U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. This content has not been altered or updated since it was archived.

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting Announcement

Thursday, October 21, 2010

8:30 a.m. to 4:07 p.m.

Hilton, Washington D.C./North Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

PRESENT:

Jeffrey R. Kirsh, M.D., Chair
Kalyani Bhatt, Designated Federal Officer, ALSDAC

ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Jeffrey R. Kirsch, M.D., Chair
Professor and Chair,
Department of Anesthesiology and Perioperative Medicine,
Associate Dean for Clinical and Veterans Affairs,
Oregon Health & Science University,
Portland, Oregon

Randall Flick, M.D., M.P.H.,
Assistant Professor of Anesthesiology Mayo Clinic,
Rochester, Minnesota

Osemwota A. Omoigui, M.D.,
Consumer Representative,
Division of Inflammation and Pain,
Los Angeles Pain Clinic,
Hawthorne, California

Daniel Zelterman, Ph.D.,
Professor and Acting Division Head,
Division of Biostatistics, Epidemiology and
Public Health,
Yale University School of Medicine,
New Haven, Connecticut

INDUSTRY REPRESENTATIVE (Non-Voting)

Mark P. Fletcher, M.D., FAAAAI,
Acting Industry Representative,
MPF BioPharma Consultants, LLC,
Clinical Drug Development Consulting,
Charlottesville, Virginia

PRESENT: (CONTINUED)

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBERS (Voting)

Elaine H. Morrato, Dr.P.H.,
Assistant Professor,
Department of Pediatrics,
University of Colorado Denver,
Denver, Colorado

Sidney M. Wolfe, M.D.,
Consumer Representative,
Director, Health Research Group,
Public Citizen,
Washington, District of Columbia

Lewis Nelson, M.D.,
Director,
Fellowship in Medical Toxicology,
New York University School of Medicine,
New York, New York

TEMPORARY VOTING MEMBERS

Warren Bickel, Ph.D., M.D,
Director,
Arkansas Center for Addiction Research,
Department of Anesthesia,
Brigham & University of Arkansas for Medical Sciences,
Little Rock, Arkansas

Warren B. Bilker, Ph.D.,
Professor of Biostatics,
University of Pennsylvania,
Philadelphia, Pennsylvania

Richard Denisco, M.D.,
Medical Officer,
Pain/Addiction Medicine,
National Institutes of Health,
National Institute of Drug Abuse,
Division of Epidemiology, Services, and Prevention,
Bethesda, Maryland

PRESENT: (CONTINUED)

TEMPORARY VOTING MEMBERS (CONT.)

Robert Kerns, Ph.D.,
National Program Director for Pain Management,
Yale University School of Medicine,
VA Connecticut Health Care System,
West Haven, Connecticut

Susan Krivacic,
Patient Representative,
Austin, Texas

John Mendelson, M.D.,
Senior Scientist,
Addiction and Pharmacology Research Laboratory,
California Pacific Medical Center Research Institute,
St. Luke's Hospital,
San Francisco, California

Edward Michna, M.D.,
Director,
Pain Trial Center,
Women's Hospital,
Harvard Medical School,
Boston, Massachusetts

Cynthia Morris-Kukoski, Pharm.D.,
Forensic Examiner,
Department of Justice/Federal Bureau of Investigation,
Laboratory/Chemistry Unit,
Washington, District of Columbia

Sharon Walsh, Ph.D.,
Robert Straus Behavioral Research Building,
University of Kentucky,
Lexington, Kentucky

PRESENT: (CONTINUED)

FDA MEMBERS (Non-Voting)

Ellen Fields, M.D., M.P.H,
Team Leader,
Division of Anesthesia,
Medical Officer,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Sharon Hertz, M.D.,
Deputy Director,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Larissa Lapteva, M.D.,
Medical Officer,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Bob Rappaport, M.D.,
Director,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Judy Staffa, Ph.D., R.P.H.,
Acting Director,
Division of Epidemiology (DEPI),
CDER, FDA

Mary Willy, Ph.D.
Deputy Director,
Division of Risk Management,
Office of Surveillance and Epidemiology (OSE),
CDER, FDA

A-G-E-N-D-A

	Page
Call to Order, Jeffrey R. Kirsch, M.D.	9
Introduction of Committee, Jeffrey R. Kirsch, M.D.	10
Conflict of Interest Statement, Kalyani Bhatt	14
Opening Remarks, Bob Rappaport, M.D.	18
FDA Presentations: Nature of the Problem of Prescription Opioid Misuse and Abuse	
Overview of the Risk of Abuse and Regulatory Discussions to Date to Reduce Abuse of Opioid Analgesics, Larissa Lapteva, M.D.	24
Premarketing Assessment of Abuse-deterrent Formulations, James Tolliver, Ph.D.	39
Abuse of Marketed Opioid Analgesics and Their Contribution to the National Problem of Drug Abuse, Len Paulozzi, M.D., M.P.H.	52
Clarifying Questions,	68
Data Resources and Metrics Used to Assess Prescription Opioid Misuse and Abuse	
Designing Observational Studies on Drug Abuse, James C. (Jim) Anthony, Ph.D.	75
Substance Abuse and Mental Health Services Administration: Resources and Methods, Albert Woodward, Ph.D., M.B.A.	94

A-G-E-N-D-A (CONTINUED)

Page

FDA Presentations: {continued)

Available Data Resources to Assist in Measuring Abuse Behaviors, Patterns, and Outcomes,
Catherine Dormitzer, Ph.D. 105

Clarifying Questions, 119

Study Designs to Assess Prescription Drug Abuse

Design Considerations in Epidemiological Studies of Abuse-deterrent Opioids,
Cynthia Kornegay, Ph.D. 134

Statistical Considerations for Epidemiological Studies of Abuse-Deterrent Formulations,
Stephine Keeton, Ph.D. 143

Lunch, 154

Clarifying Questions, 155

Industry Presentations: Purdue Pharma, LP

Introduction,
Craig Landau, M.D. 177

Overview of Rationale and Study Program
Paul Coplan, DsC 190

Overdose Rates in OxyContin Patients and Non-Patients at Kaiser Permanente,
Nancy Perrin, Ph.D. 204

Exposures Reported to Poison Centers,
Rick Dart, M.D., Ph.D. 214

OxyContin Abuse Among Entrants to Substance Abuse Treatment Programs
Theresa Cassidy, M.P.H. 223

A-G-E-N-D-A (CONTINUED)

Industry Presentation: (continued)

Using Surveys to Assess the Impact of a New Formulation of OxyContin,
Howard Chilcoat, ScD 228

Law Enforcement Events in the Drug Diversion Program at RADARS System,
Rick Dart, M.D., Ph.D. 236

Doctor-Shopping for OxyContin as Measured by Prescription Monitoring Programs,
Paul Coplan, DSc 240

Internet Discussion About Reformulated OxyContin Use,
Theresa Cassidy, M.P.H. 244

Changes in Abuse Patterns in a Cohort of People Abusing OxyContin in Rural Kentucky,
Carl Leukefeld, DSW 250

Summary and Conclusions,
Paul Coplan, DSc 255

Clarifying Questions, 258

Adjourn, 301

P R O C E E D I N G S

(8:00 AM)

Call to Order

DR. KIRSCH: Good morning, everybody. If everyone could please take their seats, we can get started. I'd like to remind everyone present to please silence your cell phones, BlackBerrys, and other devices if you have not already done so. We'll get started by going around the table and introducing ourselves.

Before we do that, I have two other short announcements.

First, as we begin our deliberation for the members of the committee, I wanted to remind you to try to be succinct in your comments and try not to be redundant. I will, at this meeting, take the Chair's prerogative to curtail discussion that I think is redundant or not directed at the question at hand.

I'd also like to take this opportunity to wish Dr. Willy a happy birthday. Happy birthday.

(Applause.)

DR. KIRSCH: We'll start the introductions with our Industry Representative, Dr. Fletcher.

Introductions

DR. FLETCHER: Good morning. I'm Dr. Mark Fletcher. I'm the acting representative for the Anesthetics Advisory Committee, and I am a non-voting member.

DR. MENDELSON: And I'm John Mendelson. I'm an internist and clinical pharmacologist from San Francisco, and this is my first meeting.

DR. NELSON: Lewis Nelson. I'm an emergency physician and a medical toxicologist from New York University School of Medicine.

DR. KRIVACIC: I'm Susan Krivacic, and I'm a patient representative from Austin, Texas.

DR. WOLFE: I'm Sid Wolfe. I'm an internist. I'm with the Public Citizen Health Research Group on the Drug Safety and Risk Management Advisory Committee.

DR. BICKEL: Warren Bickel, Center for Addiction Research, University of Arkansas for Medical Sciences.

DR. KERNS: Good morning. I'm Bob Kerns. I'm professor of Psychiatry, Neurology, and Psychology at Yale University, and I'm also with the VA as director of

the Pain Management Program for VA and director of a pain research center at VA Connecticut.

DR. BILKER: Warren Bilker. I'm Professor of Biostatics at the University of Pennsylvania.

DR. MORRATO: Good morning. Elaine Morrato, and I'm an epidemiologist from the Colorado School of Public Health and Health Systems Management and Policy.

DR. FLICK: Randall Flick, pediatric anesthesia, intensive care, Mayo Clinic.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm with the Division of the Advisory Committee, Consultants Management.

DR. KIRSCH: I'm Jeff Kirsch. I'm the chair of the Department of Anesthesiology and Peri-Operative Medicine at Oregon Health Sciences University, and the associate dean for Clinical and Veterans' Affairs.

DR. ZELTERMAN: I'm Dan Zelterman, professor of Biostatistics at Yale University.

DR. MICHNA: Ed Michna, anesthesia, pain management, Brigham and Women's Hospital in Boston.

DR. WALSH: Good morning. I'm Sharon Walsh. I'm the director of the Center on Drug and Alcohol

Research and a professor in behavioral science and psychiatry at the University of Kentucky in Lexington.

DR. OMOIGUI: Good morning. I'm Osemwota Omoigui. I'm an anesthesiologist and pain specialist, medical director, L.A. Pain Clinic, Hawthorne, California, and also the consumer rep.

DR. WILLY: I'm Mary Willy. I'm deputy director, Division of Risk Management in the Office of Surveillance and Epidemiology.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the acting director of the Division of Epidemiology in the Office of Surveillance and epidemiology at FDA.

DR. FIELDS: I'm Ellen Fields, clinical team leader, Division Anesthesia and Analgesia.

DR. LAPTEVA: Good morning, I'm Larissa Lapteva. I'm deputy director for Safety in the Division of Anesthesia and Analgesia Products.

DR. HERTZ: I'm Sharon Hertz, deputy director, Division of Anesthesia and Analgesia.

DR. RAPPAPORT: Bob Rappaport, director, Division of Anesthesia and Analgesia.

DR. KIRSCH: Thank you. For topics such as

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

In the spirit of the Federal Advisory Committee Act and the Government and 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 the proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

For the convenience of the media representatives, I would like to identify the FDA press contact, Shelly Burgess. If you are present, please stand.

PARTICIPANT: Shelly's not here.

DR. KIRSCH: Thank you.

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

I'll pass it to Kalyani, who will read the Conflict of Interest statement.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. All members and temporary voting members of the committee or special government employees or regular federal employees from other agencies and are subject to Federal Conflict of Interest Laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being

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

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

Under Section 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of the committees have been screened for potential financial conflicts of their own, as well as those imputed to them, including those of their spouses or minor children and for

purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of the design of post-marketing studies of OxyContin, controlled release tablets manufactured by Purdue Pharma and Embeda, extended release capsules manufactured by Alpharma Pharmaceuticals and King Pharmaceuticals, approved for the management of moderate to severe pain when a continuous, around the clock opiate analgesic is needed for an extended period of time. The post-marketing studies are intended to epidemiological or observational studies that will assess a known, serious risk of these products, and whether product-specific properties which are intended to discourage misuse and abuse actually result in a decrease in the risk of misuse and abuse and their consequences.

This is a particular matter's meeting during which specific matters related to Purdue's OxyContin controlled release tablets and Alpha and Kings Embeda

extended-release capsules will be discussed.

Committee members and temporary voting members, not conflict of interest waivers were 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. Mark Fletcher is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Fletcher's role at this meeting is to represent industry in general and not any particular company. Dr. Fletcher is an independent pharmaceutical industry consultant.

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

will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with any firms at issue.

Thank you.

DR. KIRSCH: I'd like to recognize Dr. Rappaport.

Opening Remarks

DR. RAPPAPORT: Good morning. Dr. Kirsch, members of the anesthesia and life support drugs, and the Drug Safety and Risk Management Advisory Committees, invited guests, thank you for your participation in this important meeting.

Many of you have attended some or perhaps all of the numerous advisory committee meetings that we have convened in the past few years to discuss applications for opioid drug products that have been formulated to provide some degree of abuse-deterrents. As you know, one of the biggest hurdles we have to face as we review these applications and decide on appropriate labeling for their abuse deterrent properties is how to measure their actual impact on abuse in the community.

For nearly a decade, we have been quite clear that we would not allow language stating that a product is abuse-deterrent into the labels without documentation that the availability of the purportedly abused deterrent product had actually reduced abuse at the community level. To do otherwise would permit the manufacturers to make unsubstantiated, promotional claims that could lead to the same types of misconceptions which resulted when OxyContin was first marketed. Those misconceptions that OxyContin was less likely to be abused and was less addictive than other potent opioid drug products were based on just a few simple words in the approved label and they played a key role in the public health crisis of abuse, overdose, and addiction that has plagued our communities every since.

Now that we have approved opioid drug products with features that are intended to limit their abuse, it has become even more critical for us to define a clear direction for the manufacturers regarding the regulatory requirements for establishing that a product has demonstrated actual abuse-deterrents. To do this, we must provide a scientifically and clinically sound

program of studies that will stand as the evidentiary support for a regulatory determination.

