the first one being the acetaminophen toxicity; we all know the public health crisis with the estimate of toxicity, and these combination medications contribute a lot because I see patients who are taking tens of

hydrocodones a day for years and years. And the second problem is that this is a short-acting pain medication, and it only works for a few hours. So patients keep taking again and again.

So I'm here to say that the problem exists with the opiate abuse. But the problem really is because the hydrocodone, current combination, is a Schedule III and the Zohydro, I hope, would be a Schedule II. So urge the board and the agency to look at it carefully and approve the drug, but mandate education, mandate risk management.

I can tell you, in the last 15 years, things have changed so much. If we go back by ten years when the OxyContin was just being launched, things were much different. We have stricter regulations now. We have regulation, risk management programs. We have the data banks by the different states. Physicians are more educated and more trained.

So by making it Schedule II, I think the patients would get access through the physicians who are much more trained and have the much better understanding of the risk of these products. Thank

you very much.

DR. FLICK: Speaker number 3?

MR. ISRAEL: Good afternoon. My name is Avi Israel, and I'm speaking on behalf of my son, Michael David Israel, and 1900 persons who belong to our group, Save the Michaels of the World. Most of them lost their kids to prescription drugs.

My son Michael was addicted to hydrocodone prescribed to him by his doctor for Crohn's disease. On the morning of June 4, 2011, after being refused help by his counselor, Michael locked himself in my bedroom, put a shotgun under his chin, and pulled the trigger.

Ladies and gentlemen, I want to ask you a question. I want you to take a moment and think about that. Think about your kids. What would you do if your son committed suicide because he was addicted to a medicine that was prescribed to him by his doctor? How would you feel?

I can tell you. My son took his last breath while in my arms. Half his face was plastered all over the wall, and he was struggling to breathe.

Take a minute to picture your kid in that position.

My son Michael had a medically sanctioned addiction. He wasn't out on the street looking for drugs. He got his prescriptions from a doctor, and then he filled them at our local pharmacy. His doctor thought that it was a great idea to prescribe hydrocodone to slow his bowel movements.

A long time ago, a committee just like you decided to approve hydrocodone for moderate pain and long-term use. They did it without knowing or thinking of the consequences, that that decision gave a license to pharmaceutical companies and their mouthpiece, the pain management people. They brainwashed our medical society into prescribing the magical pill for everything, including for an 18-year-old that weighed 87 pounds and suffered from Crohn's disease.

Let me be clear. Certain people need this medication for the end-of-life pain or for the last day on earth, to make it comfortable. For others, hydrocodone and opiates are nothing but dangerous drugs, especially when prescribed by an

irresponsible doctor for bogus reasons. This ratio is as wide as the Grand Canyon.

Today the consequences of that decision for myself and thousands of other families -- we lost our kids, and thousands more are afflicted by a disease called addiction.

So here you are today, and you could be making the same mistake. But you need to ask yourself a question: Is this medication really going to help somebody? Do we really need another pill in this country? Do we really need another narcotic pill to help anybody with pain? We can't handle what we have.

If you approve this pill, you surely will be signing a death sentence for thousands of people, especially young kids. You were selected to sit on this committee for your expertise. But you also need to consider, will your decision help the people?

We cannot handle what we have already in this country. Today we have a change, a chance to save people. So I'm asking you, please, save all

the Michaels of the world.

DR. FLICK: Thank you.

Speaker number 4?

MR. BEEMER: Hello. My name is Craig Beemer. I hurt my back approximately ten years ago. It got to the point to where I couldn't walk. I couldn't stand. I would spend days in bed. I went to a pain clinic, and that's where I met Dr. Nalamachu. And they put me in a drug trial where I was given -- I can't remember the name of it; I'm kind of nervous right now -- I'm sorry.

Anyway, I was on the drug trial for approximately a year. It was a 12-hour dose. The thing that impressed me the most about it was that it didn't have the aspirin. It didn't have the Tylenol. It didn't have the ibuprofen in it. And I could take it twice a day, once before I went to bed and once when I woke up, and it worked wonderful.

It brought my life back to normal. I could go everyday life. I could go back to work. And it really brought me back to where I could do

everything again that I could do in the past. The only bad thing is, is when the drug trial was over and I had to go back to the old way of doing things.

I'm asking that you go back to this -- I'm sorry, I just can't pronounce it -- Zydro -- God. I am so sorry. Well, that's it. Thanks.

DR. FLICK: Thank you.

Speaker number 5?

DR. KOLODNY: I'm waiting for a slide. My name is Andrew Kolodny. I'm chair of psychiatry at Maimonides Medical Center in New York City, and I'm president of Physicians for Responsible Opioid Prescribing. PROP's members include clinicians and researchers in the fields of pain, addiction, public health, primary care, and other specialties. I have nothing to disclose.

I'm here today to urge the committee to vote no on approval of Zohydro. According to the CDC, the sharp increase in consumption of opioids, demonstrated by the green line, has led to parallel increases in addiction and overdose deaths. The

CDC is calling this the worst drug epidemic in U.S. history.

The following slides show the epidemic developing over time. States that turn red and maroon have the highest rates of admissions for painkiller addiction. This slide is from the beginning of the epidemic in 1999. This is 2001, 2003, 2005, 2007, 2009. Every state in the country has had a sharp increase in the prevalence of opioid analgesic addiction.

Unfortunately, the growth in prescribing that caused this epidemic was not driven by new evidence that opioids were safe and effective for chronic pain. Instead, it was fueled by a brilliant marketing campaign that minimized risks, especially the risk of addiction, and exaggerated benefits.

Industry spokespersons will point to the increased consumption of opioids and call it a good thing. They'll say it shows that millions of people are being helped. But there is no evidence to support this claim, and there's no evidence

showing that we do a better job in the United States, where the bulk of the world's opioid supply is consumed, no evidence that we're doing a better job of treating chronic pain.

Zogenix has stated that they intend to market Zohydro for people with chronic non-cancer pain. And to potential investors, they've been quick to cite the Institute of Medicine's estimate that 100 million people in the U.S. are suffering from chronic pain. What Zogenix hasn't quoted from the IOM report is this statement: "The long-term effects and effectiveness of opioid therapy are far from certain."

So one has to wonder why we're here today. And one has to wonder how many more pain patients have to be harmed, how many more people have to become addicted, how many more lives will have to be lost, before FDA finally begins to exercise its authority and responsibility to prohibit drug companies from marketing opioids as if they have been proven safe and effective for long-term use.

When faced with a public health crisis

caused by over-prescribing of opioids, the very last thing we need are new opioids that will invariably be released with a marketing campaign to encourage more prescribing. I urge you to vote no on Zohydro approval.

DR. FLICK: Thank you.

Speaker number 6, please step to the podium and introduce yourself, please.

MS. PLACEK: Hi. My name is Cheryl Placek. The worst day of our lives, my husband Dan and I, was on January 26, 2012. That day, my 28-year-old son Daniel hung himself at the VA hospital in Buffalo.

My son Daniel was addicted to painkillers that were prescribed -- I'm sorry -- prescribed to him by a pain management doctor for legitimate pain. Daniel was on the highest dose of hydrocodone for two years without informing Daniel of the consequences of the drug.

Daniel hurt his back at work two years prior to his death. Being a very active young man and a Navy veteran, Daniel wanted to go back to work as

soon as possible. His doctor sent him back to work while continuing his treatment with hydrocodone and workmen's compensation.

After being on pills for two years, Daniel started developing anxiety and paranoia. This was a young man that served in the Navy, raced motocross, played hockey, was never afraid of anything; and out of the blue, he was starting to hallucinate. We didn't realize what was happening.

Daniel tried to stop taking the pills several times, even consulting his pain management doctor. I accompanied my son to his pain management doctor on December 21, 2011. His doctor never once mentioned addiction to him. I sat right next to him, by his side. Never asked Daniel whether or not he tried to stop. He just never mentioned the word addiction.

This pain management doctor thought it was okay to crack a few jokes, actually, when I was sitting there with my son while he was suffering from this. The medicine was prescribed to my -- Suboxone was prescribed to my son without any

counseling, without any instructions, without supervision. A pain management specialist gave him a prescription and sent us out the door.

On Christmas day, Daniel was hallucinating and was talking of suicide. We were very confused by what was happening. Nothing was said to us by his pain management doctor. We took Daniel to the emergency room and stayed with him for 16 hours, and then we were told there was no beds, and they sent him home suffering from withdrawal.

Getting no help from his pain management specialist, my son decided to go to the VA hospital. After three weeks of begging them and getting an evaluation for my son, he was admitted at 11:00 a.m. in the inpatient program on January 25, 2012.

Thinking my son was safe, after several hours my husband and I, his girlfriend Colleen, and his best friend Eric, who were there for support, went home. At 1:00 a.m. the next morning, we received a phone call from the VA hospital telling us that my son had hung himself.

We came in front of this committee where you have the option to approve or disapprove a more deadly form of hydrocodone. We have not settled the question of whether or not hydrocodone is really safe for long-term use. We have not settled the question of whether or not hydrocodone is addicting.

As a mother who is here in front of you who lost her only child, I can answer that for you. Opiates are highly addicting. Hydrocodone was approved for long-term use, and my son is proof that it is not safe. This is not just one individual. This happens every day across the country.

I urge you, do not approve hydro ER. It is a medicine that was developed for the sole purpose of profit. This is a medicine that is not tamper-proof. This is a medicine that contains more morphine than any hydrocodone that is on the market today. And if approved, you are basically inviting people to take their own lives, or it will end their lives.

My husband Dan and I have been robbed of having grandchildren, of having my son for the rest of our lives, and Daniel himself was robbed of his life. This was preventable. Do we really need another pain medication in this country? Ask yourself that question.

(Time expired, microphone shut off.)

DR. FLICK: Thank you.

Speaker number 7, please step to the podium and introduce yourself.

DR. BUSCH: My name is Dr. Daniel Busch, and I'm here at my own expense. I'm a psychiatrist at Northwestern University's Feinberg School of Medicine. Both high achievement and opioid addiction run in my family.

My beloved son Joshua, a senior at Emory University, lost his life last year due to the interaction between his addictive illness and the ready availability of prescription opioids. I'm disturbed that the FDA is even hearing the new drug application for Zohydro ER. The FDA has determined that ER/LA opioids, like Zohydro ER, present so

much greater risk than immediate-release opioids that the new classwide opioid REMS were instituted.

But can these REMS protect us from a flood of new opioid deaths if Zohydro is released onto the market? The value of these REMS in the fight against a force so irrational and so powerful as opioid addiction is untested and unproven.

Extended-release opioids as a group are moving toward more tamper-resistant formulations. Recent papers have noted the impact on abuse of OxyContin since the new, more tamper-resistant formulation was introduced.

Opana ER was recently reformulated using INVAC technology to beef up its tamper-resistance. Yet Zohydro ER uses SODAS technology, which presents no significant barrier to abuse. Immediate-release hydrocodone can be extracted simply by crushing the SODAS particles.

Hydrocodone is already the most abused opioid. Why would the FDA consider a new drug from which pure hydrocodone can be so easily extracted? The CEO of Zogenix, Roger Hawley, was quoted by the

Associated Press as saying that the FDA was not pressuring Zogenix to put an abuse deterrent in Zohydro; that he believed that the "priority of a safer hydrocodone -- that is, without acetaminophen -- is a key priority of the FDA."

Can this possibly be true? An estimated 250 Americans die annually from liver failure from opioid/acetaminophen combinations, while 15,000 die from prescription opioid overdoses. Approval of a new drug which will be a ready source of easily abusable hydrocodone has the potential to undo the work that has been done toward gaining some modicum of control of this epidemic.

Let's at least wait until Zogenix develops its promised tamper-resistant formulation before considering releasing it onto the market.

DR. FLICK: Thank you.

Speaker number 8? Please introduce yourself.

MS. LINDELL: Hi. My name is Laurie Lindell, and my travel arrangements were paid for by Zogenix.

I was told September 2002 that I have RSD, also known a Regional Complex Sympathy. I'm now a patient advocate for the United States Pain Foundation and for the New York Pain Society. In both positions, I work with patients to help them find new drugs and activities they can do in order to help them find some relief for their pain.

I make sure that they know all groups available to them, sometimes go with them to doctor's appointments so that they have a better understanding of what's available to them in terms of treatment, and sometimes just let them talk and let their fears out.

I have several friends who are on opioids, and they have taken them for so many years, a few have shown signs of damage to their liver. This makes them scared to take the drugs that they're prescribed, and in some cases they would rather live in a lot of pain and basically do nothing to help themselves. If they had another option, these people may take better care of themselves. None of these people like taking medications.

When I was being dropped off here this morning, the driver asked me why I was here. I explained to him about why I wanted a new drug like this to come out on the market, and he told me about his father, who had been on pain medications and now suffers with problems with his liver, and how a drug like this would help his father greatly because it would hopefully do no more damage to his liver.

When I go to my doctors, we talk about changing my medications, and we go over what I've taken and why we stopped the medication, and look at what medications are coming out. And we talk about the pros and the cons of taking these drugs, and we never make a decision on that day.

I go home, we do more research and the doctors do more research, and then we meet again and go over everything and decide what to do at that time. At all times, my doctors monitor what's being taken so they know it's not just me, but none of their patients are abusing the drugs that they are prescribed.

My doctors have no problems telling any patient who they believe are doctor-shopping, pharmacy-shopping, or abusing prescriptions that are written for them to leave the practice and they'll no longer be seen.

I worked for ten years with RSD before my employers -- no matter how much pain I was in and how much information I gave them, but they never understood what was going on. If I had to take off from work because the pain was bad, they would tell me, "It's in your head." I've heard the same comment from many others, and they would be angry to have such a bad reaction from their employers.

Employers need to be educated on chronic pain, as well as family members who refuse to believe there is a problem. Many people want to go back to work, but can't because their pain is so bad, myself included. But at this point, it's not an option for me. If there was a drug you only had to take once or twice a day and go back to work, most people would welcome it. I would want to go back to work, and looking for something to help

with the pain to go back to work and living a life without having your family and friends and government to support them.

I think the government definitely needs to do something so that the people who have chronic pain should be able to get the medication that they need, but at the same time they need to tighten up the rules as to who can receive this drug and, better yet, who can actually write the prescription for the drug because of the abuse and the overdose problems of the existing drugs.

DR. FLICK: Thank you.

Speaker number 9, can you step to the podium and introduce yourself?

MR. JACKSON: My name is Pete Jackson. I have no financial relations.

I am president of Advocates for the Reform of Prescription Opioids, a nonprofit organization in the U.S. and Canada dedicated to fighting the epidemic of death and addiction that rages in our countries, and that according to CDC has resulted directly from the over-prescribing of prescription

opioids.

I became involved in this issue after losing my 18-year-old daughter, Emily, to a single OxyContin pill swallowed whole in 2006. I'm speaking on behalf of families from all across America that have been similarly devastated by prescription opioids. A majority of people for whom we grieve were pain patients who got in trouble by taking their medications as prescribed.

ARPO strongly recommends against FDA approval of Zohydro ER, or any other extended-release form of pure hydrocodone. Combine the popularity of hydrocodone, its established record of adverse outcomes, and the much higher hydrocodone dose in a pure ER formulation, and you have a recipe for disaster similar to the OxyContin tragedy. We are in the midst of a public health crisis of death and addiction, and the last thing we need is for FDA to keep approving more opioids.

