FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Open Session

Monday, March 13, 2017

9:16 a.m. to 5:14 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:16 a.m.)

Call to Order

Introduction of Committee

DR. WINTERSTEIN: Good morning, everyone.

I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you have not already done so.

I would also like to identify the FDA press contact, Sarah Peddicord. There she is, waving.

If you are present, please stand. She just did.

My name is Almut Winterstein. I'm the chairperson of the Drug Safety and Risk Management Advisory Committee, and I will be chairing this meeting.

I will now call the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to order.

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

DR. MENDELSON: Hi. I am Dr. John Mendelson. I am an internist and clinical pharmacologist from San Francisco, and my most relevant job role for today is I am a senior research scientist at the Friends Research Institute, also medical director for methadone programs, BAART programs.

Thank you very much.

DR. HERRING: Good morning. I am Joe Herring. I am the industry representative to the AADPAC committee.

DR. ACRI: Hi. I am Jane Acri. I am chief of medication discovery and toxicology at the National Institute on Drug Abuse.

DR. GHANY: Hi. I am Marc Ghany. I am an investigator at the liver diseases branch at the National Institute of Diabetes, Digestive, and Kidney Diseases, NIH.

DR. WISH: Good morning. I am Eric Wish. I am director of CSAR. That is the Center for Substance Abuse Research at the University of Maryland College Park, just down the road from

here.

DR. WOODS: I am Jim Woods, Department of Pharmacology, University of Texas San Antonio.

DR. SCHISTERMAN: Good morning. I am Enrique Schisterman. I am chief of epidemiology branch at the NICHD, NIH.

MS. ROBOTTI: Hello. I am Suzanne Robotti. I am the consumer rep on DSaRM, and I am the founder of MedShadow and the executive director of DES Action U.S.A.

DR. PORTER: Hi. I am Laura Porter, and I am with the Colon Cancer Alliance. I am the patient representative.

DR. HIGGINS: Jennifer Higgins. I'm the AADPAC consumer representative.

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

DR. McCANN: Mary Ellen McCann. I work at Children's Hospital in Boston as a pediatric anesthesiologist, and I am an associate professor at Harvard.

DR. RUHA: I am Michelle Ruha. I am a medical toxicology physician the University of Arizona College of Medicine.

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

DR. ZACHAROFF: Hi. I am Kevin Zacharoff. My expertise is in anesthesiology and pain medicine, and I am a faculty and clinical instructor and member at the State University of New York Stony Brook School of Medicine.

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

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

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

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

School.

DR. WAHOLAK: Terri Waholak. I'm a pharmacist by training. My PhD is in outcomes, and my specialty is in quality and safety. I am at the University of Arizona.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist at Rutgers University.

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

DR. TYLER: Linda Tyler. I'm the chief pharmacy officer at University of Utah hospitals and clinics and associate dean at the College of Pharmacy.

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

DR. LITMAN: Good morning. I am Ron Litman. I am a pediatric anesthesiology at the Children's Hospital of Philadelphia and the University of Pennsylvania, and I am the medical director of the

Institute for Safe Medication Practice.

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

DR. BILKER: Warren Bilker, professor of biostatistics, University of Pennsylvania.

DR. CICCARONE: Dan Ciccarone, professor of family and community medicine, University of California San Francisco. My expertise is in public health aspects of heroin and opioid abuse.

DR. LO RE: Vincent Lo Re. I'm in the Division of Infectious Diseases in the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania.

DR. CALDERON: Good morning. I am Silvia Calderon, pharmacologist, controlled substance staff, CDER.

DR. McANINCH: Hi. I am Jana McAninch. I am a medical officer and epidemiologist in the Office of Surveillance and Epidemiology.

DR. STAFFA: Good morning. I am Judy Staffa. I am the associate director for public

health initiatives in the Office of Surveillance and Epidemiology.

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

DR. HERTZ: Sharon Hertz, division director, same review division in CDER.

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

Thus, as a gentle reminder, individuals will be allowed to speak only into the record and only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic

at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until it's conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I will pass it to Lieutenant Commander Stephanie Begansky who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR BEGANSKY: Good morning, everyone. The Food and Drug Administration is convening today's joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry

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

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

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

is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's closed session, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

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

The product is an approved extended-release

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

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

This is a particular matters meeting during which specific matters related to Opana ER, oxymorphone hydrochloride ER, and oxymorphone hydrochloride IR products will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they

have made concerning the product at issue.

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

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

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

DR. WINTERSTEIN: We will now proceed with

the FDA's opening remarks from Dr. Judy Staffa.

FDA Introductory Remarks

DR. STAFFA: Good morning. On behalf of the large multidisciplinary FDA review team represented here today, I would like to welcome you all to this joint meeting of the Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees.

I would like to thank all the committee members for taking the time to review all the materials we sent to you and to come here for these two days to discuss this very important public health issue, particularly in light of the challenging weather conditions we're likely to face later. I would also like to thank Endo Pharmaceuticals for providing the information we requested to support this meeting and for their participation.

In my role in CDER's Office of Surveillance and Epidemiology, I oversee all opioid-related activities in our office, which includes the planning of this two-day meeting to discuss safety

issues relating to reformulated Opana ER.

These safety issues include a potentially fatal bleeding disorder resembling thrombotic thrombocytopenic purpura, or TTP, and an unprecedented outbreak of human immunodeficiency virus, or HIV, in rural Indiana county that appeared to be associated with a shift from intranasal to intravenous abuse of Opana ER.

Although we recognize the apparent regional specificity of these outbreaks and regional differences in abuse patterns more generally, the postmarketing experience with this product is nonetheless concerning to us, as it suggests that even well-intentioned efforts to deter abuse may have unintended consequences.

Throughout the day today, you will hear from multiple speakers who will provide information on these safety issues using relevant data from multiple disciplines. Each data stream, from the in vitro extraction studies in human abuse liability studies to the local outbreak investigations and spontaneous reports, to the

large epidemiologic studies, has its own unique set of limitations, which makes forming definitive conclusions challenging.

But uncertainty is a concept we will deal with routinely as regulators and in drug safety and in general. We rarely have all the data we would like, but we must use what we have to make the best regulatory decisions possible. Our job is to look at these data critically and find the consistencies amidst the limitations, erring on the side of patient safety and the public health.

The questions we bring to you for discussion over these two days are challenging, but we look forward to the many insights you will provide to us along with your best recommendations. Thank you again for your time and your support of our mission.

DR. WINTERSTEIN: Thank you, Dr. Staffa.

We will now begin with industry presentations from Endo Pharmaceuticals.

Industry Presentation - Harris Rotman

DR. ROTMAN: Good morning. I'm Harris

Rotman, vice president, regulatory affairs at Endo Pharmaceuticals. We would like to thank the advisory committee members and the FDA for inviting us to present at this meeting.

Opana ER is an extended-release formulation of oxymorphone hydrochloride. The reason we are here today is to discuss the place of Opana ER in today's environment, considering the risks of abuse with all opioids.

To provide some definitions, I want to discuss the different forms of Opana ER that we will be talking about today. Opana ER was originally approved in 2006. We will refer to this product as original Opana ER, which is no longer available on the market. This reformulation of Opana ER was approved in 2011 without abuse-deterrent labeling. We will refer to this product as reformulated Opana ER. Reformulated Opana ER is the currently available product on the market, and we are not currently seeking abuse-deterrent labeling.

We will present data that supports the role

of Opana ER as an important treatment option for patients based on a decade of experience, which reinforces the need for an extended-release oxymorphone analgesic in the armamentarium of opioid therapies for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Opioids are an important option for treating chronic cancer and non-cancer pain that negatively affects quality of life and productivity, but opioid therapy for the treatment of pain is not one size fits all. Opana ER is one of the important opioid options for physicians to customize therapy to the patient's specific needs.

We will also present data on unintended use, often called abuse. These data are sourced from epidemiology studies to understand the effect of reformulated Opana ER on real-world outcomes. The epidemiology studies are also known as category 4 studies within the context defined in the 2013 draft FDA guidance for opioid abuse-deterrent

formulations that was finalized in 2015.

This meeting has been convened to discuss the challenges inherent with evaluating abuse epidemiology data. As you will see, these data are often conflicting and make it difficult to reach definitive conclusions on the interpretation of cause and effect.

Our category 4 studies are observational in nature and incorporated FDA recommendations. Each is a pre/post design using a baseline period of January 2009 through December 2011 during which original Opana ER was on the market. This is highlighted in blue. The post-reformulation period occurred from July 2013 through June 2016 as highlighted in yellow. The period in between is the transition period.

The FDA recommended that because of the high degree of instability of the market during that time, it would not be possible to understand the effect of the reformulation and therefore should not be included in the formal data analyses.

Endo believes the totality of the evidence

demonstrates a favorable benefit-risk profile in the intended population. Coincident with the introduction of reformulated Opana ER, intranasal abuse was lower. IV abuse initially increased in Tennessee but has stabilized and was stable or decreasing in other states.

It is important to point out that this is the first time that product-specific results from completed opioid abuse epidemiology studies will be presented to this committee. Abuse data come from real-world settings against the backdrop of the constantly changing landscape of available opioid formulations. Most importantly, Endo supports improving data collection methodology so that new studies can continue to provide even more robust and meaningful results.

Next, I will briefly describe our rationale for developing a reformulated tablet. The data from early abuse experience with original Opana ER show that intranasal abuse was most prevalent because of the ability to manipulate it into a powder with minimal effort.

Opana ER was therefore reformulated with the dual intent of maintaining the extended-release properties of the original formulation but also making the tablet so hard that it resisted crushing. The key inert ingredient is polyethylene oxide called PEO for short. Opana ER is made by a process that applies heat to the product mixture as it is being manufactured, resulting in a very hard tablet that resists crushing with extended-release characteristics.

In addition, PEO has the property of gelling in aqueous solutions, limiting the ability to form a simple aqueous solution of the active ingredient. PEO has been used to provide abuse-deterrent properties to three approved extended-release opioid products, OxyContin, Arymo ER, and Hysingla ER.

Let's review the timeline for reformulated Opana ER. Endo first submitted the NDA in 2010, well prior to the availability of FDA guidance on conduct of category 1, 2, and 3 studies. In fact, FDA and industry were all still learning how to

evaluate abuse-deterrent formulations at that time.

The FDA did not grant ADF labeling at that time, so reformulated Opana ER was approved by the FDA without inclusion of the available abuse-deterrent study results. Endo submitted a supplemental NDA in 2013 to obtain ADF labeling. However, the FDA requested a study looking at the abuse potential by the intranasal route as part of their complete response letter.

Endo submitted the requested intranasal PK/PD abuse study along with interim two-year category 4 studies in 2016 requesting ADF labeling, but there was missing information in our two-year category 4 data. Endo subsequently withdrew the submission in anticipation of the three-year epidemiology data becoming available in late 2016.

Endo completed category 1 through 3 studies requested by the FDA. As per FDA guidance for ADF submissions, category 1 through 3 studies are intended to be hypothesis generating with positive data suggesting that abuse deterrence would be expected to occur when looking at real-world

category 4 data.

Since reformulated Opana ER was available on the market and could be monitored, Endo voluntarily initiated three-year category 4 studies. These category 4 epidemiology studies were intended to provide real-world evidence demonstrating whether or not deterrence did occur with reformulated Opana ER. However, the actual results are influenced by the market evolution.

There are two major events that confound our ability to interpret the epidemiology data: the introduction of an abuse-deterrent formulation of OxyContin while original Opana ER was on the market and the launch of generic oxymorphone products immediately before and after the introduction of our reformulated product.

Now, let me show you the timing of the two confounding issues. In August 2010, OxyContin was introduced into the market with an abuse-deterrent formulation. After the introduction of OxyContin ADF, we saw an increase in Opana ER abuse during 2010 and 2011.

Secondly, low-dose strengths of generic extended-release oxymorphone became available in July 2011 prior to the availability of reformulated Opana ER, and additional generic tablet strengths became available in early 2013. These generics were approved as bioequivalent to the original non-PEO formulation of Opana ER and are easy to crush.

Endo discontinued the low-dose strengths of older non-PEO Opana ER in March 2011 and the remaining strengths of the original Opana ER in May 2012. Note that generic extended-release oxymorphone versions that were easier to manipulate were available at the same time as reformulated Opana ER.

Our goals today are shown here. First, we will detail the benefit and safety of Opana ER in the intended population of patients with chronic pain. We will demonstrate that oxymorphone has distinguishing characteristics that make it an important choice for patients with chronic pain and should remain available to prescribers as a choice.

Second, all opioids, including oxymorphone products, are abused. Our interpretation of the category 4 epidemiology data suggests that abuse patterns changed prior to and following the introduction of reformulated Opana ER. The cause-effect cannot be determined. However, taking into account all data, the overall benefit-risk profile of Opana ER remains consistent.

Let's review the remaining agenda. First, Dr. Perry Fine, a professor of anesthesiology at the University of Utah, will present the benefit of Opana ER in the intended population of chronic pain patients and the high unmet need for different opioids to treat chronic pain.

Next, I will present the results from our category 1 through 3 studies that support the hypothesis that reformulated Opana ER lowers the risk of abuse.

Then Dr. Neil Shusterman will provide a detailed review of the category 4 abuse epidemiology data from NAVIPPRO and RADARS. In addition, he will address two key issues raised by

FDA, which the panel will be tasked with discussing today, TTP and HIV.

Dr. Alec Walker, former chair of the department of epidemiology at the Harvard School of Public Health, will then discuss epidemiology principles and how they apply to the observational data.

Finally, Dr. Rick Dart, director of the Rocky Mountain Poison and Drug Center and executive director of the RADARS system, will put the epidemiology data into context.

Then I will return to the podium to address your questions.

We are also joined today by additional experts. All external experts have been compensated for their time and travel expenses.

Now I would like to invite Dr. Fine to the lectern.

Industry Presentation - Perry Fine

DR. FINE: Good morning. My name is Perry Fine, and I truly appreciate the opportunity to meet with you at this crucial joint committee

meeting, the substance of which is emblematic of the extraordinary challenges we face in balancing the needs of pain patients against the risks of prescription drug abuse.

In the throes of the current opioid abuse epidemic, it is difficult but absolutely necessary to harken back to the circumstances that motivated the changes we have witnessed over the last few decades. My entry into the healthcare world 45 years ago was met with the overwhelming and pervasive suffering I witnessed on cancer wards, neuro and rehab units, and postoperative wards.

From my early patient care experiences, it was clear that poorly relieved pain and the misery it caused were striking. Those experiences projected me on to my chosen career path. So I trained to become a board certified anesthesiologist, a pain medicine specialist, and a hospice and palliative medicine subspecialist.

At the University of Utah, we treat by referral the most difficult cases in the intermountain west. I have been treating complex

chronic pain patients safely now and effectively for more than 30 years. Without the several options among the opioids we now have, including oxymorphone, we would not be nearly as successful as we are able to be.

Let me proceed by explaining why this is and how important it is to retain this drug within the current pain management pharmacopeia. In the next few minutes, I'll review the following essential points: first, that severe and intractable pain is a major public health problem and that opioid therapy may be needed in selected patients to affect positive therapeutic outcomes, and the responses to opioids are highly variable due to first, the variability in drug metabolism among diverse clinical populations, that there are potential drug-drug interactions, and that there is receptor polymorphism.

Therefore, a wide variety of opioids are needed, including oxymorphone, to optimize outcomes. And since all medicine is driven by clinical context, let's start with the magnitude of

the chronic pain problem as detailed in the recent Institute of Medicine and National Pain Strategy reports.

Intractable pain is a high impact and potentially life-threatening condition affecting millions of Americans. Some of it is due to obvious somatic or neurological tissue injury or disease, and other persistent pain syndromes are more enigmatic, including central pain disorders and many of the commonly categorized neuropathic pain conditions. Regardless, unresolved moderate to severe pain has serious affects ranging from decreased productivity to depression and even suicide.

As such, treating physicians have an obligation to prevent and manage the most severe adverse consequences of intractable pain while mitigating treatment risks. Safe effective pain management requires comprehensive assessment and integrated care. An important part of this is differentiating those who are genuinely seeking pain relief from those merely seeking drugs for

other purposes.

Here you see examples of contemporary treatment modalities we use concurrently with pharmacotherapy such as lifestyle changes and psychological support. But many patients do not obtain satisfactory outcomes with conservative, that is, nonopioid therapies alone.

Prospective studies and clinical experience have taught that long-term opioid therapy when properly prescribed and monitored can be effective in restoring functionality and quality of life.

In our practice at the University of Utah, we have been treating cancer and non-cancer patients for more than three decades without appreciable morbidity and no known opioid-related mortality. We attribute this low fatality rate to good clinical practices that follow state and national treatment guidelines. This includes the necessary practice of opioid rotation, that is, switching patients from one opioid to another when other opioids are not effective in making a positive therapeutic impact.

Our experience mirrors that of the literature citations reporting an average range of 3 to 4 opioid switches before optimal pain control may be obtained. Practically speaking then, a one-size-fits-all approach is a failing formula. Every patient's individual circumstances need to be assessed, and plans of care require tailoring to match social, cognitive, psychological, medical, and even spiritual circumstances and values.

Pertinent to today's discussion is the pharmacokinetic and pharmacodynamic variability of opioid effects most likely due to pharmacogenetic differences among patients. New opioid polymorphism and differential opioid sensitivity, as proven in the laboratory, now helps explain what we observe in the clinic. I witness this with every patient I treat, justifying the need for the multiple opioid moieties that we now have on formulary. This is akin to the need to such a wide range of anticonvulsants for effective management of epilepsy.

Although we lack randomized clinical trials

that prospectively evaluate genetics and other predictive variables in pain medicine, we have ample experiential evidence that reinforces the importance of individualizing care as best we can, including matching drug characteristics and effects to patient characteristics and responses.

I'm optimistic that over time, translating the burgeoning science of pharmacogenetics to the bedside will lead to better initial and ongoing matching of drug to patient for greater predictability of responses.

The essence of personalized medicine is that people are not the same. Patients have different metabolisms, and they take medications with various interacting metabolic pathways. Clinical factors influence drug effects, and genetic backgrounds differentially impact drug sensitivity.

Drugs are not the same, either. Efficacy for mu receptor subtypes vary from drug to drug and from subtype to subtype, and because biased signaling varies from the drug to drug and receptor subtype to subtype, we need a wide range of options

to make sure that we can provide an effective alternative for each and every patient.

Oxymorphone has a unique metabolic profile among opioid analgesics. It is not a substrate for cytochrome P450 based metabolism, the common metabolic pathway for the vast majority of therapeutic drugs. Since the most complex pain syndromes require more than a single drug for pain control and regaining functional capacities, oxymorphone provides a useful alternative when an opioid is indicated because there's less potential for harmful drug-drug interactions.

While this remains an empirical clinical observation, certainly in my practice, oxymorphone greatly reduces concerns about these drug-drug interactions. And again, it bears repeating, the receptor polymorphism is well established in opioid pharmacology with a solid foundation of experimental data strongly supporting clinical observations of highly variable inter-individual responses.

Now that we have described how highly

variable responses of pain patients are to different mu opioid agonists, it follows that we need multiple agents and formulations for clinicians to prescribe when opioids are indicated. Insufficient alternatives limit options limiting effectiveness and driving clinical failure. Opioid rotation or switching is the accepted process used to optimized therapeutic effectiveness to minimize adverse effects and manage through tolerance to limit dose escalation.

Let me give you an example of one of my patients who is representative of tens of thousands of patients who currently rely on extended-release oxymorphone for effective pain control.

This is a recent case from my practice involving a previously healthy, professional, middle-aged woman forced into early retirement due to severe neuropathic facial pain, a particularly difficult to manage, highly debilitating, and often devastating pain syndrome.

She was referred to me expressing suicidal ideation, feeling robbed of her life, desperate for

pain relief, uninterrupted sleep, and to eat normally. By the time I saw her, she had been treated with a multitude of non-opioid and opioid therapies with only modest benefit due to the dose-limiting adverse events when combined with other neuropathic pain drugs, which she required to manage both her pain and the deleterious physical, affective, and social consequences of it.

In the prior year, she had been hospitalized four times. So I started with prescribing immediate-release oxymorphone to avoid the likelihood of drug-drug interactions for medications that affect the CYP2D6 or 3A4 pathway. As a result of this, she has now been able to tolerate co-administration of paroxetine and carbamazepine, leading to effective palliation of all severe debilitating symptoms.

Conversion to Opana ER has allowed a twice-daily medication regimen that has evened out pain relief throughout both day and night, and importantly, it has been easy for her to coordinate with other medication use, leading to improved

adherence and reducing risks.

A year later, she has not required emergency room care or hospitalization, and she has not required any subsequent non-self-directed psychological supportive care. She's been able to resume a normal diet and to travel for family events.

With this, I would like to leave you with a hard-earned lesson from the trenches. As clinicians caring for patients with debilitating pain, we have no risk-free solutions. The progress we have made in relieving excruciating and intractable pain over the last several decades is largely due to cumulative clinical experience of how to use opioids more effectively and the expanded formulary of opioids we now have to prescribe.

Expert clinicians have been feeling their way through the variability of patients' needs and have developed ways of practicing that are only recently beginning to enjoy the support of basic science. The science doesn't so much drive the

practice, but practice has been driving the science, revealing the wisdom inherent in clinical approaches.

We need to balance effective management of chronic pain when opioids are used as intended against the potential problems associated with opioid abuse. However, until such time that there is a class of drugs as efficacious and versatile as the opioids, clinicians need to learn how to select patients for opioid therapy when indicated and manage them as safely and effectively as possible while doing what we can to safeguard the public health.

Thank you. And I would now like to invite Dr. Harris Rotman back to the podium to discuss the category 1, 2, and 3 data for Opana ER.

Industry Presentation - Harris Rotman

DR. ROTMAN: Thank you. Dr. Fine.

Now turning to the results from our category 1 through 3 studies, category 1 positive study data suggests that abuse deterrence would be expected to occur when looking at real-world

category 4 data. We conducted extensive category 1 in vitro manipulation studies to demonstrate that reformulated Opana ER resists crushing and reduction in particle size and that gelling in the presence of aqueous solutions limits extraction. These in vitro studies also demonstrated that reformulated Opana ER is superior to generic non-ADF oxymorphone and is comparable to OxyContin controlled release.

I first will discuss the key results from our manipulation studies for reformulated Opana ER versus the generic non-ADF oxymorphone comparators. Let's look first at our particle size analysis.

Reformulated Opana ER was proven to be resistant to reduction in particle size compared to generic non-ADF oxymorphone. Presented here are the distribution of particle sizes following manipulation with three tools. Particle size distribution charts for tool A and tool M only show results for manipulation of the generic product. Manipulation Opana ER using both these tools does not result in particles.

When looking at more specialized manipulation techniques like tool N, reformulated Opana ER resisted manipulation better than the generic product, resulting in larger particle sizes as shown by the blue bars. In fact, the majority of the particles were greater than the largest sieve size used.

The results are consistent with the intended effect of using crush-resistant PEO technology. In contrast, the non-ADF oxymorphone ER product was easily crushable to powder less than 0.5 millimeters.

Looking now at the dissolution rate over time to evaluate simulated ingestion, both generic products, non-ADF oxymorphone ER, readily convert to immediate release when manipulated. As shown in this figure, dissolution testing of generic oxymorphone ER, products manipulated with tool A and tool B, produce a very fast release of drug in 30 minutes. Tool A and tool B had little to no effect on reformulated Opana ER. Therefore, the dissolution results are similar to that of an

intact tablet.

Turning now to extraction, reformulated Opana ER was found to have a much lower extraction rate when compared to generic oxymorphone following manipulation and extraction in 30 milliliters of solvent A. As you can see, the rate of extraction for generic products was about 80 percent in only 15 minutes. In contrast, reformulated Opana ER maintained extended-release properties.

Now, to discuss small volume extractions, reformulated Opana ER had lower percent extraction than generic oxymorphone using tool B where products were tested using the same conditions. Reformulated Opana ER gelled more and thus was harder to syringe.

As shown in the table, the generic products yielded twice as much active after extraction. Tool A was only used on generic products as it does not generate particles for reformulated Opana ER. Tool V was not needed for generic products as they are readily crushed with tool A and B in seconds. For crush-resistant reformulated Opana ER, extra

time and effort were required for manipulation.

We also compared reformulated Opana ER against OxyContin ADF because it also uses PEO, and there would be an expectation for comparable category 1 results. First looking at particle size, reformulated Opana ER and OxyContin ADF both using PEO resist particle size reduction. The most destructive tool for Opana ER was found to be tool B.

In this slide, we show a comparison of particle size results for reformulated Opana ER and OxyContin ADF using tool B. Following manipulation, both Opana ER and OxyContin ADF demonstrated similar resistance to particle size reduction.

Dissolution testing confirms Opana ER and OxyContin ADF perform similarly in vitro. We evaluated dissolution testing at 30 minutes following manipulation of both reformulated Opana ER and OxyContin using various tools. Intact tablets were used as a control.

The dissolution results presented here show

that both behave similarly when manipulated with the same tools. These data reinforce the consistency of PEO formulations to resist reduction in particle size.

Turning now to our extraction studies, both reformulated Opana ER and OxyContin ADF were very similar when exposed to five different solvents following manipulation. Reformulated Opana ER and OxyContin ADF maintained their extended-release properties showing a gradual release of the API. The extraction rate was higher at 6 hours with consistent relative differences.

Finally, we evaluated syringeability and extractability following manipulation with 3 tools. As both products are resistant to crushing, extra time and effort were required. The small volume extraction results demonstrate that reformulated Opana ER is similar to OxyContin ADF.

Results from our category 1 tests support that reformulated Opana ER is resistant to both physical and chemical manipulations compared to the non-ADF generic oxymorphone ER products. In

addition, both reformulated Opana ER and OxyContin ADF demonstrate similar physical and chemical properties against physical manipulation and chemical extraction.

As commonly seen with PEO products, both require a higher degree of effort, time, tools, and experience to crush or manipulate the products when compared to non-crush-resistant formulations.

Now let's move on to the FDA-requested intranasal category 2 and 3 study. Our category 2 and 3 abuse potential study known as study 114 evaluated the pharmacokinetics and abuse potential pharmacodynamics of manipulated reformulated Opana ER compared to oxymorphone powder when administered intranasally.

These data showed that reformulated Opana ER retained extended-release characteristics even after manipulation and that drug liking was significantly reduced with inhalation of reformulated Opana ER compared to inhalation of oxymorphone powder.

Now let's turn to the study design. The

study was a randomized double-blind, placebo-controlled crossover design. Study participants were drug experienced, non-dependent recreational opioid users. Subjects first underwent a qualification phase to confirm that they could discriminate between active drug and placebo.

Subjects then entered into the 4-period treatment phase. In each period, subjects received a randomly assigned single intranasal dose. Each period was separated by a 4-day washout period. Each subject received reformulated Opana ER 7.5 milligrams that was manipulated using tool V, placebo to match the manipulated reformulated Opana ER, oxymorphone powder 7.5 milligrams, or placebo to match the oxymorphone powder.

Let's first look at the pharmacokinetics. Presented here are the mean plasma concentration levels over 8 hours for the oxymorphone powder. As expected for a non-abuse-deterrent form, intranasal administration of oxymorphone powder demonstrates an immediate-release pharmacokinetic profile.

In comparison, we see that manipulated

Opana ER administered intranasally has a lower Cmax and later Tmax than oxymorphone powder. This profile supports the expectation that abuse-deterrent properties of reformulated Opana ER are retained even after manipulation.

The category 3 pharmacodynamic assessments were subjective patient-reported measures of drug effects. The prespecified primary endpoint was Emax, following intranasal administration for the visual analog scale that measured drug liking in the moment. The primary comparison was to oxymorphone powder. Other subjective scales were included with "take drug again" being an important one.

Presented here are the drug-liking results on the Y-axis. Note that drug liking is measured on a bipolar scale where 50 indicates neither liking nor disliking and 100 indicates strong liking.

When looking at the primary pharmacodynamic endpoint results from study 114, we see a significantly lower drug liking effect for

manipulated reformulated Opana ER when administered intranasally, shown in blue, compared to oxymorphone powder, shown in light orange. This primary comparison was statistically significant.

All results were consistent with the pharmacokinetics seen. For example, we see that mean liking scores for the 2 placebos, shown in pink and light blue, remain at approximately 50, meaning no change in liking.

When looking at "take drug again" for the 4 doses, we see a statistically significant reduction in "take drug again" for manipulated Opana ER when compared to oxymorphone powder.

To summarize our category 2 and 3 findings, the results support the conclusion that reformulated Opana ER administered intranasally results in lower Cmax and delayed Tmax compared to oxymorphone powder. This translates into significantly lower drug liking effects when compared to oxymorphone powder and a reduced desire to take the drug again.

Opana ER met the prespecified endpoints in

the intranasal study.

Thank you. Dr. Shusterman will now present a detailed review of the category 4 abuse epidemiology data from NAVIPPRO and RADARS.

Industry Presentation – Neil Shusterman

DR. SHUSTERMAN: Thank you, Dr. Rotman.

I am Dr. Neil Shusterman, chief medical officer of Endo Pharmaceuticals. I will now present the results of our postmarketing epidemiologic studies, which compare estimates for measures of abuse for reformulated Opana ER to estimates for original Opana ER and to certain other comparator opioids.

The evaluation of opioid abuse comes from three studies. First, the NAVIPPRO data are based on information from patients admitted to substance abuse treatment. As part of the intake process, patients are asked about the drugs they have abused over the past 30 days.

Second, the RADARS poison center data are based on calls to poison center hotlines across the country from or about individuals experiencing an

adverse reaction from exposure to a substance or a drug overdose. These two datasets were prespecified as our primary epidemiology studies.

Supporting these primary studies, we also conducted a third study based on drug diversion data reported by law enforcement that is collected by another RADARS tool. I will present the NAVIPPRO data first.

The NAVIPPRO study is a cross-sectional observational postmarket study of individuals who abuse drugs. The data come from NAVIPPRO's proprietary source, the Addiction Severity Index Multimedia Version or ASI-MV. They're collected from computerized structured interviews of patients entering addiction treatment.

Importantly, the interview includes images of virtually of all drugs of abuse such that individuals register their use of a substance by looking at its visual representation.

Over the study period, more than 459,000 ASI-MV assessments were collected from over 1,000 treatment sites in 40 states. From this set of

assessments, there were about 5,000 mentions of abuse of either original or reformulated Opana ER.

Prevalences were calculated using two denominators, a population denominator per 100 ASI-MV assessments and a denominator presumed to represent drug availability per 10,000 tablets dispensed.