But, as has been widely acknowledged in numerous public meetings and in the pertinent medical literature, the available databases used to track abuse were not designed for this challenge, but rather to detect signals of abuse. And no clear paradigm for which databases and which study designs would provide the best quality data for longitudinal tracking of abuse in the community has been established, though many different academic and other centers have been working hard to address the challenge.

Today, we've brought together leading experts from a number of disciplines that are key to the development of a study or set of studies that we hope will provide us with a foundation upon which we can provide the guidance that is needed to support continued development of these important drug products and that will allow us to fulfill our regulatory mandate of making decisions that are based on sound science and that are not arbitrary and capricious.

You will be hearing from a number of FDA

scientists, as well as experts from other government agencies and academia. In addition, representatives from King Pharmaceuticals and Purdue Pharma will present their proposals for studies to track abuse levels after the introduction of their own novel products into the market.

While we are not asking to judge those proposals today, as they have provided them in early draft form and without the benefit of agency feedback, we are asking you to consider the elements of these proposals as part of your discussions and in providing your recommendations to us today.

The development of a standard by which the agency can judge whether a new product has actually impacted abuse in the community is a significant challenge. As such, we recognize that these studies that you recommend for us in this endeavor will require testing and validation, and, over time, this methodology will likely change and grow. We are just at the beginning of this effort, and we may not have a true gold standard for many years.

But we do have to begin someplace if we're

going to encourage and advance the development of abuse-deterrent opioids. So, please remember that as Voltaire wrote back in 1764, "the perfect is the enemy of the good." And let's work together to come up with the best path forward for today and perhaps for tomorrow.

Again, thank you for taking your time from your busy schedules to participate in this important process.

I do have one additional matter to bring to your attention today before we begin the presentations. Yesterday, Dr. Wolfe sent us an e-mail requesting that we provide you with a copy of a warning letter that FDA issued to King Pharmaceuticals regarding a video news release for Embeda that we considered false or misleading. We have provided that document and you will find it with your package.

Warning letters are a type of enforcement action that are used by FDA to correct promotional activities that are not balanced in presenting the benefits and risks of the drug or refer to unapproved off-label uses. We did not include the warning letter in the background package for this meeting, and

generally do not include them in the background package for advisory committee meetings since enforcement actions are not the type of scientific issues for which we seek your advice.

Also, today's meeting is not specific to Embeda. Rather, we are seeking your scientific and clinical input on how best to measure the impact of abuse-deterrent opioid drug products on actual abuse in the community. Your recommendations will help us to develop policies that will affect all companies marketing or developing abuse-deterrent opioid products.

We have made the warning letter available to you since it is available to the public on our Web Site. However, the issues described in the warning letter are not directly relevant to your discussions today, and this meeting is not the proper forum to debate the issues underlying the issuance of the letter and any corrective actions taken by King Pharmaceuticals.

Thank you.

DR. KIRSCH: Thank you.

We'll now start the presentations by the agency. The first presenter is Dr. Lapteva.

Nature of the Problem of Prescription Opioid Misuse and Abuse

Overview of the Risk of Abuse and Regulatory Discussions to Date to Reduce Abuse of Opioid Analgesics

DR. LAPTEVA: Good morning, Mr. Chairman, Advisory Committee Panel Members, all invited guests, and meeting participants. My name is Larissa Lapteva, and I work in the Division of Anesthesia and Analgesia Products in the Office of New Drugs in CDER.

In my presentation today, I will give you a brief overview of the risk of abuse and measures employed to mitigate this risk. Then, briefly summarize the current recommendations for development of abuse-deterrent formulations, then describe formulations with abuse-deterrent properties developed to date, and then discuss some labeling considerations for labeling claims for abuse deterrents.

Abuse of prescription drug products, particularly opioid analgesics, has steeply increased over the past decade, and is now recognized by many as a national public health crisis. According to the recent study report of Treatment Episode Datasets, also known

as TEDS, recently released by the Substance Abuse and Mental Health Services Association, the proportion of all substance abuse treatment admissions related to serious medical outcomes associated with abuse increased more than fourfold between the years of 1998 and 2008.

This slide presents data from the Treatment Episode Dataset on the treatment admissions involving opioid analgesics between the years of 1992 and 2008. As you can see, the number of admissions for opioid analgesics has increased from less than 30,000 in the year 1992 to more than 185,000 treatment admissions in the year of 2008. Such increase in the abuse-related medical outcomes is likely multifactorial, but may in part be explained by how these prescribed products could be obtained by people who abuse and misuse opioid analgesics.

A large proportion of the prescription opioid analgesics that are misused and abused are reportedly obtained by friends and relatives from patients with prescriptions. On this slide, you see a pictorial representation of how respondents to the National Survey on Drug Use and Health, also known as NSDUH, reported

the source of pain-reliever that was taken non-medically.

As you can see, about 18 percent of survey respondents obtained it from one doctor, whereas about 70 percent obtained their pain reliever from a friend or relative, either for free or because they bought it. And, among the relatives, about 80 percent obtained their pain relievers from one doctor. Very few obtained the drugs from internet and a low proportion obtained the pain reliever from more than one doctor. Given this variety of sources from which an opioid analgesic could be obtained, measuring non-medical use may be particularly challenging. Therefore, development of novel systems providing information on the patterns of abuse, as well as development of formulations that deter drug-seeking behaviors become an important part of abuse prevention.

Because measurement of abuse is a developing field, it is important to operate with the terms and definitions that are similarly understood by all parties.

On this slide, you see the definitions of

abuse and misuse proposed by the FDA Opioid REMS Working Group at the Opioids REMS Class Advisory Committee Meeting that was held in July of 2010. These definitions of abuse and misuse will be employed by the subsequent FDA presenters at this meeting.

Abuse is the non-medical use of a drug repeatedly or even sporadically for the positive psychoactive effects it produces. Misuse, on the other hand, is the use of a drug outside labeling directions or in a way other than prescribed or directed by a health care practitioner.

Let me now briefly talk about the scope of measures that could be employed to mitigate the risk of abuse.

When a product with abuse potential is approved, the first measure to reduce the risks associated with the product is its appropriate labeling. Labeling can serve is a useful, educational tool for both physicians and patients. All approved controlled release, high-strength opioids contain Boxed Warnings that are used to convey the serious risks of this product and direct the prescribing practices.

Medication guide is the currently used form of patient-directed labeling to aide safe use of extended and controlled release opioids for patients for whom these products have been prescribed.

Strategies and public campaigns, in collaboration with other agencies and stakeholder organizations is another way to mitigate and prevent abuse. For example, in January of 2003, FDA and SAMHSA launched a joint prescription drug abuse prevention educational effort with the goal of preventing and reducing the abuse of narcotic opioid pain-relievers.

While abuse is multifactorial problem, it has to be dealt with on different levels.

In May of 2010, the Office of National Drug Control Policy released the national strategy with a five-year goal to reduce non-medical use of prescribed drugs and its consequences through a balanced policy of abuse prevention, treatment, enforcement, and international cooperation. The strategy also includes efforts to reduce drug trafficking, as well as prevention and treatment of drug abuse.

With the authorities given to the Food and

Drug Administration by the Food and Drug Administration's Amendments Act after its passage in 2007, the FDA and the manufacturers of the opioid drug products started developing risk evaluation and mitigation strategies for classes of opioid analgesics and fentanyl-containing products. These strategies would put additional safeguards to the health care system to aide appropriate drug prescribing, dispensing, storage, and safe use.

While risk mitigation by information and strategies, could achieve a certain degree of diminishing abuse, the risk mitigation at the stage of design of the pharmaceutical products appears a very promising venue. Over the past decade, designing pain-relief products with the new physiochemical features to deter abuse has been an ongoing effort of drug manufacturers and academia, highly encouraged by regulatory agencies.

Specifically, FDA has been communicating to the manufacturers about abuse deterrent formulations through development of guidance documents, written advice to manufacturers on individual drug development

programs, presentations at academic settings, and discussions at advisory committee meetings.

Now, let me give you a brief overview of the current FDA recommendations for the development of abuse deterrent products.

Before a product is tested in preclinical studies, or, as we call it, at the pre-investigational new drug application stage, the agency encourages manufacturers to include in the design of the formulation features aiming to deter abuse. Such features may include formulations with physiochemical barriers to tampering or combination products with an antagonist intended to reduce euphoria when the antagonist is released during in appropriate use, or formulations that include non-analgesic ingredients that cause unpleasant side effects when the product is used inappropriately.

At the pre-marketing stage, manufacturers would need to demonstrate that the new features of the formulation, in fact, translate into decrease in the abuse potential, observed from different kinds of data: *in vitro* data of the product's resistance to tampering,

as well as pharmacokinetic and bioavailability studies, and clinical studies, evaluating the likeability and euphorigenic effects of both manipulated and intact abuse-deterrent product.

And finally, at the post-marketing stage, manufacturers would need to demonstrate a meaningful decrease in abuse-related outcomes, including addiction, overdose, and death, as observed from the post-marketing epidemiological studies.

Moving on from theory to practice, this slide summarizes the regulatory experience with abuse-deterrent formulations developed to date. Two approved combination products formulated with an opioid antagonist naloxone, Talwin, and Suboxone do have some post-marketing data, which I will describe in the next slide.

Of the other recently discussed or approved abuse-deterrent products, OxyContin, reformulated from the original OxyContin with a change in physicochemical properties, and Embeda, oral capsule with the pellets of morphine sulfate and sequestered opioid antagonist naltrexon are both approved products, and their post-

marketing epidemiological programs are the subject of this meeting's discussion.

Remoxy, controlled-released oxycodone, formulated with additional properties to resist manipulation, and Acurox, a combination product of the immediate release oxycodone and niacin tablet, were both designed to be abuse-deterrent, and have not yet met the regulatory criteria for approval. Several other products with abuse-deterrent features are currently in development.

The story of Talwin is likely well-known to this advisory committee, and probably does not need to be repeated, yet, we come back to it as to an example when some apparent decrease in the abuse of this product was seen upon introduction of risk mitigation strategies.

Talwin, also known pentazocine, was approved in 1967 for the relief of moderate to severe pain. The first reports of dependence appeared in 1968, and in the late 1970s, increasing frequency of cases of abuse, diversion, overdose, and death were reported. In an effort to mitigate abuse, Talwin was scheduled under the

Controlled Substance Act in 1979, reformulated with Naloxone, and the original Talwin removed from the market.

With these measures, it appeared that the abuse outcomes reported with Talwin declined during the two years after withdrawal of the original formulation from the market, as you can see from the graph on the right side of the slide. However, while all of these factors likely contributed to decrease in abuse in Talwin, it was also possible that the change in the availability of heroin, which occurred at about the same time, played a role in decrease of abuse with Talwin.

This exemplifies a setting when the change in abuse trends could have been influenced by multiple factors and not necessarily only by the measures introduced to mitigate abuse.

Suboxone is another formulation product formulated with buprenorphrine and naloxone, which was approved in October of 2002 for the treatment of opioid dependence. Although there have been no formal studies done to access whether addition of naloxone decreased abuse, the post-marketing reports of intravenous and

intranasal abuse continued to support existence of abuse with Suboxone, despite the inclusion of the opioid antagonist in the formulation.

Again, on this slide and on the following slide, I will briefly discuss the regulatory history of OxyContin and Embeda, and then we'll move on to the topic of labeling claims. But, again, the story of OxyContin is well-known and does not need to be repeated to this committee. However, several aspects of it pertaining to the development of the reformulated OxyContin are worth to mention.

When the growing problem with abuse and misuse of OxyContin was recognized around 2001, it was as early as April of 2001, when the FDA and Purdue Pharma started discussing development of a reformulated product with properties that would improve resistance to product's manipulation. It took the company almost six years to put the reformulated version through the development program, and in November of 2007, the new drug application for the reformulated OxyContin was submitted.

Following the agency's review and the two

advisory committee meetings, the reformulated OxyContin was approved in April of 2010 with two post-marketing requirements: Risk Evaluation Mitigation Strategy and the post-marketing epidemiological studies. While the REMS is not the point of discussion of this advisory committee, the epidemiologic studies will be presented to the panel and discussed at this meeting.

Embeda is a formulation similar to another extended-release morphine sulfate product named Kadian, which was approved in 1996. Unlike Kadian, Embeda includes the opioid antagonist naltrexone to decrease the euphorigenic effects with inappropriate use. The sponsor of Embeda approached the agency in March 2005, before they submitted their investigational new drug application, and, at the time, already planned their post-marketing epidemiological program.

The original New Drug Application for Embeda was submitted in February of 2008, and then the product was approved in August of 2009 with the post-marketing requirement of REMS. Discussions about the epidemiological program continued in post-marketing, and are the subject of this advisory committee meeting.

Switching gears now to the important regulatory aspect of labeling claims. Before discussing the labeling claims for abuse deterrence, let me explain the difference between the indications and the claims. Indications are the approved uses and populations for a drug or biological product, and they are described in the indication part of the labeling. For example, a product could be indicated for treatment of moderate to severe pain in opioid-tolerant patients. Claims, on the other hand, may be based on any labeled information, not just an indication. They may be explicit or implicit.

For example, if one takes a possible claim of abused deterrence, then a statement in the label that the product is abuse-deterrent will be an explicit claim, whereas showing a table, demonstrating more qualities to resist tampering with the product, would be considered an implicit claim for abuse deterrence. Nevertheless, implicit or explicit, claims could be included in the labels when they're accurate and complete reflections of the product’s properties.

So, labeling claims for an abuse-deterrent product would require demonstration that a product’s

abuse-deterrent properties studied in the pre-marketing program actually resulted in a reduction in abuse and its outcomes: death, overdose, and addiction, as confirmed in post-marketing epidemiological studies. They would be dependent, as any claims would be dependent, on the adequacy of the data. Any possible promotion based on such claims would be limited to presentations of the pertinent data.