I'd like to tell you a little about my daughter Emily. She was a sweet and friendly girl,

one of those people who everyone got along with. We were a very close family, and Emily was our heart and soul. She would tell us she loved us every day. She also displayed a tremendous sense of humor and made people laugh. She was an excellent athlete in three sports, and a gifted artist. She was a good person.

She was very close with a cousin who lived in a nearby suburb of Chicago. That cousin's father, like Emily, had cancer, and it took his life in August of 2006. Emily was staying with the family to be with them in their grief, and one night her cousin offered Emily some of her dad's leftover OxyContin.

Emily took one pill, and died in the early hours of the morning on the couch in their family room. The OxyContin had caused respiratory depression, and she simply stopped breathing. It was the only time she had taken OxyContin. The last time I saw Emily alive she was telling jokes, trying to make the best of things at her uncle's funeral. They assumed that the drug was safe

because it had been prescribed by a doctor.

Emily was a teenager who made a bad decision. I tell you her story because it provides a real example of how dangerous and potent extended-release opioid medications really are. Good people can make bad decisions. This scenario will be repeated often if Zohydro is approved.

Here's a slide you've already seen. I would ask the FDA and its advisory committee members to consider why, truly, do we need this new drug? All opioids are dangerous medications, whether they are abuse deterrent or not. But several other factors make this drug especially dangerous.

One, the ER formulation gives it a potency that is up to an order of magnitude greater than the current hydrocodone products. Two, the company has requested its use for moderate pain. Three, the company has also requested its use for chronic non-cancer pain, and this is extremely dangerous, given the lack of support for long-term use of opioids for chronic non-cancer pain.

There are already multiple available

treatments for pain. Let's address the ongoing epidemic before considering additional products that will offer more of the same risks without any demonstrable benefits over currently available opioid formulations.

In conclusion, ARPO strongly opposes FDA approval of Zohydro and any other formulation of pure hydrocodone. Please vote no on Zohydro. Thank you.

DR. FLICK: Thank you.

Speaker number 10? Please introduce yourself.

DR. REYNOLDS: I'm Dr. Jeffrey Reynolds. I have nothing to disclose. I'm the executive director of the Long Island Council on Alcoholism and Drug Dependence, which is a nonprofit based on Long Island, America's first and largest suburban area.

As you deliberate here today, I hope you'll take into account what our local communities are struggling with. You've heard a lot of data this morning about overdoses and medical events. And on

Long Island last year, we lost 370 young people to fatal overdoses. That's 370 families, like some of the ones you heard here today, who will never be the same.

Beyond overdoses in medical events requiring ER care, we know that, as is the case with most opioids, abuse of hydrocodone is associated with tolerance, dependence, and ultimately, addiction. That's the part we see day in and day out as families crowd into our waiting room begging for us to do something, anything, to help them get their kids back.

The collateral damage associated with untreated addiction on Long Island became even clearer last Father's Day, when four people were executed during a pharmacy robbery. Sadly, pharmacy shootings, robberies, community violence, and car crashes by impaired individuals have become commonplace on Long Island and in many areas of the country as prescription painkillers flood our streets.

In the midst of this public health

crisis -- and we keep calling it that; it's time we addressed it as such -- we applaud FDA's risk evaluation and mitigation strategy for long-acting and extended-release opioids. Both consumers and practitioners need better information about the appropriate use, secure storage, and proper disposal of prescription drugs, especially opioids. We are also heartened that the President's Drug Abuse Prevention Plan directs the FDA to encourage the development of and prioritize consideration of tamper-proof and abuse-resistant medications.

Still, that's not enough. The technology exists to incorporate physical or pharmacological impediments that limit one's ability to alter the recommended routes of administration and/or that can limit the addictive potential of these powerful painkillers.

We know that the reformulation of OxyContin in 2010 produced a significant decrease in the misuse of the drug. Locally on Long Island and elsewhere, we saw a flight to Opana, which stopped after Endo reformulated the drug to make it tamper-

resistant at the end of 2011.

That means a couple things: first, that these tamper-proof mechanisms intuitively and empirically do, in fact, thwart misuse; and second, that unless we eliminate those products that are not formulated with tamper-resistant protections, we will forever be engaged in the proverbial game of Whack-a-Mole as we struggle with the drug du jour.

You're being asked to recommend approval of a product that doesn't have those protections and will potentially become the drug of choice for addicts in 2013. Zogenix's CEO recently told investors at a Piper Jaffray healthcare conference that they look at a tamper-resistant formulation of Zohydro "down the road," and noted that, "It is not, in our view, a requirement for approval of the product."

Given what's happening in our community, it should be. And down the road to us potentially means more addiction, more violence, more ER visits, more fatalities, and a deepening of what

virtually every public health entity in the United States has called a crisis and an epidemic.

We know that Congress is urging the FDA to move in this direction, and those conversations have likely been accelerated by introduction of the STOPP Act. Given FDA's central role in protecting public health by assuring the safety, effectiveness, and security of drugs, this shouldn't require an act of Congress. The FDA should be doing it on its own.

As you contemplate the potential risks and benefits of a painkiller that's being touted by the media, potential abusers, who I serve day in and day out, and others as the "most powerful painkiller on the planet," we hope you'll recognize what's at stake and act in a way that protects public health and ultimately saves lives. Thank you.

DR. FLICK: Thank you.

Speaker number 11, can you step to the podium and introduce yourself, please? Speaker number 11, Ms. Westrup?

(No response).

DR. FLICK: Speaker number 12?

MR. ISRAEL: I'm going to speak for Teri Kroll. My name is Avi Israel again, and I am definitely not getting paid by anybody, especially not a pharmaceutical company.

I'm here to speak on behalf of some kids who lost their life. I'm going to speak for Tom Kroll, for Adrienne McDonald, for Adam Placek, for Cassandra Lewis.

What I want to ask is, there seems to be a big discussion whether or not this pill is really necessary. We can't control what we already have on this market. We have people who are dying every day, especially kids. We're one-fifth of the population of this earth, but we use 95 percent of the hydrocodone being produced on this earth. In New York State where we're from, we have a population of 18 million people, but doctors wrote prescriptions for 22 million. We got to be all sick in this country. We're all in pain.

The FDA is the one that's supposed to be

protecting our job, or our life. But it seems like everybody's more concerned about acetaminophen than the narcotics. Mr. Rappaport, how many people die from acetaminophen that you can name or you could tell? How many people die from opiates? Well, the last number was 15,000 from opiates, and most of them are kids. One of them was mine.

Every day, every day in this country, there's people who die, one every 19 minutes. And yet we're going to come up with another pill which is not tamper-proof, has more heroin than anything else on the market, and we're going to put it out there.

This is all about money. This is not about helping people. This is not about saving somebody. This is about money. Yes, there's people who need that pill. But we don't have any control over the pills. We don't have any control over the pills that we have now. You cannot add another one that's going to destroy people.

First you've got to put in place some sort of stops, of red flags, or something to stop these

kids from dying before you go approve something and it's marketed for really to make money.

As far as I'm concerned, you need to put a face in front of the dollar. That's what we all forget. These are people. These are kids. My son was 20. I got robbed of having my son and my grandchildren.

Put a face in front of the dollar. Start thinking of the ones that are dying. Thank you.

DR. FLICK: Thank you.

Speaker number 13? Please introduce yourself.

MS. HUSKEY: Hi. My name is Joanna Huskey, and I'm here today to share a little of my life with you. I'll start by letting you know that my travel expenses were paid for by Zogenix, but my testimony is my own.

Physical activity has been a huge part of my life. I learned to swim at 18 months, and began to swim and dive competitively at the age of six. Every summer, I lived at the neighborhood pool and was undefeated as a diver until I aged out at 18.

I was a lifeguard, assistant pool manager, and a swim and dive coach throughout my high school and college years. In high school, I played volleyball and made varsity. We came in second in state my junior and senior year. I also played Junior Olympics volleyball. Since graduating from college, volleyball has been my sport. I'm a member of a women's and coed team that both play weekly in our city recreation league.

Now my reason for coming here today. For the past ten years, I have been in excruciating pain in my left foot that radiates all the way up into my hip. The first diagnosis was plantar fasciitis. After trips to the podiatrist, a cortisone injection was recommended. Unfortunately, the injection only increased the pain. The podiatrist suggested a surgery to release the fascia. The pain worsened.

He referred me to a neurosurgeon, who diagnosed the condition as tarsal tunnel syndrome. When this surgery failed, he discharged me to my primary care physician with the recommendation of

pain medication as the only alternative. The final diagnosis is severe nerve damage.

After several years of trying various narcotic and nerve medications, acupuncture, massage therapy, and more physical therapy, I went to an orthopedist. After X-rays and an exam, he felt that further surgery would only have a 70 percent or less chance of helping the pain. The other 30 percent chance included the chance that I would lose the use of my foot completely.

The orthopedist suggested I be seen at a pain clinic. On a pain scale from 1 to 10, I lived with a 7 or 8. The physical activity I loved was no longer possible. I went to work, came home, and lay on the sofa because to do more increased my pain level to a 10.

After a short time at the new pain clinic, my doctor told me of a study and asked if I were interested. I entered the Zohydro study in November 2010. All of a sudden I had my life back. I started playing volleyball again. I could swim and dive again. I joined a gym, and even began a

hula hoop exercise class. I could clean my house.

I'm blessed to have a wonderful husband who has helped me get through these difficult years. But now I could be myself again, and the kind of wife he deserved.

For a year I did all of the things I wanted to do. With extreme activity, I now had a pain level of a 2 or a 3. With what I had endured, that was nothing.

I wasn't prepared for life when the study ended. All of a sudden the pain came back with a vengeance. The new medications the pain clinic prescribed did nothing. I was back at a pain level of an 8 or a 9. I had to drop out of my volleyball league. My fellow teammates are holding my place on both teams. It's so hard to sit in the bleachers and watch as my life passes me by.

To end, let me tell you the story of a special little boy. He's the son of a close friend. Like everything since childhood, she has shared her precious children with me, and I feel like they are my own.

Her 5-year-old little boy is developmentally delayed and just learning to swim. During our annual beach trip this past summer, knowing that it was going to hurt like crazy, I swam with him, letting him ride on my back. It was a wonderful day and one that I'll never forget. But I paid the price. That night I lay in bed for over three --

(Time expired, microphone shut off.)

DR. FLICK: Thank you.

Speaker number 14? Please step to the podium and introduce yourself.

MR. BARNES: I'm Michael Barnes. I am the executive director of the not-for-profit Center for Lawful Access and Abuse Deterrence, CLAAD, and I have nothing to disclose.

Dr. Flick, Dr. Rappaport, and committee members, thank you for this opportunity and, more importantly, thank you for your commitment to medication safety and optimal care for people with pain. Like yours, CLAAD's mission is to reduce prescription drug abuse while protecting patient access to care.

Since 2009, CLAAD's national prescription drug abuse prevention strategy, a comprehensive strategy, has called for the adoption of new technologies, just one piece of the approach to impeding the abuse of prescription medications. The national strategy has earned the endorsements of 30 not-for-profit organizations, including the American Chronic Pain Association, NADAC, the Association for Addiction Professionals, and Drug-Free America Foundation.

Our position is that pharmaceutical companies have an obligation to ensure the safety and minimize the abuse of their products. Some companies have already acted responsibly, consistent with CLAAD's support for a market transition to less readily abused medications.

Public health and safety data indicates that pain relievers designed to be abuse-deterrent and now on the market are less susceptible to common forms of abuse, and less appealing to drug dealers and abusers as a result. FDA advisory committees told us that back in 2009.

I'm here today to ask this committee and the FDA to lead the market transition to less readily abused medications. So, committee members, please recommend that Zogenix resubmit its application after it embraces its commitment to merging medicine and technology and adding abuse-deterrent features to its hydrocodone product.

Dr. Rappaport and colleagues, the White House this week warned U.S. communities of the dangers of non-abuse-deterrent opioids entering the U.S. black market as a result of bad Canadian policy. Please do better than Canada.

On behalf of CLAAD and the not-for-profit organizations that we work with, I'm imploring the FDA, do not approve any additional opioids, branded or generic, without abuse-deterrent features. And specifically, do not approve Zohydro until it incorporates tamper-resistant technology. Do not allow generic versions of Opana and OxyContin to come to market unless they're designed to reduce abuse. And on this one, we need you to act within 24 days.

We are making progress on our national strategy to reduce prescription drug abuse. Don't set us back, please. Instead, lead the market transition to less readily abused medications. You have our support. You have the support of the White House on this issue. Please do it.

Thanks again.

DR. FLICK: Thank you.

Speaker number 15, can you please step to the podium and introduce yourself?

MR. LUND: Hi. My name is Bob Lund. I'm one of the test patients from Kansas City. My travel was paid by Zogenix.

A little of my background is in '84, I, after a football injury, was also found with spinal stenosis. Four years later, I broke my neck in two places. Then in 2002, after MRIs, found bulging discs in T9, T10, T11, T12, in the thoracics.

I've had over eight neurosurgeons and orthopedics that that have told me not to have surgery on those. And so after many years of successful steroid injections, I guess two years,

and after those failed, at that point I told my doctor, either find me a tall building to jump off of or something to help me with my pain. I struggled to even make it from my bed ten feet to my bathroom.

The benefits of Zohydro for me, while I was a test patient, is effective pain relief for over 12 hours. Take one pill in the morning, one pill at night. Sometimes I would also take Celebrex. The thing I liked about Zohydro is it didn't have the acetaminophen in it, which doesn't work well for me. I either have to take ibuprofen or Celebrex to help with the inflammation that I have.

I would also like to point out that as a patient, when I'm not on -- I would take 60 pills in a month of Zohydro, one in the morning, one at night. When I'm not on that, I have 90 pills of morphine or OxyContin and 90 of a Lortab. That's 180 pills. So for me, 60 pills of a Schedule I narcotic is a lot easier to keep track of, as opposed to 180 in my shelf.

So I just want to let you know that that was

a very effective medicine for me. And I would appreciate your support in passing this as there are those of us that do get a benefit from these medicines. But while they can be abused, I like to control my medicine because if one pill is missing, I know it at the end of the month because every 28 days, I can go back and get that refill. If something's missing, I'm in bad shape.

I thank you for your time. That's all I have.

DR. FLICK: Thank you.

Speaker number 16, can you please introduce yourself?

MR. LEONARD: Good afternoon. My name is Brandon Leonard, and I'm a program manager with Men's Health Network. I have no relationship to disclose.

Men's Health Network is a national nonprofit organization whose mission is to reach men and their families where they live, work, play, and pray with health prevention messages and tools, screening programs, educational materials, advocacy

opportunities, and patient navigation.

The American Chronic Pain Association has estimated that 116 million Americans suffer from chronic pain. This burden affects the ability of men and women to carry out the basic routines of daily life that many of us take for granted. It also hinders their ability to be productive in their work and to enjoy their free time with family and friends.

During the many community health fairs, free screenings, and other events I have attended while on the staff of Men's Health Network, I've heard numerous participants describe how chronic pain interferes with their daily lives.

Understanding the tremendous impact of chronic pain on so many Americans, Men's Health Network strongly encourages the availability of a variety of treatments that can help patients safely manage their pain.