The two primary objectives were to compare the prevalence of abuse of reformulated Opana ER by alternate routes of administration to the historic control, original Opana ER, and to the concurrent control, generic oxymorphone ER.

What is an alternate route of administration? It is any route of administration other than swallowing the tablet whole. However, in this dataset, it is functionally a combined endpoint of intranasal or intravenous abuse.

After looking at alternate routes of administration, it was prespecified that the components of intranasal and intravenous abuse would be looked at individually.

NAVIPPRO has some limitations. First, this

is a convenience sample. The ASI-MV was designed to facilitate the intake process at addiction treatment centers. As a by-product of that, the data are available in a HIPAA-compliant anonymized manner for research purposes.

Second, no direct abuse-related outcomes such as overdose, withdrawal, or death are monitored by this system. An endorsement is a mention of use of a drug during the past 30 days.

Third, the sampling is based on a site selection of this proprietary software system. It is non-random, and the recorded prevalence of abuse can vary extensively from site to site depending on the profile of patients served.

Also, the system is not nationally representative because it is a subscription service. Representation is greater in some regions than others and is entirely absent in certain states.

Fourth, sampling can change over time as some centers drop out and other centers drop in. Essentially, each look represents the collection of

centers contributing data over that period of time.

Finally, since responses are self-reported, they are subject to recall bias, and response accuracy and honestly cannot be verified.

The analysis I will show include all NAVIPPRO sites, which is the prespecified primary analytic dataset. The fixed-sites analysis, covered by the FDA in their briefing book, was a prespecified sensitivity analysis of a smaller set of sites that provided data in every quarter of the pre period and the post period. Importantly, the pattern of results observed was similar between the fixed-sites and the all-sites analyses.

Now let's take a look at the data. First, we are showing the historical control by the population denominator. The mean prevalence for original Opana ER during the three-year pre-reformulation period is shown in striped bars and for reformulated Opana ER during the three-year post-reformulation period in solid bars.

For the primary objective of abuse by alternate routes, the mean prevalence was higher in

the post period, 0.89, compared to the pre period, 0.73 per 100 ASI-MV assessments.

When looking by specific route of administration, the prevalence of intranasal abuse was lower during the post period compared to the pre period. However, when looking at intravenous abuse, we see the prevalence was higher during the post period compared to the pre period.

The same comparisons are now shown for the availability denominator for 10,000 tablets dispensed, and the pattern is similar. For abuse by alternate routes, the mean prevalence was higher in the post period compared to the pre period. When looking at specific routes, the prevalence of intranasal abuse was lower during the post period compared to the pre period. When looking at intravenous abuse, the prevalence was higher during the post period compared to the pre period.

Now let's move on to the second control, concurrent generic oxymorphone ER first by the population denominator. Here, the mean prevalence for reformulated Opana ER during the three-year

post period is shown in solid blue bars and for generic oxymorphone ER during the same time period in the orange bars.

For the primary objective of abuse by alternate routes, the mean prevalence during the post period is higher for generic oxymorphone ER, 1.59, compared to reformulated Opana ER, 0.89, per 100 ASI-MVs.

When looking at the specific routes, the prevalence of intranasal abuse is higher for generic oxymorphone ER than for reformulated Opana ER. When looking at the intravenous prevalence, the means are practically the same.

The same comparisons are now shown for the availability denominator. A similar pattern is seen as for the population denominator. For abuse by alternate routes during the post period, the mean prevalence is higher for generic oxymorphone ER compared to reformulated Opana ER.

When looking at the specific routes, the prevalence of intranasal abuse is again higher for generic oxymorphone than for reformulated Opana ER.

When looking at the intravenous abuse prevalence, the mean for generic oxymorphone ER is higher than for Opana ER.

Now, while Endo was receiving quarterly surveillance reports in real-time, NAVIPPRO informed us that a continually increasing proportion of Opana ER cases was coming from Tennessee. Because of this potential disproportionate representation by a single state, we prespecified an analysis of Tennessee separate from all other states when writing the epidemiology protocol. After the study period closed, we reviewed the distribution of information from individual states reporting Opana ER cases.

The single state of Tennessee accounted for 75 percent of all Opana ER abuse reports during the post period. To put this in perspective, Tennessee contributes 2 percent to the population of the United States.

To see if there was anything different about the results in the two regions, we will now show the NAVIPPRO results for all states except

Tennessee separately from those for Tennessee.

Presented here are the prevalences of abuse by route of administration for all states except Tennessee per 100 ASI-MVs. Here, we have expressed the data using line graphs as a function of time because it's important to understand the temporal pattern. This was not a static situation.

Abuse for alternate routes is shown as the top blue line and increased over the entire pre period, reaching its highest level after the reformulation of OxyContin. It was being driven primarily by intranasal abuse, shown in green. Importantly, intravenous abuse of original Opana ER, shown as the orange line, although low during the first 18 months of the pre period, doubled in the last 18 months.

In the post period, abuse by alternate routes shown in blue was lower and was principally driven by the lower level of intranasal abuse, shown in green. Importantly, intravenous abuse, shown in orange, was not higher in the post period compared to the level seen in 2011. This means

that reformulated Opana ER did not increase the intravenous abuse above that rate observed with original Opana immediately prior to reformulation.

Now, highlighted here is the Y-axis ranging from 0 to 2. In order to be able to show the results from Tennessee on the same axis as all other states, it is necessary to expand the vertical scale by 12 and a half fold.

Presented here are the exact same data from the previous slide for all states other than Tennessee. Notice that the Y-axis values now range from 0 to 25, and the non-Tennessee data basically hug the horizontal axis.

Presented here in dashes lines with the same color scheme are the prevalences of abuse for Tennessee only. In the pre period, the prevalence of abuse by alternate routes in Tennessee driven by intranasal abuse, shown in the green line, was increasing to levels much higher than that for the rest of the United States.

Notice that the peak point of abuse for alternate routes of administration for Tennessee,

20.6, is 20 times higher than that for all other states at 0.9. Importantly, similar to other states, intravenous abuse, shown in the orange line, was also increasing during 2011.

Now looking at the three-year post period, abuse by alternate routes, in blue, was lower, and intranasal abuse, in green, was lower, too. Given the greater magnitude of abuse in Tennessee, these drops are heartening. However, intravenous abuse was higher compared to 2011, yet it appears that a moderating downward trend is observed in the most recent quarters.

The marked differences in prevalences of abuse in Tennessee compared to all other states make NAVIPPRO nationwide figures uninterpretable as a measure of national trends.

What do we understand about Tennessee? First, the tendency towards greater abuse has been documented in the NAVIPPRO system as far back as 2008 prior to any significant data for abuse for Opana ER. Second, the uncommonly high intravenous abuse rate in Tennessee is not specific for Opana

ER but is evident for many opioids. Even before the reformulation of Opana ER, intravenous abuse was high in Tennessee.

This panel shows the intravenous abuse prevalence in Tennessee for 5 different opioids monitored by the NAVIPPRO system during the pre period before the reformulation of Opana ER. Original Opana ER is on the left. Intravenous abuse rates for oxycodone IR, morphine ER, and OxyContin were all higher than for Opana ER.

The contrast between Tennessee and all other states is even more evident when data for intravenous abuse outside of Tennessee, shown in blue, are displayed next to the Tennessee data for the same time period. There is clearly an intravenous abuse issue in Tennessee that goes beyond Opana ER and predates the introduction of reformulated Opana ER.

Here, we see the prevalences of intravenous abuse during the post period. Reformulated Opana ER is on the left, but notice that intravenous abuse prevalences for generic

oxymorphone ER, oxycodone IR, and morphine ER are all high during this time. And now, in blue, I have again added the intravenous abuse rates for all other states.

The first thing to note is the intravenous abuse prevalence for any drug is far lower outside of Tennessee than in that state. Even at these lower levels, several drugs, including oxycodone IR, morphine ER, and OxyContin, are injected at a relatively high rate.

So what might the NAVIPPRO data be telling us about Tennessee? It is possible that the population of individuals treated for addiction in Tennessee may be different than in other states or the sample may have changed over time. The use of inpatient treatment was higher in Tennessee compared to other states before the Opana ER reformulation but increased even more after the reformulation to almost 90 percent of subjects compared to about 40 percent elsewhere.

Similarly, the percentage of subjects coming into addiction treatment with a history of

prescription opioid intravenous use increased after reformulation across the country but was highest in Tennessee at 81 percent.

These demographic differences suggest that Tennessee individuals who abuse drugs in the NAVIPPRO system might be a more severe group of opioid abusers with more intravenous experience than those in other states. Alternatively, the population studied may have changed over time.

It is clear from the NAVIPPRO data that abuse patterns are constantly changing as the abuse environment evolves. The NAVIPPRO data demonstrate that abuse of Opana ER principally by the intranasal route but also by the intravenous route was increasing during the pre period, especially after the introduction of reformulated OxyContin.

In the post period, even though abuse by alternate routes appeared to increase nationwide, the effect of Tennessee warrants that the two regions be looked at separately. Within Tennessee, intravenous abuse was higher during the post period even at the same time that abuse by alternate

routes and intranasal abuse was lower compared to the pre period. But intravenous abuse was high for other opioids during both time periods and not specific for Opana ER.

In states outside of Tennessee, abuse by alternate routes and intranasal abuse was lower in the post period compared to the pre period, and intravenous abuse was at the same level seen with the original formulation in 2011.

Now, let's look at our other epidemiologic data. The second epidemiological study focuses on the RADARS poison center program. The RADARS poison center program gathers data from U.S. poison centers, covering more than 90 percent of the U.S. population in 48 states.

This high degree of coverage makes these data nationally representative of such calls. As prespecified, the 43 centers continually reporting data during the study period are included as the primary analysis set.

Each poison center obtains information from callers who are seeking advice regarding toxic

exposures, including exposures to prescription opioids. The data are collected across the country in a standard fashion and entered into an electronic health record. The intake process involves asking specific questions in order to accurately identify the toxic exposure. In addition, medical outcomes, including death, are captured in this process.

In total, poison centers receive over 2.3 million exposure calls per year. Incident-based data for the three-year post-reformulation period will be compared to the three-year pre period. Data adjusted for population will be shown and supplemented with tablet denominated data.

Four primary objectives were prespecified for this study. Essentially, determine if rates of Opana ER mentions by intentional abuse resulting in major medical outcome or death through non-oral routes of administration or resulting in overdose were lower after reformulation compared to the pre period.

There are some limitations to poison center

data worth noting. Poison center calls collect data on spontaneous reports, which are subject to reporting bias. Not all persons exposed to a prescription opioid who experience an adverse effect will call a poison center.

The call intake process attempts to identify the exact nature of the toxic exposure through characteristics of the pills or capsules. When a positive ID of the exact brand or generic is not possible, the data are coded as "not otherwise specified." Such data are not included in the analyses shown here.

Now let's review the results. This slide shows the increased rate of intentional abuse events during the pre period. The dotted line to the far left represents the time from January 2009 to September 2010.

In August 2010, reformulated OxyContin was launched. Just like the NAVIPPRO data showed, there was a further increase in abuse exposures of Opana ER after the reformulation of OxyContin as shown by the dotted line a little to the right.

The highest rate of measured abuse of Opana ER occurred in the fourth quarter of 2011. During the three-year post period, shown in the solid line, the rate of intentional abuse events was lower than during the pre period at the end of 2010 and all of 2011.

This lower rate of intentional abuse exposures remains stable throughout the three-year post period. The same pattern is seen here when the intentional abuse mentions are presented as a ratio of events to the number of tablets dispensed each quarter. A similar pattern was observed for these events, which include both intentional and nonintentional exposures with both denominators.

When looking at death and major medical outcomes, those events considered to be life-threatening or potentially disabling, we again saw an increasing rate throughout the pre period, particularly after the reformulation of OxyContin. However, during the post period, the rate of death and major medical outcomes was lower than during the peak. This lower rate of outcomes remains

stable throughout the three-year post period.

Again, similar patterns are seen when looking at the rate of death and major medical outcomes, when assessing results by the ratio of events to tablets dispensed.

Since 2010, RADARS has been capturing the route of administration for toxic exposures. When looking at the rate of intentional exposures via the non-oral route, the data show the same pattern as for the other endpoints, an increase during the pre period followed by a lower rate during the post period. Again, the pattern remains consistent when looking at the ratio of events to dosing units dispensed.

Since the non-oral route consists of intranasal and intravenous abuse primarily, let's look at those routes of abuse individually. Here we have the rate of intentional abuse mentions by the intranasal route. Intranasal abuse of Opana ER increased in the pre period and then was lower in the post period, similar to results for overall abuse.

Here, we are showing the data for intravenous abuse by the population denominator. During the pre period, the rate for Opana ER, the blue dotted line, increased after reformulation of OxyContin. In the post period, intravenous abuse rates remained stable at approximately the same rate as that at the end of 2011.

Now let's look at the results with the tablets dispensed denominator. As with the population denominator, the rates for intravenous abuse became higher by the end of the pre period. After reformulation, there is initially an increase followed by a stable to decreasing trend during the most recent years.

When we look at the mathematical change of the rate in the post period, we find that the numerator has stayed the same but the number of dosing units dispensed has decreased. In other words, there are not more cases of Opana ER injection reported to poison centers. The rate is driven by a decrease in the number of dosage units sold for Opana ER.

This is depicted here by looking at total doses dispensed during the pre period, in the dotted line, and in the post period, in the solid line. When we divide a smaller number in the denominator into the same number of events in the numerator, the ratio goes up, and in fact, that is just what has occurred.

Here, we have the actual counts of poison center intentional intravenous abuse cases. The number of intravenous cases increased to about 3 to 6 per quarter before reformulation of Opana ER and has remained in that range since then.

In summary, the RADARS poison center data show that abuse of Opana ER increased during the pre period, particularly after the introduction of reformulated OxyContin. However, coincident with the introduction of reformulated Opana ER, rates of intentional abuse, death, and major medical outcomes, non-oral abuse, and overdose were lower during the post period.

Let's finish up with a look at our third epidemiology study, which uses data from the RADARS

drug diversion program. This study is a supported epidemiologic study examining differences in rates of diversion mentions before and coincident with the introduction of reformulated Opana ER. The rates we are presenting are per 100,000 population.

The RADARS system collects reports from law enforcement and regulatory authorities of prescription drugs found outside of controlled distribution channels. The types of events include drug buys, pharmacy thefts, home robberies where drugs are stolen, drugs recovered during traffic stop searches, and doctor shopping events. The sample comes from 110 law enforcement agencies in 45 states.

The number of diversion cases of the drug sold in the illegal market may reflect the desirability of the drug among opioid abusers, and declines in diversion offer supportive data for less desirability. However, since oxymorphone data were only captured starting in 2011, data from the full baseline period are not available.

The drug diversion program also has

limitations. The investigators are not randomly drawn from a pool of all possible drug diversion officers. Jurisdictions volunteer to participate in the program. Furthermore, investigations may vary from one quarter to the next, and these data are unable to distinguish or predict the specific route of abuse.

Now let's look at these results. During the period of 2011, drug diversion investigations of Opana ER were increasing, consistent with the abuse data from the poison center program and from NAVIPPRO. In the post period, the rate of drug diversion events was lower and has remained lower over that time period.

In summary, the lower level of drug diversion investigations after the introduction of reformulated Opana ER suggests that the desirability of the formulation may have dropped.

Now let me summarize our conclusions from all three postmarketing epidemiologic studies. All three studies show that abuse of original Opana ER was increasing from 2009 to 2011, especially after

the reformulation of OxyContin.

Coincident with the introduction of a reformulated version of Opana ER, several observations were made in the post period compared to the pre period. Prevalence and rates of abuse by the intranasal route were lower. Intravenous abuse increased in Tennessee where such abuse was already highly prevalent, but this was not observed in other states. Additionally, drug diversion reports were lower.

The consistency of these findings across multiple data sources reinforces the conclusion that intravenous abuse rates of reformulated Opana ER remain stable at levels observed with original Opana ER in 2011.

Now I'd like to switch to postmarketing pharmacovigilance for a couple of minutes and discuss two events that were reported following the introduction of reformulated Opana ER. These two issues were specifically mentioned in the discussion topics posed to the panel by the FDA.

The first was receipt of reports of

thrombotic thrombocytopenic purpura from a nephrologist in northeast Tennessee in August 2012. These were associated with IV abuse of reformulated Opana ER tablets.

Endo took a number of actions in response to these serious reports. As soon as Endo was notified of these cases, we promptly informed the FDA and discussed the findings with both federal and state officials.

We met with our sales representatives in the area to ensure they were properly informing physicians of the risks of improper use of the tablets among their patients and reiterated our policy about notifying headquarters about potentially suspicious healthcare providers.

We met with local anti-drug organizations and law enforcement. We directed law enforcement to liaise with the National Association of Drug Diversion Investigators for assistance on training and drug take-back programs. And we have remained in touch with local healthcare providers who have been treating those patients with TTP.

Shown here are the cases of TTP associated with Opana ER by month of onset. There are a total of 65 reports, primarily from Tennessee, the majority of which occurred in 2012 and 2013. Since then, there has been a drop in the number of cases reported, and no new cases have been received by Endo since June 2016. And that was a literature report that likely occurred sometime earlier. It appears that the prevalence of reports has dropped.

The single major difference between reformulated and original Opana ER was the use of polyethylene oxide, PEO. This is a common inactive ingredient used in extended-release oral medications and listed in FDA's database of inactive ingredients. However, it has never been studied or cleared for administration by any other route.

In fact, studies by an interested researcher at FDA's Center for Biologics Evaluation and Research in collaboration with Endo demonstrated a potential link between IV administration of PEO in animals with some of the findings shown in humans.

Subsequently, similar cases of TTP have been submitted to the FDA and published with IV abuse of reformulated OxyContin, which also contains PEO. Thus, given the experimental evidence and the reports with another PEO-containing medication, this is likely to be a risk for IV abuse of oral preparations containing PEO.

The second event was the public health emergency declared in March 2015 in Scott County, a rural community in southeast Indiana. An outbreak of HIV had occurred, primarily being spread by needle sharing among a group of abusers of IV drugs.

Various state and federal agencies, including CDC and the Indiana State Department of Health, intervened and were able to contain the HIV outbreak principally through widespread screening of contacts, instituting a needle exchange program, and initiating proper antiretroviral treatment for HIV positive individuals.

Oxymorphone ER, both brand and generic, were the most prevalent drugs, although heroin,

methamphetamine, cocaine, and oxycodone were also documented as being used intravenously during this outbreak.

Overall, extensive use of IV drugs where needles and other paraphernalia were shared by a large group of individuals was the primary cause of the outbreak, not the individual medications.

Both the occurrence of TTP and HIV are serious consequences of intravenous drug abuse. While we believe the epidemiology data are not predictive of a growing trend in IV abuse, we take this situation seriously. As a result, Endo has begun activities to better understand the unique abuse situation in local communities and to make a difference in those areas.

First, Endo is committed to conducting an ethnographic study to understand patterns of abuse and the reasons behind them. We are piloting this first in northeast Tennessee where high rates of IV abuse have been documented for a long time.

Second, Endo has committed to at least a three-year program focused on targeted

interventions in problematic areas as shown here. The goals of these interventions are to intervene in youth before abuse begins, to support care in local treatment centers, to raise awareness and outreach, and to assist local law enforcement in their efforts to target the source of drugs.

In addition, we will continue to monitor the NAVIPPRO and RADARS systems as long as Opana ER is on the market.

Thank you. Now I would like to turn the presentation over to Dr. Alec Walker.

Industry Presentation - Alexander Walker

DR. WALKER: Thank you, Dr. Shusterman.

I appreciate the opportunity to address the committee. My name is Alec Walker. I am an epidemiologist who has spent his career studying the safety of medical products and procedures. I was previously chair of the Department of Epidemiology at Harvard. I am now a principal in WHISCON, a firm that specializes in drug safety.

I have been asked to speak to you today about how an epidemiologist would approach the

NAVIPPRO and RADARS data in interpreting the safety of opioid formulations designed to have abuse-deterrent properties. I will confine myself to points that I think should be part of the discussion.

In public health, decisions need to be made in a timely fashion often before there are enough data. The available information may be approximate or even biased. In agreement with the position expressed in the FDA briefing book, I believe that the information we have available is less complete, less accurate, and less representative than what we would look for if designing a study from scratch. Still, there is a coherent story here.

Let me address some important points and provide context to the data presented. First, we can't always measure what we want to measure. The quantifications of drug abuse that you have heard in this discussion are all ratios, ratios consisting of estimates of populations at risk in comparison to selectively derived product-specific numbers of abusers in NAVIPPRO or consultations to

poison centers in RADARS.

Let's first consider the number of abusers, which serves as the numerator in the presence of abuse, and the numbers of overdose events, which gives us a numerator for overdose rates.

Currently available national data sources provide only partial measures. For example, the National Survey on Drug Abuse and Health is an annual household survey that calculates estimates of past month and past year misuse of a variety of drugs by category. But it's only been since 2015 the information on specific opioid products has been available in the survey.

Thus, there's no real numerator data at the product-specific level. We have no estimates of diversion for specific entities. For overdose events, we have no national estimates. Even for deaths, we have no census estimates associated with individual products.

Events are not directly observable here, and so we need substitutes. For example, abuse events could be drawn from a registry using standardized

descriptions from active monitoring programs that cull likely events or from spontaneous reports. These are the situations with NAVIPPRO and RADARS.

We might also wish to hone in on a subset of events such as those called into hotlines or deaths and let them stand for all the events that we really want to know. This is the approach used in the RADARS data.

I said that we don't have directly measured numerators. We also don't have a true denominator for abuse prevalence or overdose incidence. Therefore, we use proxy denominators.

The simplest denominator, used for RADARS, is the sheer size of the population. This is useful for ascertaining the public health burden to the extent that you can consider the poison center calls to represent overdose events generally.

The second denominator, used for NAVIPPRO, is the number of individuals admitted to participating drug rehabilitation centers. Persons entering rehab are likely to bear some resemblance to abusers in general, and so these prevalence

measures may represent what is going on in the abuser community.

The third denominator is the number of tablets dispensed. In RADARS, a tablet denominator gives you a reference point for the poison center calls, and in NAVIPPRO, it provides an adjustment for the product-specific estimates of abuse prevalence among rehab entrants.

None of these denominators leads you directly to an estimate of the incidence of overdose or the prevalence of abuse. We can gain confidence in the findings if multiple approximate measures yield a consistent pattern of results.

I would like to say that tablets sold in a region are not likely to be a good measure of the availability of illicit drug in the same region. As this quote from NAVIPPRO indicates, prescription availability is calculated on a small region basis.

In my view, tablet denominators are shaky because they assume a correspondence between regional sales and regional illicit use. They also assume that the degree of correspondence varies

little between compared groups. So the use of a tablet denominator assumes, without evidence, a similar refraction diverted for different products within a given time period, or similar fractions of a single product over sequential time periods.

But we have strong field epidemiology to support the inadequacy of local sales as a measure of illicit availability. For example, the NAVIPPRO data, based on patients seeking drug abuse treatment, shows that two-thirds of diverted drugs come from drug dealers who often source their product far away from the point of use. This is documented in southeast Indiana when the DEA arrested the dealers and found out that the drugs had come from Detroit, Louisville, and Indianapolis.

In Missouri, drugs that are destined for illicit use are procured by individuals from many states, some as distant as Florida, because Missouri is the only state without a prescription drug monitoring program.

Thus, movement of illicit drug from areas of

high availability into areas of high demand results in higher numbers of overdoses in the area of high demand without a corresponding increase in local denominator of drugs sold. The result is a systematic exaggeration of apparent variations and risk.

Finally, the presence of potentially confounding factors introduces another challenge to drawing conclusions from these epidemiologic data. In epidemiology, we call this the ecological fallacy. For example, there appears to be an increase in IV abuse in Tennessee following the introduction of reformulated Opana ER, but we fail to account for potentially confounding factors such as changes in the composition of the sample over time.

Specifically, there was an increase in the number of inpatients that provide data to NAVIPPRO. Inpatient sites, as opposed to outpatient programs, are a proxy for severity and are more likely to report IV abuse. Therefore, we have what appears to be the effect of introducing reformulated Opana

ER as a reflection of an increased representation of inpatient programs through the post reformulation sample.

We can partially address the shift in population sites over time by attempting to hold the data sources constant. The NAVIPPRO analysis plan included a prespecified sensitivity analysis of only those sites that contributed at least one ASI-MV admission in each quarter of both pre and post periods.

This approach succeeds in holding the population of sites constant across both periods, but it substantially restricts the population to just 26 percent of the full dataset.

Importantly, it reduces the number of Tennessee sites from 53 sites in the primary analysis to just 2 sites in the fixed-sites analysis. These 2 sites accounted for 85 percent of the reformulated Opana ER reports in the post period. Such a restriction in reporting sites raises questions about the generalizability of the fixed-site analysis to the broader population of

interest.

How to proceed? You have incomplete data on the progress of a maelstrom. Wrong decisions will have consequences as well as correct ones. I would urge a middle way between summary rejection and uncritical acceptance of the information. It has been generated by processes that you can't examine. Form theories about the plausible explanations and then decide whether there is sufficient data to act.

For myself, I am persuaded that the data on the reformulation of Opana ER so far has indicated a deterral of intranasal abuse. I think that the reformulation has had little effect on the risk of intravenous abuse.

To me, the data from Tennessee suggests abuse prevalence an order of magnitude higher than in other parts of the United States, and increased intravenous use of all opioids, particularly Opana ER. I do not think that you will resolve Tennessee at this meeting, nor do I think that it makes sense to let Tennessee drive a decision about

the product when data from the rest of the nation do not show the same trends.

Thank you. Now I would like to invite Dr. Dart to the podium.

Industry Presentation - Richard Dart

DR. DART: Good morning. My name is Rick Dart, and I am the executive director of the RADARS system. I am also director of the Rocky Mountain Poison and Drug Center and a professor at the University of Colorado.

As you now realize, the amount of information on Opana ER, both in the intended and non-intended populations, is immense and challenging to integrate into a single conclusion. The details unfortunately are crucial here, and I would like to share some of those observations with you.

First, it is important to understand that the information available in the unintended population, of the many challenges inherent in the surveillance of substance abuse, the most challenging is that abusers seek to hide their

behaviors. These behaviors are not readily measurable by the usual data collection methods.

Thus, we can only measure abuse when the abuser chooses or is forced to reveal themselves. This occurs when they have an acute health event that stimulates them to call a poison center, when they are investigated for drug diversion, when they enter treatment for substance abuse, or when they voluntarily provide confidential information such as an online survey. Each of these approaches is used by a large body of investigators to study the opioid epidemic.

We know there are limitations to postmarketing surveillance techniques. Each data source has its own well-described limitations. However, the same limitations are often not present for other data sources. Thus, we can look at complementary data sources to form a more complete picture of abuse. This use of converging evidence is a common approach in public health.

Given all these challenges, how do we answer the question today? What are the benefits and

risks of a regulatory action on reformulated Opana ER? As you have heard, there is consensus that opioid analgesics are needed for chronic pain. A simple example is that while there has been a recent explosion of treatment guidelines for chronic pain, they all include the use of opioid analgesics when other treatments are ineffective.

There's good reasons for this. You've heard from Dr. Fine that chronic severe pain can be a serious condition with its own inherent risks. Treatment of pain requires multiple therapeutic approaches, including a range of opioids, to treat the unique needs of individual patients who may not achieve pain relief or develop side effects.

Yet we all know that opioid analgesics have serious risks. So to me, the question becomes, is Opana ER different? Do the data prove that reformulated Opana ER has a risk-benefit assessment that is different enough from other opioid analgesics to need separate regulatory action?

Dr. Shusterman has already shown the data that, overall, total abuse from Opana ER in both

the RADARS poison center program and the NAVIPPRO substance abuse treatment program increased after the reformulation of OxyContin but then decreased after Opana ER itself was reformulated. It is important to note that these trends for intranasal and intravenous abuse have been flat to decreasing over the three years after reformulation.

For me, the outcomes data are the most informative in determining whether the reformulation is associated with new or increasing harms. As shown by the blue dotted line, the population-adjusted rates for major outcomes and deaths are lower for Opana ER than for the other Schedule II opioids, which is the orange line.

Since 2011, they have come down and stayed down. Even after adjusting for dosing units, we do not see concerning changes in the rates of major medical outcomes or death in the poison center program. The rates adjusted for dosing units are approximately the same for Opana ER and the other Schedule II opioid products after the reformulation of Opana ER. Even if we address misclassification

of oxymorphone products, the results are the same. Major outcomes and deaths are not increasing.

As you probably realize, it is hard to find product-specific mortality data because medical examiner data, like those from the CDC, cannot identify the specific product. They only identify the active ingredient. However, poison centers do record the specific product involved in nearly all cases they receive. We receive fewer cases, but poison center data correlate well with deaths reported by the CDC.

Like the other data I have shown, deaths associated with Opana ER increased before it was reformulated but have since decreased and remain low over the three years after reformulation.

How can we incorporate this information into a benefit-risk assessment? We are all aware that the use of opioids carries risks. The data available from several sources presented today show that Opana ER accounts for a small portion of total abuse cases and has risks similar to the other long-acting opioids.

Epidemiology data indicate that abuse by non-oral routes is similar to other long-acting opioids and has now been increasing. Importantly, major medical outcomes and death have not increased. In fact, we see consistent trends in abuse diversion and medical outcomes in the three different programs.

One reason for the better than expected performance by Opana ER may be that although not labeled for abuse deterrence, Opana ER does have demonstrable physical chemical barriers to crushing for abuse.

Considering all the data, I don't see evidence of new net harms for Opana ER. We have heard from Dr. Fine about the efficacy of Opana ER in people with chronic pain and the important features of oxymorphone as a long-acting choice among opioid analgesics.

Like every opioid analgesic, Opana ER is abused, and the abuse is intravenous in some cases. The risk of TTP with injections still exist, but this is true for other products where PEO is a

major ingredient. Perhaps a label warning is needed on PEO products.

I have presented surveillance data that has many limitations, yet they represent the best product-specific data available in the United States. Perhaps we need additional data like the ethnographic study Endo is planning to conduct. These data should help us understand why abusers in Tennessee inject Opana ER. But today, the committees' charge is to make a recommendation based on their judgment using the information available.

To me, loss of Opana ER would create a major burden to a substantial number of patients without evidence of an increasing or overwhelming harmful effect. Removing any particular product doesn't seem prudent to me. These patients will have to switch to other opioids, which have their own risks, and I believe that they were on these drugs for good reasons like improved efficacy or an improved adverse event profile for that patient.

Every overdose is a tragedy, but we often

miss the fact that opioids are a tremendous help for millions of patients who otherwise would not be able to function. It is clear that patients need safe and effective options to treat their chronic pain.