And, in conclusion, let me highlight some of the challenges with evaluating the impact of abuse-deterrent formulations.

First of all, pre-marketing studies for abuse liability have their limitations, and you will hear a more extensive presentation on this topic from the Controlled Substance Staff later on this morning. It is difficult to measure abuse since abuse is not a clinical phenomenon or a drug-related adverse reaction, but rather a consequence of non-medical use. Standard data collection or measures used in population-based epidemiological studies may not apply to measuring abuse. Current surveillance systems have their limitations, of which you will hear in the subsequent

presentations today, and we are in need of novel surveillance systems.

Defining the population of abusers can be difficult, because usually, abusers cannot be adequately identified until a serious outcome occurs or a person self-identifies as a survey responder.

And finally, even when decrease in abuse to one product is demonstrated, the overall impact on the abuse problem may not be observed until more abuse-deterrent formulations are on the market.

It is not easy to measure abuse, and it is not easy to develop abuse-deterrent formulations. No single government agency, individual drug manufacturer, isolated non-profit or professional organization could defeat this big societal problem. Collaborative, step-by-step approach by multiple stakeholders will be needed to achieve the desired results. Owing to the advances in modern technology, designing and development of abuse-deterrent formulations became possible.

It is now the turn of clinical and biostatistical sciences to assess whether bringing these formulations to the market will actually result in the

decrease in abuse in the nation. Through conducting this advisory committee meeting, FDA is looking to an open and engaging discussion to help us find the path forward.

Thank you for your attention.

DR. KIRSCH: Thank you.

Dr. Tolliver?

PreMarketing Assessment of Abuse-deterrent Formulations

DR. TOLLIVER: Good morning. My name is James Tolliver. I am a pharmacologist for the Controlled Substance Staff within the Center of the Drug Evaluation and Research at the Food and Drug Administration. My presentation this morning will focus on the pre-marketing assessment of abuse-deterrent formulations from an FDA perspective.

By way of introduction, I'd like to provide two definitions relevant to this presentation. The first definition is that for abuse-deterrents. According to the FDA-CDER draft document entitled "Guidance for Industry Assessment of Abuse Potential Drugs," abuse deterrence is defined as the introduction of some limits or impediments to abuse in a drug

formulation as opposed to the outright elimination of abuse.

The second definition is that of abuse, which is defined as the non-medical use of a drug repeatedly or sporadically for the positive psychoactive effects it produces.

The pre-market assessment of formulations purported to be abuse-deterrent involves a three tier approach. The first tier is that of in vitro manipulation and extraction studies. This is followed by clinical pharmacokinetic studies on the intact and manipulated formulation.

The last tier involves human abuse liability studies. It must be stressed that the three-tier, pre-market assessment is to be conducted on the to-be-marketed product formulation. Such product formulations usually have controlled release mechanism that allow for the release of an opioid over an extended period of time. These product formulations also generally contain amounts of opioid that exceed that of immediate release product formulations, making them potentially attractive targets for manipulation with the intent to abuse.

There are a number of different types of purported abuse-deterrent formulations for opioid analgesics. Three types are presented in this slide.

There are formulations that are intended to resist physical and chemical manipulation. A good example of that is reformulated OxyContin.

A second type of formulation is that of an opioid agonist in combination with an opioid antagonist. A good example of this formulation is Embeda. With this formulation, the intent is that the opioid antagonist will mitigate positive, subjective effects, and possibly cause adverse effects such as that of opioid withdrawal if the formulated product is used in a manner other than that intended in the label.

A third type of formulation is the combination of an opioid agonist with a second component that will produce an aversive effect if the product is not taken as indicated. Here, an example would be Acurox.

The purpose of *in vitro* manipulation and extraction studies is to evaluate the ease with which the abuse-deterrent mechanism of a formulation can be defeated. Physical and chemical manipulation of a

formulation is intended to obtain the opioid in a form more amiable for abuse by desired routes of administration.

In the case of opioid agonist, antagonist combination formulations, separation and isolation of the opioid from the opioid antagonist is a consideration. For formulations of an opioid agonist with an aversive agent, a goal would be to neutralize the effects of the aversive agent by separation or other means, while maintaining opioid agonist effects.

These studies are designed while keeping in mind the knowledge of the physical and chemical properties of the formulation, including the opioid agonist, opioid antagonist, and other components, such as the aversive reagent, if present.

Another consideration in designing these studies is the knowledge of methods available to abusers with different levels of chemical expertise, constituting such groups as recreational abusers, more experienced abusers, and, finally, so-called kitchen chemists.

In vitro manipulation and extraction studies

are of three types. The first are studies looking at the mechanical manipulation of a formulation. Secondly, there are chemical extraction studies. The third type of study relates to modifying the formulation in whatever way for purposes of abuse by snorting, inhalation, or intravenous use.

In vitro mechanical manipulation studies are intended to evaluate a variety of common household tools for crushing, cutting, grading, and grinding product formulations with comparisons to appropriate extended-release reference products. Both the time required for the manipulation, as well the ease of the manipulation are noted. The intent is to reduce the particle size of the formulation, thereby possibly changing the formulation's controlled release properties.

Dissolution studies of intact versus manipulated product formulations will determine whether the controlled release mechanism is compromised. Other studies may also examine the impact of first freezing or heating the formulation on the ability to mechanically manipulate that formulation. Chewing simulators, using artificial saliva, can be used to predict the effects of

chewing the product formulation on the controlled release of the opioid agonist and other components of the formulation.

In vitro studies also evaluate the ease of chemical extraction of opioids from intact and manipulated product formulations. Comparisons are also to be made to intact and mechanically-manipulated reference products.

In the case of opioid agonist/antagonist combination products, consideration is given to the chemical separation of the opioid agonist from the opioid antagonist.

In chemical extraction studies, a variety of chemicals are tested as solvents. These include water, beverages or simulated beverages, household chemicals, buffers of different ph, and other chemicals constituting different molecular polarities. Extractions are conducted under continuous agitation and at room temperature and elevated temperature. Percent of opioid extracted is determined at selected time points out to 12 or 24 hours or until the opioid is mostly extracted.

Finally, *in vitro* studies are conducted with the intent of determining the ease with which a product formulation may be modified mechanically and chemically to prepare for abuse by intranasal inhalation and/or intravenous injection. For the purpose of intranasal administration, both particle size and the behavior of the manipulated formulation at the lining of the nasal cavity are important considerations.

With respect to possible inhalation, it is important to consider the vaporization and degradation temperatures for the opioid agonist of interest. That is abuse by inhalation of an opioid is not feasible when the temperature at which the opioid agonist chemically decomposes is less than the temperature required to vaporize the opioid agonist. In such a case, studies may be done to evaluate the possible conversion of the opioid agonist to a form more amiable to inhalation.

In the case of preparing for intravenous injection, the intent is to obtain a small volume of solution with sufficient opioid agonist concentration such that upon intravenous injection subjective reinforcing effects, such as euphoria, may be achieved.

The injectable solution must be of a sufficiently low viscosity to allow the solution to be taken up into a syringe, in other words, injectability, and subsequently to be injected via needle, that is the injectability of the solution.

Clinical pharmacokinetic studies constitute the second tier of pre-market assessment, purported abuse deterrent formulations. In these studies, the purported abuse deterrent formulation both intact and manipulated is compared to one or more reference extended-release products and to a reference immediately-release product.

Oral ingestion, in chewing or, most common modes, administration with these types of studies, but other routes are also found from time to time.

Additional studies looked at the effects of Concomitant food and ethanol ingestion on the control-release mechanism or purported abuse-deterrent formulations.

These various studies tend to be open-labeled, randomized, single-dosed, and crossover in design, using healthy adult volunteers under opioid agonist blockade.

Plasma concentrations of opioid agonists and possibly other metabolites of the agonist are followed as a function of time following dose administration. In case of an agonist-antagonist product, formulations, plasma levels of the antagonist or opioid agonist are also determined over time.

A variety of pharmacokinetic parameters are determined. The most important of these includes the peak plasma concentration, designated Cmax. The time to peak plasma concentration, designated Tmax, and the area under the concentration versus time curve for some time from zero to some time point usually just a few hours.

This last parameter reflects the amount of drug exposure over a designated time period. A compromise of the extended-release mechanism of a purported abuse-deterrent formulation is indicated when the peak plasma concentration of the manipulated formulation is greater than that of the peak plasma concentration achieved with the intact formulation and when the time to peak plasma concentration of the manipulated formulation is less than that of the time to peak plasma concentration of the intact reparation.

And finally, also, when the area over the concentration curve in a short period of time for the manipulation product formulation is greater than the area under the concentration curve for that same period of time for the intact product.

In that event that the results of *in vitro* manipulation and extraction studies and clinical pharmacokinetic studies indicate that the controlled release mechanism of a purported abuse deterrent formulation can be compromised. It is appropriate to move to the third and final tier of the pre-market assessment, namely human abuse liability studies. The purpose of these studies is to compare the subjective effects produced between intact and manipulated formulation of the purported abuse deterrent product. Additional comparisons are with subjective effects produced by intact and manipulated extended release reference products, as well as with an immediate release reference product and possibly placebo.

In addition to the subject effects, another pharmacokinetic dynamic effects measured, pharmacokinetic parameters, as previously described, are

also generally determined.

Studies are randomized. Placebo-controlled, single-dose, double-blind, crossover in design, and are conducted in a controlled setting. Studies are completed using approximately 30 subjects, consisting of opioid-experienced, non-dependent volunteers who can discriminate the subjective reinforcing effects of the opioid in question from that of placebo.

Subjective endpoints measures are obtained using a variety of standardized questionnaires used to assess the reinforcing effects, such as the Visual Analog Scale for drug liking, and also for dysphoric effects, using, for example, the Visual Analog Scale for bad drug effects. Subjective effects, as well as other measurements, are recorded just before, and as a function of time following treatment.

Maximum effect is designated as Emax. Time to maximum effect is designated as Tmax, and the area under the time effect curve from zero to some time, t are determined along with other parameters, including pharmacokinetic parameters. Both mean, as well as individual response data are analyzed. With respect to

subjective reinforcing effects, increases in the maximum effect, and area under the effect curve, and a decrease in the time to maximum effect of a manipulated formulation compared to the intact formulation suggests compromise of the controlled-release properties of the formulation.

Human abuse liability studies do have limitations. Considering that these studies involve subjective measures, it is not surprising that substantial variability may exist in the subjective endpoints. In addition, multiple scales of subjective effects may be difficult to collectively interpret. Results are specific for the route of administration and doses used in the study. Statistically, significant differences in subjective effects may not necessarily represent a meaningful difference in a potential for a drug product to be abused.

With respect to summary and conclusion, currently, pre-market marketing assessment of abuse-deterrent formulations using *in vitro* manipulation and extraction studies, chemical pharmacokinetic studies and human abuse liability studies provide information that

suggests how and to what extent a product purported to be abuse-deterrent may be manipulated and abused once the product is on the market. However, very importantly, it should be noted that only post-marketing epidemiological studies will reveal the extent to which a product purported to be abuse-deterrent will actually be manipulated and abused after the product has been on the market.

In addition, post-marketing epidemiological studies may also establish that appropriateness of the pre-market assessment studies in predicting patterns and extent of abuse of products purported to be abuse-deterrent once the products are placed on the market.

Thank you.

DR. KIRSCH: Thank you.

While Dr. Paulozzi comes up to the podium, I'd like to take a minute to have Dr. Morris-Kukoski and Dr. Denisco introduce themselves.

MS. MORRIS-KUKOSKI: Hi, Dr. Cynthia Morris-Kukoski, FBI forensic examiner and toxicology at the FBI Laboratory, clinical pharmacist, toxicologist, United States Navy Reserve.

MR. DENISCO: Richard Denisco, medical officer at the National Institute of Drug Abuse, specialized in pain medicine and addiction medicine and public health and statistics in epidemiology.

DR. KIRSCH: Thank you.

Dr. Paulozzi?

Abuse of Marketed Opioid Analgesics and Their Contribution to the National Problem of Drug Abuse

MR. PAULOZZI: Good morning, everyone. My name is Len Paulozzi. I'm a medical epidemiologist in the National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention.

I'm going to be talking about the abuse of marketed analgesics and its contribution to the national problem of drug abuse.

When FDA asked me to cover this topic, they asked me how much time I wanted. I said, well, how many days do you have? And we settled on 20 minutes. So, if I leave anything out, forgive me.

I begin many talks with this slide. It is the rater of unintentional drug overdose death from all drugs in the United States from 1970 through 2007, which

is the latest year of national mortality data being available. You can see a dramatic increase in the drug overdose death rate through the 1990s and through 2007. The rate of 2007 actually represents about 27,700 deaths. The numbers of deaths related to drug overdose are beginning to approach the numbers of death related to motor vehicle crashes in the United States, and that is an unprecedented occurrence.

Why is the rate going up? We have some data that breaks down the drug types from 1999 through 2007 shown here on this slide. The occurrence of drugs are dependent on the coroner or medical examiner putting down the name of the drug on the death certificate. Some death certificates still come in as recorded as drug overdose and nothing else or a narcotic overdose or even opioid overdose, and you can't tell what kind of drug it is exactly. This data represents death certificates where they do specify the type of drug. And, of course, many or most deaths involve more than one type of drug.

So, some deaths are represented twice on this slide. But the point is that the opioid analgesic-

related deaths have increased more rapidly than any other of the major types of drugs shown here on this slide.

Heroin deaths are basically flat from 1999 through 2007. Cocaine deaths have gone up appreciably, but the biggest increase is in the opioid analgesic category. And it was actually a few years ago that the total number of deaths involving opioid analgesics exceed the total number involving either heroin or cocaine in the United States.