We recognize that while there are existing treatments that patients may use to manage their chronic pain, no two patients are exactly alike.

Some may not respond well to the current treatments that are available to them, or they may find them completely inappropriate due to their own unique biology.

New therapies that offer alternative methods of delivery will provide more options to patients suffering from chronic pain. These therapies are particularly needed for patients who must take medications for an extended period of time, as current options may not be safe for them.

In recent decades, men have shown poorer health outcomes to women across all racial and ethnic groups, as well as socioeconomic status. This can be largely attributed to cultural attitudes that have been ingrained in American boys and men for years.

Men are taught at an early age to suck it up, and that big boys don't cry. When a boy is five years old and falls down and skins his knee, his mother or father often tells him to shake it off. And when he's 50 and having chest pain, he may dismiss it as indigestion while it may really

be the first sign of a cardiovascular event.

Many of those who suffer from chronic pain may be reluctant to seek help and treatment due to stigma and lack of understanding their condition. Men may be particularly averse to seeking help because of social norms that teach them to suffer in silence.

This dangerous mentality often leads to the exacerbation of medical conditions that only grow more severe and costly if they are not managed and treated early.

As we tackle many of the social and cultural barriers to the health and well-being of men, women, and their families, we must not lose sight of the need for safe and effective treatment options. It is also of critical importance for patients and health care providers to work closely together to determine the best treatment plan, given their own individual situation.

To conclude, there's a need for new and innovative treatment options for chronic pain patients. This is an important decision for men

and women who are suffering and will suffer from chronic pain, as well as millions of family members and loved ones across the nation who are profoundly affected.

Thank you for the opportunity to speak.

DR. FLICK: Thank you.

Speaker number 17?

DR. BERGER: Good afternoon. My name is Dr. Tom Berger. I'm executive director of the Veterans Health Council for Vietnam Veterans of America, and thank you for the opportunity to present our views on Zohydro ER this afternoon.

The wars in Iraq and Afghanistan have resulted in a growing number of troops evacuated to the U.S. for comprehensive care for their physical and mental health trauma. And despite the media attention focused on post-traumatic stress syndrome, or PTSD, the number one malady suffered by America's active duty military personnel is musculoskeletal.

Given the number of physical injuries often experienced by troops, it's not surprising that

chronic pain is a frequent problem among returning military personnel from Operation Iraqi Freedom and Operation Enduring Freedom.

Other common sources of chronic pain for these troops are in the head, such as traumatic brain injury; post-concussive syndrome; leg fractures; amputations; burns; and shoulders. And, of course, other physical injuries include spinal cord and eye injuries, as well as auditory trauma.

A paper in the March 7, 2012 JAMA described the pattern of opioid prescription for returning OIF/OEF vets. Of the 291,205 who enrolled for VA health care benefits between October 2003 and December 2008, 141,029 received a diagnosis of a painful condition not caused by cancer. And of that number, 15,676 received a prescription for an opioid drug that lasted for at least 20 days.

But chronic pain is not limited to America's newest veterans. It's also a significant malady among our older veterans, particularly Vietnam veterans suffering from PTSD, hepatitis C, and especially those exposed to the ravages of Agent

Orange. Given these morbidities, it may not be surprising to see a higher frequency of prescription opioids for these vets.

Other common chronic complaints for them often include headache, low back pain, cancer pain, arthritis pain, neurogenic pain, and/or psychogenic pain.

Frequently these veterans have two or more coexisting chronic pain conditions, including chronic fatigue syndrome, endometriosis, fibromyalgia, inflammatory bowel disease, interstitial cystitis, temporomandibular joint dysfunction, and vulvodynia. In addition, research suggests that these chronic pain patients complain of cognitive impairments such as forgetfulness, difficulty with attention; difficulty completing tasks; impaired memory, mental flexibility, verbal ability, speed of response in a cognitive task, and speed in executed structured tasks.

Most people don't know it, but acetaminophen is the most deadly ingredient in prescription pain medications such as hydrocodone. That's the reason

why the FDA started its program in 2011 to reduce the level. That's why Vietnam Veterans of America and its Veterans Health Council supports, all right, the addition of this new drug.

Thank you very much. Appreciate it.

DR. FLICK: Thank you.

Speaker number 18? Please introduce yourself.

DR. KOLODNY: My name is Andrew Kolodny. I'm president of Physicians for Responsible Opioid Prescribing. I've been asked to stand in for Giselle Jackman. I have nothing to disclose.

In the additional time that I received to speak for Ms. Jackman, I'd like to talk a little bit about the dichotomy that we heard about this morning from Zogenix.

We heard Zogenix tell us that there is a dichotomy when it comes to opioid prescribing, that we have two distinct populations: the pain patients who are helped by opioids, and then the population of people that misuse, abuse, and divert the pills. And this was presented to us as if

these are two distinct populations.

This is something that we've heard over and over again at FDA meetings. It's a theme that's sometimes presented to us as the principle of balance, in which policy-makers are told that we have two problems in America. We have the problem, the public health problem, of abuse of prescription medications; but we also have the public health problem of untreated chronic pain and the 100 million Americans with untreated chronic pain.

The message for policy-makers has been, don't do something about the drug abuse problem that will worsen the problem of untreated chronic pain. And of course, the implication there is that opioids are helpful for the 100 million Americans with chronic pain.

In fact, we don't have any evidence that supports that belief. We do know that there are millions of Americans on these medications, and we know that some pain specialists believe that there are some patients who do well. Whether they're really continuing to get effective analgesia or

whether they just manage to function okay, we don't really know. But we know that many patients are harmed by this treatment.

I'd like you to look at the green line on this graph. And what the CDC has been very clear about is that as this green line has increased, that it's dragging up the purple line and the orange line, that the over-prescribing, the over-consumption of opioids is leading to increases, dramatic increases, in death rates and addiction. And what the CDC is suggesting is that we will not be able to turn this epidemic around until that green line begins to come down.

But that's not what we're hearing from industry, and it's not what we hear from pain organizations that are sponsored by industry, like some of the folks we've heard from today. What they tell us is that the green line can still go up, and it should go up, because there are millions of people with chronic pain.

But they tell us we can have our cake and eat it, too, that the green line can continue to go

up and we can make the purple line and orange line go down, and we can do that through education. And that's the basis of REMS, that through education, we can reduce the adverse events.

But what is the basis of the education? It's something we call the new paradigm, where we teach patient selection, risk stratification, and monitoring. And I think one of the questions that Rodney Mullins asked of Zogenix this morning pointed to one of the flaws with the new paradigm, which is patient selection.

We heard from Zogenix that their safety approach is that they're going to target the medication for the people that are helped by it. But we have no way of knowing which patient is going to be helped by the prescription before starting them on the medicine, or which patients are going to develop addiction.

What we're told is that we can stratify patients on the basis of risk and monitor them closely, and that if you're monitoring the patient closely and you see evidence of addiction, then you

stop the treatment and you prevent addiction. But that doesn't work. The point at which a prescriber is going to recognize that the patient --

DR. FLICK: Thank you.

DR. KOLODNY: -- may have developed addiction, the horse is already out of the barn.

DR. FLICK: The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the charge to the committee. Dr. Rappaport?

Charge to the Committee

DR. RAPPAPORT: Thank you, Dr. Flick.

As I stated in my opening comments, your discussion and recommendations today should consider both the clinical and public health risks and benefits that would be inherent in approving Zohydro for marketing, and the regulatory framework

within which those of us at FDA must function. The word was "must" function.

The first approved single-entity hydrocodone product is likely to be a useful option for patients with pain that cannot be controlled with the currently available analgesic drug products. It is also likely to contribute to the toll that prescription opioid abuse and misuse are taking on many people in this country.

But the key question that we are asking you to address at this time is whether Zohydro does or does not post a different or greater risk of abuse and misuse than the other drugs in the class. And if it does pose a greater risk, should we require risk management tools above and beyond the ER/LA REMS? Or is it perhaps even too unsafe for patients and should therefore not be marketed at all?

If you determine that its risks are essentially the same as the other approved potent single-entity opioids, is the current level of risk management for that class adequate, or should

additional risk management strategies be considered?

Recognizing the many years of investigation, deliberation, and discussion with all of the pertinent stakeholders that went into creating the current version of the ER/LA REMS, if other risk management strategies are needed for Zohydro, would the additional risk mitigation tools the sponsor intends to put in place be appropriate for their product and only for their product? Or, if applied to Zohydro, should they be applied to all the drugs in the ER/LA class?

It's extremely important that if you recommend that FDA either require additional risk management tools to approve this application or not approve the application, you support your recommendation with clear examples of how this product is different from the other products in the class. If you cannot do that, please consider the implications of making recommendations that may not be supportable by law and regulation.

If, on the other hand, you conclude that the

risks associated with this product and the other products in this class can be managed by implementing risk management strategies over and above the ER/LA REMS, please tell us clearly what strategies you think will provide that additional level of protection.

To do other than what I'm asking you today, while no doubt heartfelt and in the best interest of patients and the public health, may not provide us with a level of guidance that will be useful as we make our final decisions regarding this application. Let me thank you in advance for taking on this difficult and challenging task.

Questions to the Committee and Discussion

DR. FLICK: Thank you, Dr. Rappaport.

We will now proceed with questions to the committee and panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will be using electronic voting system

for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. 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 would like. We will continue in the same manner until all questions have been answered or discussed.

(Pause.)

DR. FLICK: So the first question for vote, has the applicant demonstrated that Zohydro ER is effective for the management of moderate to severe

chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time?

We will open questions to the committee on question number 1. Please confine the questions to this particular question.

Mr. Mullins?

MR. MULLINS: I still come back to my question for the sponsor on exactly for what target audience this therapy is designed to be most effective for. And I don't have clarity on that because surely we know that some opioids are not effective for particular populations.

I'm also concerned we haven't addressed -- there's a number of things we haven't addressed, and that is patients with neurological diseases, patients with COPD.

So I'm wondering, who is this -- in order to answer that question properly, do we have enough information on the profile of the patient population that will receive the highest amount of benefit for this therapy?

DR. FLICK: Would the sponsor like to respond to that?

DR. BREITMEYER: Thank you. Mr. Mullins, unfortunately the state of the art doesn't allow anyone with any opioid medication to prospectively identify a patient in advance. And we are watching closely for evolving science to see whether or not predictors of opioid response and safety become available. They are not.

On a related note, several committee members asked, in a couple of different ways, how many patients are likely to end up on this medication. And so we wanted to clarify this, and the number is, we believe, lower than some of you may be imagining. If I could have the slide up.

I'm showing here the current numbers of patients -- and this is from the FDA data that you saw today; we believe they're accurate -- for oxycodone ER, morphone ER, oxymorphone ER, hydromorphone ER. And our projections, which are both based on the company's understanding -- the company's intended approach to working only with

experienced pain professionals, working only with patients with chronic pain who don't have alternatives, who need an extended hydrocodone -- and the blue bar, the 90,000 patient number, is not only the number that the company intends to have utilize this medication, but it's also a number that is exactly in line with the DEA quota that we showed you.

We cannot exceed our DEA quota. It's not that we don't intend to; we can't. And this, I hope, will provide some reassurance to you that not only do we not intend to have a mushrooming or explosion uptake of this product, but we're putting safeguards in place that we hope will prevent that.

MR. MULLINS: I'm trying to understand. It sounds like you'll be self-policing. Who will you not sell this drug to, first of all? And how will you defined a trained pain professional? Thank you.

DR. BREITMEYER: Certainly. And thank you for the follow-up question. We will not sell to -- and this is what we can control. We will not

distribute the product -- we will not allow the product to be sold -- through distribution sources that have demonstrated abuse or diversion of the product.

We will not in any form encourage the use of the medication by any physician or other prescriber who demonstrates inappropriate prescribing of the medication. And in both cases, we will report either the prescriber or the channel of distribution to DEA, FDA, and state authorities.

MR. MULLINS: If you look at study 801, we had a signal of diversion in study 801 and in study 802, and that was with close monitoring in a clinical trial. If we had this issue arise of diversion and potential abuse in a closely monitored situation with multiple professionals, then how do we control this substance in the larger marketplace where we don't have the same controls underway? And how do you propose to be a part of mitigating that potential risk?

DR. BREITMEYER: Great question. The rate of diversion that we're aware of in other extended-

release opioid product clinical trials is 36 percent diversion. Ours was one-half of 1 percent. We applied a number of additional measures in our clinical trials to ensure that -- to bring down the diversion rate, and it did do so.

Our approach to the risk mitigation program, which as you heard is substantially added to above and beyond the opioid LA REMS, has the same philosophy to it, the same approach to put extra tools in place, to put extra surveillance in place, and to act when something occurred. That was the philosophy in the clinical trial. That will be the philosophy in the marketplace.

DR. HERTZ: I'm sorry. Where did you get that 36 percent number from?

DR. BREITMEYER: CSS presentation, Exalgo advisory committee, 2009.

DR. HERTZ: Thanks.

DR. RAMSAY: And could I just comment that -- no?

DR. FLICK: The chair realizes that -- and

I'm getting a sense from the committee -- that the primary concern here may be safety. I want to remind you that the question before you is about effectiveness. And I would just ask that we try and confine the questions at this point to the question at hand. We will come back to safety when we get to question number 2. Thank you.

DR. RAPPAPORT: Can I just add that it's okay to also comment? You don't have to just ask questions. You can tell us your opinions, too.

DR. FLICK: Dr. Jevtovic?

DR. JEVTOVIC-TODOROVIC: I just want to pose another question to the sponsors. I'm sorry, Dr. Breitmeyer, you sat down, but do you mind to stand up again? Thank you, sir.

Speaking about efficacy that the chairman would like to go back to, if I understood correctly, when the chairman asked Dr. Walsh whether her sum-up as far as the effectiveness of the drug, in terms of analgesia is concerned, her response was that it was less effective than presently available formulations and yet had the

same risk potential.

Dr. Walsh, am I misspeaking? Is that what you stated? Is that correct? When the chairman summed it up, was that the summation as far as the efficacy is concerned?

DR. WALSH: You're correct that that's how the chairman summed it up. I'm not certain that those are the exact words that I would use. But the point is that, in general, hydrocodone is considered to be less potent than oxycodone on a milligram-per-milligram basis for the treatment of pain. And that's typically how prescribing practices are then carried out, so that you would be prescribing more hydrocodone on a milligram basis. But our data suggests that from an abuse liability standpoint, they're more equivalent to one another on a milligram-to-milligram basis.

DR. JEVTOVIC-TODOROVIC: What was your response to that, as far as the efficacy is concerned?

DR. BREITMEYER: Thank you. Dr. Katz will address your question.

DR. KATZ: This is a potentially very confusing area, and I'm concerned about that because I think that there's been a cloud of misunderstanding that's been created around this problem.

First of all, the question at hand is whether the potency for abuse is different than the potency for pain relief. And there's no way to draw any even remotely close-to-the-data conclusions from the information that we presented here today. The analgesic potency of these compounds is drawn from very old and very unpublished data. There's a lot of literature out there that indicates that, really, nobody knows what the exact potency ratios of these compounds are.

In any case, if we're going to try to draw a conclusion about the relative analgesic versus abuse potency, we really have to test both in the same study rather than extrapolating from one type of data to another. And I'm sure Dr. Walsh would agree that the analgesic potency was not tested in

that particular small study.