Thank you. And now I'll turn the podium back to Dr. Rotman.

(Pause.)

DR. WINTERSTEIN: I wasn't sure whether there was some concluding remarks.

DR. ROTMAN: Sorry. Thank you for the ability to present today.

DR. WINTERSTEIN: We thank you.

We will actually now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience.

We will resume with clarifying questions at 11:10.

(Whereupon, at 10:56 a.m., a recess was taken.)

Clarifying Questions

DR. WINTERSTEIN: All right. Let's start with questions. Are there any questions for Endo? Dr. Bilker?

DR. RUHA: Hi. Michelle Ruha. I have a question about the --

DR. WINTERSTEIN: I actually had called Dr. Bilker.

DR. RUHA: I'm sorry.

DR. BILKER: I have question about all the graphs that were shown for RADARS and NAVIPPRO. Do you have versions of those plots that have confidence intervals?

For example, it's very difficult to interpret without either confidence intervals, testing for trend. I didn't see any statistics other than they were all plots.

DR. ROTMAN: We will start with Dr. Neil Shusterman that can show you what we can about the confidence intervals, and we will call up a statistician as needed as well.

DR. SHUSTERMAN: I am Dr. Shusterman.

Because of the multitude of lines and the difficulties in showing lots of confidence intervals and still focusing on the lines, we chose not to, but actually in the briefing book, there are confidence intervals presented there.

Also, there were a very large number of potential inferential statistics calculated without really a primary plan of how to do so. We are really thinking of this more as a descriptive look at the information rather than an actual inferential look. But I would like to ask Dr. Davidson, who's the head of biometrics at Endo, to talk a little bit more about that.

DR. DAVIDSON: Good morning. I am Jeff Davidson. Early on, we made a decision that use of inferential testing for these data would be inappropriate. The data are best shown descriptively. To use any inference, including confidence intervals, would be inappropriate for a number of reasons, number of principles that are violated by these methods.

DR. WINTERSTEIN: Ms. Higgins?

DR. HIGGINS: I wasn't prepared for that.

A question regarding the physical manipulation tools, I am wondering what research there was done to both compare the fact that the types of tools used with other similar studies conducted by other companies with respect to standardization of the tools. Then also, what research there was done to understand whether these were indeed common tools used by abusers.

DR. ROTMAN: We utilized various tools that we think were the most destructive and that are used by abusers. We will call up Dr. Frank Diana to go into greater detail about that.

DR. DIANA: Endo evaluated many tools that involve crushing, cutting, grinding, and grating. And that's pretty much what the guidance says, so that's pretty much standard now in the industry, although tools can certainly be somewhat different.

In our case, we looked for common tools, a variety of different tools that can be used, and we listed those, and they have codes.

Then product knowledge, so we understood how

we designed the product. We understood how you might go about compromising it, and so we used those tools. Again, those would be different depending on the type of formulation that you would be looking at.

Then we did go to the online chatrooms quite a bit and see what type of methods were being used by typical abusers, and then of course, you would have your experienced abusers also who tended to use multistep-type approaches.

I think to answer your question, we looked at a lot of tools, a lot of different techniques. It is probably fairly difficult to standardize, although everybody uses similar tools, but it really depends somewhat on the formulation that you are trying to compromise.

DR. WINTERSTEIN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. I would just like to comment on Dr. Fine's presentation and references to Dr. Pasternak.

I couldn't agree more about what you said, Perry, regarding the need for this medication and

the use of opioid rotation strategies and polymorphisms, et cetera. But my question to Endo would be does any of the data that was presented today with respect to abuse distinguish between chronic pain patients who abuse versus nonchronic pain patients who abuse?

It's great to make a case about the value of another molecule, but it's not clear to me as to whether this was a situation where it was actually patients for whom the medication was prescribed versus people who were getting it through diverted channels, et cetera, et cetera.

DR. ROTMAN: It's a challenging question because there's no one way we have to determine when a prescription is given whether it's meant for the patient or whether somehow, unfortunately, it gets diverted.

Are you looking for clinical trial data or some sort of data that is in the published literature about that?

DR. ZACHAROFF: Well, I am thinking if we're talking about data streams from substance abuse

treatment centers and/or poison control centers, that there might be some information that could be gathered about the patient's medical history. And if it was somebody who had a history of chronic pain, then that might be more telling. It might be more likely that the medication was actually prescribed for them as opposed to the idea of these patients obtaining the substance illicitly.

Because it makes me think about somebody mentioning adding to the label the risks associated with PEO and intravenous injection, and I think of drug labels as being intended to make a difference in patient safety. I'm not 100 percent sure how changing the label would then have an impact on people who are illicitly obtaining the medication.

DR. ROTMAN: Well, why don't we start out, we'll call up Dr. Neil Shusterman, and he'll at least explain the demographic characteristics of the people that came into our NAVIPPRO studies.

DR. SHUSTERMAN: NAVIPPRO does collect that information for people entering addiction treatment, and I can show that to you. It is the

set of answers towards the bottom of the slide where it says "self-reported pain."

Now, this is broken up into the entire sample in the first column of data, and then the original Opana and then the reformulated Opana. Those who have had some kind of pain problem, we don't know if this is current or past because of the way it's asked, it's about a third going up to about half had some kind of reported pain problem at some time in their lives. That's the data that we have.

DR. ZACHAROFF: Thank you.

DR. WINTERSTEIN: I actually have a quick follow-up question on the value of oxymorphone in the larger scheme of pain management. Dr. Fine talked in particular about adverse events and drug-drug interactions involving cytochrome P450. I think it would be helpful for the committee to understand whether that really is relevant with the typical alternatives to opioid use.

From what I recall, those types of interactions would really be confined to methadone,

fentanyl, but not the classic oxycodone or hydrocodone, morphine types of drugs. Could we get a little bit more detail on why the adverse event issue is that relevant?

DR. ROTMAN: We'll break that question into two parts. We'll start by calling up Dr. Tony Priestley to describe what we know of the drug-drug interactions, and then we'll bring up Dr. Fine to illustrate how in clinical practice this information is used.

DR. PRIESTLEY: The body has a number of ways of eliminating undesirable substances. Let me start by showing a table showing the metabolic disposition of a variety of commonly prescribed opioid therapeutics.

What you can see here in the center column is that the vast majority of these drugs utilize cytochrome P450 based hepatic extraction as the primary route of elimination. Additionally, codeine, hydrocodone, and oxycodone progress to phase 2 metabolism using a separate system based on glucuronidation via an enzyme system called UGT.

Now, morphine, hydromorphone, and oxymorphone are somewhat different. They do not utilize any of the cytochrome P450 extraction methods that proceed directly to glucuronidation. This creates a distinct advantage, as the questioner has alluded to, in that the vast majority of commonly prescribed therapeutics, a number of nutraceuticals, grapefruit juice, many other substances that are taken in, are metabolized using cytochrome P450. So there's an incredible liability for pharmacokinetic drug-drug interactions.

Now, to exemplify this point, actually, oxycodone has a very distinct warning in its label highlighting prescribers to the potential risks for concomitant medications that might possibly be 2D6 metabolizers.

This warning is actually further substantiated by numerous reports in the clinical literature highlighting cases of DDI to pharmacokinetic drug-drug interactions with methadone, oxycodone, and other opioids, but

nothing, to my knowledge, for oxymorphone.

So I do believe that oxymorphone presents a unique situation with respect to pharmacokinetic drug-drug interactions.

DR. ROTMAN: If Dr. Fine would mind saying how this works in clinical practice.

DR. FINE: The clinical challenge that we face is really the tension that exists between trying to simplify drug regimens trying to avoid drug-drug interactions and to limit polypharmacy and almost the obligate necessity of what I'd call rational polypharmacy, recognizing that it's rarely true and in certainly complex pain conditions that a single drug will do when pharmacotherapy is indicated at all.

Other than I don't have a whole lot to add beyond what was in the chart, the fact of the matter is there are very few clean alternatives. And by clean, I mean drugs that either do not rely upon either the cytochrome P450 system, and especially 3A4 and 2D6, in terms of either opioid interactions or interactions with the commonly used

drugs, especially for the most difficult to treat pain conditions such as the neuropathic pain conditions, which is why I gave the exemplar case, almost all of which have some interactions there.

The other component of this is in those drugs that are metabolized through glucuronidation, the issue there, for instance, morphine, is that we have active metabolites that accumulate especially. Then we have to start thinking about disease interactions, renal function, et cetera.

Oxymorphone does fit into this little niche where it does not have active metabolites that accumulate, nor do we have these CYP450 problems.

DR. WINTERSTEIN: So in your case, what was the opioid that actually got replaced by Opana, and what were the adverse events? Because when I'm looking at classic drug-drug interaction tables --

DR. FINE: Right.

DR. WINTERSTEIN: -- I don't see --

DR. FINE: What had she been on prior to the time I saw her?

DR. WINTERSTEIN: Yes.

DR. FINE: She had been on, if I remember, almost everything. I saw her after she'd been on not only multiple drug trials and had been hospitalized these four times for problematic drug-drug interactions and over-sedation and similar related problems, but it just had been so desperate, she had had a gamma knife procedure that unfortunately failed. She was willing to go through brain surgery to try and overcome this.

The reason was the drugs she had tried from hydromorphone to morphine to oxycodone, levorphanol, butorphanol, buprenorphine -- I am trying to think of all -- methadone, everything that she had tried had interactions with other things she needed. Examples of what she finally ended up being able to tolerate, paroxetine and carbamazepine, both have -- one has a 2D6, the other, 3A4 pathway; the gabapentinoids, similarly of the tricyclics.

We go through all these regimens and slowly, discernibly to try and limit these interactions. But in her case, I daresay that it was a little

simpler than had been made out. I wish I had seen her a bit earlier. I'm sorry to say that this had not been tried before. But I think it was a pretty simple principle I was trying to elucidate, which is get the cleanest drug, limit the drug-drug interactions, limit the adverse event profile, and then proceed, and she was able to have a successful regimen.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: Michelle Ruha. My question is actually about the TTP with the injection of the PEO-containing formulation. It sounds like there were pretty frequent reports of this complication with the Opana ER, and we were told that it was also reported with IV administration of the OxyContin tablets that also had the PEO.

I am wondering, is it just a single case report, or is there similarly sporadic, continuous cases reported with OxyContin, also? Is it truly a PEO effect, or are we really only seeing this with Opana? Because I think there could also be a misclassification obviously with some of these, and

I am just wondering if it is really a PEO across the different products that contain PEO.

DR. ROTMAN: The data lend itself to the conclusion that TTP, as it's been reported with other formulations with PEO such as OxyContin, it could very well be a PEO effect. It is a very concerning issue. The only slight bit of possible good news is that we're not seeing it increase dramatically over time. But we'll call up Dr. Neil Shusterman to go over what we have seen and what the rates look like over time and if we've seen it with other products.

DR. SHUSTERMAN: A couple of points first about Opana and then about OxyContin. The reason this came to clinical light was because of clustering so that nephrologists in northeast Tennessee saw 5 cases in a very short amount of time, and as an epidemiologic phenomenon when you have clustering, that heightens awareness. If they had seen 1 case here and 1 case there, it would have been in the background of the occasional case that's seen in any given hospital.

That brought it to awareness, and then there were public health announcements made by regulatory agencies that even heightened further awareness of this particular molecule, and it was only about Opana.

As you can see from the graph I had shown, it all spiked in 2012, 2013, and interestingly, as we'll hear later today, even in southeast Indiana where Opana was one of the drugs, there were actually no cases of TTP observed there.

Now, as for OxyContin, it is possible that those cases were more sporadic. We have searched the FDA FAERS database, as the FDA has, and we were able to find 6 cases. Two of those are the ones in the literature, but there were also 4 others. And I'll show you those case summaries here.

Information reported spontaneously often has missing data and is often not complete, but these cases were ones that did not have confounding medications. The majority were either unknown route of administration or intravenous, but they were all coded as thrombotic thrombocytopenia

purpura, and it appears that at least 5 of the 6 resulted in hospitalization.

So these weren't random cases. These were significant cases. Three came from Australia, 1 from Canada, and 2 were identified from the United States. So given the experimental evidence that we'll also hear more about this afternoon, we believe that it does have something to do with PEO.

DR. WINTERSTEIN: Dr. Emala?

DR. EMALA: I have two questions. First one for Dr. Rotman's presentation on slide 36. I am curious on the right-hand side of this slide with solvent A at 6 hours, or all these comparisons for that matter, whether they were done side by side, same laboratory setting by the same group, or is this relying on existing data for OxyContin.

My second question for this topic is in any of these extraction procedures with any of these formulations, has anybody measured PEO extraction and compared it across Opana versus OxyContin as an example?

DR. ROTMAN: We'll bring up Dr. Frank Diana

to answer both of those questions in turn.

DR. DIANA: The OxyContin data that's presented here is our data, so it was run side by side in the laboratories. Similar results are obtained as discussed since OxyContin uses PEO similar to Opana and uses a similar manufacturing process to yield the hard tablets, and so you get fairly similar results when you do the extraction testing and a variety of other tests that we do between OxyContin and reformulated Opana.

We have not tried to measure the PEO to see if there would be any difference. I can say this: The formulations have similar levels of PEO. They're not exactly the same obviously, and I obviously don't know the OxyContin formulation exactly as I do the Opana. But it's typical to have a fairly high amount of PEO in these formulations.

DR. EMALA: It would seem based on I guess the discussion we'll have this afternoon after we discuss the concern about TTP, whether this is an important thing to measure and compare between

different formulations.

My second question actually for Dr. Shusterman's presentation -- and we can reference slide 65, although it applies to many of the Tennessee versus non-Tennessee data points that were pulled from the NAVIPPRO data. And a lot of this Tennessee data is passed off as being an anomaly.

I guess my question -- and maybe this would also -- Dr. Walker could comment on. Is it possible the Tennessee data is just better data? Is it possible that Tennessee is doing a better job of collecting this data?

DR. ROTMAN: We can explain that in detail. That's not what we see with the data. But I'll have Dr. Shusterman start by explaining what we see, and he will call up Dr. Alec Walker to further explain it.

DR. SHUSTERMAN: I don't think it's a phenomenon of a particular area because the tool that's used is used uniformly at all treatment centers. It's either a phenomenon in Tennessee or

the types of patients that are getting referred to the centers in Tennessee in the NAVIPPRO system.

I think it would actually be better to hear from Dr. Butler who runs the NAVIPPRO system.

DR. EMALA: Could I just follow up on that?

DR. SHUSTERMAN: Sure.

DR. EMALA: Is there any way of knowing if Tennessee centers do a better job than other centers even though they're using similar questionnaires and methodology?

DR. SHUSTERMAN: Do you mean better job in collecting data or something different?

DR. EMALA: Yes, in the accuracy of the data.

DR. SHUSTERMAN: I'll have Dr. Butler speak for that because he owns the NAVIPPRO system.

DR. BUTLER: Hi. I'm Steve Butler, chief science officer at Inflexxion, and Inflexxion runs and maintains the ASI-MV data stream.

As Dr. Shusterman just mentioned, part of the advantage of the ASI-MV is that it's standardized presentation to the patient across

time, across geography, and across products. The question about what's going on in Tennessee is that I think there's no reason to believe that the way that it is administered in Tennessee is any different than any other states.

If I could see the slide on the four states that we created, I think that might be helpful, the other one that we added last night. It would be more informative. Can we find that?

Well, we can get some of the information here. One of the things that you would want to consider in terms of what we're seeing in Tennessee is how many admissions are the data drawn from. If we look at this slide, what we can see here is that a similar state close by, North Carolina, if you look down the road, you see that there's about the same number of assessments being drawn during -- this is in the post period.

There are about the same number of assessments being drawn. You can see that the difference -- if you look down the second row from the bottom, you can see that although they're a

similar part of the country, that there are similar number of assessments, and also, that there are comparable numbers of Opana ER prescriptions in the state.

We're getting vastly different Opana ER abuse cases from Tennessee than we are from North Carolina. And I should add that North Carolina is the state that has the second largest N of Opana abuse cases. I think that these are the kind of data that suggest to me that something different is going on in Tennessee that's reliable.

DR. EMALA: Just to finish, can you link any of this NAVIPPRO data to availability of these various drugs of abuse? So is it possible that the rates are higher here simply because of distribution or diversion, I should say, is higher in that region?

DR. BUTLER: Well, if we could see that slide again. That's why we had on the slide there the number of tablets dispensed. It is higher in Tennessee.

Am I misunderstanding?

DR. EMALA: Well, that's prescriptions, but as one of the speakers pointed out, we can't always link where the diversion occurs to where the drug is dispensed from. So linking it to where and how many prescriptions are prescribed in one state versus how much is transported by dealers into a state, it seems to me not a great link.

DR. BUTLER: That's absolutely correct. And in our system, we do not have a way of tracking that. I'm not aware of that in any system.

DR. ROTMAN: Yes. What we can do -- and it's a shame, we were going to have Dr. Shawn Ryan, who is a nationally known addiction specialist, come and speak to those very issues, but we do have Dr. Steve Passik that has talked to many specialists and can explain what we can know about what is going on with Tennessee and the diversion into the state, perhaps some other regions.

DR. PASSIK: Thank you, Harris.

I'm Steve Passik. For the last year, I have been senior medical director at Endo. Prior to that, I was a clinical psychologist. I practiced

in pain and addiction for 25 years in various settings, including Sloan-Kettering and University of Kentucky and Vanderbilt.

Firstly, let me say by saying that it is an anomaly does not mean that it is not something that we take very seriously and care deeply about. I lived and worked in Tennessee, and I care very, very much about any loss of life to chronic pain and suicide or to drug abuse in that region.

I have spoken with multiple substance abuse experts in that area where we have found that there is a particular abuse psychology, if you will, in the Tennessee area. It's tempting to see one curve go down and another go up and immediately assume that people have been automatically shifted from one form of abuse to another.

In my clinical experience over the years, it takes a certain climate for that to happen. It takes mentors to teach you how to get paraphernalia, how to use it, how to prepare drug and so on and so forth. So there is that particular ecology in Tennessee where this signal

has been present since 2008, which has been higher than everywhere else, but is thankfully also trending downward at this time.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: Well, I have to say I'm fascinated by the Tennessee research, being from Kentucky, and I have a couple of questions to follow up the discussion that we just had. I think this is very important because I think if we don't figure out exactly what's going on in Tennessee, that we may recreate this finding in another geographic area in the country fairly soon.

My first question really relates to the volume of agent that goes to Tennessee. Does Endo have any understanding of the number of tablets that go to a specific area, a specific geographic area over time?

DR. ROTMAN: We'll call up Dr. Shusterman to explain what we do now about where tablets come from. We also have information when we investigated in Indiana, which was fascinating in that the tablets did not necessarily come from that

region. Maybe Dr. Shusterman --

DR. BROWN: I'm really interested in -- we've been to that data. I'm interested specifically for the manufacturer and whether you can determine how many tablets of oxymorphone that you ship to a specific area in any given year.

DR. ROTMAN: Absolutely.

DR. SHUSTERMAN: We do have that data because they were used obviously as the denominator in these studies. Let me show you Tennessee.

Using the same format you're familiar with, the dotted line represents original formulation, and the solid line represents the reformulation. This is Tennessee only.

What it appears is that the amount of drug tablets dispensed reached a peak at the end of 2011, and now at least in 2016, it looks like the levels are about the same, although for a period of time, they were lower.

DR. BROWN: Is there any difference in the way that Endo markets individual drugs in individual areas of the country?

DR. ROTMAN: There is not, and actually at the current time, we are not prospectively marketing with sales representatives. But there's no state-by-state difference.

DR. WINTERSTEIN: Ms. Robotti?

MS. ROBOTTI: Thank you.

We briefly saw a slide indicating -- my actual question is on subpopulations. Have you evaluated if the drug is being abused more by men or women or people of different backgrounds?

You had a slide up very briefly that seemed to show on my quick glance that the population of abusers went down by about 10 percent for men and up by 10 percent for women between the reformulation. Can you address that? Did you look at it?

DR. ROTMAN: Yes. Perhaps we can start with Dr. Steve Passik talking -- or Dr. Neil Shusterman to go over the detailed data, and Dr. Passik can go over what we see in the abuse psychology.

DR. SHUSTERMAN: I'll put up the demographic slide again from NAVIPPRO, and there are some

shifts. We specifically have not done what you might be referring to as a subgroup analysis. But overall, for example, in age, there was a little bit of a shift towards an older population during the reformulation going up from 12.4 to 23 percent. Men and women shifted a couple of percent. Race looked like it was pretty much the same.

So there wasn't a huge change from the pre period to the post period in major demographic factors. And I talked about pain before in response to a previous question.

DR. ROTMAN: And Dr. Passik, maybe just to explain the experience in the real world with subpopulations.

DR. PASSIK: There have been pockets of IV drug use amongst high school students that we've noticed in a recent publication that have come up around the country, none of which has shown an Opana signal.

I think in my clinical experience, when people are looking for drugs to use via their preferred route, we may hear a lot today about

certain drug effects or the particular likeability or whatnot of any particular chemical, but I think by and large, availability and price will trump whatever else is used by several-fold. And unfortunately, as we all know, we have a very large amount of illicit opioids, synthetic and heroin, that have probably pushed aside other drugs in many of those other locations.

DR. WINTERSTEIN: Dr. Lo Re?

DR. LO RE: Dr. Rotman, you had made the point that the reformulated Opana ER had similar indications in physical and chemical properties as OxyContin ADF, which also uses the polyethylene oxide. You had that in I think slide C33 to C038, and I thought that was very interesting that you called out particularly that comparison. You also made the point later on that oxymorphone ER was really the most prevalent abuse drug in the HIV outbreak in Scott County, Indiana.

I have actually four questions for you. First, do you have any data that actually compares the rate of abuse in the pre and post reformulation

periods between the reformulated Opana ER and OxyContin ADF? I just thought since you were calling that drug specifically out and were highlighting their similarities that you might have some head-to-head comparisons on rates of abuse there.

Secondly, given that Dr. Shusterman made specifically mention about that TTP was observed with the OxyContin ADF, do you have any -- I don't recall seeing whether the number of cases of TTP with the Opana ER was similar to the OxyContin ADF.

Then the third question I have for you is why does Dr. Shusterman or Endo think that Opana ER was the most prevalent abused drug in that HIV outbreak?

Then my last question to you is the statistician specifically made mention that the key results from the category 4 postmarketing data are really descriptive and not really amenable to statistical analyses. But we on the committee are really basing much of our decisions in terms of the risk and the benefit on those data.

I am just wondering, are there any other studies that Endo is proposing, perhaps more quantitative or more statistical, to actually consider in the future?

DR. ROTMAN: As a point of clarification for your fourth question -- and we'll get to all of them -- we could elaborate a bit more about our statistical reasons, if that would help, and then also address your fourth question, if that would help.

We'll first start with Dr. Shusterman to explain what we can show comparing with OxyContin and the abuse rates.

DR. SHUSTERMAN: I'm happy to take the first three, but you may have to repeat them because I was trying to get them down.

Let me put this up. We do have data on OxyContin contemporaneous in the same time periods, and OxyContin is shown in gray here. Similar to our color scheme, if it's a dashed gray line, it's the original. If it's a solid gray line, it's reformulated.

You can see that they reformulated in August of 2010, and their numbers have dropped further and in the post period have dropped even more. I already mentioned after the reformulation, ours went up, and then when we reformulated, ours have come down. Right now, as you can see, they are basically intertwined.

Your second question was about?

DR. ROTMAN: This was with the TTP and what are the number of cases of OxyContin compared to what we saw with Opana.

DR. SHUSTERMAN: Yes. In my presentation, there were 65 cases with Opana, and in the table I presented, there were 6 cases with OxyContin that we were able to discern from the FDA's database. All of the Opana cases were either directly reported to us as the manufacturer or came from literature, articles. So we have obviously more of a line of sight to those than to OxyContin.

Then the third question?

DR. ROTMAN Then, Dr. Shusterman, we wanted to discuss what we know about the HIV outbreak and

the prevalence or non-prevalence of Opana compared to other products as well.

DR. SHUSTERMAN: Yes. For that I'm going to say we don't know the actual reason why it was Opana, but what we do know is that Opana was not being prescribed by any local individuals, healthcare providers in Scott County, Indiana, and it was not being stocked in any pharmacies.

Of course, then the DEA found that -- the drug dealers were arrested. About 10 arrests were made. It was pretty prominently publicized, and none of the drug was coming locally. So how they got it in Louisville, Kentucky; Indianapolis; and Detroit, Michigan; they don't say in any of their public pronouncements, so I don't have any other insight on that other than the individuals who were supplying it were getting it from somewhere, of course.

DR. ROTMAN: I'd like to set up for the fourth question on Dr. Davidson. He can explain, we have shown the confidence intervals in locations. He can point out where they are and

explain a little bit more why the statistical methodologies he discussed make sense.

DR. DAVIDSON: Thank you. I believe that the question that was asked was not so much about the statistics and their use in this particular setting. The question was more about what could we do to conduct a study that would be able to enable us to do inferential testing.

With that, I think the answer is best resolved through a discussion by an expert epidemiologist since this is an epidemiological issue. Thank you.

DR. ROTMAN: We can call up Dr. Walker, if you'd like. Thank you for the push.

DR. WALKER: First, let me say that I agree with Dr. Lo Re's view and differ somewhat from our Endo colleagues. I think that examining the confidence bounds based on the numbers of events is helpful even though we're aware that there may be clustering and other things that make the bounds unreliable and that you still need some way of knowing whether you're talking about 2 cases or 200

cases in the data.

To stand for Dr. Davidson's point, though, if people commonly take confidence bounds and then turn them into informal statistical tests -- and we probably don't have the basis for doing that here.

Can I answer a further question there, or is that a complete answer? Okay.

DR. WINTERSTEIN: Dr. Ghany?

DR. GHANY: Yes. Thank you. Marc Ghany. I have two general questions. Can you give us an estimate of the size of the prevalence of the intended population for Opana ER and where this data is derived from?

My second question is, where does Opana ER fit in the management algorithm of this intended use population, and how effective are alternative treatments that are already approved for this population?

DR. ROTMAN: Yes. We'll answer that in two parts. I'll take the first part.

What we can say are the number of prescriptions that are received, and it's 100,000

prescriptions per month for oxymorphone as a molecule in the United States. Half of them are on the brand, and half of them are generic.

Why don't we call up Dr. Perry Fine to talk about the use of Opana and in those numbers of patients to address your question of prevalence rates.

DR. FINE: Let me make sure I understood the question. I don't want to opine on something that you're not inquiring about.

Other than what we know through IMS data how many prescriptions are written, what the population would be for whom Opana would be the best choice with oxymorphone would be the best choice, it would be fully in the realm of opinion and would go something like this, that of the hundred million patients for whom persistent pain is reported as a problem on a regular basis per the IOM report, 5 to 10 percent of that population may have indications for continuous or chronic opioid therapy based upon the fact that the types of -- the epidemiology of their pain problems and the likelihood of other

treatments not being effective.

Of that population, then what's the subset that would most likely respond to oxymorphone? Other than the standpoint of drug-drug interactions we talked about, I think this is a question I would like to defer to Dr. Pasternak to see if he can give some insight into where the pharmacogenetics might give some inkling, where the laboratory may start to actually inform the clinical practice in that way.

Is that -- if that's --

DR. GHANY: There was a second part to that question, and that is, how effective are the alternative agents that are already available?

DR. FINE: All I can speak since there are no prospective clinical trials, it's just once again, a compendium of opinions but a lot of clinical experience. What the literature says, and what my clinical experience would corroborate, is that oftentimes, it takes 3 to 5 opioid rotations over the course of weeks to months to find the sweet spot of where the highest degree of efficacy

is and the lowest number of adverse events or the severity of adverse events that would lead to problems as well as the intent to actually limit dose escalation to try and get more efficacy out of a drug that may not, in fact, be a good match inductively in terms of pharmacogenetic responsiveness.

The clinical answer is you start with usually what the patient can afford, it's a very pragmatic issue, what the history would dictate has been their previous experience, and then you begin to treat. I tend to prefer, as you've heard me state, cleaner drugs, drugs that have lowest likelihood of drug-drug interactions because it's likely the patients are going to be on multiple drugs, especially older patients. I take care of a lot of older patients and patients with advanced illness. So the multi-drug polypharmacy is a major issue.

Does that begin to answer? I'd love to get more incisive, but there is no prospective data or prediction that we actually depend upon in the

clinic as of yet.

DR. ROTMAN: Thank you, Dr. Fine.

DR. WINTERSTEIN: Our last question before the break, Dr. Mendelson.

DR. MENDELSON: Hi. This is a comment probably mostly for Drs. Butler and Dart, and for the general issue about this issue of opiate diversion and treatment.

You guys never expressed the data against opiate treatment availability. The other side of the coin of opiate diversion and abuse is treatment, and if you have treatment programs available to people, they probably will not inject as much drug.

It'd be interesting to see what Tennessee and Indiana's rate of treatment is, and just glancing at the SAMSHA treatment site, there are only 17 treatment sites in all of Indiana and only 13 in all of Tennessee.

My bet is a lot of this abuse and diversion issue is because there's no place to get treated, and when there was treatment in Tennessee, it's

inpatient residential care without medication, and that's a great place to get trained in how to inject drugs after you leave, so great mentorship. Although, in San Francisco, I would say we have excellent mentors for drug abuse, and we'd put them against Tennessee's anytime.

I would like to see your data expressed against treatment availability, and I suppose what I'd rather have you do than an ethnographic study is to pay for and to get treatment more available. This would eliminate a lot of your trouble, less cases of TTP, less cases of overdose, less cases of HIV.

You might also work on needle availability and needle exchange in Indiana. I think that was the vice president's epidemic, personal, because he didn't allow needle exchange to occur until the epidemic was pretty much at its terminus.

Anyway, those are some comments for both Endo and for the NAVIPPRO and RADARS people in terms of approaching how to think about these problems. Treatment is important.

DR. WINTERSTEIN: I didn't hear really a question, so we will break for lunch. We will reconvene again in this room in one hour from now. That's 1:00 p.m.

Please take any personal belongings you may want with you at this time. For the panel, you can leave your laptops here. There will be security in the room, so you don't have to put everything together.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any other members of the audience.

Also, one other comment, there is some panel members who are new to the process here. When you raise your hands and either Stephanie and I see you, you actually get on a running list so we actually have the list of everybody who indicated has a question. So there still are a few people on here. We will revisit this after the FDA presentation.

So there will be more time for more

questions. We have plenty of time, and if the snowfall starts, we might have more time than we need.

(Laughter.)

DR. WINTERSTEIN: Enjoy your lunch.

(Whereupon, at 12:03 p.m., a lunch recess was taken.)