The number of deaths shown here for opioid analgesics and unintentional overdoses shown in yellow is the same as on the previous slide. What I've added to it is the opioid sales in the United States as tracked by the Drug Enforcement Administration ARCOS Program, and computed milligrams in morphine milligram equivalents per person over time.

The opioid sales are shown on the right axis, and they have increased dramatically up to the point in 2007. Preliminary figures show about 700 milligrams per person being distributed of opioid analgesics in the United States. And, clearly, the increases have

occurred in parallel.

Turning from mortality data for a moment, this is data from emergency department visits as recorded by the Drug Abuse Warning Network. It's a sample of emergency departments across the United States and the numbers are projected upward to national estimates. And in 2008, the numbers of ED visits involving legal drugs, the first bar on the left in yellow, from misuse or abuse of those drugs surpassed 1 million emergency department visits. Therefore, the number of visits involving legal drugs exceeded the number involving illicit drugs shown in the first bar in green. Opioid analgesics and benzodiazepines were the major contributors to the legal drug category, whereas cocaine and heroin were the major contributors to the illicit drugs in emergency department visits.

Although there are thousands of deaths associated with opioid analgesics in the United States today, they really are the tip of the iceberg or the top of the pyramid, if you prefer. I put the unintentional overdose deaths related to opioid analgesics at the top here, and in 2007, there were at least 11,499 documented

involvement of opioid analgesics on death certificates in the United States.

By comparison, there are about 105,000 opioid treatment admissions, where opioid analgesics were the primary drug. There were about 306,000 ED visits for the misuse or abuse of opioid analgesics. That's about 27 ED visits for every one death. And data from the National Survey of Drug Use and Health shows that in 2009, there were almost 2 million people in the United States who self-reported abuse or dependence on opioid analgesics in the past year. And the largest figure of all is the 5.3 million people who reported non-medical use of opioid analgesics in the past month on the 2009 national survey of Drug Use and Health.

So, as the deaths have gone up, they really are just representing a small part of the morbidity and mortality associated with this problem, which affects millions of people now in the United States.

So, I'm now going to turn to some different sources of data to try to quantify the prevalence of abuse of opioid analgesics using a variety of different data sources. We're going to look at some circumstances

of pharmaceutical overdose deaths in medical examiner studies. These are state-specific studies, look at some results of urine drug testing among pain patients in brief, data on patients receiving opioid analgesics tracked in insurance claims data or Prescription Drug Monitoring Program information, and data on the route of administration or exposure of people entering substance abuse treatment because that's the topic of this meeting.

First, the overdose deaths and medical examiner data. This was one of the earlier studies that we conducted on this topic in the State of West Virginia, which, at the time, had the highest drug overdose rate in the United States. The years 2006, West Virginia was affected primarily by legal drugs rather than illicit drugs. In that year, 295 pharmaceutical overdose deaths occurred in West Virginia.

Within that group, 231 decedents, or 78 percent, had a history of substance abuse, whether alcohol or drugs. Other mental illness other than substance abuse was observed or noted in the medical

examiner's records for 43 percent of the decedents. And 63 percent of the decedents had one or more of the prescription drugs involved in their death for which they did not have any prescription recorded in the State Prescription Drug Monitoring Program. Twenty-two percent of the deaths showed some evidence of non-medical route of administration, such as injection or snorting the drugs. Twenty-one percent had a history of five or more prescribers of controlled substances in the past year in the State Prescription Drug Monitoring Program, and about seventeen percent had a history of a previous overdose.

All told, a population that had a lot of indicators of history of substance abuse and their past history and then the circumstances surrounding their death.

Another study done more recently in Utah, 2008 and 2009, involving a 155 deaths. Similar results, history of substance abuse in 60 percent, signs of non-medical use, in this case a broad definition, were found in 51 percent, but that category includes any opioid involved without a prescription, which was involved in

37 percent of the decedents. Again, linking decedents to the State Prescription Drug Monitoring Program. Eighty-two percent had a history of chronic pain. Typically, this was headaches or back pain or other muscular skeletal problems, and 57 percent had mental illness and that had been diagnosed by a provider and was available to the state medical examiner.

This is the data from a Web report put out by the Ohio Department of Death recently for data for 2006 through 2008. They were able to look at some indicators of substance abuse by linking their deaths, again, with their State Prescription Drug Monitoring Program. And they looked at unintentional drug overdose deaths in total, over 1,000 deaths in Ohio during these three years. And 16 percent of those individuals had filled prescriptions from an average of 5 prescribers per year over the three years of data that they looked at. And I'm going to show you a lot of information about numbers of prescribers that's oftentimes used as a surrogate for a label of doctor shopping, a use of multiple providers to obtain similar types of drugs.

As in previous studies, a lot of the people

had no prescriptions in the Prescription Drug Monitoring Program for the drugs in their death; in this case for the opioids. Twenty-five percent had no prescription, so, they obtained the drug by some route other than through prescription, through drug diversion, presumably. And they looked in particular at methadone because it was the leading drug among the deaths involved, and they saw that 71 percent, most of the people, had no prescription in the Prescription Drug Monitoring Program for methadone among the methadone-related deaths. Methadone, of course, is also used in substance abuse treatment programs and rather than just for treatment of pain.

And this is sort of a compilation of a number of studies focused on methadone. It was the leading drug among opioid analgesic deaths in the United States for most of this decade. It's only in the last few years that state studies have shown that oxycodone has come back up to the top. But, in general, as seen for the other drugs, a small proportion of the decedents had a prescription. That's the last column, percent with prescription. Going back to early studies through the

1990s, it's basically a third or so of the people had a prescription for methadone when examined by the medical examiner.

So, you can see a variety of different problems around the country in different states, taken a look at by medical examiners, sometimes using different definitions. It's hard to standardize some of the information, but there's a large prevalence of abuse associated with opioid analgesic deaths.

Turning to another topic, patients with chronic nonmalignant pain, a lot of literature, again, on this topic. Many studies. I chose just to present to you this one systematic review of the literature. It's prevalence of abuse-related behaviors in patients with chronic non-cancer pain and chronic opioid analgesic treatment. And Fishbain in this 2008 paper reviewed a number of these studies and pulled out a number of different prevalances from them. The clinician-determined development of addiction was recorded in a number of different ways and different studies, among 24 studies that looked at this prevalence of addiction among these patients under treatment.

Three percent were recognized as having or recorded as having addiction. However, when they looked at the percent of patients in 17 studies with aberrant drug-related behaviors, things such as reporting a loss of your prescription, early refills, calls to the office, antagonistic behavior, a variety of different measures in different studies, 11 percent was the prevalence.

And finally, in 5 studies, aberrant behaviors determined by urine drug testing showed the highest prevalence of all, about 20 percent. Aberrant behaviors in this case meant that the person did not have the prescribed opioid in their urine when tested or they had opioids that were not prescribed to them in their urine. Either one qualified as aberrant behaviors. And this generally recognized that observation and even questionnaires administered to patients are not very sensitive to the overall prevalence of this problem.

And, more recently, people are looking at large datasets, such as insurance claims and Prescription Drug Monitoring Programs to try to get a handle on this using surrogate markers for a misuse and abuse of drugs.

This a study in Maine based on insurance claims data published by White last year. They looked at behaviors during just a three-month period of time, and these are all privately-insured patients who were all opioid users. If you look at the bottom, the lowest row, opioid abuse, diagnosis, and claims data, 3.5 percent. That's actually, therefore, observed by clinicians and recorded as a diagnosis. It’s similar to the 3.3 percent I showed on a previous slide for recognized addictions by clinicians.

They also looked at combinations of prescription claims and identified people who had used two or more pharmacies for opioids; about 20 percent during 3 months. Twenty-six percent used two or more prescribers. Sixteen had one plus early refill or an opioid prescription. Certainly not pathognomonic or all indicative of misuse or abuse necessarily, but they did find the significant associations between these behaviors, these uses of multiple pharmacies, physicians, and early refills with the presence of an opioid abuse diagnosis in claims data. So, it is a marker, although a non-specific one, for opioid abuse.

The recent study from California Prescription Drug Monitoring Program using 2007 data, they looked at the prevalence of the same drug obtained from two or more prescribers and dispensed at two or more pharmacies within 30 days, a fairly tightly-circumscribed definition in 2007, they looked at different classes of drugs, and they found that for opioid analgesics prescriptions, 12.8 percent of all the prescriptions were involved in this type of a situation, use of two or more prescribers, two or more dispensers, and so on.

Benzodiazepine is 4.2 percent, smaller percentages for stimulants and so on. Eight point four percent overall for any Schedule II through IV controlled prescription drug. Again, use of two doctors and two pharmacies is not necessarily indicative of abuse, but that may happen through people legitimately losing their prescriptions or choosing to go to different pharmacies. But the percentages that might happen by such innocent occurrences might be represented by the 1 percent stimulant or an anorectic, and, therefore, the difference between that and the 12.8 percent of all opioid prescriptions meeting this

definition, I think, is remarkable.

Another study from Massachusetts in 2006 used slightly different definitions. There's really no consistent definitions of doctor shopping in studies to date. They looked at use of three or more prescribers of Schedule II drugs, which is primarily opioid analgesics in the State Prescription Drug Monitoring Program. Found that it was about 8 percent of patients had used 3 or more prescribers during one year, and about 2.5 percent had used 3 or more pharmacies.

When they combined prescribers and pharmacies, you can see the numbers in the last column. They gave the data only in terms of the percent of prescriptions. So, 7.7 percent of Schedule II prescriptions were included in this definition, 3 or more prescribers and pharmacies. Correspondingly, smaller percentages with larger numbers of prescribers and pharmacies.

Finally, some data collected by surveying State Prescription Drug Monitoring Programs. This data comes from the PMP Center of Excellence at Brandeis University, and it is a survey of Bureau of Justice Assistance Funded Harold Rogers Grantees among the State

Prescription Drug Monitoring Programs. They looked at the numbers of either individuals or doses that met their definition of doctor shopping, which was five plus prescribers and five plus pharmacies in six months. The prevalence among individuals was .4 percent, using data from 7 PDMPs, and for doses, it was 1 percent of all these Schedule II through IV prescriptions.

So, as you can see, the as definitions get tighter, as the numbers of prescribers and pharmacies goes up, the prevalence goes down. It makes sense.

Lastly, route of exposure, I included just two slides here to give what there is available about route of exposure, given the topic of this meeting. This is information from Butler from a surveillance system known as NAVIPPRO, data from 2007 and 2008. This is from adult drug-users entering substance abuse treatment using opioid analgesics, and it asked them about their routes of administration, and they could record more than one route of administration per type of opioid analgesic.

So, for oxycodone, 76 percent of the users reported that they used it orally some of the time, and

that would include chewing and sublingual exposures. Forty-five percent inhaled, thirteen percent injected, smaller percentages smoked and used other routes of exposure. For morphine, 40 percent oral, 29 percent inhaled, 56 percent injected. Again, more than one route of exposure is reported here, obviously, because these numbers add up to more than 100 percent.

There is comparable data available from the treatment data exposure dataset of the Substance Abuse and Mental Health Services Administration, also known as TEDS. This is data from 2008 shown in the last column. The difference here is that TEDS looks the at most commonly used or records the most commonly used route of exposure, and this is just oxycodone because that's all that TEDS had information on. But I think the numbers are basically consistent with the NAVIPPRO statistics, which I've repeated in the first column here. Basically, the most common route is oral, including chewing, 30 percent inhaled, 13 percent injected, and smaller percentages for smoking and other routes of exposure. And my thanks to Deborah Trunzo for generating this information for me. Deborah's with

SAMHSA Group.

And that's all I have. Thank you.

DR. KIRSCH: Thank you. We now have a few minutes to ask the speakers clarifying questions. The way that I like to run this part of it is if you raise your hand, we'll mark you down and call on you by individual.

Dr. Bickler? I'm sorry, Dr. Bickel?

Clarifying Questions

DR. BICKEL: I do like Dr. Bickler's name though overall. It's very nice.

(Laughter.)

I have sort of a comment and an inquiry for Dr. Tolliver, and I agree with your assessment, generally speaking, right, that abuse liability approaches are using methodological procedures that are in excess of 30-years-old and have certain limitations about them. however, there have been dramatic advances in the study of behavioral economics of the consumption of additive commodities that show increased sensitivity, a greater selectivity, and have been demonstrated to being increasingly predictive of subsequent behavior. I

was wondering if you have considered or the FDA has considered updating their methods to the more novel approaches that have been demonstrating those effects.

DR. TOLLIVER: I think for the most part, the abuse, the human abuse liability studies that I mentioned are the ones that we've been using. I don't know if that answers the question or not.

DR. BICKEL: So, I guess I would just suggest that you contemplate or look into the options of updating some of these methodological procedures using more recent events as an understanding how reinforcing substances are influenced choice across a broad set of conditions as indicated by behavioral economics.

DR. TOLLIVER: All right.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: Thank you. I had a clarifying question with regard to definition of claims, and since we'll be talking about what's the evidence needed to put something into label or to make a claim.

I was wondering if there's any precedent or examples that we could work from that talks about claims that might be time-dependent. So, an easy one would be

this is the drug that's number one prescribed, and that changes over time. So, are there examples within the FDA in which a claim gets into the label, it needs to be monitored over time because it's a time-dependent kind of claim, and, therefore, what's the process of taking a claim out once it's in and how long that takes, et cetera?

DR. RAPPAPORT: I can't think of an example, but, certainly, we modify the label all the time as new information becomes available. I will say it's more difficult once something gets in there to take it out. But not terribly difficult. We still can do it.

If the information in there is found to be incorrect and raises safety concerns, we can get it out of there. But to modify the label as time goes on, we do that when it's essential to do so. We can't make changes to every label, to every sentence in every label because of minor changes, but if there are significant changes, we do work with the companies to make those.

Does that address your question?