So we would have to work a lot harder to try to come to a conclusion like that. It's also not clear that the potency is really what's relevant here. Really, what's relevant is the maximal efficacy, and it's not at all clear that even if we could construct a ratio like that, that it would have anything to do with the clinical versus -- the clinical issue in the marketplace about the relative analgesic versus abuse-related potency.

The final point about this is that we actually do have real-world data. We don't need to stick with just data that we think might in some way predict what's going on in the real world. We heard a whole wonderful presentation about the epidemiology of abuse in the real world.

So I would strongly caution this committee against deriving any conclusions about the relative abuse versus analgesic potency from these bits of data that we're trying to piece together.

DR. FLICK: Dr. Walsh, did you want to comment?

DR. WALSH: I think that it would be laudable to address those questions in the same subjects in the same study. But that's not typically now it's done. And what is important is that what doctors use for prescribing are the recommended equianalgesic tables. I mean, that's what happens in practice, and that's really what my point is.

So what we understand, and how doctors will implement the medication, will be based on the references that they go to, to tell them, is hydromorphone more potent that oxycodone? What are the morphine equivalents? And that's historically how the whole field has operated from the prescribing standpoint.

So whether or not you like the way that the data look, I think that the reality is that that's how it's implemented in practice. So that's my response.

DR. BREITMEYER: Mr. Chairman?

DR. FLICK: Yes?

DR. BREITMEYER: I have a direct comment to

that. I'd like to show the equianalgesic table that is to be printed in the packaging information for Zohydro ER, and I believe is the most common and widely accepted one in use. Slide up, please.

Hydrocodone in the second line, a 20 milligram equianalgesic dose of hydrocodone to oxycodone 20 milligrams. That is a one-to-one correspondence. My interpretation of Dr. Walsh's data was that to achieve the same effect in terms of likeability or other abuse liability-related endpoints, a larger dose of hydrocodone had to be administered in order to achieve the same effect as a lower dose of hydrocodone. And I was puzzled when I was hearing the exchange earlier with Dr. Walsh, that the conclusion would be that it was of a higher addictive potential. The data didn't appear to me to go in that direction.

DR. FLICK: Thank you.

Dr. Walsh, I'll offer you another opportunity to respond to that, if you'd like.

DR. WALSH: I can respond by saying that I'm happy to see the table that they plan to include

because that's one analgesic table that's available. There are a lot of others that aren't identical to that one and that do not suggest that the drugs are equianalgesic. And that's all that I'll say about that.

DR. FLICK: Thank you.

Dr. Zito?

DR. ZITO: Yes. I wanted to clarify study 801's efficacy data, the main outcome measure, as a clinically important difference on a pain score. It's an 11-point scale in which -- a half point reduction difference between favoring the drug versus the placebo. And I'm wondering how we would convince ourselves that that is a clinically meaningful difference.

DR. BREITMEYER: Thank you for that follow-up question. I think that our statistician, Dr. Davis, has taught me that it is challenging and sometimes not the best approach to try to derive clinical meaningfulness from group means. And if you'd like, he's more eloquent on that point than I am. But I'll say a couple of other things first.

If I could have the slide up. One is that our results are not different from this class of Schedule II approved opioid analgesics. And that's shown, I think, most clearly by the fact that the confidence intervals in our meta-analysis all overlap. They wobble here and there, but you'll notice that there is more difference between the same agent studied in more than one trial than there is between our results and the combined results. So study design is a big factor.

Getting out of the statistical arguments, the individual response rates that I showed you are very robust for this product -- 30 percent responders, 50 percent responders. These compare favorably to any response rate figure that you can find for any other opioid. And if I could have the list of other secondary endpoints.

Every efficacy endpoint in this study pointed in the same direction. I think you saw that in the briefing document, and measures of emotional function, physical function. Slide up, please. And so with the exception of anxiety

score, and mine's a little high right now, too, all the secondary endpoints pointed in the same direction. This is how I'm viewing the clinical significance question.

DR. ZITO: May I just add one more point?

DR. BREITMEYER: Of course.

DR. ZITO: The dose range was quite wide, 40 to 200.

DR. BREITMEYER: Yes.

DR. ZITO: And I'm wondering if you segregated or stratified the responses according to moderate versus severe, what would the difference in the response rate be on this primary -- on the primary measure?

DR. BREITMEYER: Yes. No, I understand. I heard two questions. Let me clarify. One had to do with dose, and one had to do with severity.

DR. ZITO: I wasn't quite so much questioning -- well, I was thinking about whether -- I'm thinking about moderate, people who are classified as moderate, versus people who are classified as severe, and whether they have

differences in outcome.

DR. BREITMEYER: Yes.

DR. ZITO: And then, I guess, secondly we could then go on and talk about the dose exposure in each group.

DR. BREITMEYER: Okay. Thank you. We did not analyze the study stratified by categorized pain scores. We did, however, evaluate the primary endpoint by administered dose. And I think that that may -- it's a poor man's surrogate for severity, perhaps. And there was no difference between the patients in the high dose and the low dose in terms of significance of the primary endpoint with similar treatment effect, similar level of significance, whether the patients were above 100 milligrams a day or below 100 milligrams a day of hydrocodone ER.

DR. FLICK: Dr. Hertz, did you have a comment?

DR. HERTZ: Yes. I just need to correct for the record that there is no statement by FDA or anyone else of a 36 percent rate of diversion, even

in the Exalgo trials. That was a number picked off a slide from a former AC used very out of context.

So that 36 percent and whatever your .1 percent were, at the very least were apples and oranges. So just let's not use that in our deliberations here.

DR. BREITMEYER: We have -- I'm totally not trying to be argumentative -- the figure is "missing drug." If I --

DR. HERTZ: Right. But you said "rates of diversion."

DR. BREITMEYER: Then I apologize. It was "missing drug."

DR. HERTZ: And again, there was no evidence of rates of diversion of 36 percent in that study.

DR. BREITMEYER: Absolutely. And I apologize for misspeaking.

DR. FLICK: Dr. Maxwell?

DR. MAXWELL: Nothing.

DR. FLICK: Dr. Kramer?

DR. KRAMER: Yes. On the efficacy question, it appears that the language that's been put into

the question is the standard language that is being applied to all of these extended-release products. Is that right?

I think somewhere in the briefing packet, they said this language would be similar, that it's effective for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extend period of time.

DR. RAPPAPORT: Yes. That's the indication for all the drugs in the class.

DR. KRAMER: Right. So I just want to clarify that this is not an indication-specific term. I mean, this language does not say anything about what you're treating.

So, for instance, the sponsor chose not to study cancer patients, who would be a large number -- there would be a large number of cancer patients who would have this type of chronic pain. But they have presented us no evidence about the effectiveness or even the safety, reliably, from these studies.

I also -- I can't remember what page it's on, but there was an exclusion criteria in 801 that excluded osteoarthritis. So, once again, a very common cause of pain, even traumatic-induced osteoarthritis, we have not studied -- you have not studied or presented to us.

I just want to point out that because I think that's a very -- you're asking us for an approval that will be used much more broadly. You could almost call it off-label because you didn't study it. And I think that's a very important point to make.

DR. FLICK: If I may ask --

DR. KRAMER: Okay. I have one other thing, too, but it's a separate issue.

DR. FLICK: Dr. Rappaport, I just want to make sure that I, at least, understand that the use of this and any other medications in this class of drugs would not be off-label for any pain that is moderate to severe.

DR. RAPPAPORT: That's correct.

DR. FLICK: Thank you.

DR. KRAMER: So also on the efficacy, although it wasn't spoken or presented in the sponsor's presentation, in the packet on page 58 there's a very interesting finding on some of the secondary -- you keep referring to the very positive secondary endpoints.

But I found it very interesting that where you did an analysis, where you looked at the number of people who were very much or completely satisfied with their pain medications, at baseline, it had been 74 percent for the Zohydro ER group. However, at the end of the study it was 54 percent. But the most striking thing is that 35 percent of placebo patients at the end of your 12-week study were either completely satisfied or very much satisfied with their pain relief.

DR. BREITMEYER: So to your earlier comment about osteoarthritis -- and Dr. Rappaport may want to comment about the use of a chronic back pain model for the pivotal efficacy study, which was an agreement between the company and the FDA. However, in study 802, a high percentage of the

patients that were enrolled did suffer from osteoarthritis. So we certainly have safety data in patients with osteoarthritis.

The placebo effect is substantial, and this is known in this space. Patients who enter these studies with very high pain scores at baseline or at the time of study entry, and in all of the long-acting opioid studies, people make it to the end of the study. And they make it to the end of the study with surprisingly low pain scores, surprisingly low secondary endpoints. You see this with all these agents.

The speculation is that there is a very strong study effect, but also a lot of these people have been struggling on their own, as you heard some of the public commentators, at home without any support. And they come into a pain specialty center, and they're getting a lot of ancillary benefit. Of course, both arms on the study are, so this doesn't introduce any bias into the results.

But I think that the common wisdom in this area is that there is always a substantial placebo

effect. We didn't feel that ours was any different than the rest of the class.

DR. RAPPAPORT: Yes. Can I comment on these two things? First of all, the last statement was correct. We see this 40 percent, approximately, in almost all of these opioid chronic use studies. And we could all speculate on what it's caused by; we're actually trying to understand that with some studies that we're collaborating with some private sector people on right now to try to understand that. But it's been a problem in those trials because it's hard to tease out what's the placebo effect and what's the real effect.

We allowed them to do the single indication, the single patient population, to get this broad indication. And we have done that consistently with any reformulated opioids, old opioids. And there's a long set of deliberations that we went through in making that decision. It was a balance between getting adequate study design and studies that were feasible, and studies that would actually demonstrate an effect in drugs we knew were

effective. But because of study design issues, because of noise in the background, we were having trouble showing that effect.

So it's not unusual, and this is no different than the standard that we've held any other company that's come in with a new set. If people want to add other -- more than one population into their study populations, we won't say you can't do that. But most people have not, and we've allowed that. And we hope that we'll get additional efficacy information out of the long-term safety where they have more of a mixed population. Obviously, that's not quite as good.

The issue that's been brought up of long-term efficacy is something we're working on, trying to understand right now. And one more thing, and then I'll let you follow-up. One thing we do not do is allow people to promote beyond -- allow companies to promote beyond the studies that they have done. So what's in the label in the clinical study section is the study that they did and the patient population they studied.

So when they go out and talk to doctors, they have to say it was studied in low back pain, and they have to acknowledge that it was not studied in all those other patients you've been asking about.

DR. KRAMER: I think the thing that's troubling me, and I know there's probably not an answer to this question, is that the patients that we're talking about have tried all the other alternatives. And the decision's been made that they need an opioid alone, a sustained-release opioid, which is really -- and the average age of this group, this could be a prescription for life, I mean, if they have a cause of pain that is unremitting and is unlikely to be cured.

The question of what's effective is much greater than that they have a score at the end of 12 weeks in a very limited, controlled experiment that somehow was a little bit better than a placebo group.

I know it's philosophical, almost. I understand the requirement to have everyone use the

same criteria based on clinical trial methodology, et cetera, in trials that are doable. But the fundamental question actually blurs the issue between efficacy and safety because I would argue that the number of articles that have been, just recently in the last couple of years, published about what are we doing with treatment of chronic pain, are we really, in the long run, helping people, or are we creating an epidemic?

There's one I ran across that the title of it -- well, I can't get it up right now, but is something like -- it was a patient-oriented physician who wrote an article in Archives of Internal Medicine that says, "A Believer Losing His Faith," in terms of starting out wanting to help people to treat pain, and in the end wondering if he's done more harm than good. So it's very hard to evaluate effectiveness here in this setting.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Yes. I would like the sponsor to give us greater insight into the longitudinal data of the effectiveness of Zohydro ER over

52-plus weeks because we know that the treatment of chronic pain can be extensive and can go on for an extensive length of time. So I wanted to have the sponsor review that information with me, that data with me.

DR. BREITMEYER: Thank you. I'd be happy to do so. I showed you the pain intensity over time. Let me give you a little bit more information about that.

Slide up, please. So these are the same pain data. But if you're interested in a little more detail, this also shows the number of study subjects that were evaluated at each time point.

This rate of retention is a particularly robust one. And what I mean by that is that patients did well in the study and stayed in the study. And so I believe we have a comparison. No, it's the -- yes, it is. Slide up, please.

So this is a comparative graph of the likelihood of subjects completing one year open label studies. The green bar, our product, 67 percent, is higher than most. And so this is an

indirect indication. But time to exit is something that people in this field view as one indication of effectiveness.

MR. MULLINS: I guess what I'm looking for is the greatest stratification on subpopulation. Effective for whom? I mean, so I need to understand --

DR. BREITMEYER: Yes.

MR. MULLINS: -- in order to answer that question accurately, who it benefits the most, who is this treatment effective for. I need to understand, were there any comorbidities with this group? The demographics. I don't see anything to speak to that issue.

DR. BREITMEYER: I think as in selecting patients who you can predict in advance will respond --

MR. MULLINS: No. I'm not saying that. I just want to see the profile of the patients that were in the study -- the profile, comorbidities, that's all. Because we know -- because I'm particularly concerned about subpopulations such as

we know that this therapy -- oxycodone is prescribed for persons with respiratory illness.

So I'm curious the effectiveness of this treatment for persons with COPD, for example. So I'd like for you to give me greater detail so we can answer this question effectively.

DR. BREITMEYER: Right. No, thank you for clarifying. I appreciate that. So I can't answer down -- I can't drill down to that level of detail. I can say that the study outcomes were examined by gender, by age, age categories, by race, and there were no differences in those categorizations.

MR. MULLINS: Then can I see that? Can we see the data by race and gender? Can we see that?

DR. BREITMEYER: We don't have it on a slide. I'm sorry.

DR. FLICK: I think we'll move on to our last question in this prior to our vote.

Dr. Maxwell?

DR. MAXWELL: Yes. Can we go back to the next-to-last slide that was up?

DR. BREITMEYER: Bar graph?

DR. MAXWELL: The one before the bar graph.

DR. BREITMEYER: The pain results over time?

DR. MAXWELL: Well, pull up the last slide and then go back one.

DR. BREITMEYER: Okay. We don't organize it that way. I'm sorry. Is this --

DR. MAXWELL: All right. My question to you is -- and this is probably a typo, but this was not the day for typos -- how come we go from 292 patients to 391 at the end?

DR. BREITMEYER: Because the prespecified way of looking at pain in this study included putting the early terminators into the last visit.

DR. MAXWELL: So the early terminators are getting counted as 340 days?

DR. BREITMEYER: Yes. For the pain endpoint, yes.

DR. MAXWELL: Okay.

DR. FLICK: If there is no further discussion on this question, we will now begin the voting process. Please press the button on your

microphone that corresponds to your vote. You will have approximately 20 seconds to vote.

Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before your vote is closed.

(Vote taken.)

DR. FLICK: Everyone has voted. The vote is now complete.

DR. BAUTISTA: I will now read the vote into the record: 7 yeses, 6 noes, 1 abstention.

DR. FLICK: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and reason they voted as they did into the record.

Dr. Leff?

DR. LEFF: I don't vote.

DR. FLICK: My apologies.