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

(1:03 p.m.)

DR. WINTERSTEIN: We will now proceed with presentations from the FDA. Dr. Staffa will begin.

FDA Presentation – Judy Staffa

DR. STAFFA: Good afternoon. You may be feeling a bit overwhelmed, looking at this afternoon's agenda and seeing eight listed FDA speakers along with two invited guest speakers. I will admit that we have an unusually large number of FDA talks scheduled.

However, before we start, I'd like to take a few minutes to orient you to the information we've seen develop around the abuse of reformulated Opana ER and the emergence of the safety issues related to these changing abuse patterns.

As Endo has pointed out, the interpretation of the epidemiologic data is not straightforward. As is often the case in pharmacoepidemiology, we are faced with uncertainty because to collect data on large populations, we often lose the detailed information needed to fully understand it and

interpret it.

Therefore, we believe it is crucial to also consider other streams of data, including in vitro and human abuse potential studies, spontaneous adverse event reports, animal studies, drug utilization patterns, local outbreak investigations, and then determine how all the data fit together to understand the risks associated with reformulated Opana ER. We can then weigh these risks against the drug's benefit.

We've decided to take an approach based very loosely on the chronology of events surrounding the approval of reformulated Opana ER. After a brief regulatory history of Opana ER, Drs. Englund and Tolliver will present FDA's interpretation of the results of the preapproval in vitro and human abuse potential studies designed to test the performance of Opana ER reformulated with polyethylene oxide, or PEO, with regard to its potential to deter abuse via the injection and intranasal routes.

Dr. Tolliver will then integrate the findings of these studies with what we know about

the pharmacology of oxymorphone.

We'll then move on to examining information we have learned since the approval of reformulated Opana ER. Ms. Woods will provide an overview of the utilization patterns for Opana ER and comparators in recent years, including regional differences in dispensing and availability of this product. As you heard from the sponsor, these patterns are important to understand prior to delving into the epidemiologic data, which comes later.

We are then honored to have two guest speakers, Dr. Adams from the Indiana State Health Department and Dr. Brooks from the Centers for Disease Control and Prevention who will present information on the widely publicized outbreaks of TTP-like illness and HIV and the role that reformulated Opana ER played in those events.

Although these outbreaks were specific to certain geographic regions, we believe that the data gathered in these investigations provide important insights into specific abuse behaviors

related to Opana ER.

Dr. Patel will then discuss reports we've identified in FDA's Adverse Event Reporting System for TTP and related thrombotic microangiopathies, sharing the most current data we have available to us.

Next, Dr. Hunt, from our Center for Biologics Evaluation and Research, or CBER, will present the results of animal studies that suggest a potential mechanism whereby the specific PEO included in reformulated Opana ER might lead to TTP-like illness when injected.

Dr. Xie will discuss a number of statistical considerations in interpreting the epidemiologic studies submitted by Endo. And finally, Dr. McAninch will present FDA's view of the key findings as well as the strengths and limitations of the epidemiologic data. Dr. McAninch will then attempt to integrate all these data streams together to present FDA's interpretation of this body of evidence on the abuse and abuse-related risks of Opana ER within the context of other

oxymorphone and opioid comparators.

We have inserted several breaks in between talks for some clarifying questions, so if you could note your questions and raise them during those intervals, we will do our best to address them.

Now I will turn it over to Dr. Fields to begin our presentations.

Presentation - Ellen Fields

DR. FIELDS: Good afternoon. I am Ellen Fields. I am the deputy director in the Division of Anesthesia, Analgesia, and Addiction Products.

I am going to briefly present the regulatory history of Opana ER. Some aspects of my talk have been covered by the sponsor, so I will try to not be too repetitive and focus only on those issues that have not been covered.

I will start by talking about some characteristics of oxymorphone and then move on to the approval history of oxymorphone products, including Opana and Opana ER. I will spend some time on the approval of the reformulated Opana ER,

and then talk about a citizen's petition that had been submitted by the sponsor related to Opana ER. I will finish my talk with some brief points that apply to Opana ER and the entire extended-release long-acting opioid analgesic class.

Just for your reference, I've included the acronyms that will appear in my slides.

Oxymorphone is a semi-synthetic opioid analgesic. It is listed as a Schedule II drug under the Controlled Substance Act. It is a pure agonist and is relatively selective for the mu receptor, and its pharmacologic effects are consistent with other mu opioid agonists.

Oxymorphone has a relatively low oral bioavailability of approximately 10 percent and is principally metabolized by the liver as was discussed earlier by the sponsor. The potency of oxymorphone compared to morphine by the IV route is approximately 10 to 1.

Oxymorphone has a relatively long history. This slide includes some corrections of the regulatory history as written in the background

document you received.

In 1959, three formulations were approved under the brand name Numorphan, a parenteral product, an immediate-release tablet, and rectal suppositories, which were later withdrawn from the market. The brand name of the parenteral product was later changed to Opana, and all three of these formulations have the same indication: relief of moderate to severe pain, preoperative medication, supportive anesthesia, obstetrical analgesia, and relief of anxiety in patients with dyspnea associated with pulmonary edema due to left ventricular function.

The sponsor stopped marketing and distributing the IR tablets in 1971, and they were officially withdrawn from the market in 1982 for commercial reasons. Of note, there were anecdotal reports of abuse by injection of Numorphan tablets in the 1960s and early '70s.

The sponsor covered this, that in 2006 both Opana and Opana ER were approved. Three studies in postoperative pain supported the approval of Opana,

two in orthopedic surgery, and one in abdominal surgery. The approved strengths of this immediate-release tablet were 5 and 10 milligrams to be dosed 10 to 20 milligrams every 4 to 6 hours as needed for pain. Opana has a significant food effect whereby food increases the systemic exposure by approximately 40 percent, so it is labeled to take on an empty stomach.

The Opana ER approval was supported by two double-blind placebo-controlled trials done in patients with moderate to severe chronic low back pain. One of the trials was in opioid-naive patients and the other in opioid-tolerant patients.

Safety data was obtained in more than 2,000 subjects. The original approval included 5, 10, 20, and 40 milligram strength tablets, and additional intermediate strengths were added in 2008. This formulation also had a significant good effect and must be taken on an empty stomach.

As the sponsor stated, this formulation was not intended to have abuse-deterrent properties, and the label contains instructions to swallow the

tablet whole and that crushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose a significant risk that could result in overdose and death.

The sponsor has covered that the characteristics of the Opana ER tablet regarding the inclusion of polyethylene oxide, and you'll hear more about that excipient from Dr. Englund in her talk.

In the application for the reformulated Opana ER, the sponsor submitted in vitro and in vivo studies that assess its abuse-deterrent properties. The agency determined that the data did not support abuse-deterrent labeling. However, the reformulation was approved in December 2011, and the label does not include any abuse-deterrent labeling.

This approval included a risk evaluation and mitigation strategy, or a REMS, and the reformulated Opana ER replaced the original Opana ER in the first few months of 2012. Generic products to the original Opana ER continued to be

marketed, and currently, there are no generic products referencing the reformulated Opana ER.

Following the approval of the reformulated Opana ER in 2012, Endo submitted a citizen petition to the agency requesting FDA make a determination that the original Opana ER was withdrawn from the market due to safety concerns.

A consequence of this determination would have been withdrawal of generic products referencing the original Opana ER from the market. However, the petition was denied in 2013 due to insufficient data to conclude that the original Opana ER posed increased risk of abuse compared to the reformulated product.

You may refer to your background packets for details of the agency response to the citizen petition.

A supplemental NDA, or an sNDA, was submitted in February of 2013 to request abuse-deterrent language for Opana ER. The submission included the same studies as the first reformulated submission plus preliminary postmarketing

epidemiology data on Opana ER. And the agency determined there was insufficient data at that time to support abuse-deterrent labeling.

The application was resubmitted in January 2016, requesting labeling for abuse-deterrent properties for intranasal abuse, and also, the submission included additional epidemiologic data on abuse patterns of Opana ER.

Concurrently with this submission, there were reports of serious illnesses associated with the IV abuse of Opana ER that you heard about earlier. The agency became concerned that there may be a shift in the preferred route of abuse for Opana ER from intranasal to IV abuse, so an advisory committee meeting was planned to discuss these issues. However, the supplement was withdrawn by the sponsor, as they stated, in August 2016, and the AC was canceled.

Subsequently, Endo submitted three years of postmarketing data for Opana ER to the agency to inform discussion at this AC, which brings us to today. And as the sponsor said, they are not

currently seeking any abuse-deterrent labeling.

Finally, I would like to provide a high-level summary of three things that apply to the entire class of extended-release and long-acting opioids, and that class includes Opana ER.

The ER/LA opioid analgesic REMS was approved in July 2012. It applies to all members of the ER/LA opioid analgesic class, and its objective is to ensure that the benefits of these products outweigh the risks of serious adverse outcomes of addiction, overdose, and death resulting from inappropriate prescribing, abuse, and misuse while at the same time maintaining patient access to pain medications.

It is a shared system among this class of products in order to minimize the burden to the healthcare system and includes an education program for prescribers, patient counseling document, and a medication guide.

Second, the agency determined that routine pharmacovigilance for postmarketing adverse events for drugs in this class is not sufficient to assess

the safety of these products. The postmarketing requirements for this class include 11 studies to assess misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ER/LAs. Sponsors are encouraged to work together to complete these studies, and there are milestone dates for each study.

Finally, there have been two major safety labeling changes for opioid analgesics. The first occurred in 2014 and affected the extended-release long-acting opioid analgesics. Language in the labels was clarified in order to ensure safe use, proper prescribing, and patient selection, and to better describe serious risks of the class, including abuse, addiction, overdose, death, hyperalgesia, and neonatal opioid withdrawal syndrome.

In addition, the indication for all of the extended-release long-acting opioid analgesics was revised to the one that you've currently heard; trade name as an opioid, agonist indication for the management of pain severe enough to require daily

around-the-clock long-term opioid treatment, and for which alternative treatment options are inadequate.

Recently, in 2016, a second safety labeling change occurred that affected both the immediate- and extended-release opioids. A number of changes to the labels were made, and importantly a warning about the interaction of opioids and benzodiazepines and other CNS depressants was added to all labels.

That is the end of my talk. I'll hand it off to the next speaker.

FDA Presentation - Erika Englund

DR. ENGLUND: Good afternoon. My name is Erika Englund. I am a chemistry reviewer in the Office of New Drug Products in CDER at the FDA.

Today I will be discussing the in vitro abuse-deterrent studies of Opana ER. This presentation will focus on interpretation of in vitro studies conducted by both Endo and the FDA laboratories to evaluate the abuse-deterrent properties of Opana ER. Although there were a

number of different studies that were submitted to the new drug application, today I will only be discussing the particle size reduction and small volume extraction in vitro studies, abbreviated SVE.

In 2015, the FDA issued a guidance for the evaluation and labeling of abuse-deterrent opioids. The guidance recommends laboratory-based in vitro manipulation and extraction studies. These studies are used to evaluate the ease with which a potentially abuse-deterrent formulation can be defeated or compromised.

For example, the ability to crush or grind the tablet with different tools is assessed. This provides information about the potential of the product to form a powder that can be abused by the nasal route.

Other recommended studies include the extraction of the opioid from intact or manipulated tablets in a small volume of solvent and at different temperatures. The ability to withdraw this extract through a needle is assessed, and this

provides information about the ability of the product to be abused by injection.

The tablet manipulation techniques discussed today will be blinded, but the advisory committee, Endo, and FDA have the codes. And the codes in my presentation are the same as the ones used by Endo.

The codes will be written in bold red letters in this presentation. For example, tools that are used to cut, crush, or grind the tablets will be represented with codes A through W, and the temperatures used for the small volume extraction of tablets will be coded as T1, T2, and T3.

I will also be using several different acronyms in today's presentation. ADF is abuse-deterrent formulation. Original Opana ER is the original formulation of Opana ER as approved by the FDA. Reformulated Opana ER is the currently marketed formulation of Opana ER. API is the active pharmaceutical ingredient or the drug substance. For Opana, this is oxymorphone hydrochloride. SVE are the small volume extraction studies, which I introduced on the previous slide,

and ER is extended release.

I would like to talk briefly about the formulation. Reformulated Opana ER, original Opana ER, and Opana immediate release all contain the same API or drug substance, which is oxymorphone hydrochloride. However, these all differ in their excipients or the components of the tablet.

Of these three in this list, only reformulated Opana ER contains polyethylene oxide, which I will be abbreviating as PEO. There are a number of examples of FDA-approved PEO-containing products. PEO is listed in the inactive ingredient website in 9 different entries for extended-release, controlled-release, and sustained action tablets. All entries for PEO listed for products approved for the oral route of administration.

Some examples of FDA-approved PEO-containing ER products are Arymo with morphine sulfate, Hysingla with hydrocodone bitartrate, OxyContin with oxycodone hydrochloride, and Zohydro with hydrocodone bitartrate.

I would like to now discuss a little bit more about what exactly PEO is. Polyethylene oxide, as the name indicates, is a polymer of ethylene oxide. The number of oxyethylene groups, which is shown in brackets in the structure at the top of this slide, can vary from 2,000 to 200,000, and this would be indicated in the end subscript.

PEO is not a single molecule and can have a range of molecular weights. PEO is a white to off-white powder and is available in different grades that can vary in the viscosity profile, and the different grades of PEO can vary in their ranges of molecular weights. For example, one grade of PEO can have an average molecular weight of 100,000, whereas a different grade of PEO can have an average molecular weight of greater than a million.

The viscosity of PEO in the National Formulary monograph is measured in isopropanol and water solutions. PEO powder initially swells in water, and then it forms a viscous solution.

I will not be discussing PEO further in my

presentation, but several other speakers today will discuss PEO as a component in Opana. I would like to now switch topics to discuss the laboratory studies of reformulated Opana ER.

I will be starting with the particle size reduction. Crushing and grinding studies included common physical manipulation techniques used by individuals who manipulate products. For example, tools A, B, E, I, J, and N through W were all studied. The reformulated Opana ER was compared to original Opana ER, OxyContin ADF, and two generic oxymorphone hydrochloride ER products. The two generic products were from two different manufacturers and had two different formulations.

In these studies, reformulated Opana ER was more resistant to crushing and grinding than most of the comparators. Of these comparators, OxyContin ADF performed the most comparably. Of all the tools that were studied, tool V reduced the median particle size range of reformulated Opana ER to the greatest degree to less than 1 millimeter.

To switch gears to the small volume

extraction studies, all of the small volume extraction studies that I will be discussing in my presentation were conducted with the highest strength of product, which is 40 milligrams. The SVE studies were conducted in solvent A predominantly, but I will be using some examples later on in this presentation that were conducted in solvent E.

Reformulated Opana ER was compared to OxyContin ADF, two generic oxymorphone hydrochloride ER products, and the original Opana ER. There was one set of conditions that was used to compare the small volume extraction of reformulated and original Opana ER, and this was submitted to the new drug application in 2010.

The original Opana ER could be crushed or ground with many common tools. In this list, A, B, E, and N could all crush or grind original Opana ER, whereas reformulated Opana ER could only be ground with tool N and was flattened with tool B.

All tablets in the small volume extraction studies were manipulated with tool B. This

resulted in original Opana ER tablets being crushed, and the reformulated Opana ER tablets being flattened. Original Opana ER was described as forming a highly viscous gel, and as shown in entry 1, only 0.3 grams of the extract was withdrawn through a needle. This contained 0.4 percent of the API.

I would like to discuss briefly what these values mean. 0.3 grams represents the total mass of solution withdrawn into a needle. This includes the mass of the extraction solvent. 0.4 percent represents the percentage of API extracted from the 40 milligram tablet, and this is 0.16 milligrams.

In the small volume extraction studies, reformulated Opana ER formed a hydro gel layer around the tablet, and 4.23 grams of the extract could be withdrawn through a needle. This contained 26 percent of the API.

In 2016, additional small volume extraction studies were submitted to the NDA. The same extraction conditions that were used on the previous slide were used for these studies. Tool B

was used to manipulate the tablets, which flattened the reformulated Opana ER and OxyContin ADF, but this crushed the generic oxymorphone hydrochloride ER products. As stated previously, the generic products were from two different manufacturers.

A broader percentage range of API was extracted in this study, and a slightly higher percentage of the API from OxyContin was extracted in comparison to reformulated Opana ER. For reformulated Opana ER, between 26 to 40 percent of the API was reported as extracted. For OxyContin ADF, this was 42 to 46 percent. In comparison, over 60 percent of the API was extracted from both generic products, but the volume of extract that can be withdrawn through the needle was more variable with 2 to 5 milliliters.

Small volume extraction studies were also conducted with tablets that were manipulated with different tools. Reformulated Opana ER when it was manipulated with tool V was not syringeable through an N3 needle. Reformulated Opana ER when it was manipulated with tool W was syringeable. However,

only one set of extraction conditions was studies for the W manipulated tablets, and these differed from the extraction conditions described on earlier slides.

For the tablets that were manipulated with tool W, 1 milliliter of solvent A at temperature T2 was withdrawn through the needle N1 5 times. Cumulatively, 39 percent of the API was extracted. The results from OxyContin ADF in terms of percent API extracted were comparable.

The pretreatment of the tablets was also studied. All tablets were manipulated with tool V and extracted in 5 or 10 milliliters of solvent A or E. The pretreatment conditions, P3 through P8, were studied. The pretreatment did not impact the median particle size range of the tablets when they were manipulated with tool V.

For the results, the 5 milliliter extract of reformulated Opana ER could not be filtered in the extracts from solvents A or E. In comparison, 67 percent of the API could be extracted from P4 with tablets that were pretreated in solvent A when

there was no filtration step.

Some of the 10 milliliter extracts in solvent A were filterable, and 50 percent of the API could be extracted from P4 pretreated tablets and withdrawn through an N3 needle. In comparison, for the 5 millimeter extracts of the generic tablets in solvent A, the products were filterable through an N1 needle, and 58 percent of the API could be extracted with the P5 pretreated tablets.

The FDA laboratories also conducted some extractability and syringeability studies. The FDA laboratory studied syringeability of the reformulated Opana ER in only solvent A. All samples below were extracted at temperature T3. The temperature of T1 was also studied. However, the maximum percentage of API that could be extracted was 25 percent, and these results are not shown below.

All samples were withdrawn through an N5 needle, and the extractions in 2 milliliters in solvent were described as more viscous, but all samples were syringeable.

There's no significant difference in the API extracted from either the intact or the manipulated tablets, which are shown in the left- and right-hand columns respectively. There was also not a significant increase in the API extracted when the volume increased. After 5 minutes, the 2-milliliter and 5-milliliter extracts were measured with 15 and 16 percent of the API, respectively.

The variable which most significantly impacted the percentage of API extracted was time. The increase in time resulted in over a twofold increase in the percentage of API extracted.

The FDA laboratories also studied the effect of pretreatment on the tablets. The reformulated Opana ER was pretreated with condition P4 and extracted with solvent A at temperature T3. All samples were withdrawn through an N5 needle, and the samples were described as easily syringeable and easily filterable.

There was no significant increase in the API extracted from the tablets that were pretreated and

not manipulated. The pretreatment conditions resulted in close to a twofold increase, however, and the percentage of API extracted from tablets that were manipulated with tool J. After 30 minutes, 72 and 79 percent of the API could be extracted from the manipulated tablets with tool J, which were pretreated. Note that the amount of API was also more concentrated in the smaller extracts.

In conclusion, the reformulated Opana ER was resistant to crushing and grinding by some common physical manipulation techniques. The API could be extracted from reformulated Opana ER tablets and 5 milliliters of solvent A and withdrawn into a needle.

In the Endo small volume extraction studies, 40 percent of the API could be extracted from tablets that were not pretreated through an N3 needle. In the FDA's small volume extraction studies, 44 percent of the API could be extracted from tablets that were not pretreated through the N5 needle. However, do note that the extraction conditions used for this result were slightly

different from those used by Endo, and 79 percent of the API could be extracted through pretreated tablets, which were manipulated with J, and these could be withdrawn through an N5 needle.

Thank you. Jim Tolliver will be presenting next.

FDA Presentation – James Tolliver

DR. TOLLIVER: Good afternoon. My name is James Tolliver. I am a pharmacologist for the controlled substance staff within the Office of the Center Director, Center for Drug Evaluation and Research at the FDA.

This morning I would like to briefly discuss two intranasal human abuse potential studies submitted under NDA 201655 for reformulated Opana ER. The first is a pilot study designated EN3288-113. The second was a pivotal study designated EN3288-114. Afterwards, I will interpret these results within the context of what we know about oxymorphone pharmacology and the findings from the in vitro studies.

For the pilot and pivotal studies, the

subjective measures I will discuss include the Visual Analog Scales, abbreviated VAS, for drug liking, high, take drug again and overall drug liking. Drug Liking VAS, the only primary measure assessed at the moment drug liking and various time points post-dosing out to 24 hours. Subjects responded to the statement, "At this moment, my liking for this drug is" using a 0 to 100 millimeter bipolar scale anchored on the left by 0, strong disliking; in the center by 50, neither like or dislike; and on the right by 100, strong liking.

High VAS and at the moment assessment of euphoria consists of a 0 to 100 millimeter unipolar VAS with anchors on the left of 0, not at all, and on the right by 100, extremely.

It was administered pre-dose and at selected times points post-dosing out to 24 hours. Subjects responded to a statement, "At the moment, I am feeling high."

Take Drug Again VAS is an overall global assessment taken only at 8 and 24 hours post-dosing. Subjects were required to respond to the

question, "Would you want to take this drug you just received again if given the opportunity?" Using a 0 to 100 millimeter bipolar VAS anchored on the left by 0, definitely not; in the center by 50, indifferent; and on the right by 100, definitely so.

Overall, Drug Liking VAS is a global assessment also taken at 8 and 24 hours post-dosing. Subjects were required to respond to the statement, "Overall, my liking for this drug is" using a 0 to 100 millimeter bipolar VAS anchored on the left by 0, strong disliking; on the center by 50, neither like nor dislike; and on the right by 100, strong liking.

Oxymorphone plasma levels were determined as a function of time following treatment. The purposes of this presentation, pharmacokinetic parameters for plasma oxymorphone are limited to maximum plasma concentration, designated Cmax, and the time to maximum plasma concentration designated Tmax.

Specific parameters used for the subjective

measures in this presentation include the maximum effect designated Emax and the time to peak effect designated TEmax.

Study EN3288-113 was a pilot study utilizing a randomized double-blind, ascending dose, placebo-controlled design using nondependent recreational opioid users. The purpose was to assess the safety and dose-response relationship of intranasal oxymorphone hydrochloride API powder for producing subjective reinforcing effects to assist in selecting a dose for the pivotal study, EN3288-114.

Subjects were divided into two cohorts. Cohort 1 with 10 subjects was used to examine the effects of intranasal doses of 2.5 milligrams and 7.5 milligrams oxymorphone hydrochloride API powder. Cohort 2 consisted of 9 subjects who received intranasal doses of placebo, 5 milligrams, and 10 milligrams oxymorphone hydrochloride powder.

In total, placebo treatment was given to 12 subjects while each oxymorphone hydrochloride dose was given to 6 subjects.

This slide provides the mean and standard

deviation Emax for the 4 subjective effects as a function of dose of oxymorphone hydrochloride API. Over the dosage range of 2.5 milligrams, 7.5 milligrams, intranasal oxymorphone hydrochloride, there was a progressive increase in the mean Emax for drug liking, high, take drug again, and overall drug liking.

For all 4 subjective measures, the scales were maxed out following intranasal 7.5 milligrams oxymorphone hydrochloride API and achieving maximum oxymorphone plasma concentration of 7.84 nanograms per milliliter. The decision was made to use 7.5 milligrams reformulated Opana ER and 7.5 milligrams oxymorphone hydrochloride API in the pivotal intranasal study EN3288-114.

Pivotal study EN3288-114 was a randomized, double-blind, single dose, placebo-controlled, 4-period crossover study to evaluate the abuse-deterrent effect of manipulated reformulated Opana ER towards intranasal abuse.

Subjects were nondependent and had experience in the intranasal administration of

opioids. Intranasal treatments included manipulated reformulated Opana ER 7.5 milligrams, reformulated Opana ER placebo, oxymorphone hydrochloride API 7.5 milligrams powder as the positive control, and placebo powder.

Statistical analyses of the subjective measures were conducted by the CDER Office of Translational Science and Biostatistics using a mixed effects model in which period, sequence, and treatment were fixed effects with subjects nested within a sequence as a random effect.

Primary treatment comparison was manipulated with reformulated Opana ER 7.5 milligrams versus oxymorphone hydrochloride API 7.5 milligrams.

All four measures were validated as evidenced by statistically significant increases in mean Emax following oxymorphone hydrochloride API 7.5 milligrams compared to placebo.

This slide provides the pharmacokinetics for plasma oxymorphone following intranasal active treatments. The mean Cmax following intranasal reformulated Opana ER was approximately 47 percent

that achieved following intranasal oxymorphone hydrochloride API.

The median Tmax was delayed approximately 6-fold following intranasal reformulated Opana ER compared to following intranasal oxymorphone hydrochloride API.

Both these observations do support a possible deterring effect of reformulated Opana ER to intranasal abuse.

This slide provides the mean Emax values for the four subjective measures following intranasal treatments as evidenced in the completer population consisting of 38 subjects. Both placebo treatments had little effect on the four measures.

Compared to the oxymorphone hydrochloride API powder, manipulated reformulated Opana ER produced statistically with a p of less than 0.0001 and very likely clinically relevant reductions in Emax for all four subjective measures. These results, along with the pharmacokinetic data, do provide support for a possible deterrent effect of Opana ER to intranasal abuse.

Now I would like to discuss how these findings, along with what we know about the pharmacology of oxymorphone and the in vitro study findings discussed in the last presentation by Dr. Ingram, might predict changes in the routes used to abuse Opana ER following its reformulation.

First, the results of study EN3288-114, using the subjective measures of Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS, support a deterrent effect of reformulated Opana ER to abuse by intranasal administration.

Secondly, oxymorphone has very low oral bioavailability, approximately 10 percent, thereby requiring larger doses, somewhere in the range of possibly 40 milligrams to really produce subjective reinforcing effects when taken orally.

Third, at this time, we do not know the dose-response relationship between intravenous oxymorphone and subjective reinforcing effects. However, high levels of subjective reinforcing effects were documented following intranasal

administration of 7.5 milligrams oxymorphone hydrochloride API in pilot study EN3288-113.

Although intranasal bioavailability of oxymorphone hydrochloride in humans is not known, it is most likely less than 100 percent. Within intravenous injection of 7.5 milligrams or higher of oxymorphone hydrochloride, subjective reinforcing effects would likely occur.

Finally, as discussed in the presentation by Dr. Englund, category 1 studies conducted by the FDA laboratory demonstrated that reformulated Opana ER tablets can be manipulated by selected methods to produce solutions suitable for intravenous injection and containing sufficient amounts of oxymorphone such as 7.5 milligrams or higher to likely cause subjective reinforcing effects when injected.

With limitations to oral and intranasal abuse of reformulated Opana ER, individuals may be more likely to abuse Opana ER by intravenous injection. Such abuse may be facilitated by the ability to manipulate reformulated Opana to prepare

solutions for intravenous injection and the potency of oxymorphone for producing subjective reinforcing effects by this route.

In conclusion, the results of the study EN3288-114 using, again, the subjective measures of drug liking, high, take drug again, overall drug liking, support a deterring effect of Opana ER to abuse by intranasal administration. In vitro studies indicate the ability to manipulate reformulated Opana ER tablets to produce solutions suitable for intravenous injection and likely to produce subjective reinforcing effects.

These findings together with the low oral bioavailability of oxymorphone might predict a higher likelihood of abuse by the intravenous route for reformulated Opana ER compared to original Opana ER. Thank you.

FDA Presentation - Corinne Woods

MS. WOODS: Good afternoon. My name is Corinne Woods, and I am a drug utilization analyst in the Division of Epidemiology in the Office of Surveillance and Epidemiology. I will be

presenting drug utilization patterns for brand and generic oxymorphone extended-release, or ER, as well as selected opioid analgesics from 2009 through 2015 to provide context for today's and tomorrow's discussions.

The focus of this presentation is to summarize recent trends in drug use patterns of oxymorphone ER.

The outline of the presentation will be as follows: First, I will discuss prescription utilization data for brand, generic oxymorphone ER and selected opioid products with a focus on the outpatient retail setting. Then I will present the findings on the diagnoses associated with the use of oxymorphone ER and selected opioid comparator products. I will discuss limitations of the analyses and finish with a summary of findings.

These analyses focused on oxymorphone ER products, including Opana ER and generic oxymorphone ER. Our analyses also included other extended-release long-acting, or ER/LA, products as these provide context regarding the prescribing

trends and settings of use for Opana ER and comparator opioid products. Additionally, immediate-release oxymorphone was included to provide comprehensive analyses of oxymorphone utilization.

To conduct these analyses, we used two databases with differing features. I will briefly describe each database before presenting the results of each analysis.

We obtained prescription utilization data from the IMS Health National Prescription Audit. This database measures the dispensing of prescriptions from outpatient retail pharmacies to patients and is projected to provide national estimates of drug utilization.

This figure displays brand and generic oxymorphone ER utilization within the opioid analgesic landscape in 2015. Prescriptions for ER/LA opioid analgesics comprised approximately 9 percent of prescriptions for all opioid analgesics in 2015. Correspondingly, prescriptions for oxymorphone ER comprised approximately

5 percent of prescriptions for all ER/LA opioid analgesics.

Focusing on ER/LA opioid products, this graph displays the nationally estimated number of dispensed prescriptions for ER/LA opioid analgesics from U.S. outpatient retail pharmacies between 2009 and 2015. Oxymorphone ER is shown as a red solid line. The annual number of oxymorphone ER prescriptions dispensed increased from approximately 583,000 prescriptions in 2009 to 968,000 prescriptions in 2015.

Other trends were an increase in morphine ER prescriptions as well as decreases in oxycodone ER and methadone prescriptions during the time examined.

In this graph, we focus on the nationally estimated number of dispensed prescriptions for oxymorphone from U.S. outpatient retail pharmacies between 2009 and the second quarter of 2016. Prescriptions for the original formulation of Opana ER, shown as a red solid line, peaked in the fourth quarter of 2011 with approximately 328,000

prescriptions dispensed, and prescriptions decreased sharply thereafter.

A supply disruption and limited production occurred starting in December 2011 followed by the market introduction of reformulated Opana ER. Shipments of reformulated Opana ER, shown as a blue double line, began in February 2012, plateaued between the third quarter of 2012 and the third quarter of 2013, then steadily decreased afterwards.