DR. MORRATO: I think so. So, the norm is you get data and you put a statement into the label as

opposed to a type of claim that you know could be changing and evolving over time, such as is it abuse-deterrent? That's not the normal type of claim that ends up in a label. It's more like an absolute fact. It has this benefit, it has this side effect, but still evolving --

DR. RAPPAPORT: Yes, we only allow into the label whatever is supported by data. So, if there's no data at this time to support that something is abuse-deterrent in the community, it's not going in the label. If that changes in time, we'd be only too happy to get it into the label because I think that would be beneficial to the community and to prescribers.

DR. MORRATO: Right. I was just talking about the case in which it got into the label, but then, over time, you don't see it, and --

DR. RAPPAPORT: We had to change it. We could take it out.

DR. MORRATO: Yes.

DR. RAPPAPORT: Yes.

Sharon, did you want to add something?

DR. KIRSCH: Dr. Nelson?

DR. NELSON: Thanks. Just another question for Dr. Tolliver.

DR. KIRSCH: Okay.

DR. NELSON: Just my assumption is that the three-tiered approach you outlined is a regulatory requirement. Is that right? Or is that just something that most companies do before they market a drug?

DR. TOLLIVER: I don't know that it's a "regulatory requirement." I don't think that we have specific guidance in place right now. However, the kind of data that I provided to you today or the kind of studies are what are provided to the Food and Drug Administration for us to look at with respect to evaluating the abuse --

DR. NELSON: Okay, can I --

DR. HERTZ: These are -- excuse me.

DR. NELSON: Sorry.

DR. HERTZ: These are recommendations that have evolved as we started to interact with companies who have been seeking different approaches to developing these products. It's been informed in part by discussions at advisory committees, as well. So, it's

not a regulatory requirement, but it is the recommendation so we can begin to understand sort of in a step-wise manner what different formulations' characteristics are.

DR. NELSON: That makes sense. Just the reason I actually asked that was because you had said that if the *in vitro* or the clinical pharmacokinetic studies show that a tablet can be compromised, then there are the likeability studies, which implies that if they don't show in either of those first two phases that there's a potential problem. Likeability studies aren't required or required or anything like that.

DR. HERTZ: We know that for the Schedule II Opioids, there's a certain amount of likeability associated with the drug substance.

So, we generally don't require that type of study. If the goal of the development of a formulation is, for instance, to avoid manipulation that can defeat extended release characteristics and the formulation was actually able to resist attempts to dose-dump, it still has the abuse liability of the Schedule II Opioid.

So, we don't think it's not attractive or

likeable, but we know that it resists dose-dumping, which can contribute to some of the morbidity and mortality. The trouble is these are opioid analgesics, so, they have to be able to deliver the opioid. So, no matter what, an overdose is going to be possible, it's going to be likable to some extent because it's got to deliver the opioid in order to function as an analgesic. And so, it depends on what the actual intent is and what the results are. The reality is no product that we've seen so far is completely capable of resisting manipulation.

So, when it is manipulated, then the question is how much do we need to know about what that does to the likeability and that's when we start asking for likeability studies.

DR. KIRSCH: We have three other people on the list to ask questions, but we need to go on to the next speaker, and I will start in order at our next question period with Dr. Wolfe, Mendleson, and Omoigui.

So, we're going to go on to the next speaker, who is Dr. Anthony.

Data Resources and Metrics Used to Assess Prescription

Opioid Misuse and Abuse

Designing Observational Studies on Drug Abuse

DR. ANTHONY: Good morning. I'm aware I stand between you and your break. So, I will move along. You can see I'm Professor of Epidemiology at several universities, as listed here, and I thank the FDA for inviting me to give this talk. I've been coming to advisory committee meetings for 35 years or more, and when they asked me to talk about this topic, I wondered whether there was anything I could say that the advisory committee wouldn't already have heard and why they needed me to say anything else.

And as we looked into the issue a little bit more, it turns out that my research group has been working on some population rate perspectives on evaluation of drug experience and that these were novel with respect to some ideas that have, perhaps, not previously been seen here.

So, what I'm going to do today is work around the topic I was requested to cover, mainly focusing on some conceptual issues and introducing some new ideas for evaluation in the post-marketing context. Most of

the drugs I've studied are not pharmaceuticals, and I'll be giving you some examples outside the domain of pharmaceuticals, but I think you'll be able to see how the concepts and the research approaches can carry over to the evaluation of products that at least where the attempt is to improve patient safety.

I've given you an outline so you could see where I'm headed. I'm not going to read through this outline in the interest of time, but it's there just if you'd like a roadmap of where I'm going.

The points of departure, I'm mindful that you all are trying to focus on and clarify concepts and approaches for risk management plans, and some of the products that are to be evaluated have at least in theory some safety advantages over already-marketed products, but I also am mindful that there is a good bit of knowledge and history and expertise in the room, and there's no need for me to go over issues that have to do with the basics of epidemiology and design of observational studies in epidemiology as one might do with a less-educated audience.

I'm going to focus on a Cross-Sectional

Approach that we are using mainly because that Cross-Sectional Approach finesses some problems that have to do with differential mortality. Mortality, for example, that occurs quickly between the onset of drug use and a follow-up at three, six, or one-year intervals, which is the type of study that I've generally been doing over the past three years. We find very often that the people who are engaged in what would conform to the current FDA definition of drug abuse often are not to be found when we go to look for them in our follow-up studies, and that's caused us, in part, to work on Cross-Sectional Approaches. So, I'm going to focus on that.

This will come as somewhat of a surprise to those of you who have studied epidemiology because one of the principles of basic epidemiology is that the prospective and longitudinal design inherently is superior to a cross-sectional design. That actually is not always the case, and we'll see that in this context it may not be the case.

I was asked to talk a little bit about societal perspectives on drug abuse, and I have to say I

teach my trainees not to use the concept of drug abuse because it's stigma-laden. In public health, we have to pay attention to the communication value of the words that we use, and it doesn't turn out to be very useful to use the concept of drug abuse. So, we think of that as a piece of baggage.

If you go back to Latin, the term impediment is *impedimentum*. It's baggage that the Roman Army had to carry along that kind of impeded their fast progress, and abuse is a piece of baggage. We can reach inside and pull out selected facets of abuse that can be studied, but as a scientific concept and as an object of study for an observational study, it probably is not very helpful to us. Congress, however, is very fond of it.

Same is true for abuse liability, but, here, the problem is mainly that it conveys the idea that abuse liability or dependence liability is a property of the drug, and there are more productive ways of thinking about becoming dependent or becoming a drug abuser if you want to think about it that way, and I've sketched one here on this slide.

So, in coverage of societal perspectives on drug abuse, I think we have to realize that this is a pejorative stigma-laden term, and it may be wise for us not to think about abuse-deterrent products because it's unlikely that any product is going to be deterrent of abuse across all the range of facets of abuse that we might be studying.

In my own work, I focus on drug dependence, and a point of departures, this early study by L. Lasagna in which he tried to find out what the response of healthy volunteers would be to placebo and a profile of other drugs, one of which was heroin.

What you can see here is that among 20 exposed to heroin, 4 said they would have liked to repeat it and 70 of the 20 would not like to repeat it at all. So, you can see that in contrast to the popular conception about heroin, this isn't a drug that if you take it once, you'll become hooked, and certainly that is true of the marketed opioid analgesics that are in discussion here.

Now, using that as a point of departure, in our studies on drug dependence, which is not exactly the

same as wanting to repeat a drug experience, we focus on a definition that has to do with three facets: One is a disturbance of the mental life. This is where craving comes into play. The only way we'd know about it is by asking people about their mental life, and these are obsession-like ruminations about the drug experience and cravings.

Another domain of disturbance and dependence running together with those in the mental life is compulsion-like behavior. So, that here, something manifest, you could actually see it. You wouldn't necessarily have to ask about it, but it's like a compulsion in psychiatry, and it may in some cases be a compulsion. Its repetitions are rounds of drug-involved behavior.

And then, finally, the third facet of this syndrome is neuro-adaptation, as typically manifest in tolerance, which might be subjectively felt or demonstrated in the lab or a withdraw syndrome. So, if you think about this syndrome definition, what we've tried to do is ask how often people who use different types of compounds develop this drug-dependent syndrome.

This is a summary of work that we've done. We're updating these values with more recent data, but we're not getting much change, and if we work our way from the top to the bottom, if we look among people who smoke tobacco cigarettes, even one cigarette, and ask what proportion of them become dependent or develop a dependent syndrome, as we've just defined it, it's about one in three. If we do the same for heroin, it's about one in four or five, and notice the similarity to the Lasagna experimental evidence.

Going around the circle, you can see crack-cocaine is followed by a crack-dependent syndrome slightly more often than cocaine-hydrochloride powders, followed by a cocaine-dependent syndrome. And we can work our way around to the opioid analgesic drugs to about 1 in 11.

I should note here that the context is extra-medical use. This is not a medically-prescribed user. I think the values would be much smaller if we were to include in the denominators people who are getting these medicines from the doctor in a prescribed context, such as a pain management clinic.

These are people who will acknowledge to us that they've used it outside the boundaries of what's been prescribed either for feelings that it produces or they've taken it for reasons the doctor didn't prescribe it. So, they might have gotten a pain medicine after foot surgery, and they woke up in the morning and felt a hangover after heavy drinking and took the medicine to help relieve that hangover. That would count as extra-medical use, and we're including those people in these denominators. We're not including people who are taking the medicine as the prescriber intended.

So, these are the relative proportions that we get when we go out into the population and accumulate over the experiences of drug-users drug-by-drug, looking at each form of the dependent syndrome.

In terms of the design, you're going to hear more about this because the National Surveys on Drug Use and Health, which will be discussed next, is often a source of data for our studies. Typically, these are pre-designated U.S. population studies. We're now working in 22 different countries. So, we should have estimates for other countries before too long. We have

multi-stage area probability sampling of dwelling units, and then probability sampling of the respondents. We recruit with IRB-approved protocols. There are standardized assessments that are either anonymous or confidential. Nowadays, they tend to be computer-assisted self interviews or personal interviews. The assessments include standardized, prewritten items, and routing patterns, branching patterns through the assessments so that we can follow-up and give details about experiences as they're expressed.

For the drug-dependent syndrome, we have what we call testlets, each facet of the syndrome is evaluated with multiple items. We then estimate cumulative incidence proportions for each drug group, and we pay attention to variants in the constraints.

Now, one of the questions that was raised in pre-discussions of this talk is whether there process phenotypes on the way to the full dependent syndrome that might be investigated in the marketing of new products, and the answer is yes, there are, and I’m going to focus for the next few minutes on that topic.

They typically are going to require fairly large samples to identify them.

The idea of the process phenotype can be seen in this graphic. It's a stage transition model. At number one, you see the onset of drug use. At number two, a building up of count of drug experiences for those who use the drug more than once. Number three, sometimes after repeated drug experience, you'll get the formation of the clinical features that I described earlier, the craving, the ruminations, the compulsive-like behavior, and so on. And then, number four, that those features can coalesce into a syndrome which we would call the drug-dependent syndrome. And then, at number five, there could be secondary complications of that syndrome.

Now, of course, there is potential cessation of use at each step, and one of the questions is how many people use the drug once and then will continue to use the drug and how many people are not likely to use it again? This brings us to the concept of a population rate perspective on drug abuse as opposed to the individual risk perspective. The heritage of this

concept goes back to an early geneticist, Wilhelm Johannsen, who coined the terms "genotype" and "phenotype," and most of the time nowadays, because of prominence of molecular genetics and biology, we think about the individual type of genotypes and phenotypes. Johannsen thought more broadly, and he thought about a population perspective on phenotypes and thought of them as population characteristics.

A related idea was introduced more recently by Epidemiologist Rose, who drew distinctions between causes of incense and causes of cases.

In the interest of time, I'm not going to be able to say much about this, except I'm going to illustrate with an example that has to do with drug dependence, and you have the references here if you're interested in that.

If you want to think about this idea of the process phenotype, you can think about a population that studied from birth to death. Some of them try a drug or take a marketed product one time, never repeat it again. Others will repeat it. Sometimes this will happen quickly after the first try, which could be a

manifestation of liability to dependence, or it could happen after a lengthy lag interval.

If we observe these people longitudinally to death, we can know the count and lag times of these drug experiences, but in a cross-sectional survey, we cannot know. We take a slice in time and we'd see whether someone was recently using the drug, but we wouldn't know among those who were not using it whether they would ever use it again.

Well, if we set up the problem appropriately, we actually can estimate those who would never use it again not at the individual level, but at the subgroup level, and if we think about ethanol as a drug understudy and if we were to take into account potential protection, and here, I'm thinking of the protection that you might like to have in a so-called abuse-deterrent formulation, what we would expect to see with respect to ethanol is that in population subgroups that have an excess prevalence of a null variant of liver metabolizing enzyme alleles, we would have less likelihood to become dependent upon that drug, and this should be manifest in a process phenotype that shows up

very soon after the onset of the drug, and this is where I think these ideas might be portable to the context of post-marketing surveillance of new products where the goal is to try to confer some protection by virtue of the product characteristic. Here, the protection we're hypothesizing has to do with genetic variation and responses to ethanol.

So, I can't point to any Asian-American in a cross-sectional sample and declare whether this person might be in the future a persistent drinker or never again drink, but if I look at the Asian-Americans who very recently have started to drink and I ask whether in the most recent interval of time, say 30 days, whether they have had even one drink and then what is the rate of drinking in those 30 days, I then can estimate whether Asian-Americans are over or under-represented in a group of people who are not likely to drink, again, versus those who are likely to drink again. I can also estimate the rate of drinking conditional on the membership in these classes.

And what you can see here in data that are just submitted, the PP is the persistence parameter of

this regression model, and we get an inverse association, non-Hispanic, Asian-Americans compared to non-Hispanic whites are less likely to persist in their use of ethanol, and we hypothesize this is related to the pharmacokinetic substrate. I'll come back to that later.