Dr. Denisco?

DR. DENISCO: Richard Denisco. Vote was yes. I felt that the one study that was shown,

there's no difference in giving this medication with or without acetaminophen that I could envision. And we could look at the studies upside down and it's not going to show a difference.

It's going to have the same effect that hydrocodone does with acetaminophen. And we know from perhaps not adequate studies, but we know by long history of clinical impression that it is an effective medication.

DR. FLICK: Dr. Rosenberg?

DR. ROSENBERG: Yes. I thought that the applicant demonstrated effectiveness given the caveats about chronic opiate therapy in general.

DR. FLICK: Dr. Kaye?

DR. KAYE: I voted yes. I believe that that is the correct answer to question 1.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Yes. I voted no because I felt that there was insufficient evidence on the details of the effectiveness of the treatment for the study population.

I felt like the sponsor could not respond to

particular questions on details, the effectiveness for the study group. So I felt like we had limited data, and particularly, limited data on the usage of Zohydro ER over an extended period of time. And that was my question on effectiveness over an extended period of time, effectiveness within the study population with greater detail.

DR. FLICK: Ms. Gravois?

MS. GRAVOIS: I have to apologize. It says no but I thought I hit yes.

DR. FLICK: Bob, how does the vote get recorded, then?

DR. BAUTISTA: We'll just note it for the record. That's all we can do.

MS. GRAVOIS: I believe the effectiveness was shown.

DR. FLICK: Dr. Ware?

DR. WARE: I voted yes. I thought the body of evidence submitted in this application was modest, but I thought the responder analysis was helpful. And I thought there was a larger body of evidence about the efficacy of the combination

product. So I concluded that it is effective.

DR. FLICK: Dr. Wesselman?

DR. WESSELMAN: I voted yes because I was convinced by the data regarding the efficacy. But I look forward, actually, to the next question because I'm worried about the safety for different patient populations.

DR. FLICK: Dr. Ware, can you turn off your microphone for me, please?

Dr. Jevtovic-Todorovic?

DR. JEVTOVIC-TODOROVIC: I voted no because I'm not convinced that this is an effective treatment for chronic pain, which is what we are talking about today. I don't think that follow-up for 360 days would convince me that this is a true chronic pain management.

Listening to our speakers from the public side, we realize that these patients have been on different medications for years. So I would like to see data that are longer than a year before I would say that truly it is effective.

DR. FLICK: Dr. Ramsay?

DR. RAMSAY: I voted yes because the studies that were presented were developed in consultation with the FDA. They followed standard techniques. They were compared to other similar studies of similar drugs, and met the same successful endpoints. So I think the effectiveness was shown.

DR. FLICK: Dr. Kramer?

DR. KRAMER: So I knowingly pressed the abstain button in a moment of complete dilemma as to how to vote, and I probably should have pressed no. My reason for the confusion or the concern about what to say here is that I don't believe that the 12-week study does give us indication that this is effective in the long term.

I think that the fact that, in fact, compared to baseline, the treated group was worse at the end of the study but not quite as bad as the placebo group is worrisome because that's just 12 weeks. And this is really -- once we write these prescriptions, people stay on this much longer than that.

So I'm not sure that in the long run, if we

looked at all of the effects on people's lives, that this would be an effective treatment for patients.

DR. FLICK: Dr. Perrone?

DR. PERRONE: I voted no. I was concerned that there's a very modest change in the pain scores. With a lot of methodologic reworking, it is convincing as a study, but not that convincing, I think, when you look at it in the picture of effectiveness. I have my doubts.

DR. FLICK: Dr. Zito?

DR. ZITO: I voted no, for the reason that I presented earlier to the manufacturer, that I don't see that clinically significant difference that I think could impact effectively in practice; and also that the second study, where the longer-term work was done didn't really address -- does not address effectiveness. So that's the reason.

DR. FLICK: Dr. Maxwell?

DR. MAXWELL: I voted no because I don't think that the effectiveness has really been proved for a long-term, more than 60-day, study.

DR. FLICK: I voted yes. I think the sponsor has met the burden of demonstrating that a medication that's long been in use in a different formulation has similar characteristics in this formulation.

The next task I have is to summarize the comments that surround this question. And I would summarize the discussion here as the committee has significant concerns about the efficacy; does not unanimously believe that the sponsor has demonstrated clearly the efficacy of the drug.

However, the weight of the evidence would seem to suggest that this is indeed efficacious, especially in light of the long history of use of this particular medication.

We'll move on to the second question, and we'll go ahead and take questions and comments regarding question number 2.

Dr. Perrone?

DR. PERRONE: I had a question earlier of the information about the adverse effects, specifically the deaths, in the 802 study. There

were five deaths that were described. Arguably, three of the deaths occurred in the setting of some kind of depression or substance abuse.

I was wondering if you had screened those patients prior to entering the study for those kinds of risk factors or whether or not those things developed in the study, and how you would propose that primary care doctors or prescribers would be able to offset those results in their own prescribing.

DR. BREITMEYER: Yes. We did screen, and there were two forms of screening at study entry. One was a direct question to the patient about any history of a major depressive disorder. The second one was to apply the HADS score at baseline. And if I could have the slide up.

The criterion that was used was a score greater than 12 in either depression or anxiety was an exclusion criteria. The patient who committed suicide well after the study, like all the patients in the study, had had scores tested periodically over the course of his experience in study 802, and

it wobbled up and down a little bit.

But there was no -- first of all, the study staff who interviewed him had no indication of concern about exacerbating a depressive disorder while he was on study. And the scores wobbled but didn't spike and didn't -- I think there was one at 13 that wasn't a criterion to go off the study.

They watched him more closely. It settled right back down at the next visit. Of course, the episode that led to his suicide was 13 months later.

So as to recommendation for use in primary care, we are -- thank you. Patients were also screened for substance abuse, either a history or with urine screening, being in the study, I'm reminded.

There's an unfortunate linkage between opioid abuse and suicide. And that will be an important part of the training that we do. It will be an important part of the training that NAVIPPRO will be doing -- through us, that NAVIPPRO will be doing for both patients and practitioners.

We believe that anyone that treats with opioids, whatever kind of specialty they're in, needs to be constantly alert for any interaction between the medications and the patient's state of mind.

DR. PERRONE: Can I just make a point here? How much time did you spend with these patients on each visit?

DR. BREITMEYER: Yes. Dr. Rauck was an investigator on the study. I think he may be the best positioned to describe that.

DR. RAUCK: Certainly there's a fair bit of time spent on the visits, and it's spent by different people with them. So most of the visits would exceed an hour. Sometimes it's less if it's a routine visit with them. But certainly, between getting their case report form data and the other data, it is a substantial amount of time at each visit.

DR. PERRONE: So I commend you for spending that much time with the patients. Despite that and despite all the screening that you did, you still

have a 1 percent, almost, death rate from this drug if you go down to the 250 patients and the two or three deaths that we would try to have screened for.

How could you relate that to a primary care practice, where they would never have the ability to screen at that level, even to obtain the results that you've obtained?

DR. RAUCK: Yes. Your point's well made. And the problem, a little bit, exceeds in the complete chronic pain population and, as you know with cognitively active drugs, not just opioids but other types of cognitively active drugs, and compiled issues with suicide and suicidality.

So chronic pain often leads itself to suicide, and certainly untreated pain does as well. So it's a problem, there's no question. But it's part of what we have to deal with as clinicians. Certainly, even after 26 years, we're not always successful in preventing that or recognizing it as well during screening processes in clinical trials or in practice.

DR. PERRONE: Thank you.

DR. FLICK: Dr. Kramer?

DR. KRAMER: So I have questions about how the sponsor described the safe marketing practices that you're planning on instituting if this drug is approved. And there's two components. One has to do with the incentives for your sales professionals, and the other has to do with your plan to limit the launch.

On page 92 of the briefing packet that we had, in describing the fact that there are 330,000 opioid prescribers, you talked about targeting to 15 percent of those prescribers. And in the course of that, you also said, and I quote -- I think in your presentation this morning you said the sales representatives would be given incentives just for education in the first year.

But in this packet, it says, "The Zogenix sales representatives will not be compensated" -- oh, wait a second. Excuse me. "The sales-related portion of their incentive compensation will be capped and will be based only

on prescriptions written by this approved group of prescribers."

That seems to imply to me that they will receive financial incentives for every prescription written by these prescribers. Is that correct?

DR. BREITMEYER: Well, thank you for pointing that out. The decision to go to 100 percent compensation for education was made --

DR. KRAMER: For one year?

DR. BREITMEYER: For the first year, possibly longer. But --

DR. KRAMER: Let's talk about the second year.

DR. BREITMEYER: But our initial commitment is for one year. It was made after the briefing document shipped, as we thought about what we could do in this very complicated -- in the midst of this complicated public health crisis.

DR. KRAMER: Okay. For the second year. Let's talk about year 2.

DR. BREITMEYER: So Dr. Farr can address that.

DR. FARR: Yes. We will certainly continue the incentive around education in the second year. I think what we want to try and do is really start to pilot things and see if they make a difference towards pushing education to the physicians.

With respect to will the sales reps be compensated one day on prescriptions in their prescriber audience, the answer to that is, yes, they will be. They will not be compensated on prescriptions that are outside their target audience.

DR. KRAMER: Okay. So I want to talk about, then, your marketing plan. So you talk about limiting by this DEA quota and limiting the manufacturing.

DR. FARR: Yes.

DR. KRAMER: But how does this play out? If this is approved, any physician who's licensed to prescribe narcotics could prescribe this drug.

Are you telling me that you wouldn't fill a prescription from a community practitioner, a primary care doctor, even if they would want to

refer their patients to pain specialists, they lived in a community where there aren't pain specialists receiving referrals from primary care doctors?

DR. FARR: Well, what we've done in looking at our target list is really identify the doctors that we know today are really treating patients with chronic pain and are highly experienced in the use of extended-release opioids. We see that as the obvious place to go.

We have a surveillance system in place that will really look at who else is prescribing the product. We have weekly prescription data that we'll be able to analyze per physician and really see who else is prescribing.

If we see a signal of prescribing outside of our target audience, we will certainly investigate that. And the way we would do that is, first, we would send our information to that physician. We would ensure that we'd follow up with a call from our medical affairs group, just to establish whether or not that physician understands how to

use Zohydro, the intended use of the product.

If the answer to that is yes, then of course we hope that the materials that we provide him would be helpful -- him or her -- would be helpful, and also, they would get access to the NAVIPPRO tools that I mentioned earlier.

DR. KRAMER: I'm having a problem because the FDA materials that talked about use patterns in this country show a very large percentage of opioid prescriptions coming from primary care specialists.

I understand that the longer-term supplies were more likely to come from pain specialists. But there is a vast part of this country where primary care specialists are the ones seeing these patients with chronic pain. And it seems like you're saying that you'll target all of your efforts on pain specialists who might be the most knowledgeable --

DR. FARR: Right.

DR. KRAMER: -- and that those primary care doctors who might need the education or might need the help are going to be left aside and scrutinized

as to whether they should be able to prescribe it, once again left with the dilemma of how do they treat these patients in their office.

It's really a problem. Their medical boards are looking at them very carefully as to whether they're using the drugs correctly, and you're going to the pain specialists. So I'm having a hard time understanding how this is going to help the epidemic.

DR. FARR: Let's see if this slide starts to address your question. Slide up, please.

So this is really the makeup of our target list for prescribers that we feel would be appropriate prescribers for our product. And you can see there are primary care physicians there. And we do acknowledge that primary care physicians do see a lot of chronic pain patients, and a lot of them adequately treat chronic pain. So they are certainly part of our call list. So it's not just pain specialists.

DR. KRAMER: Your briefing document says, "Other product promotional efforts will focus

exclusively on scientific meetings and media dedicated to pain management. General primary care congresses and journals will not be part of the promotional strategy."

DR. FARR: That's correct. But I don't think it changes the fact that we have primary care physicians on our call list because these physicians are attending such conferences. They are experienced in the treatment of chronic pain.

DR. BREITMEYER: If I could add something, Dr. Kramer, we agree absolutely that the misuse and misunderstanding about hydrocodone itself probably resides out in this larger arena of Vicodin writers, if you will. And we are -- I'm not sure how to put this.

I think that there's a very wide-held belief that excessive enthusiasm in marketing for general practitioners may have had something to do with the excessive use of extended-release oxycodone products in the past. And we're acutely aware that we -- we're taking a position at the beginning that we will in no way replicate that mistake of the

past.

You're describing an unintended consequence of that policy, which we thought about. And so for the broader audience, the first coverage is that everybody -- slide up -- everybody gets REMS materials. And so we're supportive and enthusiastic about the REMS program itself. We've joined the consortium. Everybody will get the REMS materials. And they're already getting some of the Inflexxion tools.

Then when somebody starts to use our drug, we identify them through our weekly prescriber database, and then they get more attention and more teaching and more training.

If I could have the diagonal response slide? And at that point, we also are committed to making a specific assessment about whether that uptick in behavior is appropriate or inappropriate prescribing. We think that this is a critical moment in the introduction of this product.

Slide up. So everyone will have gotten the core materials. Then when someone writes more than

a handful of prescriptions -- we're going to have a low trigger here -- they will get, first of all, a notification letter. If they're an inappropriate prescriber, they're going to know in their mailbox that someone is watching their behavior. We think that's a very important initial intervention. They'll also get a call from medical affairs, a specific request whether they need more training, more information.

Then, if in the course of assessing that prescribing behavior we find evidence of any signal, any suspicion, around inappropriate prescribing, the bottom half of the slide kicks in, an in-person visit from one of our medical affairs professionals and, as appropriate, actions up to and including reporting to DEA.

So I hope that was a little closer to your concern.

DR. KRAMER: If you're concerned about that accusation in the past, I think the simplest thing would be to not have financial incentives, counting the number of prescriptions your sales

representatives get people to prescribe.

DR. BREITMEYER: Yes.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Yes.

DR. BREITMEYER: Our incentives will be capped, which was -- and off-target prescribing will not be compensated. But I take your point. Thank you.

MR. MULLINS: I have three quick questions. One, if a salesperson encountered someone that called in, a dentist that called in and wanted to purchase this drug, would you say no? My first question.

DR. BREITMEYER: Yes, we would.

MR. MULLINS: Okay. So you're going to refuse sales for everyone that's not on your approved list.

Secondly, do you have additional data on the neurological impacts of Zohydro ER?

DR. BREITMEYER: Could you clarify the question, please?

MR. MULLINS: Do you have additional -- on

slide CO-30, we saw that there was some adverse effects as far as headaches and anxiety and some other issues. But we know in postmarketing analysis of opioids that there are hallucinations as one of the adverse effects. We have severe -- some mental fogginess.

So I'm curious. In looking at the data, postmarketing analysis of other opioids suggests neurological impacts. So I'm just wondering why we didn't see too much of that in study 802.

DR. BREITMEYER: No. Great question. It didn't make the briefing document because the numbers are low. When we looked at the overall integrated safety population, there were two cases of euphoric mood, one auditory hallucination, three altered moods, four cognitive disorders, six sedation.

MR. MULLINS: Okay. And my additional question was, do you have a sample of your proposed packaging for this product?

DR. BREITMEYER: Do we have a sample with us? I don't know the answer to that. No? No.