Generic oxymorphone ER prescriptions increased steadily between 2012 and the second quarter of 2016 while oxymorphone IR prescriptions remained relatively steady during the time examined.

To understand the geographic variations in oxymorphone ER utilization across the U.S., we analyzed state level data on the prescribing of oxymorphone ER. This data may help address some of the questions posed by the panel. This data was not available at the time of the FDA briefing document.

This graph shows the population-adjusted rates of prescriptions per capita for total brand and generic oxymorphone ER dispensed from U.S. outpatient retail pharmacies in 2015 where darker grays indicate more prescriptions per capita. The state with the highest number of prescriptions per capita was Tennessee, which had approximately 18.5 total oxymorphone ER prescriptions dispensed per thousand residents in 2015.

Other notable states were North Carolina with 9.9 prescriptions per thousand residents and Nevada, Delaware, and West Virginia, which ranged from 5.9 to 6.7 prescriptions per thousand residents.

In these graphs, we looked at the nationally estimated number of prescriptions per thousand residents for Opana ER, on top, and generic oxymorphone ER, on bottom, dispensed from U.S. outpatient retail pharmacies from 2009 through 2015. We included only the 10 states with the highest number of prescriptions per capita for each product.

Looking at the top graph, from 2009 through 2014, Tennessee residents had the highest number of Opana ER prescriptions, peaking at approximately 16.1 prescriptions per thousand residents in 2011, then declining each following year.

Looking at the bottom graph, from 2011 through 2015, the number of generic oxymorphone ER prescriptions dispensed annually to Tennessee residents increased to a peak of approximately 12 prescriptions per thousand residents in 2015, while utilization among residents of other states increased to a lesser degree.

Now we will transition to the analysis of diagnoses associated with the use of brand and generic oxymorphone ER and selected opioids. To determine this, we used Inventive Health Treatments Answers database, which was derived from monthly surveys of 3200 U.S. office-based physicians who reported all patient activity during one typical workday each month.

These data are nationally projected by physician specialty and region and are based on the

number of office visits where drugs are mentioned, thereby providing insight into prescriber intent.

This table shows the top diagnosis categories associated with the use of brand and generic oxymorphone ER and selected opioids from 2011 through 2015. Diseases of the musculoskeletal system and connective tissue included conditions such as back pain and arthritis. Diseases of the nervous system and sense organs included conditions such as migraine headache and chronic postoperative pain. Injury and poisoning included bone fractures and sprains as examples.

Similar to the other selected drugs, diseases of the musculoskeletal system and connective tissue followed by diseases of the nervous system and sense organs to a lesser extent were the most frequently mentioned diagnosis categories associated with oxymorphone ER use during the time examined.

Limitations of these analyses were that only outpatient utilization was assessed. Therefore, no inpatient or mail order data were included in the

prescription analyses.

The diagnosis data were not linked to prescriptions, rather they represented mentions of a drug at a physician visit. The diagnosis data were derived from surveys of office-based physicians and may not have captured prescribing patterns of physicians who practice in other settings such as hospice care, pain or cancer clinics located within hospitals, or urgent care clinics.

In summary, total oxymorphone ER utilization comprised 5 percent of the extended-release, long-acting opioid product market in the U.S. in 2015. Overall utilization of the brand product Opana ER peaked in the fourth quarter of 2011, then declined through the second quarter of 2016.

Utilization of oxymorphone ER varied by state. Total oxymorphone ER was most often associated with conditions affecting the musculoskeletal system and connective tissue. Diagnosis patterns for oxymorphone ER were similar to those of oxymorphone IR, morphine ER, and

oxycodone ER.

If I could pull backup slide number 2, please? Thank you.

We would like to make a minor correction. If you would please disregard table 3 in appendix C on page 286 of the FDA briefing document as it was included in error, and please refer to the corrected graph above on the display. However, this correction did not affect or have any impact upon our findings or our conclusions.

Thank you very much.

Clarifying Questions

DR. WINTERSTEIN: This concludes the first set of presentations from the FDA. We will start with questions specific to the FDA presentations, and then get back to questions for the sponsor that were left over from before the break.

Are there any clarifying questions for the FDA?

Dr. Zacharoff?

DR. ZACHAROFF: Thank you. Kevin Zacharoff. This question is regarding Dr. Englund's

presentation, slides 8 and 9 with respect to the small volume extraction.

I see on slide 8, it seems like the same mechanism, the same solvent, the same timeframe was used with respect to extraction for the reformulated Opana ER when it was flattened, and that resulted in 26 percent of the API being retrieved.

On the next slide, it looks as if the same scenario was used, and again, reformulated Opana ER was flattened. This is in a volume measurement, not a weight measurement, but the percent of API now says instead of 26 percent that it's 26 to 40 percent.

So I am just looking for some clarification. If the conditions were the same, why are those different?

DR. ENGLUND: It was a variability in the results. These results were done in triplicate. The range of the triplicate results are 26 to 40 percent, but the extraction conditions were the same.

DR. ZACHAROFF: Okay.

DR. ENGLUND: It's just variability within the results.

DR. ZACHAROFF: If we go back to slide 8, just one more question with respect to the comparison between original branded Opana ER and reformulated. The percent API was significantly larger, if I'm understanding this correctly, than the original percent API.

DR. ENGLUND: Correct. In the original NDA, only a 0.4 percent of the API was reported extracted from the original formulation.

DR. ZACHAROFF: Thank you.

DR. WINTERSTEIN: Ms. Higgins?

DR. HIGGINS: This is a question for Dr. Woods. Did you look at diagnoses as they varied by state? Because as I'm looking at the top two diagnoses for use of opioid prescriptions, and I am just wondering if there's any possibility that Tennessee diagnoses differently somehow or disproportionately.

MS. WOODS: That's a very good question.

Our data comes from a small survey of physicians, and the granularity is limited as it is with the utilization of Opana. If we were to be able to look that up, the data would not inform us very well with any degree of accuracy. Unfortunately, it's just a very small database. That's a good point, though.

DR. WINTERSTEIN: Dr. Gupta?

DR. GUPTA: This is a question for Endo. Do you want me to ask this now or -- this was for the industry from this morning's, okay?

DR. WINTERSTEIN: Hold off. Let's finish FDA first.

Dr. Craig?

DR. CRAIG: Thank you. A question for Dr. Woods, I think again. Tennessee sticks out to me as an outlier, probably to most people. It's pretty obvious. Any ideas what's driving the trends in Tennessee?

I think that just doing some preliminary research on my laptop, it seems like there was a change in formulary status in Medicaid around that

time in 2009 to a preferred status, which correlates to the trends that we're seeing.

Do you think that that could have been a driver for use in Tennessee, and why is Tennessee using more than other states per capita?

MS. WOODS: We had very limited information for state-level data. Unfortunately, most of our data is collected and aggregated and then projected to national estimates. That would be wonderful to look up if we had that resource, and let me get back to you on that. Thank you.

DR. WINTERSTEIN: Dr. Schisterman?

DR. SCHISTERMAN: Yes, Dr. Woods, thank you so much. A follow-up question to your previous question. I was wondering if you have any data indicating this concern about Tennessee being an outlier or whatever we want to call it. Is the number of hospitalizations related to pain higher in Tennessee than the rest of the country or any indication that this is not surveillance bias?

MS. WOODS: I'm sorry. Could you repeat your question? My apologies.

DR. SCHISTERMAN: Sorry. Is there any data supporting that the hospitalizations due to pain or any other data that supports the rates in Tennessee being much higher than the rest of the country, that it's not an issue of more prescriptions but actually maybe there is a cluster of more pain-related conditions in Tennessee?

MS. WOODS: We actually don't have access to much state-level databases. So while that would be excellent to investigate, I don't believe that we have access to information with that granular level. I wish we did.

DR. SCHISTERMAN: Okay. Thank you.

DR. WINTERSTEIN: Dr. Brown?

DR. BROWN: I'm going to ask you another question.

(Laughter.)

DR. BROWN: I'm sorry. But I just have to. Did you guys investigate the more granular Medicaid data that is available on the state level rather than the CMS data that is where all these states are put together? It seems to me this gets to Dr.

Craig's original question, that it might be possible for us to get a better idea of why Tennessee became an outlier.

DR. STAFFA: Hi. Judy Staffa. I'm going to just try to save Dr. Woods.

You're raising great questions. Unfortunately, most of the data we have comes from claims data. That's where they come from, and they provide evidence of a prescription being dispensed. But there's very little in the information anywhere in the healthcare system about the reasons behind that, and that's always a frustration to us.

You've heard us before at these committee meetings not being able to differentiate between appropriate and inappropriate prescribing. We can only look at what's being dispensed and then speculate, as you can, too, over the reasons why.

These data were obtained from IMS Health. They were also obtained -- the prescribing data is actually looking into diagnoses, but that's not available at the state level. That's just office-based surveys.

So we're not really able to see into the minds of the prescribers or to get much more granular into Tennessee. But there are individual state Medicaid data available, but we've not been able to look at them. If we did, I'm not sure we'd be able to find them because there is no link between a prescription and the indication that it's treating even in those data.

DR. BROWN: Judy, does it really matter why -- we're worried about the drug being out there, and why it is more consistently out there in the population in one state over other states. One of the last things that Dr. Woods showed, pretty profoundly demonstrated, that it seems to be out there more in Tennessee than anywhere else.

I'm wondering if it really matters why it's out there just to say I'm not certain it matters what was in the mind of the prescriber as long as we look at some database that's large and view the fact that it actually was prescribed. I think that's what I'm getting to.

DR. WINTERSTEIN: Let me translate. I think

Dr. Craig suggested that there are differences in formularies across Medicaid across states and the fact that Tennessee may have a formulary where oxymorphone would be preferred might be able to explain that --

DR. STAFFA: It certainly could. It could.

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: If you look at the ARCOS data -- I was just looking at Tennessee compared to other states, just data I have access to; it's not very scientific -- over the time period from 2009 to 2011 in Tennessee, oxymorphone use, according to ARCOS, tripled from 55,000 grams to 150,000 grams over that time period before the oxymorphone reformulated.

Using my state as a comparison, the trend is not anywhere close to that steep. So if you're looking at the magnitude of change, it's in the sea. It's substantial, which is showing what the IMS data compared to again, using the ARCOS, which is not perfect. But just looking at Florida versus Tennessee, it's substantial, the differences.

DR. WINTERSTEIN: Any other questions about the FDA presentations?

(No response.)

DR. WINTERSTEIN: I think the decision is to continue with the guest speakers first, and then go back to the industry questions.

We will now proceed with the presentation from our guest speaker Dr. Jerome Adams.

Guest Speaker Presentation - Jerome Adams

DR. ADAMS: Great. Well, thank you all very much for having me here today. I am Jerome Adams. I am the Indiana State Health Commissioner. That's my public health hat. I also am a staff anesthesiologist at Indiana University. That's my clinical hat. And I'm also the pharmacy and therapeutics chair at my hospital where I work.

So I have, in sort of a micro way, a conceptualization for the regulatory side of things. I am also deciding whether or not we're going to make these drugs available to our patient population.

I want to say I'm not here to bash Opana ER

or Endo Pharmaceuticals or the FDA. I am simply here to tell you all a story, and a story that's gained traction throughout the country and, quite frankly, throughout the world. I was in Switzerland, and people were asking me about our HIV outbreak and about the contributions of Opana.

Three takeaways I want you to take from this. Number one, we need to ask ourselves if the risk is greater than the benefit in terms of making new and more potent opioids more widely available. You have probably all heard that a person is dying every 20 minutes from an opioid epidemic. That number is now approaching a person dying every 10 minutes.

So while I agree that untreated chronic pain is a public health concern, I would respectfully suggest that you should consider whether or not a person is dying every 10 minutes from untreated chronic pain and take that into consideration as you're looking at what to do with all of these medications, not just Opana.

Number two takeaway is that addiction is the

mother of all invention, and people will find a way. So we've got to think about that.

That leads into takeaway number 3, there are unintended consequences of both your new approvals and of new formulations, and you're going to see this throughout the talk that both I give and that Dr. Brooks is going to give in concert with mine.

No disclosures here.

In December of 2014, we had 3 new people diagnosed with HIV linked to Austin, Indiana. For reference sake, only 5 people had been reported with HIV in Scott County in the entire preceding 9 years, so we were up to 3 people very suddenly.

Two had had a common needle sharing partner. Contact tracing showed 8 more people diagnosed with HIV by January, and as of March 5th, we have 215 people now diagnosed with HIV. Nearly all had experience injecting Opana ER, and we did testing via the CDC to determine that the infections were all recent from a single strain of HIV. 204 of those infections, 95 percent, are co-infected with hepatitis C. So again, there's lots of offshoots

of this situation.

This is just for reference. Scott County, as you can see, is in the red located in the southeastern part of Indiana about 30 to 40 minutes north of Louisville, Kentucky. Scott County's population is about 24,000, and the epicenter of the outbreak is the small rural town of Austin, population size of about 4200.

Some reference when you're looking at the data I'm about to present, this is a small rural town, much like the one that I grew up in just south of here in Maryland.

The two pharmacies in the town, you can see them from each other. Nobody goes into Austin to get their prescriptions. If you are getting prescriptions dispensed from the Austin pharmacy, they are staying in Austin.

As a matter of fact, my father-in-law works for Marathon Oil and has a gas station down there. He travels all over the region and said, "I didn't even know we had a gas station there." This is not a place where there's a lot of in and out.

Overall, Scott County is experiencing high poverty, unemployment, and low educational attainment. The county ranks last among our 92 counties in Indiana on a variety of health and social indicators, including life expectancy.

As far as the demographics of our outbreak, the median age of those infected with HIV was 33.5 years, 58 percent were male. All were non-Hispanic white, and 94 percent reported injection drug use.

All of them, A-L-L, reported use of Opana, and I say Opana with air quotes here, and then we're going to get into teasing out what they mean when they say Opana. An early report found that over 40 percent of females diagnosed also engaged in commercial sex work, but again, everyone reported injection of Opana.

Why are we talking about Opana ER? I'm not going to belabor the points that were made earlier. In 2010, there was a reformulation of OxyContin. People went from OxyContin to Opana. Opana ER could be snorted and injected originally, and in

2010, you heard about the reformulation, which was impossible to crush and snort, and people transitioned over to injection. It has a very short half-life when injected, resulting in multiple injections per day, from 25 to 30 injections per day.

So the point here isn't that Opana encouraged new drug use amongst people, but the way people were injecting drugs definitely changed. High street cost, $160 per 40 milligram tablet during the outbreak peak now reports of over $200 per tablet.

Potency is high, morphine milligram equivalent dose higher than heroin. People liked it because you know what you're getting. What's interesting is following the overdose trends throughout this outbreak.

This is our prescription drug monitoring data, and I keep hearing people say Tennessee is different. Well, I'd ask you to look at that data a little more closely because Indiana is pretty different, too, when you look at our data.

This is per capita dispensed. The reason why I look at pills dispensed as opposed to prescriptions is because when you look at prescriptions, are you talking about a 30-day supply? Are you talking about a 60-day supply? Are you talking about BID or TID?

The real measure for me in terms of trying to figure out the amount of pills in the community is looking at the number dispensed, and so that's why I'm looking at that. When you look at my data versus other data later, take that into consideration.

If you'll look here, 2010 is again when you had OxyContin reformulated, and you see a precipitous uptick in Opana usage in the state, which is the dark orange, and also, in Austin, Indiana, which is the yellow.

In 2012 when we hit our peak, there were 29.7 pills per capita being dispensed in Austin, Indiana. If you back up into prescriptions, let's say an average prescription is a 30-day supply. Let's just say that for sake, and it's taken BID.

So you're getting a half a prescription per citizen in Austin, Indiana per year. That means for every 10 people in Austin, Indiana, you were getting 5 prescriptions. That means to put it in the per thousand terms, that's 500 prescriptions per thousand per year in Austin, Indiana. Again, just so folks can back their way into those potential numbers.

Why is this happening? Well, we've got marketing. You've got patient request. You've got prescriber perception. I practice myself. People perceive that it's safer, that it's better. Could be any or all of those reasons. That's up to you all to decide, but we've heard all three of those potential reasons for why you're seeing these regional variations and this big uptick.

I do want to quickly point out an excerpt from a 2012 publication. "Opana is the hot new prescription drug of abuse, sometimes with tragic consequences. At least nine people have died so far this year in 2012 from prescription overdoses in Scott County, Indiana."

This is a Reuters report. "Most of the fatalities involved Opana, according to county coroner. Opana abuse can be deadly because it's more potent. People who are not familiar with how strong it is may be vulnerable for overdosing.

"State Police Sergeant Jerry Goodin says, 'This Opana pill has really kicked us in the rear. We've never seen an addiction like this.'

"Endo is reformulating the medication, but the old form is still available. And pharmacy and home robberies are on the rise as addicts search for a way to get their fix.

"Fort Wayne, Indiana reported 11 pharmacy robberies related to Opana since Endo announced the reformulation."

I talk about unintended consequences. Indiana led the nation in pharmacy robberies in 2015.

Regarding doubts about dispensing being correlated to diversion, I will point out 29 million pills dispensed in Indiana in 2015.

There were comments made about this is safe

for the intended population. We've got to ask ourselves is the risk-benefit in theory versus in reality the same thing. Are 29 million pills about right? Too many? Is that what we'd expect for Indiana?

I would say respectfully you can't have it both ways. You can't say this drug is safe if we use it for the intended population but then look at the data and see that it's clearly being used well beyond the intended population.

That was all Opana doses. I dug in a little deeper to find out from our PDMP what percent of Opana ER dispensed in Austin and in Indiana was the actual ER versus the immediate release. Showed all Opana prescribed.

If you look here, 90 plus percent of the Opana prescribed in Austin, Indiana was ER, and 63 percent of the Opana prescribed in Indiana was ER. Both of those numbers are significantly higher than anything that you're hearing nationally in terms of the proportion of ER to IR being prescribed.

What's the take home point here? At least in Scott County, Indiana specifically and in Indiana in general, there was a clear preference for Opana ER.

If you look here at just Opana ER prescribed, breaking down these numbers a little bit more, again, you still see that same trend in 2010 shooting up to a peak of 27.2 pills per capital in 2012 prescribed in Austin, Indiana. Per capita, ER dosing is higher in 2015 still in Austin, Indiana than at any point statewide in all the preceding years.

In 2015, you still had 6.75 pills being prescribed per capita in Austin, Indiana. We never even got close to that high on a state level. So there's something different going on here.

Considering legit dispensing versus what's being diverted, if you take a BID dosage, that's 2 pills times 365, that's 730 pills. If you take 212 under 2012, which is the number of ER doses prescribed in Scott County, Indiana divided by that 730, that means that 290 people in the city of

Austin, Indiana could be taking an Opana ER twice a day for the entire year. That's 7 percent of the entire population of Austin, Indiana is getting enough pills to take an Opana ER twice a day the way it should be prescribed for an entire year.

Is that unusual? Is it not? I don't know. What I do know, as we heard earlier, and I agree with those statistics, that 100 million people have chronic pain, 5 to 10 percent of those people should be getting an opioid in general. If you take 10 percent of 100 million, that's 10 million. Divide it by the U.S. population of 326 million, that means less than 3 percent of the entire U.S. population should be getting prescribed opioids, period. That's not Opana ER. That's opioids, period.

Let's be generous and say that 25 percent of all people who are supposed to be prescribed opioids are candidates for Opana ER. You're still looking at less than 1 percent of your population who you should expect to be getting Opana ER, and at Scott County, 7 percent of that population is

getting Opana ER.

It's going somewhere, and respectfully, I agree with our epidemiologist friend who said that you can't say that correlation equals causation, but those pills are being dispensed and they're going somewhere. And they're being dispensed at 7 times the rate they would be expected to for normal usage.

I also want to say that I've talked to the police officers. I'm in the governor's cabinet with the state of police chief, and it started with prescribing. If you look back at our PDMP, he's right. There is a lot of illicit Opana going on, coming into the community right now, but it started with legitimate prescribing. And then once that supply dried up, it shifted over.

I would respectfully suggest that we're here today not so much to look back at what happened but to make sure it doesn't happen in another community. So I do want to challenge you and say we want to make sure it doesn't happen in another community. We want to learn the lessons about what

can happen if we allow prescribing to happen originally, and then let it shift over to illicit use.

My final point I want to make is, again, it's still being prescribed. 2016, most recent numbers, still being prescribed in Austin, Indiana. You heard it was not being dispensed anymore. It actually still is on top of illicit at a rate of $240 per pill.

Again, you all now know I like math. $240 a pill times 30 is $7200 a month. So again, I challenge the FDA to ask, if you're going to give someone a 30-day prescription that's worth $7200, what are the incentives you're creating out there for diversion compared to the average Social Security benefit check in the United States of $1400?

This is not again picking on Opana. It's not picking on Endo Pharmaceuticals. It's not picking on the FDA, but it's simply saying $7200 for a 30-day prescription, what's the message you're sending out there? What position are you

putting people in? Are you putting them in there -- even if you're giving them these prescriptions legitimately, even if they legitimately have chronic pain, you're in the poorest county in Indiana, and you're giving them a 7200-dollar piece of paper. What do you think they're going to do with it?

I want to finish on a happy note. We had 215 HIV cases identified total. At the peak of the outbreak, we were getting 22 new cases in a week. We have not had a new case in the past several months, fortunately. So we have fortunately suppressed transmission through our syringe exchange program, which not only passes out syringes but connects people to addiction and recovery treatment, to health insurance, to testing for HIV and hepatitis. And the folks down there are doing a great job in some trying circumstances. We've seen 99 people enter addiction treatment.

Why have we been successful? Our viral suppression rates are off the charts. National viral suppression rate's estimated between 25 to

50 percent. I think most people are familiar, but viral suppression is the level of HIV that's detectable in the blood.

The best way to prevent transmission of HIV is to suppress the HIV levels to undetectable levels so that a person can't transmit it. In Scott County, our HIV viral suppression levels are 73 percent. They are truly off the charts.

I want to leave you with, again, three points. Unintended consequences. There is no doubt that Opana changed and accelerated substance use disorder behaviors, and John's going to talk about that. It also increased pharmacy robberies and had an unpredictable effect on overdoses.

Overdoses first went up when people are introduced. Now, actually Scott County has one of the lower overdose rates in our state because people know what they're getting when they're getting Opana versus when they're injecting heroin in other counties, they may be getting fentanyl. They may be getting heroin.

Again, we don't know what's going to happen

with overdoses, but we do know we need to pay attention or you're going to have unintended consequences.

You need to ask yourself, are you helping more people than you're hurting? Opana ER in Indiana is absolutely being over-prescribed. It is. I showed you the data. It's absolutely being diverted, and it's absolutely causing a unique change in injection practices. Again, no blame here, but the numbers don't lie. All those three things are true.

Finally, since I have to run out and try to beat the storm home, I'll offer a potential solution. Perhaps you should consider a labeling change to more adequately address over-prescribing and better restrict use to the intended population.

Again, I am also a clinician. I want to keep tools in the hands of physicians. I want it to be available for people. There are unique situations out there, but these pills are not being currently restricted to this unique population. They're being widely distributed, and they're

contributing to some unique situations occurring.

With that, I'll be happy to take questions along with John Brooks once he gets over his part. Thank you, John.

Guest Speaker Presentation – John Brooks

DR. BROOKS: Thanks, Jerome.

Well, good afternoon, everybody. It's a pleasure to be here. Thanks for the opportunity to speak to you.

My name is John Brooks. I work at the Centers for Disease Control. I'm presently the senior medical advisor to our HIV division. I'm an infectious disease internist. During this event in Indiana, I was the CDC incident manager who interfaced with Jerome's team, managing what was going on in Indiana, so I have a pretty good insight into many of the details of what took place during that outbreak.

I have nothing to disclose. I was asked today to speak about two events that CDC investigated where Opana ER was involved. The first we've already talked about this morning.

This was the story of TTP in Tennessee. I'll be very brief there, and I'd like to go into a lot more detail about the Indiana outbreak and some of the work that we did to try and better understand why did HIV spread so explosively in this community.

You heard earlier from Jerome that we know the infections were very recent. We think that most of the people became infected within the 12 to 6 months before we arrived on the scene. What was going on there that really facilitated that rapid spread of infection?

With regard to the Tennessee event, this was an MMWR 2013 about an event in 2012. In total, there were 15 cases of TTP diagnosed, no deaths. Seven of those persons notably also had sepsis. Sepsis can lead to a condition called DIC, which mimics TTP and can sometimes be confused with it. But apart from sepsis, they ruled out other potential causes of TTP such as shiga toxin, e. coli infection, or exposure to quinine.

To better understand what was associated

with TTP illness in this outbreak, they conducted a case control study, 15 cases and 28 controls. The 15 cases had TTP. The controls were injectors who had not had TTP.

The really key finding here was that when you limit the case control study to only the 8 cases who did not have sepsis, so the healthy, if you will, 8 cases to the 28 controls, Opana ER when injected was associated with a TTP-like illness.

Now, the odds ratio here seems high. It's 17.5, but I'll caution that the confidence interval is quite wide. This is a modest association, but it was interesting; 7 out of 8 case patients had injected Opana, that's 88 percent, compared with 8 of 28 controls or 28 percent of controls.

Exposures to other drugs were not associated with the TTP-like illness. Those other drugs are shown here. FDA as well as CDC issued warnings, as have been described previously, at the time. The etiology was unknown. Importantly, despite extensive, extensive exposure to injected Opana in Indiana, we have not seen any TTP yet.

Let me talk a little bit about the Indiana experience and a qualitative study we did to try and better understand drug-use practices. This is a qualitative study really aiming to understand the challenges and behaviors of people who inject drugs in this area and how that may have contributed to the rapid spread of blood-borne infection.

We had a CDC- and Indiana University-approved protocol by our IRB. Eligible study participants were 18 years or older, resident of Scott County, had to have injected drugs in the past 12 months, and were able to provide informed consent.

We used a targeted sampling strategy, selecting people from the syringe service program, which at the time of the survey had been in place for about three to four months, street recruitment and peer-to-peer referral. Interviews were conducted in a local church or at the syringe service program to ensure privacy.

Data collection occurred during the summer of 2015, and it was two different forms of

qualitative assessment for a focus group of 31 individuals total plus 25 private interviews. These were all audio recorded as well. Notes from the interviewers were kept and reviewed. And no identifying information was collected from these individuals at the time of the survey.

If interviewers [sic] could not accurately describe the formulation of drug that they said they were using, they were presented a photo card of tablets to aid their accurate recall, like the one shown here, which contains the various ER formulations of oxymorphone.

Data were analyzed by having the interviews transcribed. These were then cross-checked and prepared for descriptive content analysis using standard methods for qualitative studies. Two researchers independently reviewed the transcripts and compared them for inter-coder agreement, and then these were reviewed by scientists to find themes that were associated with the preparation and injection of the drug.

This is just a brief description of the

demographics of the focus group versus private interviewers. They were interviewed -- patients rather, very similar to the demography of what Jerome showed earlier, young white adults about half male, half female. At the time of interview, most were enrolled in the syringe exchange program. About 50 percent were HIV infected of those interviewed. The majority were already hepatitis C infected.

Information about the drug they were injecting were collected differently, however, between these two groups. In the focus groups, folks were asked about past drug use. When asked have you used any drugs in the past week, thankfully, we got 31 or 100 percent since using drugs was an enrolling criterion. But when asked what drugs have you used in the past year, 30 or 97 percent reported Opana ER in the past year.

In contrast, during the private interviews, people were asked about what is the primary drug you are injecting right now. In that case, 22 or 88 percent were Opana ER, 1 person was IR, and 2

folks were injecting methamphetamine.

Just want to talk a little bit about pill and drug recall here. We learned -- and this was evident from early in the outbreak. But as we got to know what was going on, and as we from a community of mostly infectious disease experts learned a lot about medications that we don't usually prescribe, we learned that this community was very, very knowledgeable about the drug of choice that they were using, Opana ER. And almost every person we interviewed could accurately describe the tablet. It was a biconvex yellow tablet with the number 40 imprinted on it.

This was like a quality control measure. That's how they knew what they were getting. Very few participants needed to be shown the card to aid recall. And the one person who was injecting Opana ER spontaneously said, "My pill is not on your diagram." So we felt that it was useful that way.

We also conducted a survey of 148 of the early participants in the SSP to understand what their experience was and how well it was going.

While doing that, one of the questions we asked was at the time of enrollment, what is the drug you were presenting injecting. Again, a majority of folks, in this case, 89 percent, reported currently injecting Opana ER compared to a smaller percentage, 17, injecting heroin, and 3 percent other drugs.

A couple of key findings. Something that is truly remarkable about this situation as compared to anything else that I've seen reported is that these people were injecting very, very frequently. They injected from 3 to 7 times a day, and at each of those injection events, they may inject 2 to 4 times. Typically, they used one-quarter of a 40-milligram tablet, and they shared that with 2 to 4 injection partners. People consistently reported this was the common practice among people who inject drugs in this community.

Another key finding was how they prepared the drug for injection. You've heard a lot today about the FDA experiments used. I'm sorry. I don't know what the A's and W's are, but I can only

tell you about what we saw here. What they were doing -- and we don't know how they learned this. They would take -- you know now that this drug has PEO in it that deters crushing and forms a viscous gel but also facilitates this extended release.

These folks learned that if they applied heat to the pill by either browning it in the cooker with a flame underneath or putting it in a baker like a toaster oven or at low heat in a regular oven, the pill would literally go from the yellow color to turning a brown. When that brown color was present, they found that that facilitated dissolution in water and reduced some of the gelling properties that made it easier to inject.

The last thing is the key themes that we learned of reviewing all of the interview data, and I want to go over each of those separately because to illustrate how these were associated with frequent injection of the drug.

The first relates to opioid potency and the duration of action of the drug. Then the next two relate to the deterrent, both preventing crushing

and insufflation as well as the gelling capability. Fourthly, I want to talk about rinse shot. I'll explain what that means in a minute, if you don't know, and then the economics of supply and demand that I think Jerome alluded to earlier. This is a community where this drug was becoming scarce and had a very high street price.

Just to remind folks that the morphine equivalent dose of oxymorphone is high compared to morphine. If you look at parenteral, 10 milligrams of morphine as equivalent to 1 oxymorphone, and they both have a duration of action of about 3 to 4 hours.

The first aspect of potency was that the increased potency of the drug seemed to increase the intensity of withdrawal symptoms in persons. What we do in these qualitative studies, to illustrate for you what the themes were like, we often include quotes from different persons, and I've included key ones here.

The first person reported that "after taking OxyContins off the market, they came out with the

Opanas, which was 10 times worse than OxyContin, which was like the intensity of the withdrawals."