The RR parameter is the rate ratio, so, conditional upon membership in the persistent drinking or using class, we have a negative sign; the rate for the Asian-Americans is lower than the rate for whites. And so, here we're seeing before anyone has developed an alcohol-dependent syndrome or actually a few of these individuals will have developed it, but even if we set aside the alcohol-dependent individuals, we can see a subgroup in which there is an apparent protection against the risk of becoming drug-dependent.

In theory then, in terms of post-marketing surveillance, this type of approach could be used within 12 to 24 months of release of the drug in order to see if, in fact, we would see manifestations of reduced risk of these process phenotypes.

We don't find these relationships for Asian-

Americans for tobacco, cocaine, or cannabis. We're now studying them for opioid analgesic compounds, but I'm not ready to report that yet.

Now, I will show you some process phenotypes that have to do with the opioid analgesic drugs, and this may overlap a little bit with a talk that'll be given later on, but these process phenotypes are the actual clinical features of drug dependence, and they're listed here.

So, without asking who has developed the drug-dependent syndrome, we can ask about the accumulative incidents soon after onset of use of each of these clinical features of drug dependents as steps on the way to the full phenotype.

Here, the subgroups under study are kids, adolescent onset drug-users, kids who start using these drugs; in this case, it's opioid analgesics, before age 18, and the contrast group is those who start as young adults or a little later. Most of them are 18 to 25. And what you can see, if we look across the profile of these process phenotypes, at the individual clinical features of dependence, among people with or without

respect to whether they're become dependent, we see five aspects where the adolescent onset kids seemed to be at greater risk. One is getting over the effects of the drugs, spending a lot of time getting over the effects of the drug, needing more drugs to take to get the same effect, having emotional problems connected with their drug use, reducing other activities, non-drug activities, in order to use drugs, and then having withdrawal experiences.

So, this would be another example of a phenomenon of drug dependence related to drug dependence, but not the full dependent syndrome that could be studied in the post-marketing context within 12 to 24 months after onset of use. We're actually estimating these parameters for a lag time of 180 days elapsed since first use of the drug. So, we could get data in a fairly timely fashion via cross-sectional surveys on these topics.

And then, I'm here just going to contrast male/female differences, and here, we're looking at the newly incident opioid analgesic users using outside the context of medical practice. They're about half and

half male and female, and what you can see here on the left of the gray bars for males and females combined, the white bar, you can't see very well, but it's the one in the middle is for males and the yellow bar is for females. Here, you can see that, in general, females are more likely to develop these clinical features. There's one exception of the set. And again, you can see how this type of approach, evaluated within 12 to 24 months after onset of the use of the drug can be used to study steps on the way to becoming drug-dependent.

Now, in all of these studies, there's a need to pay attention to potentially confounding variables. If you consider the Asian-American example, we're hypothesizing a protection based on a null variance of the alleles, but Asian-Americans are different from other parts of the population in other ways. There's often more family cohesion, more family attention, parental monitoring, and the like, and those would have to be taken into account before we could attribute the protection to one factor or another.

I do want to note though that in this context, there is a potential for over-control of what is

suspected as a confounding variable. So, if someone says well, why don't you control for school dropout or income levels, well, those may be responses to the drug use.

I made some notes for future directions, but I want to turn the time over to you for questions, and if anyone wants to talk about these issues, I'd be happy to talk about them. The one point that I was encouraged to emphasize is that there are other domains of pharmaceutical products where, in theory, manufacturers are trying to improve the safety profiles, and we're not just talking about FDA, but also about other devices, other consumer commodities. And it may be that it's useful to look outside of the narrow boundary of the drugs that we pay attention to in this advisory committee in order to borrow some experience.

Now, the Energy Department, for example, is asking for some evidence of the firm's financial capacities to deal with the damage if something happens in offshore oil drilling. We could think of collective insurance plans in order to protect the society and the firms against a potential hazard or catastrophe with a

product that, from a theoretical and pre-marketing point of view, looks like it has advantages. I hope that that perspective is brought to bear in the advisory committee's work on these problems. The tendency may be to block out the gate and not let any new products out because we're worried about a repetition of past experiences, but the American public needs products and needs innovations that are trying to improve safety of these products, and we may need to look outside narrow boundaries of abuse context in order to borrow from other domains of FDA or federal government regulation.

Thank you very much.

DR. KIRSCH: Thank you. Before you leave the podium, can I assume that you'll be here throughout the day?

DR. ANTHONY: Yes.

DR. KIRSCH: So that at the question period, you'll be able to answer questions?

DR. ANTHONY: Yes.

DR. KIRSCH: Okay. So, with that, we're going to take a break. The break is going to be 15 minutes in duration. Committee members, please remember that there

should be no discussion of the meeting topic during the break amongst yourselves or with any other member of the audience. And we will resume at 10:32.

(Break.)

DR. KIRSCH: While you are taking your seats, I will ask our next speaker, Dr. Woodward, to approach the podium, please.

(Pause.)

DR. KIRSCH: Okay. Dr. Woodward?

Substance Abuse and Mental Health Services Administration: Resources and Methods

DR. WOODWARD: First of all, thank you for inviting me to talk briefly about the datasets that are of interest to FDA and the field.

CBHSQ is an acronym you may not be familiar with. It's the Center for Behavioral Health Statistics and Quality. You may be more familiar with the old Office of Applied Studies. The name was changed in July, and I'll explain a little bit more about that in a second.

I have no conflicts of interest being a good government bureaucrat, keeping my head as low as I can.

Let's see. The Center has more responsibilities than the old office did, but I'm not going to be talking about the new responsibilities; I'm going to be talking about the three main datasets that the CBHSQ, or, if we had IT would be CBHSQIT, has, and they were consistent with the Office of Applied Studies. There are three main datasets, the National Survey of Drug Use and Health, the Treatment Episode Dataset, and, finally, the Drug Abuse Warning Network that I'll talk about. I'm going to give a very high-level, 10,000 foot view of the datasets, given the time that I've got.

The first is the National Survey on Drug Use and Health, as you can see from the slide; these are the main features of the dataset. It's an interview of about 68,000 people per year. It takes an hour, it's very detailed, it's computer-assisted so that we're able to provide the questionnaire in a number of different languages. It's only for people over the age of 12. So, there's a component of the population we don't capture in the NSDUH that's of interest to this field so that we're able to present prevalence/incidence data for the nation and in each of the states. In each state, we

can provide direct estimates. The others are indirectly estimated.

There are two main changes of historical note. In 1999, the computer-assisted approach was used so that produced a break in the trend. 2002, we introduced a payment of $30 per individual, and both times, the prevalence went up, the response rate improved.

The overall response rate for this large a survey is just about 70 percent, which we'd like to improve, but given how difficult it is to collect survey information these days, it's pretty sound.

The household survey started out with an emphasis on illicit drug use. So, what I wanted to do is to just briefly review the kinds of information that's collected. So, including both with illicit drug use and non-medical use of prescription drugs, there's recency of use, frequency of use as much as daily so that we can report on, say, somebody who uses every day in a given year. The initiation data for particular drugs are captured. Dependence and abuse resulting from drug use is captured in the diagnostic, statistical, manual criteria. Also, we collect whether or not

treatments received is the result of a particular problem.

As far as prescription drugs, the strategy of the NSDUH is to try to report on the four major categories of drugs: therapeutic classed as a pain-reliever, stimulants, sedatives, and tranquilizers. There is information collected on specific pharmaceuticals, including brand names and generic drugs. What the respondent gets is a set of photographs, what we call pill cards, showing each of the drugs by their categories. They report what they have. If they don't see anything, they can type in other drugs.

The reporting of the drugs is largely aggregated at the therapeutic class level. Right now, the NSDUH is trying to improve the definition of drugs of what is considered drug use so that we won't really be able to collect information on dose, but we will be able to get a better sense of the type of use, whether it's over medication or misuse. Right now, the NSDUH really can't distinguish very well in that area.

The second major dataset that I want to talk

about is the Treatment Episode Dataset. It's part of larger data collection system called the Drug and Alcohol Services Information System, DASIS, which has some other components with it. This is an administrative dataset that states report to our office. We crosswalk the data to make sure there's consistency in what we collect from the data. It's an episode data system, very few states collect individual patient identifiers.

So, we can't really track patients very well. Most of it is treatment admission data. We do collect some discharge data. A lot of the states are now reporting discharge information.

It's facilities that the states keep track of, and these are largely public-funded, specialty treatment facilities or clinics, if you will. And there are something like 13,000 of them throughout the nation. Of course, with the economic downturn, there are fewer. We estimate that we're picking up about 80 percent of the facilities. We don't have the private-funded facilities, as much information on them. And there are slightly under 2 million admissions every year.

The information that's collected, as you can see, our demographic variables, the discharge dataset includes some socioeconomic information, employment history, and insurance coverage. There is a link between admissions and discharge records.

So, the information in the state report is the three main substances, at admission, route of administration, how the drug's taken, frequency of use, age at first use. Treatment variables largely focus on the type of treatment, where the individual's going. There is some limited information on treatment outcomes, length of stay. So, this particular database isn't as useful, if you will, for the field because there isn't really information collected on brand names or formulations. It's general. There are groupings that we can't really disaggregate further.

For example, opiates are aggregated into a class, and we can't really drill down further, if you will. In a minority of states, 16 report on opioid analgesics. So, it's probably a limited use to this field.

The last dataset I want to touch on briefly is

the Drug Abuse Warning Network, which has been around, like the NSDUH, for quite awhile. Initially, the intent was to design a sentinel public health surveillance system. It's now sort of focused on nationally public health problems that are captured in emergency departments throughout the nation.

The information is collected by trained recorders who go to about 250 hospitals throughout the nation. Some of the hospitals have their own recorders who are also trained to report the data that we collect directly from the hospital emergency record. And what we focus on, it's a fairly short data collection form with about 20 data elements. It is where an ED visit has drugs reported either as a direct cause or contributing factor, either determined from toxicology records or what's in the notes in the reports from the medical record.

There are about 4 million drug-related visits that we capture each year. That's out of about 110 million ED visits throughout the nation. So, it's about 4 percent. So, as you can imagine, it takes a lot of effort to try to get to that 4 percent in terms of

screening.

What we do is to select a representative group of EDs throughout the hospital. The criteria for inclusion is short-term, general, non-federal hospitals with 24-hour emergency departments. We over-select for 12 metro areas, and we have a remainder sample of hospital EDs so that we can, along with the metro areas, provide nationally representative information for the country.

Now, the estimates include the usual statistical adjustments for sample design. The biggest strata size is the most important. Strata size is hospitals where we don't have data reporting. They're adjusted for if the hospitals don't report for a full year, we make adjustments for that. We also have introduced one in three sub-sampling; that is every third ED record is reviewed or screened. And that's simply so that we can save costs without sacrificing efficiency. There isn't much increase in bias when we do that.

This gives a sense of the information that we collect, how it breaks out for use in analysis. In the

left, you can see pharmaceuticals under "medical use." This represents the adverse effects that we can pick up. Non-medical use can be broken into pharmaceuticals, illicit drugs, and alcohol. For alcohol, I need to clarify that if the only drug onboard, if you will, that is associated with the ED visit for somebody under the age of 21, we don't have any age restrictions as the NSDUH does. We capture that, but if the individual is over 21, we only capture alcohol if there are other drugs present. In alcohol for somebody under 21 is basically an illicit drug.

Non-medical use is defined, as you can see, exceeded prescribed or recommended doses. Somebody using a particular drug when it was prescribed for somebody else. An intentional poisoning, intentional administration of a drug to somebody intentionally, as well as any substance abuse that we pick up from the medical record. We exclude suicide attempts and the non-medical use, and we include suicide thought and plans.

Finally, for the DAWN, the value of the DAWN to the field is that it provides detailed brand level

specific drug information at the ED visit, which is important because any ED visit where there are drugs as a part of the visit indicate a fairly serious consequence.

We aren't able to collect dose and source of drug. As you can imagine, it's very difficult to collect that information if the patient really isn't fully conscious. Oftentimes, patients, they aren't able to provide that. If they bring in a bottle, they may know how much they've taken, but, oftentimes, they don't.

The ED record often doesn't have enough specificity for the recorder to enter the detail level of information that we would like to collect. So, often, there's some ambiguity. By and large, I think the databases -- most of the drugs reported are fairly well documented. We used the Multum Lexicon which we adjust for street level names, and we use that to try to get to as great a specificity and the types of drugs that are included in the ED visit.

If you want to find out more, you can go to the Web Site under the old OAS. The Web Site, we're

trying to improve it. But it will provide a wealth of information and various publications.

We have public use files for the NSDUH and for the TEDS under SAMHDA. That's the Substance Abuse Mental Health Data Archive. It's part of ICPS, our University of Michigan public data file archives, and it's a very powerful source of information. You can build your own tables, download your own files, and do a certain amount of statistical analysis, variance calculations, regressions with the SAMHDA. We're trying to put the more current DAWN information on there, and we hope to have that public use files, data tables ready in the next few months.

Finally, I just wanted to say that we are working with FDA through an interagency agreement to provide data requests. Sometimes, our office feels as if we're subcontractor to FDA to try to answer specific requests. So, we've set up an interagency agreement to try to extend our limited staff resources, and we have been working with FDA to make them understand to make sure that we comply with the federal privacy and confidentiality laws. Even though we don't collect any

information that's directly identifiable, that is where there's personal health information collected, we are aware that through triangulation and other data sources it may be possible to identify individuals, which is against every federal law dealing in that area. So, we're very careful about that.

And that's it. It's a very high-level level, and, so, once again, thank you for allowing me to talk.

DR. KIRSCH: Thank you. Our next speaker is Dr. Dormitzer.