DR. FLICK: Dr. Hertz, did you have a comment?

DR. HERTZ: Yes. I want to clarify something. It's sort of bouncing around a little bit.

This product is not typically sold to physicians for dispensing. It's typically dispensed through pharmacies. Right now, there is nothing in place for any patient with a legitimate prescription who arrives at the pharmacy to have that prescription filled.

So there's no restricted distribution plan in place for this. So anyone who is written a scrip, prescribed the drug with a valid DEA holder/registrant, will be able to have a prescription filled by a pharmacy. Okay? Just to clarify that piece.

DR. FLICK: Can I follow up? The sponsor tells us that DEA gives them a certain allotment. Does FDA have any input into that allotment? And how does that work? And can the committee be reassured that that allotment is as it's described

and won't change?

DR. KLEIN: Michael Klein, controlled substance staff. We make a recommendation annually, based on estimates of medical need, that provides information to DEA on setting an aggregate for the United States for how much drug is needed.

As far as how DEA parses out the aggregate to the individual companies, that's work that's done strictly between DEA and the company. So we don't know the details of those transactions.

DR. FLICK: Let me make sure that I and we understand that. When you say the amount of drug is determined, we're talking about the amount of hydrocodone, which may be used to make immediate-release or sustained-release?

DR. KLEIN: Yes. The aggregate of the active pharmaceutical ingredient needed in the United States. But the amount that each individual company needs for its own individual products is a transaction that's worked on only between DEA and the companies.

DR. FLICK: So I think what each one of us, or at least certainly I, would like to understand is that the sponsor will get what they have described as their allotment, and that allotment is determined by DEA.

DR. KLEIN: That's correct.

DR. FLICK: And we can be reassured that that allotment will stay as described by the sponsor?

DR. KLEIN: No. There are a lot if issues that go into the parsing out of each procurement quota for each company. And we don't know all the issues, the capacity issues, of all of the manufacturers. We don't know any sort of problems they might have in the future with recalls. We also don't know how much drug they have had on hand in the past, which is going to impact current quotas as well as future quotas as well.

DR. FLICK: Does the sponsor want to respond to any of those comments?

DR. BREITMEYER: Yes. Thank you. Slide up.

So our understanding, based on our

discussions with DEA, is that we have a firm and immutable quota, and that on a yearly basis, we apply for a quota for the next year.

Our understanding is that -- practice is that quotas won't rise more than 20 percent per year. And if we exceed our quota, we are at risk of a substantial legal remedy.

DR. FLICK: Dr. Maxwell?

DR. MAXWELL: Yes. This raises another question. Dr. Klein, does this mean that if this drug is approved, that DEA will increase the overall amount of hydrocodone available? Or does this come out of -- in other words --

DR. KLEIN: I can't answer yes or no to that question. I can't say that with a new NDA being approved, DEA will certainly figure it into their calculations.

DR. MAXWELL: Okay. Well, I was just trying to figure out if this means there'll be more hydrocodone going out just because of this, and we may not know the answer.

One other thing I do want to point out,

you've discussed private physicians and the marketing. But I want to remind us all of the diversion, the fact that we just saw CVS chain in Florida shut down because they were not following good practices. It took forever to get DEA to close them down.

In Texas, I have six pain clinics that in a 15-month period wrote between almost 24,000 and 43,000 scrips in a 15-month period. Those guys are still in operation.

So we need to be very aware that these people who are into making the money, just because you call DEA doesn't mean things are going to happen quickly. So it just muddies and muddles this picture.

DR. BREITMEYER: Yes. Understood. And we're well aware of those concerns.

If I could have slide up. So our action -- so this is our algorithm for distribution. And if there is -- our wholesalers have their own systems for suspicious hoarder behavior. And we get that on a weekly basis.

If there's a signal, it goes to our trade relations department. In parallel, we get raw data. It's 867 data; that's just what they call it, these forms that come in about prescribing information.

What our actions are is that we report to DEA. But we will stay on top of it, and we will stay on top of DEA. And we're making a commitment to cease distribution to that organization if have -- if we feel that we have reached a level of evidence, we're not going to wait for DEA, and we will cut that distribution entity out of the supply chain.

DR. FLICK: Dr. Rappaport?

DR. RAPPAPORT: In the interest of time, this discussion is very interesting, but I think it applies to the next three questions and not this one. This question, the last clause in there is "for the intended population," is it safe for the intended population. I just wanted to remind everybody of that.

DR. FLICK: Thank you.

We have about five minutes before a break. I would like to move toward a vote. Are there other comments that you would like to make before we move to that vote? Dr. Rosenberg?

DR. ROSENBERG: Yes. This is for Dr. Rappaport. Is the intended population to be specifically for the patients that it's prescribed? Or are we talking about the patient and their family?

DR. RAPPAPORT: No. The intended population is the person who it was prescribed for.

DR. FLICK: Dr. Denisco?

DR. DENISCO: And is this intended for the patient it's prescribed for and as prescribed? Or are we allowing that the patient who it was prescribed for may well start to get into diverting in levels higher than we saw on our studies?

DR. RAPPAPORT: Well, that's a difficult one. I would say for the intended patient, the intended population, misuse is an issue you should be considering here. Will patients misuse this? Because there are aspects of this formulation that

will lead them to misuse it. But if they divert it, it's really not a problem for the intended patient.

DR. FLICK: Additional questions or comments?

(No response.)

DR. FLICK: We'll move to a vote. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote.

Please press the button firmly. After you have made the selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button before the vote it closed.

(Vote taken.)

DR. FLICK: Everyone has voted. The vote is now complete. The DFO will read the vote into the record from the screen.

DR. BAUTISTA: 5 yeses, 9 noes, zero abstentions.

DR. FLICK: Now that the vote is complete,

we will go around the table and have everyone who voted state their name, vote, and reason they voted as they did into the record.

Dr. Denisco?

DR. DENISCO: Yes. This is Richard Denisco. I voted yes. I believe the sponsor provided adequate evidence that it was safe if used as directed in the intended population.

DR. ROSENBERG: Rosenberg. I believe that they've demonstrated that this medicine, if it's given to the chronic pain patient, will be safe in the same way that the current products are.

DR. KAYE: Dr. Kaye. I voted no. I happen to live in the real world, and I would think that the study population is very different than the real world population. And as such, I certainly feel there would be quite a bit of morbidity and mortality that would result. Thank you.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Yes. I voted no, for a couple of reasons. One, I felt like the sponsor did not assure me, from a public health perspective -- and

that's the area I want to deal in -- from the person that is receiving this prescription.

I think there are a lot of safety signals, and one -- my characterization of the packaging issue was for tamper resistance because a lot of the problems with safety are unintended use by a person that was not prescribed that drug.

The sponsor did not offer any remedies to address the issue of limiting unintended use. So that concerned me. They didn't offer any suggestion on how they would limit use to only the prescribed patient or subject. There was not even a prototype given to this body.

My other issue is that with a drug this highly addictive, we certainly have neurological impacts, and we should have studies from a neurological standpoint. There were no studies. We know opioids are highly addictive, with neurological impacts. And so I didn't see enough details to address that issue.

I also wanted to see greater detail of -- the question is, are all populations -- are

some populations more at risk than others? The sponsor didn't tell me who was at risk with this drug, does everyone share the same level of vulnerability,

So there were a number of questions that I had about the safety issue --

DR. FLICK: Ms. Gravois?

MR. MULLINS: -- so they led me to that response.

MS. GRAVOIS: I voted yes.

DR. FLICK: Your microphone, please.

MS. GRAVOIS: I voted yes. The intended population would be patients with chronic pain. And I believe, if it's used as prescribed for chronic pain patients, it would be safe.

DR. FLICK: Dr. Ware?

DR. WARE: I voted no. I first would like to say I'm unhappy about the question. I think asking whether the drug is safe is a standard that a lot of approved drugs wouldn't meet. So I interpreted it as, is the safety profile acceptable?

I thought even from that point of view I had concerns. Number one, the question does not specify "when used as intended," so I took the question really to mean, is it safe to prescribe this drug and to have patients begin using this drug? And in that context there are at least two areas of risk that are pretty significant, one in terms of long-term psychological risks, and second is the risks of addiction.

So I think one can ask whether there's an acceptable risk profile, but I don't believe that one can conclude the drug is safe.

DR. FLICK: Dr. Wesselman?

DR. WESSELMAN: Yes. Ursula Wesselman. I voted no because I'm concerned about the safety. In addition to reasons that the others have mentioned, I'm worried about the long-term effects on immune suppression in populations that are likely to use these drugs, the cancer population and the HIV population, because there are more data coming out now showing that opioids, at least in the cancer population, will result in recurrence.

There have been enough data shown in breast cancer patients. But in colon cancer patients, it did not show up, so I think we need a lot more data.

DR. FLICK: Dr. Jevtovic?

DR. JEVTOVIC-TODOROVIC: I voted no because the intended population is just as susceptible to adverse side effects as unintended population. And the majority of that, that we encounter, are actually from prescribed medications just like the one we are hearing about today. So the answer is no.

DR. FLICK: Dr. Ramsay?

DR. RAMSAY: I voted yes because I believe that the study -- that 802 documented a similar adverse event profile to other similar drugs, and that it was safe in the population for whom it was prescribed. And I think there's a real difference between this question and the next question, where I'm much more concerned. But I do think that, according to standards, it was reasonably safe.

DR. FLICK: Dr. Kramer?

DR. KRAMER: I voted no. In a way, it's striking me, as I'm listening to people give their reasons, that this drug is, in a way, held to a lower standard because of all the other drugs that we've accepted this kind of profile on and have the history that we have with their approval.

This drug will almost certainly cause dependence in the people that are intended to take it. And the consequences of taking chronic, very long-term, longer than 12 weeks, of this type of medication are not very well studied in terms of the kinds of testimonials we heard today from the public hearing, but the effect on operating machinery, on driving, clearly, high abuse liability.

Then the non-deterrent formulation I think is particularly worrisome because of the very high doses that are contained in an individual tablet, and the potential of abuse from family members and others.

DR. FLICK: Dr. Perrone?

DR. PERRONE: I voted no. I think the study

population -- they didn't demonstrate safety in the study population in the ideal world of being able to monitor for risks and risk assessment. And I think translating that to even an intended population of prescribed patients is substantially risky.

DR. FLICK: Dr. Zito?

DR. ZITO: I voted no, in part for many of the comments that have already occurred, but in particular because I'm disappointed that the independent Safe Use Board, which would have the potential, if it truly was independent -- it could have the potential to really do serious oversight of the population.

But I just didn't hear anything about the authority that the group would have other than to pass along their concerns. And in the absence of really solid epidemiologic data to monitor the use, I think it's a rather weak role.

The second point I would make is that I'm thinking about physicians who would refuse to have salespeople come in on a regular basis because of

time. Time is always a big constraint in clinical care today.

So you don't have a restricted policy here. And yet you're promising that this is going to stay in a very small, targeted, appropriate population, which sounds very appealing. But then I don't understand how it's going to work in practical terms if every physician in the country is entitled to ignore you, your program, and prescribe the drug as they choose.

DR. FLICK: Dr. Maxwell?

DR. MAXWELL: I voted no, for two reasons. One, I have the data on the number of people coming into treatment in Texas with a primary problem with hydrocodone. So clearly, people get addicted and end up in treatment. And number two, there are too many deaths already.

DR. FLICK: Dr. Rappaport?

DR. RAPPAPORT: Why don't you -- you haven't commented on your vote. And then I'd just like to make a comment before the break.

DR. FLICK: I voted yes. I believe that the

sponsor has met the requirement to demonstrate that this application meets the regulatory standard of being safe in the intended population. I share the concerns of those who voted no.

DR. RAPPAPORT: So because of the regulatory issues that I brought up both in my opening comments and in the charge, it would be very helpful to us -- and I'm basically going to direct this to you, Dr. Flick -- if you would consider asking as a transition to the next question, which I think it would be a good segue after the break, for the people who said that they had not demonstrated safety in the intended population, whether you feel that it is equivalent -- that the level of risk, is equivalent to the other drugs in this class, or there's something different.

We need to understand, and I keep trying to get that out of you. Is there something different about this product than the other extended-release long-acting opioids? That would be very helpful to us.

DR. FLICK: So I think, if I may take the

liberty, Dr. Rappaport, the question here is that the sponsor expects a level playing field, and that this application represents another member of a class of drugs. And in order for the agency to address the issues that we raise here, we must be specific in what is different about this drug than the other members of that class.

So I think we'll open discussion on that point. Dr. Rappaport, have I summarized it reasonably well?

DR. RAPPAPORT: Yes. What is different? Or, if it's not different, if it's all the same, should we be doing more with the class?

DR. FLICK: So with that in mind, we'll open for discussion -- well, I apologize. It is past 3:30, and we have a break scheduled at 3:30. So we'll now take -- instead of 15 minutes, can I ask that we take 10 minutes, and come back at 10 minutes before 4:00? Thank you. Please, no discussion.

(Whereupon, a brief recess was taken.)

DR. FLICK: Please, everyone, take your

seats. I think we'll get started. Could I have the discussion question, please? Thank you.

The chair recognizes that this is a challenging question, or series of questions, before the committee. I would like to ask a couple of favors.

One favor is, please do your best to address the question at hand and to keep your responses as concise and succinct as possible because we have a lot of ground to cover and relatively little time to do that.

One of the important considerations we have before us is recognition that this Zohydro ER is a member of a class of drugs, and we are being asked to very clearly define why this drug is different than the rest of the class of drugs, if indeed it is different.

So with those things in mind, we'll move to question number 3 for discussion. This is not for vote. Do I have folks who -- we'll move to discussion. Dr. Denisco?

DR. DENISCO: In this question 3, the

postmarketing experience associated with other approved Schedule II extended-release opioids, a little clarification. Is that postmarketing experience with those that have abuse resistance, or just as they came out? In other words, am I comparing this to oxycodone pre-2010?

DR. RAPPAPORT: So I guess the important comparison is to the non-abuse-deterrent formulations because this is non-abuse-deterrent. You can comment on the abuse-deterrent formulations as well. But what we're trying to get at is there's a group of products that are out there and approved, and is this different from those?

So it's both, but I think the primary comparison is with the non-abuse-deterrent. And then you could also feel free to bring in the others and how that impacts any decisions we should make.

DR. DENISCO: I'll just follow up, then. Thank you for the clarification, Dr. Rappaport. I'll follow up that I believe that this would be the same as any of the other Schedule II extended-

release opioids.

However, I believe that we have the ability -- I learned a little bit about what you mix these active ingredients with. I took the time to do that on another meeting. And the excipients are what you mix it with. They're very inexpensive. You can order 50-gallon drums from China for what you have in your pocket change.

Why that isn't being done for this Zohydro, I don't understand. I can't understand it at all. All this exotic marketing -- we're going to tell physicians that they can't market even though only the state that they practice in can tell them that, or the United States Congress.

So I don't think a pharmaceutical can tell a physician that they cannot market or write a prescription for their magic pills. So, number one, I have a problem that that's going to be any advantage by not marketing to general practitioners because they can write a prescription. It is valid. Unless they change the state law --

DR. FLICK: Dr. Denisco, I'm going to just ask that we move on.

DR. DENISCO: I'm sorry.