Another person said, "I couldn't find any OxyContins. Someone called to me with an Opana, and that's how I ended up doing Opana. But I had a lot of people telling me, 'Don't do Opana because a lot of people say you do it one time, you're hooked. You'll be sick the next day so you'll need to get another one.' And that's what happened. I did one that night, and the next morning, I woke up, and I just felt -- I felt terrible. So I had to get another. You get hooked on them really fast, Opanas, very fast."

The other aspect is its short duration of action, which led to people having to inject frequently. By way of comparison, if you're using heroin or cocaine, you may need to inject once or twice or maybe three times a day. With Opana with the short half-life, you have to keep injecting.

This person said, "The Opana don't last nearly as long as the other stuff. The feel of Opana will last 30 minutes. It takes 4 to 5 hours

before you start to feel sick or develop symptoms of withdrawal, and then you got to do it again or you feel really bad again. If you don't do enough Opana, then in a couple of hours, you feel really bad again. Have to inject. Inject 6, 7, 8 times but using small amounts" because the drug is expensive.

The aspects of the deterrent to crushing was reported by a number of -- repeatedly by our interviewees, that the inability to crush this tablet was the reason, they said, they moved to injecting it. One person said, "I was probably 24. I snorted Opana." That must have been the prior formulation. "It was when the government put the formula in where you have to cook them. It pretty much forced me to have to inject really. If there was a possible way I could snort them, I'd snort, then shoot."

Another person, "I couldn't find Opana or any other type of pain medication to snort. It became almost nonexistent so I was turned on to shooting up. So that's pretty much how that went

down. That was a couple of years ago. I hadn't injected before a couple of years ago, after I couldn't find anything to snort. But I couldn't handle the withdrawals. Opana was the first drug I injected."

I'll skip to the last one. "These Opana, you can't. They're like plastic, real hard. Well, I shot two, but I mostly would snort it. And then when you couldn't snort it at all, I started shooting it."

The gel also increased the amount of solvent needed to adequately divert the diverted Opana ER in order to inject it. Basically, once they had browned it and figured a way to begin dissolving it, to overcome the gelling property, they had to add more and more water to make it adequately dilute to inject, which produced a volume of material that exceeded the 100 units in a 1 mil syringe or maybe half of that. To get the whole dose into their body if I was a single person not sharing it, you'd have to inject potentially multiple times.

"You can take a lighter and you can melt it, but it gels up if you put it in water. It kills the gel in it, but that way you can draw it up. It takes so much water. If you wanted to work the whole thing up, it would get so thick and be hard to draw up. You can't get all in one shot. You got to put more water in there, and that's what you can draw. You can get by with 120 units, but it's real thick. It's really hard to draw up. You still have 50 left," meaning he or she could only draw about half of an insulin syringe.

"Then after that, you got to put more water on it and mix it some more because there's stuff left over."

Let's talk about what rinse shots are. Users would rinse the cooker. That's the device in which you prepare the drug with heat after the first injection. This was called a rinse shot, and that would create at least one more injection to ensure all of the drug was used.

When they were heating these tablets in these cookers, it often left a visual burn residue,

and that was a visual cue that there might be usable drug left behind. They would go back reconstitute that and inject that until most of that dark color was gone. That's in contrast again to drugs like heroin, which if very pure, are fully dissolved in water and you have no visual cue that there's residue.

As this person said, "And then after that," when they'd taken 2 shots of the first time with a quarter of ER oxymorphone, "you put more water on it and mix up some more because there's stuff left over. So that's 3 shots right there just off a quarter piece. Some people rinse it more than once. They'll rinse it again, so they're doing 4 shots."

We had people reporting to us that rinse shots were not common with other drugs. "If you get decent dope like methamphetamine, you do a shot, and you're good. You know, heroin, I've seen people try to take or get 3 or 4 shots off it, but you can't, you know, because heroin is 1 shot and you're done."

Then lastly, the economics of supply and demand, which really aren't so much a quality of the drug itself but do speak to the problems that happen when scarcity occurs with the medication folks are using, the increasing price and diverted drug created pressure for folks to inject together. When they were injecting together before the syringe service program, they were sharing equipment, which also facilitated transmission of hepatitis C and HIV.

"Well, if you buy these pills, a whole pill is like $200 if you buy it. We always -- sometimes we have just enough money to get high for a quarter of one. Sometimes 2 or 3 of us would do a quarter of a pill. There are times another person I inject with, and it's usually to help us because we can't make enough money to get that quarter. And it's usually like the first quarter of the day because I'm sick and I've only made $20. I'm short 15. There might be another person that's short the other 20, so we'll all get together, throw our money in together, and then we'll do a quarter 3

ways."

I wanted to summarize by going through what it was about the characteristics of how the drug was used that led us to believe that they were doing things that would increase infection risk and really sped up the spread of hepatitis and HIV under the circumstance.

With any opioid, there's an addiction potential. For those persons who may be injecting an opioid, if it has a short duration of action, then you've got to do more injections per day in order to keep withdrawal away. Moving to oxymorphone, this is a drug with substantial potency, which is very beneficial as a pain medication, but it can also lead to more intense withdrawal, which may entrain someone into having to inject again. It's more likely that they're going to be pushed into continuing to use drugs.

Then with the ER formulation, the crush resistance was cited by users as a main reason for them moving to injecting drugs. The greater solvent needs due to gelling, as well as the

practice of rinse shots, led to more injections per event, and the higher cost ultimately led to increased equipment sharing.

Opana ER is one prescription opioid out there, but there are many prescription opioids that are being abused. I just want to highlight this study conducted by CDC during an outbreak of hep C in 2011 in New York state where a variety of prescription opioids were being injected by folks, and the researchers wanted to better understand to what extent where prescription opioids and other drugs associated with being hep C positive.

They looked at 34 persons who were hep C positive, 66 who were negative, and then did a multivariable analysis to determine what was the association. Prescription opioids were not only the most used injectable, but they were associated with being hepatitis C positive.

True, the bath salts and the other category had near statistically significant results, but I'll just say that the low numbers would lead me to look at that finding with some caution.

They weren't all necessarily injecting Opana in this case, although Opana turned out to be the most common drug being injected. There was also other people who were using trade forms of oxycodone, hydromorphone, and hydrocodone.

In summary, in 2012, the injection of Opana ER was associated with TTP. The mechanism for this was not fully understood at the time, and importantly, we have not observed TTP in the 2015 Indiana outbreak.

In that outbreak, certain factors, including some factors associated with the latest formulation of Opana ER, appeared to unintentionally increase risk of transmitting blood-borne infection when the tablets were diverted for injection. But in at least one other outbreak prior to the Indiana event, injection of prescription opioid tablets in general was associated with increased risk of having a blood-borne infection, in this case, hepatitis C, compared with injection of heroin and cocaine.

My agency, of course, were very interested

in what are the public health research questions that might stem from an outbreak like this so we can learn from them and not repeat the same problem again.

I think, of course, one that interests me and I think everyone here, is what is the biological mechanism by which PEO compounds may cause TTP-like illness, and was perhaps this browning that they did, this cooking of the drug, did that somehow alter the PEO in a way that it took away whatever antigen or other material were there that turned on the TTP cascade?

How does browning this drug alter its crush deterrence and gelling properties? It looks as if FDA is beginning to look at that.

Are there alternative means of achieving crush deterrence and extended release so that if tablets were diverted, if they were diverted -- and today we've heard repeatedly that it's inevitable that a drug like this will ultimately be diverted. If they're diverted and prepared for injection, what can we do to reduce the risk of TTP-like

illness and frequent injection, which might lead to blood pathogen transmissions so that these are minimized?

Then why might prescription opioids as a class be associated with greater risk of transmitting blood-borne infection than routine street drugs?

I'll stop there in the interest of time. I have many, many people to thank here, and we'll be answering your questions shortly.

Clarifying Questions

DR. WINTERSTEIN: Thank you.

I have the sense that there were a lot of questions. There was actually no slot for questions planned in the agenda, but we just changed the agenda so now we have time for questions.

I saw Dr. Ciccarone raise his arm, and there were some here if you could raise.

DR. CICCARONE: Hi. Dr. Ciccarone, USCF.

One of the things I do in my research is observe injections. I'm an ethnographer and a

clinician and an epidemiologist. I actually spend a lot of time with injection drug users. I've seen the browning technique. I've seen the high volume solutions.

I'm going to keep it simple, Dr. Brooks. I wonder if you can give the committee some sense of the volume per pill because the reason why is I believe it's the linchpin between the epidemiological and observation findings from the ethnographers and the extraction data, which I have not heard yet from industry, but I'm going to ask that question when they allow me to.

DR. BROOKS: Sure. We do have those data. On average, when we asked them to show us the volume with a syringe or something, it was usually somewhere between 120 and 200 units of an insulin syringe. They do a little over the whole thing or a whole other one.

Some of that volume evaporated in the course of further warming it, so they got probably back down to somewhere between 100 and 200 units or 1 to 2 mLs to inject.

That's the volume they ended up with. They couldn't necessarily, as I mentioned, pull that all up into the syringe because the gelling property wasn't entirely gone. It didn't become perfectly fluid, and that would also lead to more injections. But those were the volumes.

DR. CICCARONE: Just to be clear for the committee, so let's just say 150 units. That would be about 3 injections for a typical user with a typical injection.

DR. BROOKS: That's right, yes. Given the combination of the gelling property and the excess volume, it could be as many as 3 injections.

DR. WINTERSTEIN: Dr. Gupta?

DR. GUPTA: This is a question for Dr. Brooks.

Regarding what you had mentioned -- and I'm grappling with trying to understand the PEO and the TTP, and trying to understand all these cases. For the committees' understanding, there's several cases of people that have TTP. My understanding, there's over 60 cases outside of the state of

Tennessee.

In your experience when you look at outbreaks, when you're looking at TTP in general, anyone that takes a drug outside of Opana, is it possible that you could just have this outside of IV drug abuse, just taking a drug and getting TTP, if we're not abusing it and a patient who's just taking a tablet?

If that is the case, has that occurred with Opana? And if it has occurred, what would be the mechanism? Could you hypothesize that.

DR. BROOKS: I can answer those backwards. Regarding mechanism, I have no idea.

With regard to understanding the association of a clinical outcome with a certain exposure, outbreaks are useful because you have a very fixed set of people, and you can do good interviews and get very good information about all their other exposures, so that you can compare and contrast and try and isolate it down to the one that's most significant. In this case in the Tennessee event, we had that opportunity.

When you have -- as was shown earlier, the cases seem to taper off from the graph I saw earlier today where there have been sporadic cases throughout the country, to really understand to what those may be related would require a more in-depth epidemiologic study where each person who's identified with the condition -- what we typically do in public health is each person identified with the condition is extensively interviewed with a standardized instrument and then two or three controls. People who were like that person but didn't have the outcome would be interviewed, and we'd look to see what exposures may be playing a role.

That hasn't been done yet, to the best of my knowledge. Of course, I work mostly in infectious disease, not blood disorder.

DR. WINTERSTEIN: Ms. Higgins?

DR. HIGGINS: No, not me?

DR. WINTERSTEIN: If you won't mind to hold off, I think there's a clarifying question for this?

DR. BATEMAN: A quick clarifying question on the TTP investigation. Can you talk about how you define the cases and the controls?

DR. BROOKS: Well, TTP was by standard criteria, which I'd have to go back -- I was actually corresponding with the first investigator today. But it's not a diagnosis that's often missed if it's diagnosed properly. Most of these cases, he was a nephrologist, the first five, given his clinical background, he would have been very good at making that diagnosis.

The controls were people who were injecting but had not experienced anything like TTP so no --

DR. BATEMAN: Were the cases brought to your attention as potentially Opana-related TTP cases or --

DR. BROOKS: That's a good question. I don't know. I think most of them probably came to medical attention by -- at least 7 of them by presenting with sepsis, and they needed to be evaluated. They may have been found to have TTP at the time of -- I would imagine this would be a

typical course, I think, is they'd have been admitted with a coincidentally TTP and the Opana exposure.

DR. BATEMAN: I guess my point is if you're not collecting them in a systematic way from a population sample, then you could induce an association with Opana if they were brought to the attention as Opana related?

DR. BROOKS: That's right. That's an excellent question. In an outbreak investigation, you don't often have the opportunity to grab a representative sample. But the advantage of a case control method is that if you can match them in a way that doesn't over-match so you mask what you're looking for, you can begin to get a better feel of what the association might be with.

DR. WINTERSTEIN: I think that's exactly where Dr. Bateman was trying to get at. What is the defined population that gave rise to the cases in epi terms, so essentially the controls, how similar were they to the cases? They were all sepsis patients?

DR. BROOKS: Right, they were all sepsis cases. And I didn't show this, but they were demographically matched in terms of age and gender.

DR. WINTERSTEIN: They were all sepsis cases, and they were all patients who had a history of injectable --

DR. BROOKS: The cases were all people who had TTP, and 7 had sepsis.

DR. WINTERSTEIN: Yes, but the controls had all the sepsis.

DR. BROOKS: Then the controls, no sepsis, no TTP, but they were injection drug users. So they were interviewed about the drugs they were injecting as compared to the drugs that the TTP cases were injecting.

You compare what the two groups were injecting. Is one group injecting something at a -- more of one drug than another? If you look for an outbreak of salmonella due to a number of things you've eaten, you ask everybody, what did you eat, and you compare what the people who got sick ate to those that didn't get sick, and try to

find the one that was most associated with illness.

DR. WINTERSTEIN: Ms. Higgins?

DR. HIGGINS: I am trying to get a sense of the qualitative methods that were used for that study. The focus groups were self-report data, I'm assuming.

With respect to the private interviews, was the 88 percent of Opana ER users also self-report, or was there independent validation of that finding?

DR. BROOKS: It was self-report. They had to describe the pill, and if they described the pill correctly, then we didn't bother going further.

DR. ADAMS: One of the things we were most shocked at about this community is truly how intelligent they were. I'm a biochemist. I used to work for Eli Lilly pharmaceuticals. These folks knew exactly what they were taking. They knew exactly what it looked like. They knew exactly how to prepare it. It truly was amazing.

DR. BROOKS: It was that 40-milligram

embossed tablet, which had all the value. That's what people wanted.

DR. WINTERSTEIN: Dr. Litman?

DR. LITMAN: Thank you.

Dr. Adams, in the beginning of your talk, you said that every action has a reaction, and it's often the opposite. What do you think would happen to the people of Indiana if Opana was not available today or tomorrow? Would they be in pain? Would they use OxyContins or black tar heroin? What do you think would happen?

DR. ADAMS: I think the answer is yes, and that's what makes it tough to all of your questions. I think now we -- the situation is very different than when Opana was approved. We now fully acknowledge that we are in the midst of an opioid epidemic that has not yet --

DR. WINTERSTEIN: I'm sorry. I need to interrupt you. You cannot answer this question because that's a panel question. So it's for us to answer this, not for you.

DR. ADAMS: I'm sorry.

DR. WINTERSTEIN: I'm sorry, too.

(Laughter.)

DR. ADAMS: No, I get it.

DR. WINTERSTEIN: Dr. Craig?

DR. CRAIG: Thank you.

A question for Dr. Adams on his PDMP data. What was the payer mix from that data you presented, if you know? What was it? Was it Medicaid? Was it third party? Was it cash paying? Do you know?

DR. ADAMS: It was Medicaid and third party, and that's actually what's interesting about our PDMP data and why -- you have to be careful because every state collects this data differently and reports this data differently. And what's important about Indiana is that self-pays weren't put in there. Even the numbers you got are an underestimate of the true toll in our state because we have a substantial number of people who would self-pay.

DR. WINTERSTEIN: Just for clarification, pharmacies do not enter their dispensing data. You

get the data from insurance essentially, from the PDMP.

DR. ADAMS: In Indiana, the pharmacies enter the data, yes.

DR. WINTERSTEIN: So that would include cash pays then?

DR. ADAMS: That would not include -- that would only include cash pays at pharmacies, but they --

DR. WINTERSTEIN: But if they were paying cash on the street, that would not be --

DR. ADAMS: Or paying cash at a doctor's office.

DR. CRAIG: So the cash-paying people were not collected in that data, so you are arguing that this could underestimate the true incidence of --

DR. ADAMS: Exactly. This is mostly Medicaid and insured data through the pharmacies. Exactly.

DR. WINTERSTEIN: Dr. Ruha?

DR. RUHA: Michelle Ruha. I had a couple questions.

For Dr. Adams, I guess I was just curious. The graph that you showed where Opana was dispensed, it was really high in 2012, and then it's decreased dramatically. One thing I was wondering is do you think that could be because of the reformulation or public health interventions? And also, do you know how that compares to other opioids in Scott County versus Indiana at that time? Was it mainly Opana that was being abused, or was it still much less than other opioids?

Then I have another question, and then they tie together for a third question. But Dr. Brooks had mentioned oxymorphone being so much more addictive based -- he gave examples of some user commentary.

I don't know if anyone from the FDA can answer this, but is there good objective evidence that oxymorphone is much more addictive than other opioids? Because I just wasn't aware of that.

To tie the two together, if oxymorphone is so much more addictive than other opioids, why are we only seeing these clustered areas, this one

county in Indiana and Tennessee? Why hasn't Opana abuse taken off all over the country since it's more addictive than the other opioids?

DR. ADAMS: That's a wonderful group of questions. I'll let the FDA answer a few, but I'll start with your last one.

Again, there are so many factors that affect the availability of a particular drug in a particular area, whether Medicaid pays for it, whether a particular doctor happens to prefer it, particularly in rural areas where you can have one dominant prescriber really change the distribution and the choice of medications in an entire area, whether it's you have an aggressive marketer.

I'm not pointing at anyone. Again, I used to work for a pharmaceutical company, and we have some areas where you see big blips in prescribing of a certain medication because you have a dominant marketer from that area.

So there are a number of different reasons. Our belief, based on the many folks we talked to, is that folks perceive this medication to be a lot

more potent and a lot more addictive. And once they get exposed to it, then they -- I've heard many folks say this is better than heroin, consistently say it's better than heroin.

But to answer your question, a lot of folks have not yet been exposed to it, particularly in an IV form. You saw the cost of it also. And so until you get in a situation where you've got substance use disorder related to Opana, you're not going to choose to go for the medication that's $240 a pill. You only do it to maintain your habit once you've been exposed to it.

To your question about 2012, yes, overall, prescribing did go down with Opana because remember again, folks could crush it. They could take it by mouth. There are all sorts of different things they could do to it. So the actual numbers did go down for Opana, but that's when we started to see the way that they took it change, and they started injecting it. So the actual numbers went down, but the injection of it went up precipitously.

As far as compared to other drugs, I don't

have the exact data. I can provide that to the panel. But I did look at that data, and there was a clear preference for Opana in Scott County over and above anything else that was out there.

DR. STAFFA: This is Judy Staffa. I'm going to ask Silvia Calderon to address the other part of that question about the objective information about Opana.

DR. CALDERON: We don't have objective data to show that Opana is more addictive than any other opioids. I wish we could have that type of data, but we don't.

DR. ADAMS: When you say objective data, John had a great slide. I don't know if you all saw that or not.

DR. BROOKS: Morphine equivalence.

DR. ADAMS: About the morphine equivalence, particularly for PO versus IV. So if you ask yourself -- and again, we've got lots of pain docs in this room, and I've received training in it -- what makes a drug addictive, it's the duration of action, and it's the potency.

While we don't have objective saying that Opana is more addictive, we do know that it has a much higher potency, particularly when administered IV, and it's got a very short duration, which makes it the perfect drug to get addicted to. It's super powerful, and you need to take it a lot because it's got a short duration of action.

DR. CALDERON: We don't have head-to-head comparison trials to say Opana --

DR. ADAMS: Exactly.

DR. CALDERON: -- oxymorphone is more addictive than morphine or hydromorphone. So that's what I meant. I do agree, yes, it's a high potency. Compared to morphine, it's more potent than morphine and also more potent than oxycodone.

DR. HERTZ: I'm sorry. This is Dr. Hertz. I know we're trying to get as much information as we can from Drs. Adams and Brooks, and I appreciate that, but we have to be careful that we don't go into the discussion and that we just really focus on questions about their experiences and their presentations because, one, we're not prepared yet

for discussion. We haven't gone through everything. And two, we need to have the open public hearing first before we get into that element.

DR. WINTERSTEIN: So focus on clarifying questions.

DR. BROOKS: Exactly.

DR. WINTERSTEIN: I have one follow-up question on the utilization pattern. In your analysis of the PDMP data as well as the interviews that you had with patients, did generic oxymorphone ER come up? Because it seems like it's way more troublesome to get Opana into an injectable version than a non-abuse-deterrent equivalent.

DR. BROOKS: Absolutely. In fact, that was my first question when I learned about this practice. Why aren't you using generic? It's easily dissolved. But the supply wasn't there, and I don't know why the supply wasn't there. But when they've had -- like the guy who had access to the IR, the reason he liked the IR was it's very easy to prepare to inject. But we don't know -- maybe

you know. I don't know why there wasn't more generic available in the community.

DR. ADAMS: Well, it goes to the question of whether this medication was being provided through legitimate prescriptions or whether it was being provided illicitly. The evidence that we have suggested in the beginning of the epidemic, it was being provided through legitimate prescriptions.

So my belief is that there were doctors down there who really thought this was abuse-deterrent, and it was safe to give to folks. So there was a lot more of that being prescribed than the actual generic version. And that's what people got accustomed to, got used to preparing, and that continues to be the medication of preference down there over heroin or over anything else in Scott County to this day. I was down there a week and a half ago.

DR. BROOKS: We were down there together.

DR. WISH: Can I ask a question to Dr. Brooks?

DR. WINTERSTEIN: You have a question on

that?

DR. WISH: Yes.

DR. WINTERSTEIN: Okay.

DR. WISH: My question is can you elaborate at all on the drug use history of the people you studied. In other words, was Opana misuse just one of many drugs that they had been misusing for most of their lives?

DR. BROOKS: That doesn't seem to be the case. Many of the people that were injecting drugs had come into drug use actually with oral pills first and then had moved on to injection.

Many of the people had preferred OxyContin before this outbreak was identified, had been using that. It wasn't necessarily that they started Opana and that's what they ended up using from that point forward. It was more as if you had a population of people who were engaged in addictive behavior, and then when the supply began to change, they had to learn how to adapt and use the drug that became available, which is Opana.

DR. ADAMS: The most common story that we

hear over and over is oxies and Vicodins were what people initiated their foray into substance use disorder with, and then made that quick transition over to Opanas in the community, and then to injecting.

DR. WINTERSTEIN: Dr. Emala? Dr. Mendelson?

DR. MENDELSON: Yes, hi. There are several other important complications of injection drug use, including abscesses and endocarditis. Did you observe an increase in endocarditis or abscesses during this outbreak? That's question one.

Question two is, was the epidemic of HIV terminated by decreased use of the drug or by needle exchange?

Question number three is, does anyone think the PEO had anything -- the excipient in this case had anything to do with stabilizing either the hep C or HIV virus and allowing greater infectivity?

DR. BROOKS: In terms of endocarditis and deep abscess, they were prevalent in this community. That was the main way people died was

either from sepsis or endocarditis. But when the syringe service program came into place as well as the other interventions to reduce use, endocarditis reports to the hospital have gone down steadily.

DR. MENDELSON: It didn't go up?

DR. BROOKS: It didn't go up. That's correct.

Your second question?

DR. MENDELSON: The needle exchange.

DR. BROOKS: Needle exchange, right.

DR. MENDELSON: That the epidemic was terminated by needle exchange more than anything else --

DR. BROOKS: That's correct.

DR. MENDELSON: -- not by just decreased prescribing.

DR. BROOKS: That's correct. People were still finding drug, albeit not through a prescription source but through a diverted source to use. It was still continuing to be used in the community even till pretty recently. It's only in the last couple of months -- when we were there

about a week and a half ago, the supply is dwindling, and more and more people are beginning to experiment with heroin and methamphetamine.

DR. ADAMS: And respectfully, I know this is political, and so I have to say that the syringe exchange itself was not the key ingredient, and that's not subjective for me. That's when you look at the data.

Things started to turn even before we started to institute the syringe exchange program. It was a combination of education, of getting people signed up for insurance and viral suppression.

The SSP was a touchpoint, and it was a critical touchpoint, particularly when you talk about endocarditis and cellulitis. Those, I think, were directly related to the syringe service program, but the stopping of the HIV outbreak was related to a multitude of factors and the touchpoints and services that we provided throughout the community.

DR. MENDELSON: I understand. Needle

exchange is just symbolic of the tip of the iceberg when addressing an entire epidemic.

Is there opiate treatment programs available? Are there now programs available --

DR. BROOKS: Programs are --

DR. MENDELSON: -- buprenorphine?

DR. BROOKS: Yes. A buprenorphine program is coming on board. Ninety persons, we understand, are now enrolled in a buprenorphine program. Many of the folks in this community, unfortunately, due to their drug addiction, cycle through the jail, perhaps as many as 50 percent of the users.

The jail has been a great place for people to sober up. They leave not smoking as well. We're working hard to now ensure that they get linked back into the community, to addiction resources so they don't fall back into addiction.

DR. ADAMS: With that said, Scott County is not unlike any other county throughout the country. We are still severely short in terms of options for people who want to go into addiction and recovery. And the fact of the matter is, we're going to have

to change our paradigm in terms of the way we approve drugs, the way we talk to our children, the way we prescribe medications as a physician.

I'm going back to actually argue with my fellow docs about a new prescribing rule that we want to put into place. We've got to change all that until we can provide more addiction recovery options for people and change stigma, change this opioid epidemic that has not yet reached its peak.

DR. WINTERSTEIN: Dr. Bateman?

DR. BATEMAN: This question is for Dr. Adams. From the data you have from your prescription monitoring program, were you able to characterize the physicians that were responsible for these high rates of Opana prescribing in this small community? Was it one physician or a small group of physicians?

DR. ADAMS: That is a great question, and one of the challenges of PDMPs is if you've seen one, you've seen one. Our PDMP is one of the oldest in the country. It was started initially as a law enforcement tool, and there was strict

privacy provisions put in there. I was on the state medical association board and fought for those strong provisions.

That said, to answer your question very directly, we are not allowed to go fishing in our PDMP to find out which doctors are prescribing until they reach a certain threshold. When I say we, still it's only the law enforcement community that's allowed to.

As far as going back, our belief is that the word very much got out to folks that were paying attention to what's going on with Opana prescribing, and you saw that prescribing start to precipitously decrease in accordance with the word getting that Opana was being over-prescribed and that folks were being looked at.

I'd love to be able to give doctors report cards, but right now, we're not in that place in Indiana.

DR. WINTERSTEIN: We'll have a break here now. We will break until 3:25, a short 15 minutes. I'm hoping that our presenters will still be with

us for the questions if needed, but we'll continue after the break.

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

DR. WINTERSTEIN: We will now continue with presentations from the FDA beginning with Dr. Patel.

DR. ZACHAROFF: Thank you. This question is for Dr. Adams. Oh, I'm sorry.

FDA Presentation - Chaitali Patel

DR. PATEL: Good afternoon. My name is Chaitali Patel. I am a safety evaluator from the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology.

You have heard the previous speakers discuss the utilization patterns for oxymorphone ER and reports of a primary thrombotic microangiopathy described as TTP-like illness. I will therefore continue this topic with an analysis of postmarketing adverse event data from FAERS to evaluate Opana ER's reformulation on non-oral abuse and review recent reports of thrombotic

microangiopathy, TMA, associated with injection of Opana ER and conclude with a summary of findings.

This slide explains how voluntary adverse event reports are submitted to the FDA. Two pathways exist for patients, consumers, and healthcare professionals to report an adverse event. First, they can be submitted through FDA's MedWatch program, which encompasses 5 percent of all reports, or they can be submitted to the product manufacturer who will them submit all such cases to the FDA according to regulatory requirements.

As you see listed on this slide, FAERS has many strengths that allows the FDA to use it as a postmarketing drug safety surveillance tool. FAERS is a computerized database, which as of February 2017 contains over 13 million adverse event reports.

While FAERS has many strengths, it does have some limitations. For example, for reporting purposes, the FDA does not require a causal relationship between an event and product to be

proven. Some reports do not contain enough information or detail to fully evaluate an event, and misclassification of reports as brand and generic is common where brand names may be more likely to be reported due to familiarity with the name. Reports may be entered into FAERS by the various data sources identified on the previous slide, leading to duplicate reports, which are then manually adjudicated.

Further, the FDA does not receive all adverse event reports that occur with a product. Manufacturers can influence whether or not an event will be reported such as the time a product has been marketed and publicity about a drug or event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event in the U.S. population.

Now that I have provided you with the strengths and limitations associated with the data, I will provide a qualitative assessment of non-oral abuse cases before and after the formulation change. We searched the FAERS database for reports

of Opana ER from approval of the original formulation through June 1st, 2016.

All cases reporting administration of Opana ER, an event date or year, and the narrative keywords listed on this slide were reviewed to assess routes of non-oral abuse.

We identified 108 cases reporting Opana ER use via a non-oral route. This includes 31 cases of non-oral abuse prior to the approval of reformulated Opana ER and 77 cases of non-oral abuse after approval.

This graph illustrates the 108 cases of non-oral abuse by case count and event year. The blue bar represents cases describing nasal insufflation, which we see emerging soon after the approval of Opana ER. As previously mentioned, reformulated Opana ER was approved December 9th, 2011. It is expected that there would be a time period where both formulations were available to patients.

The following red bar represents cases describing injecting. Reports of injecting Opana

ER emerged in FAERS in 2012. This coincides with the introduction of reformulated Opana ER and also the introduction of the lower dosage strengths of the generic oxymorphone ER products.

Next, I will be reviewing FAERS reports of Opana ER and TMA. Before I begin, I would like to cover a few key points about TMA. TMA is a group of disorders, which may be hereditary or acquired. These disorders are characterized by small thrombi or clots that occur in the arteries and capillaries due to endothelial injury. Clinically, it manifests as macroangiopathic hemolytic anemia, thrombocytopenia, and frequently signs of organ injury.

George et al. described 9 primary syndromes comprising TMA, which they distinguished based on their pathophysiologic mechanisms. There are overlapping clinical features which make distinguishing these a challenge. The common names of two primary TMA syndromes may be familiar to some of you, thrombotic thrombocytopenia purpura and hemolytic uremic syndrome.

In general, TMA is considered a rare disorder in which the incidence of acquired TTP is 2.9 cases per 1 million per year in adults. Treatment generally involves supportive care, and in some cases of TTP, plasmapheresis may be required.

We heard Dr. Brooks from CDC explain how Opana ER was implicated as a possible cause of TMA following a reported cluster of unexplained TTP-like illness cases in 2012. Subsequently in 2012, FDA had released a statement regarding the association of IV abuse of reformulated Opana ER and TTP-like illness. Following review of the data, the drug abuse and dependence section of the product labeling was updated to reflect the risk of TMA.