Available Data Resources to Assist in Measuring Abuse Behaviors, Patterns, and Outcomes

DR. DORTMITZER: Hi, good morning. My name is Cathy Dormitzer. I'm an epidemiologist in the Division of Epidemiology in the Office of Surveillance and Epidemiology. I will start with a brief background. I'll present standard data sources, both public and proprietary for numerator and denominator data. I will give a brief description of the Prescription Drug Monitoring Programs, and then finish with a summary of the challenges with the current data sources.

But, first, what are numerators and

denominators, and why do we need them? Well, numerators measure outcomes. So, in absolute numbers, what are the numbers of events of interest, and denominators provide some context of the burdens of these outcomes.

These are a few data sources that contain information on -- there are very few data sources that contain information on both numerator and denominator information and are actually able to link them. So, we use both numerator and denominator sources of data.

So, the data sources presented are ones that measure events related to drug misuse and abuse. They are reports on the non-medical use of drugs, events such as emergency room visits, and outcomes such as drug dependence or drug-related deaths. In the past, these measures of misuse and abuse were mainly used for illegal drugs, but now we are using these same data sources for prescription drugs that are approved and regulated by the FDA.

So, standard data sources, most of them are nationally representative, usually multi-stage probability sample. There are data sources that have been used for many years, and they've also been

presented both by Dr. Woodward and by Dr. Paulozzi.

It's not exhaustive. It does include the sources that FDA has used in the past though, and we use them to examine drug abuse outcomes.

So, as you can see from the list, half of them are funded by SAMHSA and were previously presented by Dr. Woodward. They are sources of numerator data. So, the number of events related to misuse, abuse, and related outcomes, and all of these are publicly-funded data sources.

So, DAWN provides national estimates of drug-related emergency room visits, and they also provide it as numbers per 100,000. And particularly important are the SAMSHA-defined constructs of non-medical use of pharmaceuticals that Dr. Woodward related to, and they are the cases that are classified as over-medication and other, as well as malicious poisoning, but malicious poisoning is usually very low. But they are considered abuse-related, and, so, that's called NMUP. And then, in addition to NMUP, there's also ALLMA, which are all the NMUP cases plus ED visits where alcohol or illegal drugs were present in the patient. And FDA also

examines DAWN medical examiner data. Now, these data are not nationally representative, but they do provide data on a consistent panel of medical examiners on a number of drug-related deaths.

And the strengths of DAWN are that it is nationally representative. And we do have data that's specific to substance, formulation, and sometimes even brand. And it’s very limited, but there is also data on route of administration, but it’s very limited.

Now, the limitations of these data is that there is lag time because national estimates are generally not available until 9 or 10 months after the end of the calendar year from which the data is produced, and ME data did not provide information on drug formulation, and it’s also not nationally representative.

And the last important limitation of DAWN data is that it provides data on misuse and abuse that resulted in a medical outcome, either an ED visit or a death, not on the behaviors.

The National Survey on Drug Use and Health does collect data on drug abuse behaviors, and the

questions are taking the drug not prescribed for you or just for the feeling it caused? Now, it does ask these questions on prescription drugs, but it's pain-relievers, tranquilizers, stimulants, and sedatives.

And notice the strengths are that it collects data on behaviors. So, we're interested in that. And it collects it directly from the respondents, and it's behaviors that may not have resulted in a medical event. The limitations are that it's got the same nine-month lag time and that it focuses on drug classes. So, it's pain-relievers, not specific opiates, although there are questions that were added for OxyContin in 2002.

The last SAMHSA dataset I'll be discussing is TEDS, and it collects data on the number and characteristics of a person's admittance to substance abuse treatment program. So, we do get information on the top three substances of abuse at the time of admission. We get information on route of administration, as well as frequency of use and age of first use.

And the strengths of TEDS are that it collects data on drug substance, but it's fairly limited in terms

of classes. So, it's not always very specific, and it also does provide some insight on the public health burden on opioid analgesics.

The limitations are that these data are not always completely nationally representative, and that fact that 16 states report on specific opiates, but the rest don't.

Now, Monitoring the Future, which is conducted by the Institute for Social Research at the University of Michigan, and it's funded by NIDA, which is the National Institutes on Drug Abuse, is an in-school survey of drug abuse behaviors, attitudes, and values of high school and college students, as well as young adults, and it includes questions on attitudes and perceived harmfulness of prescription drugs, including opiates.

The strengths on Monitoring the Future are that it examines drug abuse behaviors among a population that's usually recently begun to start using and abusing drugs. It's nationally representative, and it's been conducted over many years.

The limitations are that respondents are asked

on their use for drug classes, such as sedatives, amphetamines, or narcotics other than heroin, not on specific drugs, formulations, or brands. But they are asked on Vicodin and OxyContin, and usually adolescents really can't distinguish between brand or generic. So, it's not a perfect measure. And it only collects data on youth that attend school.

The Adverse Event Reporting System is a database of FDA's Post Market Safety Surveillance Program for all approved drugs. And it's used to monitor adverse events and medication errors that might occur with these products. It's voluntary and receives some adverse event and medical error reports directly from health care professionals and consumers, but manufacturers, by regulation, are required to send these reports to FDA.

And the strengths of AERS is that it can provide information on signals related to drug misuse, abuse, and dependence, but it's not complete reporting. In fact, there is substantial underreporting, so, it cannot be used as a surveillance tool.

Dr. Paulozzi actually cited most of these

datasets, but he also presented data on overdose deaths involving opioid analgesics from the National Vital Statistics. It's data extracted from death certificates, and it includes information on all deaths in the United States.

And the strengths of these data are these data are not a sample. It is the true population. But the limitations are that is provides data on opiates as a class except for methadone, and that the data are usually available a few years after the calendar year has ended. So, that's another long lag time.

Now, I will discuss data sources that are proprietary data sources, and these are just some examples. Some are newer, may use different sources of information, such as the Internet. Some may not be nationally-representative, although they are increasing their coverage. And since these data sources are part of both Sponsors' proposals, they will be probably giving more detailed prescriptions. So, again, I'm going to be brief.

NPDS, which is the National Poison Data System, provides data on poison exposure phone calls

into poison control centers. They collect calls from poison control centers across the United States, and includes both calls on drug exposure as well as calls on information for specific drugs.

It is a large data source, and it can provide some data that is specific, even down to the level of formulation and sometimes brand, but this information is limited, and there is lag time for the annual reports.

RADARS was developed in 2002 by Purdue, but in January of 2006, RADARS became a non-profit and operation administered by the Rocky Mountain Poison and Drug Center, and a representative from RADAR will be presenting today, so, I'm not going to go into the details of these data. But one strength of RADARS is that it does provide timely data that can be brand-specific, it's published their findings in numerous peer review journals so others in the research community have reviewed their work, and that's also true for actually most of the datasets. And one limitation is not all components of their data are nationally representative.

NAVIPPRO is a system that collects information on prescription opioid abuse, and it's also included in

the Sponsor's proposal, so, I'm not going to be providing a lot of detail.

One of their strengths is also a limitation because they gather a great deal of detailed information from people seeking treatment for their drug dependence. So, these are people who actually have quite a bit of knowledge about the abuse of opiates, and that provides information, and that's probably, like I said, their biggest strength and their biggest limitation, but that might not be generalize-able to the population as a whole.

So, now I will present denominator data. When providing the number of drug abuse events, the default denominator is the U.S. population. And these data can be refined by getting the number of events per 100,000 population, by age group, as well as the geographic region, such as state or ZIP code. We can also get information from the amount of drug utilization either from ARCOS, which is the Automation of Reports Consolidated Order System, which is ARCOS, and that's administered by the EA, and that was also presented by Dr. Paulozzi. But FDA also purchases excess to drug

utilization data sources.

So, the U.S. Census data is readily available, it's easily understood, and it provides data on the public health burden of these events and provides data on groups that are at risk. It does not, however, provide data on drug utilization. Drug utilization can be considered exposure; how much of the population is exposed to the drugs that are being examined.

So, ARCOS, which is DEA's dataset, it tracks all schedule drugs that are in Schedules I, those are the illegal drugs, and II, and both morphine and oxycodone are C2s, as well as all narcotics from all the schedules. And opiates are considered narcotics, so, all levels. And it is from the point of manufacturer to the time they are delivered to the pharmacies. For the most part, it reports the number in kilograms sold by drug. This system also has some information on formulation and substance.

This is not a projection. This is all drugs sold. The limitation is that it does not provide information on the numbers of prescriptions sold. So, it's once it's reached the pharmacy, we don't have any

further information with this data source.

So, FDA has purchased access to many data resources that provide estimates on the amount of drug sold by substance, formulation, and brand, and this is detailed information that includes data on the prescriber, the patient, and the indication for which the drugs are prescribed. And it also provides information on concurrent use of multiple drugs.

So, these data are used as denominators, and it does put drug abuse events into context. And we use these data to assess the amount of risk within the U.S. population. We are also using these data to understand drug-prescribing patterns and abuse, and, also, we use it to assess risk management, plans, and practices such as labeling.

So, it does provide very specific information on substance formulation and brand. The limitations are that they are projections. It is not the amount sold. And we still don't know how the drug is taken by the individual patient. The patient may have left the drug in their medicine cabinet and that could have resulted in a family member taking it, or they could have sold

it. And all we need to keep in mind that these data are in no way linked to the outcomes associated with drug abuse.

Okay, now I will discuss the Prescription Drug Monitoring Plans, which are the PDMPs. And PDMPs are statewide electronic databases that collect data on controlled substances that are dispensed in pharmacies by state. They were first started in 2002, and there are currently 34 states that receive federal funding. And there are two federal funding sources for the PDMPs. The first is the Harold Rogers Prescription Monitoring Plan, and that's administered by the Department of Justice. The second source is NASPERA, which is the National All Schedules Prescription Electronic Reporting Act administered by HHS, the Department of Health and Human Services. And this program enables states to create PDMPs or enhance existing ones.

And these programs were just started, they’re very new, and they were started to make sure that there was access to legitimate drugs that work, controlled substances, and, at the same time, identify people that have multiple prescriptions for the same substance, and

to intervene and offer treatment for people who are addicted to prescription drugs. It also provides data for finding drug abuse trends. It also began to address the issue around doctor shoppers. So, doctor shoppers are someone may go to different physicians to get the same prescription multiple times for drug abuse purposes.

And FDA can use these data in a few different ways to identify which drug substances and formulations are targeted by doctor shoppers. The data though are still very new, understand development, so, they continue to evolve and change. And, to data, not all states have PDMPs. So, that's still a challenge. And we are still learning how to use this data.

So, in conclusion, as we think about all these data sources and how we will use them, we are faced with the challenges that new drugs and formulations that address the issues associated with drug abuse are currently being developed or are currently under review. And when we're looking at new ways to evaluate these abuse-deterrent formulations, we are using current and new data sources, which are just being developed, and

how these data sources will be used to sustain a labeling claim of abuse deterrence is something that we're working very hard on.

Thank you.

DR. KIRSCH: Thank you.

We're now going to go to the question and answer session again. Our first question will be given by Dr. Wolfe.

Clarifying Questions

DR. WOLFE: I was out of the country in September of 2009, when these committees met to decide whether or not there was enough evidence of some improvement with OxyContin in the formulation to go forward. And so, I read the transcript of this meeting yesterday just to see what happened, and there were a few people, including Dr. Flick, Dr. Kirsch, who were concerned about going ahead, and I'll just quote this because it's a comment and I have a question afterwards. Dr. Kirsch voted against this because he said it's "unconscionable to move forward without well-defined REMS." I am mainly an optimist, and I think that one of the purposes of this meeting today and tomorrow is so

that the next time one of these drugs comes forward, there will be a REMS at the beginning rather than a year later.

But I want to move back one step and ask questions of really the speakers this morning. as you look at the submitted ideas for epidemiological studies by the company, FDA's ideas, and so forth, are there not some of these studies that could be done prior to approval? I mean, when you're sort of struggling for a comparator group and knowing that OxyContin old is not around anymore, is it not possible to--I mean, I am all in favor of post-market surveillance. It's necessary, and a lot of these databases need to be utilized. But, so, my question is to any of these people who spoke this morning.

Can you see any studies that could be done prior to approval or more definitively answer the question of whether there is a reduction in abuse potential. Again, OxyContin, but the same is true for Embeda before naltrexone was embedded in it. It did not have naltrexone, and the comparison would be useful. That's really the question open to anyone who spoke.

Any kinds of studies, whether it's using these processes phenotypes that Dr. Anthony described or any other means? Cross-sectional studies. Anything that could be done prior to approval so we'd have a better idea about whether there appears to be a risk reduction, as not to say that you still don't need the post-marketing studies.

DR. KIRSCH: Dr. Rappaport, would you like to take that question or appoint it to somebody?

(Laughter.)

DR. RAPPAPORT: Well, I can try to speak to some of it, perhaps. I think there may be components, as you mentioned, if there's baseline work or comparator work that could be done prior to approval, and then once a drug gets on the market, we could do those comparisons, but I think we'd have to be careful about secular trends. I think Dr. Lapteva pointed out that there's a lot of other things going on during this timeframe other than just FDA's actions. So, we'd have to be very careful if those comparisons span a number of years.

DR. RAPPAPORT: I would just add, if you're

trying to measure whether there's a reduction in abuse in the community based on the change in formulation, I don't see how that could be possible if a drug hasn't been marketed out in the community.

DR. WOLFE: I agree fully with that, I'm just simply saying the question a year ago was: Is some reason to think that the new formulation is better? And all I'm suggesting, that the community is essential, the longitudinals are essential because people may get wise to some of these tamper-resistant methods and everything, but prior to approval, not in the community in some kinds of studies, whether they're observational studies or whatever, cross-sectional studies, randomized trials between the two. Is it not possible to do more of these studies before, some of them? Not as a substitute.

DR. HERTZ: So, to do observational studies of a non-approved product, what exactly do you mean?