DR. FLICK: I appreciate it. And I apologize for breaking in. But we really have to allow as many people as possible.

Dr. Wesselman?

DR. DENISCO: Thank you.

DR. WESSELMAN: Yes. I don't think that the abuse potential of this drug as compared to the ones that are out on the market is different, based on the data that were presented to us.

But unfortunately, the playing field has changed since the studies that were done to convince the FDA of this drug. So the playing field is different in the way that there is a lot more abuse now of these drugs that are originally written as pain prescriptions.

I think that is a concern, although there are now some mechanisms, some new mechanisms, in place to prevent abuse. But I am not convinced that those are good enough. We probably need to go

a little bit further.

DR. FLICK: Dr. Ramsay?

DR. RAMSAY: I would just say that the way that I put this together is that there's potentially a large amount of drug in these pills, up to 50 milligrams, with no additional deterrent for somebody who wants to try to extract the drug.

It's the best-known and widely abused of the oral opioids. So it's likely to be the choice of illegal use. It's got the most drug, and it's going to be relatively easy to extract.

So although the small amount of drug that's going to be used by this company is relatively, in a way, slightly reassuring, I would say that this will be the choice drug for diversion and extracting hydrocodone. So that's what makes it different.

DR. FLICK: Dr. Leff?

DR. LEFF: Yes. I sort of I guess have a two-part question. One is related to abuse potential and the liability, given the liability, I guess, of the formulation per se. And the

formulation, I believe, is similar to that with Avinza with morphine. Is that correct? The SODAS? Yes. So that may speak to extractability and ease of access.

I guess a question for Dr. Walsh. We talked a lot about oxycodone. But how does it compare, do you think, in the liability compared to morphine, which is the one that's in a similar formulation? And any other insights you might have.

DR. WALSH: Well, from a pure pharmacological standpoint, if we're thinking about what we've been talking about earlier, relative potency for abuse potential signal, it would be similar to morphine. And morphine -- I don't have access to the sales for the morphine product that you're specifically asking about. And I should also say that I did not have the sponsor's brochure. So I don't know exactly how their formulation is created.

I think that Dr. Ramsay's point I would agree with, that we already have an existing population, fairly large population, of hydrocodone

abusers for whom this would be attractive because it does not have the acetaminophen in it.

I think I had mentioned earlier that a likely other risk, which is a risk with the other single-entity products, is that you'll see more parenteral abuse with the absence of the acetaminophen.

I'm not aware of -- I think -- and I might be mistaken, but I think that more than half of the patients that were in the studies that were reported today were taking more than 100 milligrams per day. And so that's more than twice the maximum dose that is being marketed. So that means that people are already taking more than one pill at a time, or at least half of them are.

So I don't think that we have data on the pharmacokinetics and effects at those higher doses as single bolus doses. I don't think that those are available. And perhaps the sponsor made them available to you, but I don't think that they're available in the published literature.

DR. FLICK: Dr. Maxwell?

DR. MAXWELL: I need a clarification. Some of these drugs are old drugs. So in one sense, this is very similar to the old hydrocodone. But if FDA -- is there an option of saying, those old drugs that were approved 20 years ago, we can now say they need to be changed also?

Because you're posing it almost like I need to say this new formulation, if it's the same as the current hydrocodone, I can't change.

DR. RAPPAPORT: Okay. So the options that I laid out here, first of all, you make a determination whether this is the same or different than other extended-release long-acting opioid products that have been approved.

If it is different, if there is something in the data that show that this is likely to have a much different -- significantly different abuse profile or other safety concern, we can single out this product and make a decision about whether to not approve it on that basis, or implement other risk management tools, strict risk management tools, or whatever.

However, if they are the same, essentially, within a range -- they're all Schedule IIs, and the schedule is put together for a reason -- so you've got Schedule IIs; this would fall within that. Somebody said -- a couple of people have said -- well, there's a community out there that likes hydrocodone and so, yes, it's going to be abused.

There's a community out there that likes oxycodone, and there's the balloon effect that we're all familiar with. So people move from one to the other, whichever is easier to get. That doesn't make it different from the other products.

So in that case, what I need to understand from you, is it that there really is something different, or that you're holding it to a different standard. Because you're punishing this company and this drug because of the sins of the previous developers and their products. And we can't -- from a regulatory standpoint, that's not something we can do.

So I really need you to focus on dividing it

up in that way. Is it different? If it's not different, then, Jane, you're right. Your question is the next step. If it's similar, falls within the same class, no big differences to these old drugs that were evaluated differently 20 years ago, then we can consider imposing new restrictions, additional restrictions within the REMS. And that's the next part of the discussion, is should we be imposing additional risk mitigation strategies under the ER/LA REMS?

DR. FLICK: Dr. Rappaport, if one were to look back at the recent applications for sustained-release narcotics, would the studies that have been done for this application with regard to safety and efficacy be substantially different? Do you understand my question?

Has this application gone through a roughly similar process than the previous ones that have been considered by this committee over years?

DR. RAPPAPORT: Well, it depends how long you want to go back.

DR. FLICK: Well, certainly we are not --

DR. RAPPAPORT: The way that FDA reviews new drugs -- there's something -- okay. It's just very distracting. The way that the agency has reviewed drugs over various decades has changed dramatically.

DR. FLICK: Sure.

DR. RAPPAPORT: So if you go back and look at the Duragesic studies, they are not of our standard at all today. But for the recent extended-release long-acting products, this is exactly the same type of program that we've required of the other approved drugs.

DR. FLICK: Thank you.

Dr. Rosenberg?

DR. ROSENBERG: The one thing about this drug that's substantially different from the other is that Vicodin -- the hydrocodone is already the widest misused drug, and it's being misused at the grade school level. And some people are comparing its use in the schools as being comparable to that of marijuana.

If they find a vial that says "hydrocodone"

in their medicine cabinet at home, they may think it's the same drug because they're not experienced. We're talking about young kids. I mean, fourth grade, they've documented that in the --

DR. FLICK: Dr. Rosenberg, I think -- and please, Dr. Rappaport, correct me if I'm wrong -- but I think that you just addressed that very question, that the fact that this drug is widely used, the most widely used as a Schedule III, when it becomes a Schedule II -- its use as a Schedule III is not important or not the factor that we're being asked to address.

Did I hear you correctly?

DR. RAPPAPORT: Well, I think I've said a couple of things that applied to your concerns. One is that there are degrees of abuse, and abuse moves from one drug to another depending on the mood of the public and the abuse community.

But the other thing is that the fact that Vicodin is so -- first of all, is the most widely prescribed drug in the country, so the numbers are very high -- but you do have to adjust that based

on actual -- you need to look at both the numerator and the denominator. So that's one issue that was brought up.

The other issue is that because it's been a Schedule III, many people have the impression that it's less dangerous. And it's more accessible to people because it's a Schedule III. All of those things have made it -- probably are reasons why it is widely abused. That may lead to people's impressions that the new product in Schedule II can be abused, too.

Should we take that into consideration? It's not really the problem for this new drug.

DR. ROSENBERG: I'm talking about the uneducated substance user who's trying stuff that he thinks -- he has a friend who took some Vicodin and had a good time. He's got some hydrocodone in his cabinet. Why can't he take that? And that will be his last choice.

DR. RAPPAPORT: No. I think that's a legitimate concern. I mean, obviously it's --

DR. ROSENBERG: And so that's how it's

fundamentally different, is we're taking something that people assume to be mild --

DR. RAPPAPORT: Right. Right.

DR. ROSENBERG: -- and in fact, it's not mild at all.

DR. RAPPAPORT: Right. So the other part of the discussion is, is that enough to not approve this product? Or does that mean that we need some type of tighter risk mitigation?

DR. FLICK: Dr. Kramer?

DR. KRAMER: Yes. I think it's important for all of us to hear what the panel members think is different rather than debate who's right about it. So let me just say that the fact that this formulation has, as far as I'm aware, the highest -- at the highest level, the highest dose of unprotected, non-deterrent formulation -- am I wrong about that? I think that it has higher abuse potential.

I think, in my view, what's different, given that we're here to protect the public health -- and I realize there has to be a level playing field in

terms of business practice, but the primary thing has to be the public health.

It seems to me that what's different is our experience of what happened with OxyContin before it was reformulated. And I don't understand how we could not see this as a promised repeat performance.

DR. HERTZ: I just want to clarify one point. I mean, I take what your comments are. The 50-milligram dose of hydrocodone is not the highest morphine-equivalent extended-release opioid dose available. There is higher amounts of morphine-equivalent doses in other products that are currently marketed. Exalgo, some of the morphines, the oxycodone, come in higher milligram equivalent strengths. So this is not the highest. It's the highest hydrocodone-containing product as proposed, but not the highest amount of opioid in an extended-release tablet, as proposed.

DR. FLICK: Dr. Rappaport or Dr. Hertz, Dr. Kramer raised the question of the public health. You raised that point in your opening

statements and your charge. Could you please address the role of the committee and the role of the agency with regard to public health?

DR. RAPPAPORT: Okay. I have a statement I'm going to read in regard to this.

So the question we asked ourselves is what authority do we have to approve a drug because it's likely to be widely abused and result in significant increases in addiction and overdose? And the answer to that question is that the FDA will only approve a drug if its benefits outweigh its risks.

All opioid analgesics have at least some potential for abuse, and abuse of these products can lead to and not infrequently does lead to very serious events, including addiction, overdose, and death. However, opioid analgesics also have great therapeutic value for treating patients in pain.

For all currently approved opioids, we have previously concluded that the therapeutic benefits of these products make their very serious risks acceptable from an approval standpoint if the

products are appropriately labeled.

We have also required REMS for certain opioids when we determine the elements beyond the approved labeling are necessary for the benefits of the drug to outweigh the risks. I've already given you examples of when we used REMS for opioid drug products in two classes.

DR. FLICK: Thank you.

Dr. Kaye?

DR. KAYE: I think we're a little bit challenged in that the reformulation of OxyContin and Opana now make us think very, for me, strongly that this, though an extended release, compared to an extended release, which is what you asked us to do, clearly, because there is not this type of reformulation, the safeguard, however we want to call it, that we would be opening up a Pandora's box. Why not raise our standard or our bar as we move forward for society?

DR. RAPPAPORT: So I'm going to read another statement because that's the other question we asked ourselves. What you're asking is, what

authority does the FDA have to not approve a highly abusable drug that does not have abuse-deterrent features?

I will refer you back to the previous answer that I gave. But also, historically, we have not required opioids or any other drug category to contain abuse-deterrent features. But as we gain experience with both laboratory and real world data concerning the new opioid products formulated to deter abuse, we are actively considering whether and under what circumstances we can and should require an opioid, or any other highly abusable product, to have abuse-deterrent features as a condition of approval.

Unfortunately, this inquiry involves many complex and novel legal and policy questions that FDA hasn't fully resolved. So therefore, I can't go further into detail except to say that the issue is receiving our serious attention.

DR. KAYE: Well, I would say go for it.

DR. RAPPAPORT: I would love to be able to just go for it, believe me.

DR. HERTZ: So I kind of feel the tension between trying to answer these questions the way you want to and trying to answer these questions within the context that we're asking.

So I think, in terms of trying to free up the speech a little bit, what I would just say is perhaps you can answer them from both perspectives, within what you perceive our regulatory perspective to be, and then if you feel like there's additional things you need to say, please tell us.

DR. FLICK: And me just ask, I think, a question that addresses that. Dr. Hertz or Dr. Rappaport, could you please inform the committee about the differences between the regulatory requirements of the agency and the requirements of the committee, if there are any differences?

DR. RAPPAPORT: Yes. There are. There are differences. I mean, we are obligated at the agency to operate within the regulatory framework. And that includes providing a level playing field

for industry. We don't have a choice by that. It's the law.

If I were to do otherwise, then there would be a different division director sitting here tomorrow, and that person would do it the right way. So perhaps there are a lot of people who would like to see that, but that's a different issue. Thank you.

So I think that in response to your specific question, that the committee is being asked for your opinions from any perspective, but to consider whether we can really act on those from a regulatory perspective. You have to take that into your consideration.

You can tell us to go and remove certain drugs from the market because you don't think they're good and people shouldn't be using them. They're unsafe. They could be abused. We can't do that. It's not within the regulatory authority we have, unless certain other pieces are brought to our attention, new data.

So we want to hear what you think. We want

to hear your clinical perspective on this. And that's important. But in making your recommendations, I do hope you'll keep in mind -- and that's what I said in my opening comment -- that we may not be able to act on all of your recommendations because of our regulations and the law.

DR. FLICK: I think, as time passes here, we'll move to discussion of question number 4. Please discuss whether the data support the need for additional postmarketing risk mitigation requirements beyond the extended-release long-acting REMS.

I think we've touched on these things, but in the interest of time, I'd like the discussion to focus on that area, if that's okay with the committee. So if we could post that question, I would appreciate it.

Dr. Ramsay?

DR. RAMSAY: I think we're skirting a little bit around things. I just want to put a few summary statements out there for challenge.

I don't know how we can argue that this drug is really any different than any of the other pure mu agonists. It's very similar to all of these drugs. So to select out hydrocodone as different is just not fair. It's just not correct.

The concerns of the committee are about all of these drugs, in light of the public health crisis that we have. It's not about any one of them. We're particularly concerned about the most popular one, which is this drug. But the concern is for all of them.

The sustained-release pure products without tamper-proof are more likely to be abuse-prone. I think everybody would agree with that. Right? If you can extract the drug easily. But we don't know for sure about tamper-proof. It's new. Right? The tamper-proof formulations are relatively new, and we don't have a lot of experience with how effective they are.

So I would suggest that things that are concrete that we could recommend as a committee, because of our concerns about all of these drugs,

are:

A restrictive prescribing practice that does not allow anybody, just anyone, to prescribe them;

A requirement that patients keep them in locked storage -- we do that in hospitals; we have to have opioids in locked storage, but we just send them home with patients and just say, put them in your cupboard. So I think we should have a requirement for that; and

We should have a requirement for surveillance programs, at least for all of the extended-release pure opioids.

DR. FLICK: So I want to make sure that I'm hearing you correctly. These are suggestions or recommendations for an extension of the current REMS?

DR. RAMSAY: Yes.

DR. FLICK: That was a yes.

Dr. Zito?

DR. ZITO: I concur with the recommendation for restricted prescribing. It has worked very well, as far as I know, for Accutane. So we have

examples, and I would imagine that what we're talking about in terms of public health risk here is equivalent to why we went to such a strong position on Accutane.

If these numbers of specialist prescribers that you are seeking, and the number of patients that you seek is so small, then it would seem to me that both the idea of a registry and/or restricted prescribing could be dealt with.

The second point I'll quickly make is that we have lessons learned from clinical pharmacology over the years, and it doesn't seem like the OxyContin story and its need to be reformulated -- and then it's the only example I see in the trends data, which shows a drop in use, and no one seemed to offer an explanation for that.

So I don't know if that's just bad press, and so we switched to another product to avoid the fact that the patients know so much negative about that.

But in any event, I think there's not a lot of logic to saying that these are impractical

solutions to this problem if it's going to be as restricted as you suggest.

DR. FLICK: Dr. Jevtovic?

DR. JEVTOVIC-TODOROVIC: I would actually like to reserve my comment right before the voting because it doesn't have much to do with this.