Next, I will provide an update of FAERS reports of Opana ER and TMA. Therefore, to capture all potential cases of TTP-like illness described with the abuse of Opana ER, we searched FAERS for reports of the broader description of TMA, recognizing that individual cases may reports signs

and symptoms of TMA but not a specific diagnosis.

Consistent with the known clinical presentation of TMA and that described in the CDC case series, we used the criteria listed on this slide for FAERS case adjudication. Cases meeting all three criteria were included.

We have searched the FAERS database for reports of TMA since the approval of reformulated Opana ER through June 1st, 2016 using the search strategy described here. Our initial FAERS review included reports from December 2011 through March 2013 in which we identified 29 FAERS cases.

Since our 2013 review, we have identified an additional 30 FAERS cases describing TMA associated with the injection of Opana ER. These include 20 cases derived from the medical literature. The remainder of my presentation will focus on these 30 cases received after March 2013.

The 30 FAERS cases have been reported from six known states in the U.S. We continue to receive cases. As the slide shows here, we received 4 cases in 2015 and 1 case in 2016. There

was one new diagnosis of TMA in 2015. The majority of these cases resulted in hospitalization.

The analysis of the laboratory data is provided for you on this slide. In general, all patients had some or all of the findings of thrombocytopenia; varying degrees of renal insufficiency; MAAJ, macroangiopathic hemolytic anemia; elevated LDH; and schistocytes, similar to the reports in the MMWR.

This graph shows the FAERS cases of TMA associated with the injection of opioids, including the 59 cases I noted previously that were associated with the abuse of reformulated Opana ER. Additionally, we did not identify any reports for generic oxymorphone ER products and the original formulation of Opana ER.

We also searched for reports of other opioids containing PEO and TMA. These included OxyContin, Hysingla ER, Nucynta ER, and Zohydro ER. We did not identify any reports for Hysingla ER, Nucynta ER, or Zohydro ER. However, we did identify 3 foreign FAERS cases of TMA, two of which

are published case reports describing TMA following the injection of the foreign reformulated OxyContin.

In January 2017 during routine surveillance, we received a U.S. FAERS report describing TMA associated with the injection of OxyContin. There are similarities in the case details of this OxyContin case compared to those reported with Opana ER that are of clinical relevance. Therefore, it is represented here on this slide and described in detail on the next slide, although it is not included in the FDA briefing package that you've received.

The U.S. case details are as follows. A 43-year-old female with a remote history of substance abuse presented with abdominal pain to a hospital in eastern Tennessee. Her laboratory evaluation showed thrombocytopenia and schistocytes with an elevated LDH indicating hemolysis. She was treated with two courses of plasma exchange, and a subsequent assay of her ADAMTS13 activity was normal.

Initially, she denied intravenous drug abuse, but with close questioning, she eventually admitted to intravenously injecting OxyContin 60 milligrams 6 days prior to admission. She denied Opana ER use.

Her method of preparing the tablet for injection is similar to what we just heard Dr. Brooks describe for Opana ER. After her drug abuse came to light, plasma exchange treatments were halted. Her complete blood count did normalize, and the caring physician attributed the TTP to her recent intravenous abuse of OxyContin.

In conclusion, we identified FAERS cases of non-oral abuse associated with Opana ER before and after reformulation. Abuse via the nasal route was primarily reported before reformulation, and the injection route was primarily reported after reformulation. These findings are qualitatively consistent with the shift in abuse from nasal to injection following its reformulation.

FAERS continues to receive reports of TMA associated with injection of reformulated Opana ER,

which is a known risk and consistent with the current labeling. Thank you.

The next speaker will be Dr. Ryan Hunt from the Center for Biologics Evaluation and Research.

FDA Presentation - Ryan Hunt

DR. HUNT: Good afternoon. My name is Ryan Hunt. I am a research fellow at the FDA Center for Biologics Evaluation and Research. Today I'll spend a few minutes digging a little deeper into the mechanisms that may underlie these cases of thrombotic microangiopathy associated with IV Opana ER use.

I just want to explain quickly how CBER became involved. The genesis for our interest was this initial case report that many speakers have been referring to, and at CBER, we regulate therapeutic plasma proteins that are essential to TTP pathophysiology, namely, ADAMTS13 and von Willebrand factor. So our interest was quite natural in this topic.

The investigation was CBER was actually headed by two groups led by Drs. Chava

Kimchi-Sarfaty and Paul Buehler. But there were other people that were very key to this study, including Neil Shusterman at Endo who provided key materials and facilitated conversations with clinicians that were seeing these patients.

I just want to take a second again to reiterate the definitions here. TTP refers to one syndrome of thrombotic microangiopathy. What the reality is, is there's actually many entities of thrombotic microangiopathy with unique causes and approaches to management.

Despite this diversity, they all share some common pathologic features, namely, vascular damage, which manifests in thrombosis of the small arteries, and they also share some clinical features, including microangiopathic hemolytic anemia, which just refers to the mechanical breakdown of red cells in the microvasculature under high shear stress.

Other common clinical features include thrombocytopenia, which refers to a low platelet count, and importantly, ischemic organ injury. So

most commonly, kidney injury and stroke are seen.

To better understand this phenomenon, we've been talking to clinicians that have been seeing and treating these patients. This table summarizes some clinical characteristics and laboratory abnormalities seen in three patients who simultaneously presented to the care of the nephrologist in Chattanooga, Tennessee.

In this case, there was a mother, her daughter, and her daughter's boyfriend who all presented simultaneously. They all had very diverse presenting symptoms, which included numbness of the extremities and vision loss, and they had laboratory abnormalities that were suggestive of TMA, including evidence of microangiopathic hemolytic anemia, thrombocytopenia. And two of the patients had evidence of acute renal injury. Importantly, in the two patients that were tested, the ADAMTS13 function was within normal range.

Renal biopsies were taken in these patients as well, and these showed strong evidence of

thrombotic microangiopathy. Panel A shows a large thrombus within the vascular pole of the glomerulus. Panel B is highlighting endothelial swelling and damage.

Then there's also some interesting findings on electron microscopy. Panel C shows what renal pathologists call a fibrin tactoid. That's that black electro-dense material that's highlighted by the red asterisks. This is not specific for TMA, but it's highly suggestive of thrombotic microangiopathy.

Panel D shows something quite unique. You see these areas of clearing highlighted by the arrow, and this is called vascularization. This suggests the presence of foreign material within the blood of these patients.

Finally, given the loss of vision experienced by two of the patients, a retinal fundus photograph was performed, and there are two interesting findings here. There are extensive cotton wool spots, which are these white cloudy areas, as well as microhemorrhaging, and both of

these are suggestive of retinal ischemia.

Eventually, the patients were managed with therapeutic plasma exchange, and they demonstrated partial recovery of kidney function. Unfortunately, the male patient continued to inject Opana ER extracts and became hemodialysis dependent.

At the FDA, we asked a pretty simple question, can we recapitulate the TMA in animals by administering IV injection of the inert ingredients found in the Opana ER tablet? With the help of Endo, we started with placebo powder, the raw material that is used in the tablet, and we solubilized this and injected this into guinea pigs. We chose guinea pigs because they display nephro-sensitivity to toxins and insults that are quite close to humans.

As many presenters have discussed this, we know that the injection patterns in the community are quite diverse in terms of their frequency, so we tried to achieve different peak levels of the inert ingredients in the animals by establishing

four dosing groups.

We first looked to the peripheral blood to see if we could see any evidence of thrombotic microangiopathy in animals that were injected with the inert ingredients in the Opana ER tablet. One of the most striking findings we found was a dose-dependent elevation of plasma free hemoglobin. This is the product generated through the hemolysis of red cells. This was accompanied by decreases in RBC hemoglobin and hematocrit and also declines in platelet count.

Also in the peripheral blood, we saw evidence of the mechanical shearing of red cells, and this results in fragmented red cells called schistocytes, so the small black arrows highlight three such schistocytes in the peripheral blood of one animal.

We also analyzed the multimeric distribution of von Willebrand factor, and under a high shear stress, this plasma protein is proteolyzed in greater amounts. Animals that were given repeated injections of inert ingredients show increased

levels of low molecular weight von Willebrand factor, which is suggestive of high shear stress in the microcirculation of these animals.

Given that kidney injury was a common finding in humans that were treated for TMA associated with IV Opana ER abuse, we also looked at pathologic outcomes in the kidneys of these animals. So we saw evidence of both tubular and glomerular damage.

The top middle panel is highlighting dilated glomerular capillaries, which are suggestive of TMA. The upper right panel is showing acute tubular necrosis, which was seen in a very patchy fashion amongst animals that received multiple injections of the inert ingredients.

This was accompanied by increased fibrin deposition within the glomerulus and the small arteries of these animals.

We also measured some very common blood markers for acute kidney injury. Animals given repeated injections showed elevations of plasma creatinine, elevated levels of NGAL expression,

which is suggestive of tubular damage, and elevated amounts of albumin in the urine, which is suggestive of glomerular damage.

As I said, these animals experienced high levels of hemolysis, and what's generated from that is something called cell-free hemoglobin, which eventually reaches the kidneys. This can be appreciated in a few ways.

Grossly, you can see the hemoglobin discolors the kidney brown. You also can measure elevated amounts of hemoglobin in the urine of these animals and also quantitate the amount of iron that's deposited in the renal cortex of the animals. And as the stain in the middle shows, this iron has a tendency to deposit primarily in the proximal tubules of these animals.

The problem with cell-free hemoglobin is that it has a capacity to generate oxidative damage, and one way to assess this is by looking at expression of protective enzymes, protective antioxidative enzymes. So what we did was we probed the kidney tissue for an enzyme called heme

oxygenase, and we saw a relative dose-dependent increase in the expression of heme oxygenase in the kidneys of these animals.

We also wanted to look at the tissue distribution of high molecular-weight PEO in the kidneys of these animals, and quite expectedly, we saw most of the PEO tends to stay within the vasculature of the animals. But we were also struck by this intraluminal occlusions that stain positive for PEO. So we next asked the question, is the tissue oxygenation of these animals impaired in any way?

To do this, we probed the kidney tissue for something called hypoxia inducible factor 1 alpha, which is something that is expressed under diminished levels of environmental oxygen. And what we saw was a variable but dose-dependent increase in the expression of HIF-1 alpha in the kidneys of these animals.

From this study, we could conclude a couple things. There appears to be a mechanistic link between the constituents of the Opana ER tablet and

cases of thrombotic microangiopathy. What we saw in our animals was a dose-dependent intravascular hemolysis and kidney injury.

We believe this is driven primarily by high molecular-weight PEO. From data I wasn't able to show today, if we used high molecular-weight PEO alone, we can generate some of the similar findings that I just talked about.

Now, the question of the determinants for the likelihood of the thrombotic microangiopathy are quite important, and we think based on this study, that dose and frequency of injection might matter quite a lot. Things we haven't looked at are the method of preparation.

There are definitely some unanswered questions we have, including the reasons for the higher rates of TMA associated with IV Opana ER abuse versus other opioids formulated with high molecular-weight PEO. And things we're thinking about are both tablet specific factors and the multitude of external factors that many presenters have talked about.

Also, the best treatment approach for these patients still is unclear. Some groups have advocated for supportive care alone while others are using an early initial plasma exchange therapy.

There are a lot of people, like I said at the onset, that were involved in this investigation, and I just want to thank all of them.

Are we doing questions now? No? Okay.

DR. WINTERSTEIN: You have to hang around a little longer.

We'll continue with Dr. Xie.

FDA Presentation - Diqiong Xie

DR. XIE: Good afternoon, everyone. My name is Diqiong Xie. I am a statistical reviewer in the Office of Biostatics. In this presentation, I will talk about some statistical considerations for evaluating the abuse-related outcomes of reformulated Opana ER.

Here's an outline of this presentation. I will first briefly describe the observational studies submitted by the sponsor, then I will

discuss the statistical considerations in four categories: data quality, estimability, causality, and interpretation.

A lot of this work is based on Dr. By's paper listed here. Last, I will give a summary of this presentation.

To start, I'll briefly describe the observational studies and key design elements related to the statistical considerations I'll address later.

The sponsor submitted two formal observational studies. I'll refer to them as the NAVIPPRO study and the RADARS poison center study. Note that data utilized in these studies are based on convenience samples instead of probability samples from a well-defined population. A few time periods were defined in these studies, according to the time of Opana ER reformulation and OxyContin reformulation.

This illustration shows Q1 as the time periods before OxyContin reformulation from 2009 to mid-2010. Period 2 is the time period between

OxyContin reformulation and Opana ER reformulation from mid-2010 to the end of 2011. The transition period is the one and a half year time window following the reformulation of Opana ER.

Also, starting in January 2013, generic oxymorphone ER became available in a full range of dosage forms. Because the market availability during this time is unstable, the transition period is excluded from all analyses, then period 3 is the time period after the transition.

These boxes mark the time periods that were used in the primary analyses in the two studies, NAVIPPRO on the top and RADARS poison center in the bottom.

In the NAVIPPRO study, there were two primary comparisons. One compared the abuse of Opana ER between the three-year period before Opana ER reformulation and the post period. The other compared the abuse of Opana ER and other opioids during the post period. The outcomes of interest were overall abuse, which includes abuse through all routes; alternate routes of abuse included

routes associated with tampering; route specific abuses were abuse through oral routes, snorting, and injection separately.

The measures of abuse used different denominators. Prevalence referred to the measure using the number of assessments as the denominator. An assessment, as we recall, is a computer-based questionnaire answered by one individual. Tablet rate refers to the measure using number of tablets as the denominator. The number of tablets reflects the availability of various opioids.

The RADARS poison center study compares abuse patterns of Opana ER among three time periods: before OxyContin reformulation, period 1; after OxyContin reformulation but before Opana ER reformulation, period 2; and after Opana ER reformulation, period 3. The change of abuse from period 1 to period 3 was also compared between Opana ER and other opioids. The comparators were morphine ER and oxymorphone IRSE.

The outcomes of interest were phone calls to the poison centers that involve intentional abuse,

death, and major medical outcomes, and overdose. Three metrics were used to measure the abuse. Prevalence uses estimates of population as denominator.

This was estimated from the 2000 and 2010 United States census data by calculating the sum of population within the 3-digit ZIP codes covered by the participating poison centers. Note that this is different from the NAVIPPRO study. In NAVIPPRO, prevalence uses the number of assessments as the denominator. Tablet rate used the number of tablets, and prescription rates used the number the prescriptions as denominators.

The first statistical consideration is data quality. Does the data support what we want to measure, in particular, whether the data recorded correctly what opioid the participant used. The next presentation will cover this in detail. I just want to mention that any misclassification may led to bias in analysis.

I will now start the discussion of estimability. To illustrate the issue, I will use

the NAVIPPRO data as an example, however, the same issues exist in RADARS poison center data.

Estimability is a term I use to describe the phenomenon of whether the sample can be used to estimate certain qualities in the population. Specifically, can the data be used to estimate the extent of overall abuse of Opana ER in absolute or relevant terms in the underlying population? In addition, can the data be used to assess whether there is a shift in the abuse of Opana ER from snorting to injection following its reformulation?

To answer these questions, what is the ideal data? Population data would be ideal. To illustrate this, I use the big circle A to represent the underlying population. For different studies, A can refer to different populations. For example, in the NAVIPPRO study, A includes all residents in the catchment area of NAVIPPRO treatment centers. Given the population A, we then count all the opioid abusers denoted here as X.

If in the pre period we could count the total number of individuals in population A and

count every abusers of every type of opioids in circle X, and in the post period we do the same counting, then we can compute and compare the prevalences in the pre and post period. Unfortunately, we do not have access to the population data.

The study data from NAVIPPRO and RADARS poison center are based on surveillance samples, which are represented by the shaded square Z in this figure. It captures some known opioid abusers in population A and some opioid abusers in the circle X, but these surveillance samples have some limitations.

Not all opioid abusers in the population interact with the treatment centers in NAVIPPRO, and these surveillance samples are not random. Certain types of abusers or abusers of certain drugs might be more or less likely to interact with the surveillance systems.

Second, the surveillance samples only capture a small fraction of the population and also a small fraction of all abusers in that population.

Third, as the data [sic] abuse dynamic changes, centers drop in and out of the network, the catchment area of surveillance system changes over time. As new drugs enter the market and new abuse epidemic arises, the questions that are used in these surveillance systems may change over time, too.

These critical limitations determined that the surveillance sample may not represent the population data. However, can we estimate some abuse-related quantities in the population using data from these samples?

I will first define some metrics to measure abuse starting with prevalence. I use capital P to denote the population prevalence, the subscript Z is for the pre period, and 1 is for the post period.

The population prevalence in the pre period equals to the number of all abusers in the pre period divided by the size of population in the pre period and similarly for the post period.

I use little P for the sample prevalence.

The sample prevalence in the pre period equals the number of abusers divided by the total number of individuals being sampled in the pre period and similarly for the post period.

Having introduced the notation, due to sample prevalences, the little Ps, estimate the population prevalences, capital Ps. In order for this to hold, we need assumption 1. Selection into the sample is independent of substance being abused. In other words, an Opana ER abuser must have approximately the same chance of being assessed as any abusers of any other drug or any non-opioid abusers.

If Opana ER abusers tend to interact more with treatment centers compared to abusers of other opioids, then assumption 1 doesn't hold, and the sample prevalences do not estimate the population prevalences.

The prevalences just discussed are absolute measures of abuse. Without assumption 1, these absolute measures in the population are not estimable. An alternative to absolute measures

would be relative measures as there is interest in how the abuse of Opana ER changed with regard to reformulation.

Here, I used capital RP to denote the population ratio of post versus pre prevalence and little RP to denote the sample ratio.

For relative measures to be estimable, one needs assumption 2. If selection into the sample depends on the substances being abused, then the nature of dependence does not change over time. In other words, Opana ER abusers can be more likely to be assessed by treatment centers relative to abusers of other drugs. However, the magnitude of such change over time has to be the same for abusers of any drugs as well as for non-opioid abusers. Under this condition, the post versus pre ratios are estimable.

Now let's check the data against the assumption. The data seem to suggest that this assumption may not hold. This table lists the states with double-digit changes in the number of ASI-MV sites over time.

In the pre period, the states in red had relatively higher abuse prevalence of Opana ER, and those in blue had relatively lower abuse prevalence. The states in red seemed to have more increase in sites from the pre to the post period, which suggests that the increase in sites may have been associated with high prevalence of Opana ER abuse in the pre period. This suggests that assumption 2 might not hold.

Another example here would be that if policy changes to encourage or to discourage people to be assessed by treatment centers in the post period compared to the pre period. For example, in the post period, public concern about opioid abuse may have arisen, and law enforcement may have increased their efforts in referring abusers to treatment centers. In these cases, the prevalences are not estimable, and the post/pre ratio is not estimable.

Another relative measure is the ratio-ratio comparison. The ratio-ratio measures the relative post/pre change between drug D and Opana ER. If abuse of Opana ER increased but the increase is

substantially less than the increase observed in another drug, then under certain conditions, it could suggest a positive health impact due to the reformulation.

I used capital RRP to denote the ratio-ratio of prevalence in the population and little RRP to denote the sample value. Subscript D is for the comparator drug.

Under assumption 1 or 2, the sample RRP estimates the population RRP. When they do not hold, meaning selection into the sample depends on the substances being abused and the nature of dependence changes over time, then assumption 3 is needed. It says that the change in the dependence is the same for Opana ER and the comparator opioid.

Assumption 3 would not hold if there were dramatic changes in the number of assessments in some states and if these states had different opioid abuse prevalences. In such case, the change in the sample selection trend over time depends on the substance being abused.

This table here shows the states that

contributed most data in either pre or post period. For example, data contributed from New Mexico decreased more than 20 percent, and data contribution from Tennessee increased 10 percent. If these two states had different abuse prevalence with regard to different opioids, then assumption 3 would not hold.

Now let's switch gears a little bit about talk about the shift in abuse. Do the data show a shift of Opana ER abuse from snorting to injection?

For the sample data to reflect route of abuse change in the underlying population, similar assumptions are needed, as mentioned before, with a slight twist. First, selection into the sample must be independent of the route of abuse. If not, then the nature of dependence cannot change over time. If this doesn't hold, then the change in the dependence has to be the same for Opana ER and comparators with regard to route of abuse.

This ends our discussion of estimability. Let's move on to causality. If studies show some changes in the abuse of Opana ER, can we attribute

the changes to the reformulation? This is the question of causality.

To attribute the observed changes to the reformulation of Opana ER, one must consider external factors. For example, DEA could increase their efforts to reduce Opana abuse. State and local government could amplify their law enforcement or education efforts to change the abuse pattern. FDA's risk evaluation and mitigation strategies, social trends, availability and cost of alternate drugs can all change the abuse pattern.

Can one separate the effect due to reformulation from that due to external factors, or as I call it, secular trends?

One solution is to use comparators. The idea is that the change in Opana ER included effects from both reformulation and secular trends, and the change in comparators included only effect from secular trends. Then by using the comparator, the change due to reformulation of Opana ER can be separated.

However, not any comparator works here as one has to assume similarity between comparator and Opana ER. The comparators have to be similar to Opana ER in the pre and the post period and be different from Opana ER only in the reformulation. In this sense, oxycodone ER cannot be a comparator because it was reformulated, too.

In cohort studies, similarity is usually verified by comparing baseline characteristics of two cohorts. However, since there was no fixed cohort followed over time in these convenience samples, similarity is difficult to verify. But the data might provide some hint about similarity in abuse rate, abuse rate trends, and throughout specific abuse patterns.

This plot shows the overall abuse trend during the three years before Opana ER reformulation. The X-axis is time in quarters of year, and Y-axis is the tablet adjusted rate of abuse.

We can see that the upper two lines representing Opana ER and oxymorphone IR seem to

have similar trends over time for the overall abuse, which is just quite different from the bottom two lines representing morphine ER and oxycodone IRSE. While not shown here, the trend of abuse through snorting and injection showed the same similarity.

Moving on to interpretation, how do we interpret the observed effect in the context of data quality, estimability, and causality? Note that I haven't discussed much about data quality. This will be covered by Dr. McAninch later. Therefore, bear in mind the data quality issues when interpreting any result shown here.

In this section, I use period 1 as the pre period, which is before OxyContin reformulation. I use this because there was more homogeneity between Opana ER and comparators without the impact of OxyContin reformulation. Nevertheless, period 2 could also be used as pre period which may present another aspect to look at the changes.

I compared the abuse of Opana ER between period 1 and period 3 using the post versus pre

ratios of prevalence, tablet rate, and prescription rate. I also used the ratio-ratio comparison intending to separate the effect of reformulation from the effect of secular trends.

These are the comparators I will use in this section. Recall that in the abuse trend plot, oxymorphone IR seems to be similar to Opana ER. Also, given the similarity requirements, generic oxymorphone ER might be a good comparator since it's bioequivalent to Opana ER. In this sense, generic oxymorphone ER could be considered as a contrafactual version of Opana ER, which might represent the abuse pattern of Opana ER if the reformulation had not occurred. However, the generic form did not exist in the pre period. For such a comparison to be possible, assumption 4 is needed. The abuse pattern of generic oxymorphone ER in the pre period, if it existed, should have been the same as the abuse pattern of Opana ER.

This plot shows the post versus pre ratio for abuse of Opana ER by route of abuse. The Y-axis denotes different routes of abuse, and the

X-axis is the ratio. It shows that for the overall abuse, abuse through alternate routes, injection, and oral, the ratio, and their 95 percent confidence interval were all to the right-hand side of the dotted line, which means more abuse in the post period. Only for abuse through snorting, there was less abuse in the post period.

It is important to remember that such changes might be due to secular trends in addition to the reformulation. To single out the effect of reformulation, comparators need to be used.

This plot shows the ratio-ratio comparison for overall abuse. The post versus pre ratios of the comparators were compared to that of Opana ER. The Y-axis shows different comparators with different measures of abuse prevalence or tablet rate. The X-axis is the ratio-ratio.

If the ratio-ratio is larger than 1, to the right-hand side of the dotted line, then the abuse of comparator was worse. And by worse, I mean that the comparator had more increase in abuse than that of Opana ER from the pre through the post period.

In this case, generic oxymorphone ER, oxycodone IRSE, and oxymorphone IR were worse than Opana ER in overall abuse. Morphine ER was better in overall abuse than Opana ER. Recall earlier, I mentioned that oxymorphone IR and generic oxymorphone ER seemed to be good comparators due to their similarity to Opana ER.

These plots are similar to what was just presented. They are the ratio-ratio comparisons for abuse through injection, in green, and abuse through snorting, in black. It shows that for snorting, Opana ER was better than all comparators. But for injection, Opana ER was worse than most comparators except for generic oxymorphone ER based on the tablet adjusted rate.

Again, as I mentioned earlier, oxymorphone IR and generic oxymorphone ER seem to be good comparators due to their similarity to Opana ER.

Now, let's look at the results from the RADARS poison center study. This plot shows the post versus pre comparison for Opana ER. The outcomes of interest here are intentional abuse,

major medical outcomes or death, and overdose. They are denoted by the Y-axis together with different metrics: prevalence, prescription, and tablet adjusted rate. The X-axis shows the post versus pre ratio.

Since the event count in RADARS were much smaller than those in NAVIPPRO, the confidence interval here is wider. We can see that the change in intentional abuse and major medical outcomes or death were not significant for Opana ER, but overdose significantly decreased in the post period compared to the pre period.

Again, I will use comparators to tease out the effect from reformulation. This plot shows the ratio-ratio comparisons for all three outcomes in RADARS poison center study using morphine ER as comparator.

Intentional abuse is shown in the top part, major medical outcomes or death in the middle, and overdose in the bottom. We can see that compared to morphine ER, Opana ER had more increase in intentional abuse from pre to the post period.

For major medical outcomes or death, since the counts were low in the RADARS poison center study, the confidence interval in the middle are white and show no difference between morphine ER and Opana ER. But for overdose, it shows that Opana ER was worse or at least not better than morphine ER. That means even though overdose decreased for Opana ER in the post period, it decreased even more for morphine ER.

Here is a summary of this presentation. I started this presentation by asking what the ideal data are to evaluate the abuse-related outcomes of Opana ER reformulation. Ideally, one would identify a population and capture all the opioid abusers and follow them over time. However, such population data are not available.

The next best thing would be a probability sample with data of all important confounders that allow us to do causal analyses.

This is the common foundation in observational cohort studies, but the data we have are not such a probability sample but rather a

convenience sample. Therefore, to make inference of data from a convenience sample, one has to make certain assumptions.

I discussed the essential assumptions for these two observational studies. With regard to estimability, the assumptions require that the sample selection all is changed over time to be independent of abused substances. In causality, I emphasized the assumption of similarity between Opana ER and its comparators.

Even though I listed a number of assumptions and talked about situations where these assumptions might not hold, our discussion here does not preclude reaching judgment about the data. It only reminds us to use caution when interpreting the study results.

In the interpretation session, I examined the study results in the context of estimability and causality. Our interpretation focused on the comparative aspect of the studies. I showed the post versus pre abuse ratios of Opana ER and the ratio-ratio comparisons between comparators and

Opana ER.

Coming next, Dr. McAninch will present a detailed look into misclassification in the data and the results from the two observational studies.

FDA Presentation - Jana McAninch

DR. McANINCH: Good afternoon. I am Jana McAninch. I am from the Office of Surveillance and Epidemiology, and I am giving the last presentation of the day. I will be discussing the postmarketing epidemiologic data on Opana ER and selected comparators.

First, I will review the two formal epidemiologic studies that were submitted by Endo, the NAVIPPRO and RADARS poison center studies, which you've heard some about today already. Then I will briefly discuss some additional epidemiologic data, including publicly available data from the National Survey on Drug Use and Health as well as data that we have recently acquired from another abuse surveillance program, the RADARS treatment center program. Finally, I will provide our overall interpretation of the

data.

First, the NAVIPPRO study, just as a reminder, this study analyzed self-reported on data on drugs abuse in the past 30 days in a sample of individuals being assessed for substance abuse triage and treatment planning in a variety of settings.

NAVIPPRO uses the ASI-MV computerized assessment, which undergoes periodic updates to incorporate changes to the prescription drug market and to improve the accuracy of data collection. This screenshot shows how individuals are asked about their use of oxymorphone products as it looked at the beginning of the post-reformulation period.

If a respondent endorses use of any of these products, he or she is directed to a series of questions to determine the routes used and whether the use was non-medical, which in this study was defined as abuse.

There are several ways to examine abuse of a particular drug in a population. First, we can

look at a drug's so-called route of abuse profile or the proportion of abusers of a drug who report using it via specific routes. Next, we can calculate the abuse prevalence or the number of abuse mentions as a proportion of the total number of assessments. This metric is useful to understand the relative frequency of abuse of different drugs within the population.

However, as more of a drug is prescribed, availability for abuse and diversion also increases. We also look at the tablet-adjusted abuse rate, which refers to the number of abuse mentions for a drug relative to the number of tablets dispensed from pharmacies within the study coverage area.

Adjusting for utilization in this way, although it has limitations, does facilitate comparisons across drugs with very different market shares as well as comparisons over time that account for changes in prescribing trends.

Many factors can influence opioid prescribing trends. First, reformulation might

reduce demand by those intending to abuse or divert it. However, many other factors can also affect prescribing of a drug. For example, drug shortages, introduction of generic products, advertising and detailing practices, use of prescription drug monitoring programs, changes in insurance coverage, and law enforcement practices such as pill mill crackdowns. Therefore, it's useful to look at both metrics when trying to understand the impact of a drug's reformulation on abuse levels or on the relative abuse rates for different products.

One question that we attempted to answer in reviewing these studies was how did Opana ER abuse patterns change after its reformulation compared to what would have happened without the reformulation. As Dr. Xie mentioned, this comparison of what was observed to a hypothetical scenario without the intervention, often referred to as the counterfactual, is a useful concept for making causal inferences.

Although we can't measure the counterfactual

directly, trend analyses and comparators can help to disentangle the effect of the reformulation from secular trends in drugs abuse, for example, due to changes in the availability or substitutable drugs such as heroin, changes in the study population, or the effects of concurrent interventions.

Because generic oxymorphone ER products are bioequivalent to original Opana ER but are not designed to deter abuse, this product group may offer a clue to what might have happened to Opana ER abuse patterns had it not been reformulated.

This map shows the sites and ZIP codes included in the NAVIPPRO analytic sample. As you can see, while the coverage area is fairly large, it does not represent the entire United States, and some areas are much more heavily sampled than others.

This is a convenience sample with sites dropping in and out of the network in a nonrandom fashion as contractual agreements change, and a relatively small proportion of sites contributed

data in every quarter. The number of sites and assessments, as you have heard, changed quite dramatically for several states, most notably Tennessee and New Mexico.

Several other states are also shown here to illustrate that some areas known to be suffering from particularly severe opioid problems, for example, West Virginia, Kentucky, and Utah, have little representation in the NAVIPPRO study sample. Also notable is the lack of assessments from Indiana mentioned earlier today as the location of the large HIV outbreak associated with Opana ER injection.

Because abuse patterns can vary widely by geographic area as well by the setting in which individuals are assessed, for example, an inpatient rehab center versus a probation office, there is potential for bias due to these shifts in the study sample over time.

We therefore focused on sensitivity analyses that used a fixed set of sites that contributed data in every quarter of the study period. So

restricting the sample in this way stabilizes the sampling frame and mitigates bias due to changes in the distribution of both geographic regions and type of assessment site. However, it does also reduce both study power and generalizability including only 53 sites in 15 states.

Importantly, it does not account for external factors that in part determine whether a person abusing or addicted to prescription opioids is assessed for treatment, for example, changes in judicial policies and availability and funding of substance abuse treatment. These factors are extremely difficult to measure and control for and remain a limitation of these type of data.

Because of the high number of Opana ER abuse reports from Tennessee and the increasing proportion of assessments from this state, stratified analyses examining Tennessee and non-Tennessee sites separately are also informative.

This table shows the number of sites, assessments, and Opana ER abuse cases in the full

3-year pre period and the 3-year post period, first for the overall network; for Tennessee sites only; for non-Tennessee sites; and finally, for the restricted set of fixed sites.

I just want to point out a few things on this slide. First, we see the large increase in Opana ER abuse cases within the Tennessee sample coinciding with an increase in both sites and assessments from this state. As noted previously, the number of Opana ER abuse cases relative to the total number of assessments is many times higher in Tennessee compared to the non-Tennessee sample.

Another important thing to note is that in addition to the almost 1700 reformulated Opana ER abuse reports in the post period, there were more than 500 abuse reports for original Opana ER during this same time period after the product had been off the market for more than a year.

These post period original Opana ER abuse reports were not included in the pre/post analyses, and it's unclear what exactly these cases represent. Some might represent residual supply of

original Opana ER or even of a counterfeit product. Some respondents may have misunderstood the question as asking about lifetime rather than past 30-day abuse. And finally, respondents may have misidentified other products, for example, reformulated Opana ER, generic oxymorphone ER, oxymorphone IR, or even another opioid as original Opana ER, which was the first selection on the oxymorphone screen for most of the post period.

Despite the limitations of the NAVIPPRO data, there were some important findings. First, using the fixed-site sample, this figure depicts the change across three time periods in the routes reported by people who indicated abuse of Opana ER and comparators. The blue bars on the left represent the pre period before the introduction of reformulated OxyContin, the red bars represent the time from the introduction of reformulated OxyContin to the introduction of reformulated Opana ER, and the green bars on the right represent the post period.

We see that after Opana ER was reformulated,

there was a notable reduction in the proportion of Opana ER abusers indicating that they had snorted the product. None of the comparators showed a similar magnitude of reduction in the nasal route among abusers of the products.

Now using the same fixed-site sample and time periods, this figure shows the percent of abusers of each drug who reported injecting the drug. Here we see a sharp increase in the proportion of Opana ER abusers who reported injecting it. An increase of this magnitude was not seen for any of the comparators. Of particular note was that there was not an increase in injection among oxycodone ER abusers following the reformulation of OxyContin.

This shift from snorting to injecting among Opana ER abusers was observed in both the Tennessee and the non-Tennessee subsamples.

Oral abuse was quite low in all three time periods for Opana ER, generic oxymorphone ER, and oxymorphone IR products.

The analyses just shown were limited to only

those reporting abuse of each specific product. However, individuals might, of course, also choose not to abuse the reformulated product at all. In order to understand the impact of the reformulation, we must also look at changes in route-specific abuse rates in the overall study population, not only among those who abuse the product.

This is in many ways a more challenging task because estimates may be more vulnerable to the type of sampling issues that have been discussed. Again, fixed-site analyses and stratified analyses are useful. Possible misclassification bias must also be considered, and pre/post comparisons may be confounded by secular trends, so use of comparators is important.

I know this is a busy slide so I'll try to orient you. On the Y-axis is nasal abuse prevalence per 100 assessments per each opioid, and on the X-axis is time by calendar quarter with the vertical green arrows marking the introduction of reformulated OxyContin, the introduction of

reformulated Opana ER, and the beginning of the 3-year post period.

The solid gray line shows the increasing prevalence of Opana ER nasal abuse during the pre period. The gray dashed line indicates Opana ER nasal abuse prevalence in the post period, showing a decline in nasal abuse prevalence following reformulation. The red solid line shows the prevalence of generic oxymorphone ER nasal abuse was higher than that for reformulated Opana ER during the post period.

Now looking at tablet-adjusted nasal abuse rates, we see a similar pattern in the tablet-adjusted rates for Opana ER and generic oxymorphone ER, again with a pre-reformulation increase followed by a decline in Opana ER nasal abuse rates after reformulation with substantially higher rates for generic oxymorphone ER.

Now let's look at injection abuse prevalence using the fixed set of sites. Again, we see some increase in Opana ER injection abuse during the pre period followed by further increases after

reformulation, shown here with the dashed line. During the post period, however, we also see that injection abuse rates for generic oxymorphone ER, shown with the solid red line, were essentially indistinguishable from reformulated Opana ER.

Stratified analyses do suggest that Tennessee is largely driving the increases in Opana ER injection abuse in this study population as well as the high post period generic oxymorphone ER injection abuse prevalence, although more modest increases in Opana ER injection abuse prevalence were seen in the non-Tennessee sample as well.

Adjusted now for utilization, Opana ER injection abuse increased modestly during the pre period and then markedly after the reformulation. Reformulated Opana ER injection abuse rates were again similar to those for generic ER oxymorphone. Also notable were the relatively high rates for oxymorphone IR during the post period.

Comparing abuse rates across drugs during the post period can also be valuable in considering the risk-benefit balance of a product. Here, we

focused on the full NAVIPPRO sample to cover the largest geographic area, although the non-representative nature of this sample must be kept in mind. In addition, product misclassification could affect these estimates.

First, the top panel compares the abuse prevalence for each opioid overall and via the oral, nasal, and injection routes during the post period. Among the opioids included in this study, the most common drugs abused were oxycodone IR single entity and oxycodone ER.

The bottom figure depicts abuse rates per 10,000 tablets dispensed. Here, generic oxymorphone ER had the highest overall in nasal abuse rates. Generic oxymorphone ER and reformulated Opana ER had the highest injection abuse rates followed by oxymorphone IR.

In summary, the NAVIPPRO study has considerable limitations. However, the data consistently show that following Opana ER's reformulation, there was a shift from snorting to injecting the drug among Opana ER abusers. This

shift was seen in the stable set of fixed sites as well as in the Tennessee and non-Tennessee samples, and a shift of this magnitude was not seen in any comparator opioid.

The data also suggests that in this study population, Opana ER nasal prevalence and utilization-adjusted rates decreased following its reformulation. Given the limitations of the data, it's difficult to determine the magnitude of this apparent effect.

Opana ER injection abuse rates increased across the study period. This increase began before reformulation and appears to be driven primarily by increases within the state of Tennessee. Finally, injection abuse rates were similar for generic oxymorphone ER and reformulated Opana ER during the post period.

During the post period, abuse prevalence was highest for IR and ER oxycodone among the opioids included in this analysis. However, adjusting for prescribed availability, generic oxymorphone ER had the highest overall in nasal abuse rates in this

population, and generic oxymorphone ER and reformulated Opana ER had the highest injection abuse rates followed by oxymorphone IR. Again, we have to consider the non-representative sampling and potential misclassification when making these comparisons.

Let's move on to the RADARS poison center study, which analyzed calls to regional poison centers covering most of the U.S. population. The study time periods were similar to those used in the NAVIPPRO study. The pre period was divided into two parts, before and after the reformulation of OxyContin, called ORF in the study; then a 6-quarter transition period after the introduction of reformulated Opana ER, which was called CRF in this study; and finally, the 3-year post period.

Both population- and utilization-adjusted call rates were calculated. Outcomes included intentional abuse exposure calls with additional analyses on the route of administration reported in these cases; a composite outcome called overdose which consisted of both intentional and

unintentional exposures; and finally, calls resulting in major medical outcome or death. I will focus today primarily on the intentional abuse calls.

The poison center data showed a sharp increase in Opana ER abuse call rates during the pre period followed by a significant decline after reformulation with rates returning to those seen during the early pre period prior to the reformulation of OxyContin. Abuse calls rates also decreased significantly for ER morphine and IR oxymorphone.

After adjusting for utilization, the relative reduction in Opana ER abuse calls was not significantly different from that from ER morphine or IR oxymorphone. The abrupt change in slope for Opana ER abuse call rates was, however, not seen for these comparators. These patterns were similar for the other outcomes examined.

An important thing to note is that there were only 6 intentional abuse exposure calls for generic oxymorphone products during the post period

despite prescription volume for these products that by the end of this period was nearing that for Opana ER, which had almost 200 abuse calls in the post period. Therefore, reliable rates could not be generated for oxymorphone generic ER, and it was not useful as a comparator in this study.

As shown in this table, there was a shift observed in the routes of abuse mentioned in Opana ER abuse calls after the product was reformulated with a decrease in the proportion of calls reporting the inhalation or nasal route and a marked increase in the proportion involving injection. Such a shift from inhalation to injection was not observed for ER oxycodone abuse cases following the reformulation of OxyContin.

This figure depicts changes in mean rates of Opana ER intentional abuse calls involving the inhalation or nasal route with population-adjusted rates on the left and utilization-adjusted rates on the right. Using either denominator, you see that there were significant decreases in inhalation abuse call rates following Opana ER's

reformulation, again returning to rates seen in the early pre period prior to reformulation of OxyContin.

This figure depicts changes in mean rates of Opana ER intentional abuse calls involving the injection route, again, population-adjusted on the left and utilization-adjusted on the right.

Using either denominator, there was an increase in injection abuse rates across the full study period. Comparing just the pre period after OxyContin's reformulation to the post period after Opana ER's reformulation, there was a significant increase in the utilization-adjusted but not the population-adjusted injection abuse call rates.

If you recall, in the NAVIPPRO study, it appeared that Tennessee may be an outlier with regard to Opana ER abuse rates, so we requested some additional analyses using poison center data to further examine this apparent geographic heterogeneity.

In the left column of this table are population-adjusted Opana ER intentional abuse call

rates for the total study period shown for the 10 states with the highest rate. The right column shows the tablet-adjusted rates for these states.

We see more than a 10-fold difference in the population Opana ER abuse call rates with West Virginia and Kentucky having the highest rates followed by Tennessee and then Indiana. With the exception of Tennessee, these top four states contributed very few assessments to the NAVIPPRO study sample.

This figure compares the post period intentional abuse call rates for Opana ER and comparators, population-adjusted in the top panel and utilization-adjusted in the bottom panel. Of the opioids included in this analysis, ER oxycodone had the highest population-adjusted abuse call rates while Opana ER had the highest utilization-adjusted call rates. Again, there were only a handful of calls mentioning generic ER oxymorphone.

It is possible that some of these exposures could have been reported as the brand product. We've seen this phenomenon in poison center data

for other drugs with a highly recognizable brand product names. However, even if all dispensed generic oxymorphone ER tablets were included in the denominator for the utilization-adjusted Opana ER abuse rate, it would still remain higher than any of the comparators included in this study.

To summarize the RADARS poison centers study findings, following Opana ER's reformulation, there was a shift observed from nasal to injection among Opana ER abuse cases. Nasal abuse call rates decreased significantly, returning to levels seen before OxyContin's reformulation, while utilization-adjusted injection abuse call rates increased.

In the post period, utilization-adjusted Opana ER abuse call rates were substantially higher than those for ER morphine, IR oxymorphone, or ER oxycodone. But the state level data suggest substantial geographic variation in Opana ER abuse with the highest call rates in the Appalachian states of West Virginia, Kentucky, and Tennessee followed by Indiana.

The relative lack of generic oxymorphone ER calls suggests that some degree of misclassification is likely occurring, and again, this complicates the interpretation of the postmarketing data.

Finally, although these data have nearly national geographic coverage, poison center calls capture an unknown and likely small proportion of actual abuse occurring, so these estimates cannot be interpreted as representing the true prevalence of abuse of these products. And as was pointed out in the last talk, making inferences about relative abuse prevalence in the population based on poison center call data relies on certain assumptions about the fraction of abuse events captured both over time and across different products.

Given the uncertainties remaining in the postmarketing evidence, we sought out additional information that might help to inform the discussion about the risk-benefit balance of Opana ER and the abuse of oxymorphone products.

The National Survey on Drug Use and Health,

or NSDUH, is a nationally representative household survey that provides estimates on the use and misuse of various types of drugs in the United States, including prescription pain relievers. The survey uses pill photo cards to assist in the identification of the drugs, and the results from the redesigned 2015 survey now allow comparisons of past year use and misuse across opioid subgroups.

The 2015 NSDUH survey defines use as either use of one's own prescription medication as directed by a doctor or misuse which is broadly defined as use of the drug in any way not directed by a doctor.

This table shows the estimated national number of individuals aged 12 and older who have used and who have misused various opioid analgesics in the past year. The first column shows the estimated number in thousands who have used each opioid, the next column shows the number who have misused each opioid, and the last column shows the percent of past year users of each opioid who report misusing it.

We see that oxymorphone products represent a very small proportion of both use and misuse of prescription opioid analgesics. However, the percent of past year oxymorphone users who report having misused it was 28.9 percent, almost twice the next highest percentages for oxycodone and fentanyl.

These data suggest that while oxymorphone compromises a small proportion of total opioid analgesic use and misuse of those who have used an oxymorphone product in the past year, a relatively high proportion report misusing it.

Finally, I want to briefly discuss some additional analyses that we recently commissioned to try to better understand what we're seeing in the submitted studies, particularly the conflicting findings regarding generic products seen in the NAVIPPRO and RADARS poison center studies.

These data are from the RADARS treatment center program, which surveys individuals entering treatment for opioid use disorders, asking them to identify specific products that they have used in

the past month to get high. This program began collecting data on abuse of oxymorphone products in second quarter of 2011. It began collecting data on injection abuse in third quarter 2011 and on other routes of abuse in third quarter of 2015.

This map shows the site locations and coverage areas for the post-reformulation period. The total number of sites and participants is quite a bit smaller than for the NAVIPPRO network, but the coverage is more widely distributed. Like NAVIPPRO, this is a convenience sample that can change and does change over time.

This program uses a paper survey instrument organized into sections by opioid molecule. This image shows the section asking about abuse of oxymorphone products. Note that Opana immediate-release tablets are listed first with Opana ER farther down in the section.

This table shows in the left column the number and percent of respondents reporting past month abuse of each drug and in the right column, the tablet-adjusted abuse rates. The most striking

finding is the relatively high proportion of respondents reporting abuse of Opana immediate-release compared to the proportion reporting abuse of Opana ER, which is far more widely prescribed. The very low prescription volume for brand Opana IR in combination with the relatively large numerator resulted in extremely high utilization-adjusted abuse rates for this product.

Of note, this survey does not use pill photographs to aid in the identification of specific products, and Opana ER is commonly referred to in the media and on internet drug discussion forums simply as Opana.

We believe that these estimates likely reflect some differential misclassification of other oxymorphone products, likely including Opana ER as Opana, which was the first product listed in the section. This would inflate abuse estimates for Opana IR while underestimating abuse of Opana ER and possibly generic oxymorphone products.

The almost 400 reports of generic oxymorphone ER abuse do call into question the near

absence of generic oxymorphone ER abuse cases in the poison center data and suggest that substantial abuse of these products is occurring, but it's difficult to determine with any degree of confidence the abuse rates for specific oxymorphone products relative to one another.

If one were to assume that most mentions of Opana ER do actually represent abuse of this product, then the RADARS treatment center findings are qualitatively consistent with the RADARS poison center and NAVIPPRO studies that following Opana ER's reformulation, the proportion of Opana ER abusers who reported injecting it increased. They also suggest that Opana ER injection abuse prevalence increased in this population both as a proportion of respondents and relative to prescription volume.

The increases in injection were not unique to Opana ER. There were also increases in injection seen for the other oxymorphone products as well as IR oxycodone. Again, comparisons are complicated by sampling issues, although in this

study, the proportion of surveys from Tennessee was relatively low and remained stable from the pre- to post-reformulation period.

As you have heard throughout the day, the postmarketing data have many limitations. However, it has been said that the art of epidemiologic reasoning is to draw sensible conclusions from imperfect data, in this case, to try to inform the discussion about the appropriate regulatory course of action.

Despite the noted limitations and uncertainties, we believe that the data are compelling that among those abusing Opana ER, the reformulation caused a shift from the nasal to the injection route. This shift was temporally associated with the reformulation. It was a consistent finding in multiple studies and populations and is qualitatively consistent with the pattern seen in the FAERS data and the anecdotal information from Indiana. A shift of this magnitude was not seen for comparators.

Finally, the observation is biologically

plausible, given the experimental evidence suggesting a deterrent effect for the nasal route, the ability to prepare a suitable solution for injection, and the very low oral bioavailability that may be pushing abusers towards IV abuse if nasal use becomes more difficult in this drug and this is the drug of choice or the one that is available.

As far as Opana ER abuse in the population, the data suggests that Opana ER's reformulation caused a decline in nasal abuse of this product. However, because of data limitations, it's difficult to determine the magnitude of this apparent effect.

Multiple data sources indicate that Opana ER injection abuse rates increased across the study period. However, it is unclear whether the increases in Opana ER injection abuse rates in the population were greater than they would have been without the reformulation.

Contributing to this uncertainty are that increases began prior to the reformulation, that

the post period rates were similar to those for generic oxymorphone ER at least in the NAVIPPRO study, and that there seems to be remarkable geographic variation in abuse patterns with specific regions appearing to drive the observed increases.

Multiple data sources suggest that Opana ER and other oxymorphone products represent a small proportion of total opioid analgesic use and abuse in the United States. Adjusted for prescribed availability, however, Opana ER and other oxymorphone products may be relatively likely to be abused and misused, although abuse of these products appears to vary widely again by geographic region.

The NAVIPPRO study suggests that generic oxymorphone ER has high nasal abuse rates and that both reformulated Opana ER and generic oxymorphone ER have high injection abuse rates with only slightly lower rates for oxymorphone IR. Again, geographic variation and non-representative sampling as well as potential misclassification

complicate the interpretation of these data.

Finally, we have seen examples of serious health consequences associated with injection of Opana ER. First, the more than 50 reported cases of thrombotic microangiopathy associated with Opana ER injection following its reformulation. We have animal model data suggesting that PEO is the causal agent. However, it remains unclear why cases were not seen in Scott County, Indiana, and why this phenomenon has not been widely seen with other PEO-containing opioids, including OxyContin, which the epidemiologic data suggests is still being injected.

Second, of course, with the large HIV outbreak associated with injection of reformulated Opana ER, investigations suggest that there were several forces driving the practice of multiple shared injections. First was the short duration of effect and intensity of withdrawal leading to many injection events per day. Second was the need for increased volume of solvent and rinse shots, and finally, the sharing of the expensive high potency

Opana ER pills and the equipment used to prepare and inject them.

It's difficult to parse out exactly how much excess risk of disease transmission can be directly attributable to properties of reformulated Opana ER specifically versus high dose extended-release formulations of oxymorphone versus the oxymorphone molecule in general compared to the baseline risk of injection drug use.

This concludes my presentation, and we will be taking clarifying questions for the last four FDA presentations.

Clarifying Questions

DR. WINTERSTEIN: All right. Any questions? Dr. Emala.

DR. EMALA: I have a comment and a question for Dr. Hunt. I can't help but applaud this study design. It's not usual that we see a case series married to an in vivo animal model that offers a plausible mechanistic explanation.

My question, in the paper itself, it's described that to determine the amount of PEO to

administer to the animals that an adulteration process was performed with a 40-milligram tablet to estimate the amount extracted and then extrapolated that to a volume of distribution of the entire plasma volume of 70-kilogram individual.

Two parts of my question, do you think that's a valid way of estimating the volume of distribution of this? Because it's a such a large series of molecular weights, perhaps it would stay only in the plasma compartment.

Secondly, do you know if anybody's ever actually measured PEO concentrations in humans after abuse?

DR. HUNT: To your second question, this is something we're trying to do right now partially to validate our findings and to ensure that the doses we used are relevant for exposure levels in humans. So actually, we've been in discussion with some physicians in North Carolina that may have blood samples taken from these patients as they were admitted.

In terms of getting to the best estimate, I

think actually that was something that Endo was quite helpful with in arriving at appropriate dose levels, but again, these were just our best estimates. With such a large molecule, it's likely that the majority of it is staying within the blood. So I think using the plasma volume is a reasonable volume of distribution to use.

DR. WINTERSTEIN: Dr. Mendelson?

Okay. I have a question for Dr. McAninch. Slide 12 where you show the NAVIPPR results for the time comparisons for these three observation periods, I'm still trying to get my arm around the generic oxymorphone.

Why is there nothing, no blue and no red bar? There was generic oxymorphone available during those time periods as well.

DR. McANINCH: Not in the first time period. In the second time period for part of that period, there were just 7.5- and 15-milligram doses of generic ER oxymorphone. Because there weren't equivalent dosing ranges, we didn't feel it was a fair comparison.

DR. WINTERSTEIN: So that would mean this is really catching up now --

DR. McANINCH: Yes. So we really started looking at the generic ER oxymorphone in the post period after there were two quarters of the full range of dosage forms available on the market.

DR. WINTERSTEIN: Okay. Thank you.

Any other questions?

(No response.)

DR. WINTERSTEIN: We still have some questions from this morning for the sponsor. It might have been forgotten by now.

Dr. Gupta was next on our list. She's shaking her head. Good.

Dr. Ciccarone had another one from this morning.

DR. CICCARONE: Thanks. You caught me off guard, though. We spent a fair amount of time looking at data and talking about intravenous route of misuse, and we've heard from our CDC and Indiana colleagues about high volume injections and some of the risk factors that were leading to HIV. I think

they also connect to some of the stuff we saw with the Zibell paper, for example, with increased hepatitis C in Appalachia.

Now I have my computer up.

Dr. Rotman, referring to tables 2.3 and 2.4 in your submitted briefing documents, we have extraction results. I applaud you and the FDA for doing studies that sort of replicate the real world of multiple procedures that folks who want to misuse the tablets are going to go through. For example, we have grating followed by heating. We have heating by various physical manipulations followed by trying to get into solution. The ultimate goal is how much of the active substance then winds up in the solution, and then you also go into what kind of needle is needed to then pull it up.

Could you summarize those data in table 2.3 and 2.4 for the committee?

DR. ROTMAN: We'll call up Dr. Frank Diana to talk about that. Thank you.

DR. DIANA: These are pretreatment results, as I think you've mentioned, different techniques. I'm not sure I can talk about these techniques other than to say there is a variety of extraction amounts that could be taken. I think that ultimately, the reformulation takes a lot of time and effort and tools and experience for people.

We tended to look, earlier on anyway as we were developing the formulation and the first few years after it was on the market, at more efficient and effective methods to extract. And only recently have we really looked now at these methods that really take quite a long time to do and lead to materials that are very difficult to filter, but you can syringe them.

I guess it's very difficult to draw an ultimate conclusion from all of this data other than to say we have very similar results in terms of in vitro properties and in terms of in vitro data we've generated for OxyContin versus Opana.

The generic products can be crushed and dissolved in really very short periods of time.

It's difficult to go any further, but just one more point I think that maybe we can make is it's fairly complicated. There's a lot of factors that have to be taken into account here. I have a bunch of them up here on the slide to talk about what you have to take into account with syringeability and extractability. Of course, the particle size of the sample.

One of the interesting points from Dr. Englund's talk was the results from our NDA where we had seen very little extraction from the original formulation and higher extraction from the reformulated products. One of the reasons was because the samples weren't at all the same.

At that time, many years ago now, we couldn't filter the sample for the original product, and so we just stopped there and we left it at that. But now as we've learned, both products gel, abusers will find ways around these things, and they'll look at all of these different

factors, and they'll take those into account.

I guess, again, just saying that the reformulated product takes a lot of time and effort, and you really have to know a lot about these products. There's got to be a lot of experience to understand how to defeat them.

DR. CICCARONE: My look at this chart, between the 5-milligram and the 10-milligram extraction, it seems to me that the more volume you have, the more extractability you have. I was just hoping whether you would -- even within the 5-milliliter chart, the difference between 2, 3, and 4 milliliters solution, you get higher extractability.

We have extractability percentages here of 50 to 60 on the 5-milligram chart and up to 80 percent on the 10-milligram chart. I just want to point that out, that a large proportion of the drug can be, if you're clever enough and as you say, take enough time and have enough expertise as an illicit drug user, that extractability rates can be quite high.

DR. DIANA: Just to comment quickly, the volume is definitely one of the factors that is important. As we went to 10-mL, but if you think about it, 10 milliliters is not all that easy to do something with, so you have to think about that. But the bottom line is the more volume, the more you're going to dilute the viscosity agent, the PEO, and then the more you're going to dilute the oxymorphone, so any other drug that's being handled through 10, 5 or 10 mLs.

DR. CICCARONE: The reason I bring it up is it ties together the Indiana data, and that is, if you have 4 people who were sharing a 200-dollar pill, they can share that volume, and it leads to a lot of injections and a lot of potential bloodborne transmission because there's a lot of pokes going on. I just wanted to highlight the extractability, high volume, multiple injections, sociability connection with the Indiana HIV outbreak.

DR. WINTERSTEIN: Let's make sure we focus on clarifying questions. We have time for discussion tomorrow.

DR. DIANA: So I'd just comment real quick that I think the same thing would be with any product. It's not just oxymorphone.

DR. WINTERSTEIN: We have Dr. Schisterman from this morning. Anything still lingering around? No.

Dr. Acri? No.

Dr. Wish? No.

And Dr. Ghany?

It's a good strategy. You see, I just let you wait long enough, and it's not an issue any longer.

(Laughter.)

DR. WINTERSTEIN: Then Dr. Zacharoff.

All right. Any other questions?

DR. ROTMAN: We did want to offer up, if the panel would like to see it, we put together some figures with the confidence intervals. We know it was a subject of some discussion, and we're happy to throw some up and see what you think of them. We don't think it changes the results in any way. That was the reason why we didn't highlight them

before, but we can do so now, if you'd like.

DR. WINTERSTEIN: My sense is this has been addressed, but I give that back to the panel.

Does anybody want to see confidence intervals?

Dr. Bilker wants to see. We can do it tomorrow, too.

DR. ROTMAN: We'll do that. No trouble.

DR. WINTERSTEIN: We won't have much time tomorrow, just as a warning, because from what I understand, we will start tomorrow at 10:00 a.m. instead of 8:00 or 9:00 a.m. because of the anticipated snowfall, so tomorrow we will have to compress everything into a much shorter time period.

He really wants to see the confidence intervals so two minutes confidence intervals.

DR. ROTMAN: We'll call up Dr. Shusterman to show you some. Thank you.

DR. SHUSTERMAN: I can actually -- if it's all right with you -- dispense with the RADARS confidence intervals because they were shown on the

FDA slides. Let me just show you the first one as an example because the FDA used exactly what came out of the RADARS report.

The means were modeled in the three different periods, and then 95 percent confidence intervals were calculated around those. But this is the same figure that the FDA showed. This is for intentional abuse mentions during the two pre periods and the post period.

I also have that for major medical outcomes and death and for the non-oral route, if you would like to see that, but the FDA has seen it.

Would you like to see it? Yes?

DR. WINTERSTEIN: We're good. I think we're good. Thank you.

DR. SHUSTERMAN: I do want to show on the NAVIPPRO side, if I could, I would like to start with AA-22, please.

The way that NAVIPPRO worked is that they did a pre period and post period, and then a percentage change, and constructed a confidence interval around that percentage change. So that's

how the data were calculated in the original NAVIPPRO report.

What I'm showing here are the top panel is Tennessee, the bottom panel is outside of Tennessee, and this is that combined endpoint of alternate routes of abuse. This actually shows the same thing that was on my slides earlier.

Within Tennessee, you can see that alternate routes of abuse went from 8.26 to 5.69, and that recapitulates that blue line that I was showing this morning. Then for non-Tennessee, the same thing but at a much lower level because everything was happening higher in Tennessee than in non-Tennessee.

Then if we go to the individual routes here, we have intranasal. This is where I showed that intranasal was lower in the post period. You can see the percentage change there, the confidence interval around the percentage change, and the top is for Tennessee and then for outside of Tennessee.

Then importantly, here we have intravenous, and this is where you see that in Tennessee it went

up from 1.24 to 4.53; percentage change, 264 percent; and the interval around that. But look at the order of magnitude for outside of Tennessee. It's a tenth of that. It's an order of magnitude lower.

It also did go up, but this takes into account that entire 3-year pre period as I showed, but remember that the second half of that was actually much higher. So when you do that comparison, it's very similar outside of Tennessee.

DR. WINTERSTEIN: That does include all sites, and we have seen that the composition of the sites has changed fairly dramatically among pre/post periods.

DR. SHUSTERMAN: That is true, but if you actually look at the fixed-site analysis, it's actually very similar to the full analytic set as well in terms of the patterns.

DR. WINTERSTEIN: But I think in terms of sharing confidence intervals, that's probably not as relevant as using the fixed-site comparison to look at that. I just wanted to recall for the

panel that there really are different types of -- but that's fine.

I think we have -- everybody I think seems to feel we have enough. Thank you.

DR. ROTMAN: Thank you.

DR. WINTERSTEIN: Before we adjourn for the day, are there any last comments from the FDA? I think everybody is keen on --

DR. STAFFA: No. We just wanted to thank you for your participation and your active listening all day. We know we've hit you with a lot of information, so thank you very much and thank you for coming despite the weather. And hopefully, we'll see everyone in the morning at 10:00.

Adjournment

DR. WINTERSTEIN: Yes. If you don't hear anything with your email, I suppose, right, if there is a major blizzard that the meeting is canceled, you will be informed via email. Yes? If you do not hear anything, we will reconvene at 10:00 a.m. tomorrow morning.

The meeting for today is now adjourned. Panel members, please remember that there should be no discussion of the meeting topic amongst yourselves or with any members of the audience. Please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. We will reconvene tomorrow morning at 10:00.

(Whereupon, at 5:14 p.m., the open session was adjourned].