DR. FLICK: Dr. Kramer?

DR. KRAMER: I think I would say yes to this. And I think what I'm concerned about is our reliance on REMS. And if I could add something to what Julie just said, my concern is that I do think there are really big challenges here because, basically, the prescribers are all prescribers. It's not a limited -- it's not just dermatologists that are prescribing Accutane. I think it is a challenge. And short of something like DEA connection and requirement for a certain educational packet, it would be difficult.

But my bigger concern is I was involved, before there were REMS, when there were the first risk management plans. And we were involved in evaluating Tikosyn, the dofetilide risk management

plan. And, essentially, if you make it difficult enough, it will manage risk because doctors will stop prescribing it because it's too burdensome on their practice.

But short of that, what really worries me is we have no -- I don't think we have good evidence that the educational programs have any effect in terms of what we're trying to accomplish, and yet we're completely depending on them.

So I do think we need to think about something different, and I think we have as much information about abuse deterrence, seeing the OxyContin curve starting to come down, than we do the educational benefit of REMS.

DR. FLICK: Dr. Rappaport, do you have a comment?

DR. RAPPAPORT: Well, I was just curious if you would maybe comment on whether you think that the result of excessive or extra restrictions resulting in doctors not prescribing this is a problem.

DR. KRAMER: I mean, the Tikosyn example is

extreme. Patients had to be hospitalized, and there had to be certification, and limited distribution -- it had everything on it. So it had all the bells and whistles. And I think the agency's more judicious about -- and realistic.

But it is a problem. The primary care practitioner is in the crosshairs of everything that's wrong with our current medical system. Right? Everyone wants a little more information from them, and they fill out the disability forms, and they get the education for this, and everyone's focusing on them. And it's untenable for us to believe that three hours of education is going to fundamentally change what they do here, I think.

DR. RAPPAPORT: Well, and I agree with what you said. I was actually asking you whether putting those kinds of restrictions on would be a problem in terms of the other side, of access to patients who really do need the drugs.

DR. KRAMER: Well, I think what I was thinking of as an alternative was requiring that we have abuse-deterrent formulations, things that

aren't going to more predictably repeat the OxyContin story.

DR. FLICK: Dr. Rappaport, could you remind me of how the committee received the REMS? And when the REMS was brought before the committee, the ER/LA REMS, how did the committee receive that and what was the vote on that?

DR. RAPPAPORT: I don't recall the numbers. But I know that they were disappointed that the educational materials were not mandatory.

DR. FLICK: Thank you.

DR. RAPPAPORT: I think that was the biggest sticking point for them.

DR. FLICK: Dr. Leff?

DR. LEFF: I guess mine's just a clarification, sitting here, just about Dr. Ramsay and Dr. Zito and others. Are your additional recommendations for the specific product or for the ER/LA REMS in general?

DR. RAMSAY: I suggest this for the whole class. I don't see a difference between the different drugs. So it should be for all the

single-drug extended release.

DR. FLICK: We have time for one more brief comment. Dr. Denisco?

DR. KAYE: And I -- oh, I'm sorry.

DR. DENISCO: I agree with Dr. Ramsay. I think we've evolved so that we can get it right in the future.

DR. DENISCO: Dr. Rappaport, you asked about the effect of situation. Well, the same area, exact same area of Florida, the same pharmacists that Dr. Maxwell mentioned, the CVSs were involved with, that area now, there was another thing in the newspaper, a set of articles in the newspaper, the local newspaper, that was picked up by a national paper that said that -- interviewed a number of pain patients.

They're having a tremendous problem getting their medications filled, and you have to know the pharmacist. And they went through this. And some of these were very distinguished, responsible people in the city who were having trouble. So I think where one area happens, the other one's going

to happen, too.

DR. FLICK: I'm going to close discussion on question 4. And I will take a moment to summarize both questions 3 and 4.

With regard to question 3, I think the committee is divided as to whether the postmarketing experience with Zohydro would be expected to be different. Some members of the committee believe that because of the prolific use of hydrocodone as a Schedule III drug, that it would lend itself to a different postmarketing experience, a more robust postmarketing experience when formulated as an extended release.

Other members of the committee believe that Zohydro does not represent a significant difference from other members of the class; therefore, the postmarketing experience would likely not be different.

With regard to question 4, a discussion whether the data support need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS, it appears to me that the committee

believes that the current REMS is probably, at best, modestly effective and additional strategies could be incorporated into the REMS that may -- and I think I would emphasize the word "may" -- be effective.

We will move on now to a relatively brief discussion prior to our vote. So question 5, based on the data presented and discussed today, do the efficacy, safety, and risk/benefit profile of Zohydro ER support the approval of this application?

Are there concerns or questions about the wording of this question?

(No response.)

DR. FLICK: If not, we'll begin the discussion with Dr. Maxwell.

DR. MAXWELL: This may be a question. But at what point can this committee recommend reformulation to be tamper-resistant? Because we've talked about it, but where do we get it into the record if the committee thinks it's a good idea?

DR. RAPPAPORT: You can recommend it. I think what my answer was intended to say was that we can't at this time require it. So, really, we have to deal with the application we have on the table, the formulation we have in this application.

DR. MAXWELL: So you could turn it down, and then turn around and tell them they should reformulate.

DR. HERTZ: SO yes. When you give us your vote and then we go around and find out why you voted, you can say you voted for this answer and here's your comments as to why you voted that way. That would be one opportunity.

DR. FLICK: Dr. Jevtovic?

DR. JEVTOVIC-TODOROVIC: What I would just like to do before we vote, express to the whole committee, I'm an anesthesiologist, and I've been practicing in this field for quite a long time. When you talk to pain specialists in our field, they will all tell you one indisputable fact: Opiates are lousy drugs to treat chronic pain. They only have about 10 to 15 percent of patients

who truly respond to opiates when it comes to chronic -- I mean chronic, months and years -- type of pain.

Let's just have that out here up front. And you can find those data anywhere. It is everywhere if you need to look it up.

DR. HERTZ: We would appreciate some references for that because I don't think it's quite that easy to find.

DR. JEVTOVIC-TODOROVIC: It is.

DR. HERTZ: So if you can maybe send us some after the meeting.

DR. JEVTOVIC-TODOROVIC: We can actually send you some slides, not immediately but when I come home.

DR. HERTZ: Great.

DR. RAPPAPORT: Well, but I think there's an important distinction here, and we discussed this at the workshop we had last spring for whether opioids are effective in treating chronic non-cancer pain.

The question is not whether there's an

absence of evidence to show that they work longer than 12 weeks, but whether there's evidence to show that it doesn't work longer than 12 weeks. And I think that's still up in the air. And we've been looking at the data now for at least a year, and I'm not sure we're convinced one way or the other.

DR. FLICK: Dr. Ramsay?

DR. RAMSAY: Do we need to vote on this question exactly as phrased? Because if we want further additions to safety, such as we discussed on question 4 --

DR. RAPPAPORT: No. I would vote on what exists in this application. You can comment that the reason you voted to not approve it is because you would want to see additional safety mitigation tools. But that's not what's in the application.

What's in the application is the REMS that exists and the additional tools that the company has discussed.

DR. WARE: May I ask a question?

DR. FLICK: Sure.

DR. WARE: So are you saying that if our

view is that we think that approval should include a more robust REMS, that we should vote no and then indicate that that's the reason?

DR. RAPPAPORT: Yes.

DR. WARE: Thank you. I just wanted to be sure that's what you --

DR. FLICK: Dr. Zito?

DR. ZITO: I know what it was. When you were summarizing number 4, there were several things that you omitted, which were the issues that Dr. Ramsay proposed. And I added to that around registries and restricted prescribers.

So I'm hearing now that we will recommend them as we go around after we give our votes.

DR. FLICK: Thank you. I appreciate the addition. I hope that my summaries are all-encompassing rather than specific, and I hope and I think I captured the need for the committee's belief that the REMS should be extended or improved.

Other questions or comments before we submit this to a vote?

(No response.)

DR. FLICK: Hearing none. I have to go to my script, and I can't find it. There we go.

If there's no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote.

Please press the button firmly. After you have made the selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. FLICK: Everyone has voted. The vote is now complete.

DR. BAUTISTA: I will now read the vote into the record: 2 yeses, 11 noes, one abstention.

DR. FLICK: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and reason they voted as they did into the record.

Dr. Denisco? And remember, please, brief, clear, concise.

DR. DENISCO: I voted yes because I believe the sponsor showed the same status that any other extended-release class II would have. I would strongly like to see, but I understand it cannot be mandated, abuse deterrence built into the formulation. I think that will do more than any of the REMS or any other activity to reduce abuse.

DR. FLICK: Dr. Rosenberg?

DR. ROSENBERG: I voted no because I would like to see a very strong restrictive REMS, including registered practitioners, very few. I think that for someone to come out with a -- instead of a hydrocodone ER, an LA preparation, which would not be as restricted an intention by that manufacturer. And I would not like to have this product on the market with too few safeguards.

DR. RAPPAPORT: Can I just ask that if you are making recommendations about changing the REMS, adding things to the REMS, that you specifically

say whether your recommendation is only for this product or you think that it should apply to the class?

DR. ROSENBERG: I believe that stronger REMS for all products in the C-II class would be appropriate, but in particular, for this particular product.

DR. FLICK: Dr. Kaye?

DR. KAYE: I voted no. Although we talked about the efficacy and the history, I believe I voted no because of the need for enhanced safety mitigation tools such as reformulation. And I believe that the standard for this drug should be looked at with all of the drugs in the class. Thank you.

DR. FLICK: Mr. Mullins?

MR. MULLINS: Earlier I heard a representative from the sponsor state that this drug comes with -- opioids come with baggage. Well, they come with a little bit more than baggage, and I think we've seen -- if you look at the regression analysis, we can see that there is a

proven pattern of addiction.

I would love to see the FDA take leadership, and I think the FDA is poised to take leadership, in addressing this issue of addiction in this class of drugs. I think we need greater restrictions.

I travel around the country and I see the repercussions of opioids, and they are a threat to public health because of this particular reason. The public does not have the amount of information to make an intelligent decision on the dangers of opioids, so they don't know how dangerous these drugs are.

So a parent or an individual does not have the acumen or the level of warning and red flags to say no when they are prescribed these drugs. So I think we need to move the level of information to the parents and to the individuals. Also, the Vicodin issue is concerning to me.

DR. FLICK: Thank you, Mr. Mullins.

I'm going to skip over to Dr. Ramsay, who has a flight that he's going to be late for.

DR. RAMSAY: Thank you. And thank you,

everyone, for this meeting today.

I wanted to vote yes because I think the company did what was essentially required compared to other drugs in this category. But I voted no because I think that the FDA and the DEA and whoever else is required needs to, for this entire class of drugs, enhance the REMS in the way that I suggested before, which is restrictive prescribing, mandatory education of the prescribers, a mandatory lockbox organization or some kind, mandatory surveillance, and once we know that tamper-proof works, incorporate that as well for the whole class. Thank you.

DR. FLICK: Thank you, Dr. Ramsay.

Angela Gravois?

MS. GRAVOIS: I voted yes because I believe the data that was presented to us is the same as for the other drugs in this class on the market now. However, I do believe that it would be beneficial for all drugs in this class to have a tamper-resistant --

DR. FLICK: Dr. Ware?

DR. WARE: I voted no. I think the sponsor -- as I understand it, the sponsor fulfilled the expectations of FDA with respect to the data they provided. I also believe, as Dr. Ramsay said, that this drug is not materially different from others in the class. However, I think that the entire class is problematic in terms of abuse and safety issues. And so my negative vote was not about this drug per se, but it was about the class.

I'm troubled about the equity issue because other drugs have been approved with similar evidence. So I just want to acknowledge that I think this sponsor has met the expectations of FDA with respect to the evidence they provided.

DR. FLICK: Dr. Wesselman?

DR. WESSELMAN: Yes. I can only reiterate I voted no for similar reasons. I think the sponsor really did what was required to be done, but there is a problem with this class of medications at the moment. They are needed for certain patients; definitely, we need them. But there need to be

different regulations, as has already been pointed out.

DR. FLICK: Dr. Jevtovic?

Dr. Ware, could you close your microphone for me, please? Thank you.

DR. JEVTOVIC-TODOROVIC: I voted no. I really appreciate everything that the sponsor did today. It's an incredible amount of work that went into that. But I do agree with what Dr. Ware and Dr. Wesselman said, so there is no need to repeat myself.

DR. FLICK: Dr. Kramer?

DR. KRAMER: I voted no. And I also struggled with the issue of equity. But I ultimately think, although several years back FDA could give a study design that would be acceptable similar to other classes, I think that it's ultimately the sponsor's responsibility to understand the whole environment around bringing a new drug to market.

I think that public health has to be primary. So do think that this applies to the

whole class. I think that -- I would be very uncomfortable approving a non-abuse-deterrent product. And although I want to strengthen REMS, I'm very concerned that we really don't have enough evidence about whether the REMS works.

DR. FLICK: Dr. Perrone?

DR. PERRONE: I voted no. I think when you look at the risk/benefit assessment, the risk is great, and I'm concerned that the benefit overall for a new product might be not in favor of it.

In terms of the REMS, I'm concerned as well that we could mandate REMS for this drug, but I'm concerned that REMS are not enough. I would favor the tamper-resistant formulation and even informed consent for prescribing these drugs to anyone.

DR. FLICK: Dr. Zito?

DR. ZITO: I voted no, for the reason that I thought the efficacy data was modest at best; that the REMS is quite weak and has no mandatory powers, and its independent safety issues -- its board issues are quite vague, and that we seem to be ignoring the whole problem that OxyContin

experienced, and then developed new technology. And while it might be new and in need of validation, we certainly should be demanding such things from all the REMS-related opioids.

(Pause - audio problems.)

DR. FLICK: Okay. Where were we? Dr. Maxwell?

DR. MAXWELL: I voted no. I very much want to see a reformulated, tamper-resistant product. I also would like to see a much stronger REMS with better quality control of the training to be provided and much better oversight and quality of the data collection, the surveying, whatever they termed it on the field. Give me the word. The monitoring -- yes, the surveillance.

DR. HERTZ: Utilization data.

DR. FLICK: The chair voted to abstain. I voted specifically to abstain because I believe that the sponsor's application is essentially no different than any other application in this class. I think the sponsor has met the requirement put forth by the agency, and I applaud them for the

work that they did.

However, I think, with the committee, I struggled with what I believe is also part of the charge of the committee, and that is to see to the best interests of the American people and the public health. And it is my view that emerging evidence would suggest that tamper-deterrent formulations are likely to reduce the incidence of morbidity and mortality associated with this class of drugs, and we should not be approving new formulations in that setting.

I will then summarize the sense of the committee. And it is my view that the committee felt most strongly, first, that the sponsor met the requirements that they were asked to meet. However, as a member of the class, the committee believes that the public health is not served by this addition to the class until and unless the REMS program is strengthened and/or this application is brought back to the committee in an abuse-deterrent form.

I hope that I've summarized your sense

reasonably well. I know I've missed some specifics in that. If I've missed something of great significance, please don't hesitate to speak up.

(No response.)

Adjournment

DR. FLICK: Hearing nothing from the committee, the committee is then adjourned.

(Whereupon, at 4:48 p.m., the committee was adjourned.)