DR. WOLFE: You literally could do a randomized trial. I mean, prior to approval, you have old OxyContin, it is around, still approved, you have the new version, which has not yet been approved, but

it's obviously being subject to other kinds of studies prior to approval. To get some better idea in addition to the post-market studies what the evidence is that it really has some improvement over the old product.

DR. HERTZ: So, you are envisioning a multi-thousand patient study of new and old OxyContin, looking for aberrant drug behavior?

DR. WOLFE: That would be one way of doing it. There might be other ways of doing it. I'm just raising the question. It just seems as we're struggling--

DR. HERTZ: I mean, I think that it's very easy to throw out a concept.

DR. WOLFE: Right.

DR. HERTZ: Without having thought it through because the concept of trying to look at abuse aberrant drug-taking behaviors in a clinical trial of patients is extremely difficult because they don't tell you that their intent is to misuse or abuse. So, typically, we get pretty low rates of this type of behavior, particularly, I would imagine, if that's what the intent of the study would be. So, I think we would love to be able to come up with a design to look at this

pre-approval, but if you have actual thoughts on how it can be done, that would be helpful, other than to say something, because that's where we're here for.

DR. KIRSCH: Well, I think the question has been asked and answered. We'll go on to the next question.

Dr. Mendelson?

DR. MENDELSON: Yes, hi. Thank you. This comes to about three different people who presented. But the question for the Prescription Drug Monitoring Programs, a big question would be: Do they capture data from the mail-in pharmacies like Merck-Medco? Increasing numbers of patients fill their prescriptions in three-month intervals through long-term pharmacies, and I think this may be fueling some of the supply of licit opioids that become illicit. It would seem to me important for epidemiologists to begin capturing who pays for the medications and how many dose units are dispensed at a time.

Dr. Lapteva, your wonderful slide there that's the scariest slide I've seen as a practicing doctor, says that most of the diverted opiates are coming from

single physicians prescribing to single patients. And that sort of suggests that a large number of dose units are going out to those individuals, and that is probably occurring because o the way they're paid for. So, this gets to Dr. Bickel's point that economics are important, but they may not be the economics we think.

So, my question would be: How would we capture payment sources for medications and how those relate to the amount of abuse-able drug there is, and this is something the FDA could possibly take a stand on to say that there is going to be a limit on the number of dose units dispensed in a per unit of time per patent. This will not please the cost people because it will drive costs up as people will need to be seen more often for management. But it's an important point, I think. It's not covered in any of the presentations so far, it's who's paying for these drugs, for the most part, and I think it's insurance is paying for all the abused, and, therefore, we are all paying for them, everyone who pays a premium for an insurance plan is paying for medication. So, I'd like some comments from the epidemiologists as to how would they capture who's

paying for the drugs and how would that be captured in Prescription Data Monitoring Systems, as well, for out-of-state prescriptions, which are probably not showing up, at least on my prescription monitoring reports.

DR. STAFFA: Well, I can address that at the population level, the drug utilization data that Dr. Dormitzer talked about does capture mail-order prescriptions, it captures all different sources, whether it's retail, and so, that type of use is being captured if we use that type of denominator. I'm not as familiar with the Prescription Drug Monitoring Plans. I don't know if someone else can address that.

MR. PAULOZZI: I can comment on that. Some Prescription Data Monitoring Programs in states do capture mail-order prescriptions to their state residence. They don't necessarily capture them mailed out of the state elsewhere. Others do not. So, it's incomplete. I don't know what percentage of states fall in each camp. I think that it's an important point that it does need to be captured. The net effect of not capturing it, of course, is to underestimate the total number of prescriptions, the number of doctor shoppers

if people getting multiple prescriptions through that route. Of course, there are limits in terms of how many months' supply controlled substances can be prescribed, but even single-month supplies could be ordered through mail-order pharmacies.

If there's somebody from the DEA, they might be able to comment more on that topic.

DR. KIRSCH: Dr. Omoigui?

DR. OMOIGUI: A couple of things. The first question is to Dr. Paulozzi. There's a significant difference in the percentage of injectable OxyContin compared to injectable morphine. Is that a difference because the injectable formulation of morphine is commercially-available or has that been broken down into what is being injected from commercial formulations and what's being injected by kitchen chemists with respect to the morphine? We know that OxyContin does not have any commercially-injectable formulation. That's the first question.

And the second thing I wanted to point--

DR. KIRSCH: Let's take one question at a time, okay?

MR. PAULOZZI: Yes. Thank you. That data that was not broken down by the formulation of the kinds of drugs. So, I don't have really the answer to your question. And it may be related to the injectable form of morphine, but I don't know.

DR. KIRSCH: Okay. Your second question?

DR. OMOIGUI: The second question, there has been some reference to a behavioral economics. As a physician on the frontline, I can see that one of the studies not being done here and which I believe would be a leading indicator of the success of the new reformulated OxyContin is what is the price point at which OxyContin is being sold on the street?

Right now, one of the greatest problems we have with OxyContin is 80 mg tablets, which is being sold at $1 per mg, you're getting like $80 per pill, and maybe with a little bit of discount, the person doing a diversion gets $50 a pill. Now, if you're talking about prescription of 90 tablets, you're getting $50 a pill for a month's supply. You're essentially making after tax income of $100,000 a year.

So, I think if we're going to analyze the

success of this abuse-deterrent formulations, we also need to know are the street prices dropping because that would be an indicator of the desirability of this new formulations. I don't know if anybody would be interested in incorporating that into any of the studies.

DR. KIRSCH: Would someone from the FDA like to address that or should I call on somebody?

DR. RAPPAPORT: Let me just say, I mean, it's an interesting concept, but I think really that's part of the discussion that we're asking you all to have tomorrow in response to the questions. What we're looking for right now is that you get clarification from the various speakers.

DR. KIRSCH: Thank you.

Dr. Flick?

DR. FLICK: Dr. Woodward, I just want to better understand some of the datasets here. You talked about in the TEDS dataset that most states do not collect identifiers, which suggests that some states do collect identifiers, and is there an opportunity in those states to do longitudinal studies?

DR. WOODWARD: We've looked into that. It's difficult because the data isn't really that well collected. We also face restrictions on doing that kind of analysis, the confidentiality privacy issues that I alluded to. The states have their own regulations. I'm not really in that group, so, I can't really respond as fully as I might want to or you might need, but I know the others in that group have looked into it, and it's been difficult logistically to get those kinds of studies going on. We haven't been sure that the data quality is that good that it would be that useful. I know certain states do have good data. They've done their own analysis, done their own reporting on that.

DR. FLICK: I would think that the ability to collect identifiers and the ability to do longitudinal studies is crucial to having good data with regard to this question, and I would think or I would hope that we could answer that question clearly. So, if there is an opportunity to do those studies and select the states, that we avail ourselves of that.

I also wanted to ask with regard to DAWN, this is a probability sample of short-stay federal hospitals.

Does that include rural hospitals? Is there a bed size cutoff for that? Are we eliminating rural hospitals where I think a good proportion of this problem exists? And do we include children's hospitals in that dataset?

DR. WOODWARD: We include rural hospitals. Obviously, they're not going to show up as part of the metro area over-sampling; they're going to be part of the remainder sample. We can do some reporting on rural versus non-rural, but EDs, the sample is strong enough for that. We would only include children's hospitals if they have an emergency department that's open 24 hours, 7 days a week. But, generally, I mean, we only use short-term general hospitals, so, I can't think of any in the 200, 250 hospitals that would be children's specialty hospitals.

DR. FLICK: All right. I would think that is going to be a problem from an epidemiologic standpoint if the age that we're considering here is 12 and over, especially in metropolitan areas, where a lot of the pediatric emergency care takes place in a children's hospital. You will miss all of those or many of those patients.

DR. WOODWARD: Well, the DAWN does pick up under 12; it picks up all age groups. It's the NSDUH that's 12 and over.

DR. FLICK: If it doesn't sample, then they won't be represented or they won't be accurately represented. If you're not sampling children's hospitals, then you're sampling metropolitan areas. They'll be missed.

DR. WOODWARD: No, it's a limitation. I agree. It's also expensive to add to--I mean, we'd also like to sample especially psychiatric facilities, too, which that would be more consistent with SAMHSA's missions.

DR. FLICK: I certainly understand the limitations.

DR. WOODWARD: Yes.

DR. FLICK: And I'm not being accusatory here.

DR. WOODWARD: Yes.

DR. FLICK: I'm just saying if we're going to plan studies, we need to understand what the datasets contain and what they more importantly don't contain.

If I could just ask one more question of you.

DR. WOODWARD: Sure

DR. FLICK: Do any of these datasets communicate with one another or can the data from one be merged with another to gain a more accurate picture?

DR. WOODWARD: Could I, if it's okay, elaborate a little more on your prior question?

DR. FLICK: Sure.

DR. WOODWARD: One of the things that we have been looking into, the staff has been looking into is working with other ED databases. NCHS has the NHAMCS and also ARHQ has the SIDS and SAIDS part of the HCUP, the Hospital Cost Utilization Project. Again, they're largely focused on general hospitals, but they do get into specialty hospitals more than we do. So, we're trying to supplement.

DR. FLICK: Right. The Age CUP database contains an additional sub-database called the KID dataset, which, if I'm not mistaken, has identifiers and can accurately represent pediatric care. So, it might be an opportunity to utilize that dataset to better form a picture of pediatric care.

DR. WOODWARD: Yes, we're starting to talk

with AHRQ, and we've started to talk to NCHS.

DR. KIRSCH: We're going to go to the next presentation.

DR. WOODWARD: Okay.

DR. KIRSCH: For a point of clarification, Dr. Morrato is shaking her head no, and so, I'll give one second.

DR. MORRATO: Yes, I've done research with KID. KID is admissions, it's the identified. If you're really interested in pediatric, there's a semi-proprietary PHIS dataset which would allow you to get to that.

DR. KIRSCH: So, our next speaker is Dr. Kornegay.

Study Designs to Assess Prescription Drug Use

Design Considerations in Epidemiological Studies of Abuse-Deterrent Opioids

DR. KORNEGAY: Good morning. My name is Cynthia Kornegay, and I'm an epidemiologist in the Office of Surveillance and Epidemiology at FDA. I'm going to spend the next several minutes discussing some general design considerations related to epidemiological

studies of opioid abuse.

First, I will outline the purpose of this talk. I am also going to briefly review the definitions of abuse and misuse. Then I will provide some background information, and, finally, discuss comparators and issues related to measuring change in abuse-related outcomes in studies. I will conclude by summarizing the concerns highlighted in my presentation.

The purpose of this presentation is to provide general comments based on preliminary proposals submitted by the Sponsors and to provide a framework for considering the industry presentations later this afternoon and tomorrow. My talk will relate mostly to study design, while the next talk will address some of the statistical considerations. This presentation is not a detailed critique of the specific proposals, but general comments based on the submitted documents.

To review, abuse is defined as the non-medical use of a drug repeatedly or sporadically for the positive psychoactive effects it produces, while misuse is defined as the use of a drug outside label directions or in a way other than prescribed or directed

by a healthcare practitioner. The difference is intent. For abuse, the intent is non-therapeutic, that is to get high, while the intent is still therapeutic for misuse. These definitions are independent of anything that may be done to the drug, for example, crushing, dissolving, chewing, et cetera, to achieve the desired effect.

The proposals that you will hear about will use differing approaches, measuring a particular population versus studying several different populations and measuring the severe end of the abuse spectrum versus including occasional or recreational use. Both proposals attempt to measure change, but that raised the question of change from what?

Prior to measuring change, the baseline abuse potential for a product would need to be established. This would also be important in targeting studies and interventions to where they will have the largest impact. One of the basic considerations is defining who is at greater risk for abusing a particular product, including demographic, social, economic, and geographic considerations in defining at-risk populations may help define the limits of abuse deterrence efforts. In

addition, other risk factors such as family history and certain psychological conditions may also be important in determining the at-risk population.

Along with who at-risk individuals are, how they are manipulating the product or not is also important. In other words, are a product's abuse-deterrent properties designed to affect the typical routes of abuse? Before a change in abuse-related outcomes can be measured, the baseline abuse level population and risk factors must be known. This information can be determined from historical data on the same or similar products. This baseline should be derived from real world, that is post-approval, product use.

The next few slides will discuss the important issue of comparators. The appropriate comparator is vital to providing the big picture or context for changes in abuse-related outcomes. There are several different choices for meaningful comparators, but, usually, multiple comparators are required. Multiple comparisons can be historic by class, drug schedule, and/or individual product. Specific attributes of

comparators will be discussed in more detail shortly. Although multiple comparisons on many levels are necessary to understand the big picture. They can be confusing, and conversely make it more difficult to understand what is going on.

In some cases, it will be possible to compare non-abuse-deterrent and abuse-deterrent formulations of the same product from either a historic or concurrent perspective. This could be a particular problem, however, for novel drugs introduced with abuse-deterrent formulations. Once an abuse baseline is established, how will it be possible to determine if abuse-deterrent properties are effective?

Although these challenges are familiar, when deciding on what comparators to use, this is a partial list of some of the attributes that should be considered. Ideally, comparators should be similar in population, indication, active ingredient, time-released formulation, single ingredient or combination, and time on market. One should also consider the strength, route of administration, and the scheduling. The next section will provide some thoughts on interpreting a change in

abuse.

Although none of these questions have easy answers, some are more abstract and may require a paradigm shift to address effectively. The most obvious question is what is a significant change and how can that be defined? Close on heels of that is what types of change are most meaningful from a regulatory perspective, a change in the common methods of abuse or an overall reduction as an example? Other questions are over what time period should the change occur and in what population?

A second consideration in measuring change is how time will be incorporated. It would be unrealistic to assume that the abuse profile of a drug would be static once established. The abusing population and the method of abuse are both subject to change.

To address this, should updates be triggered at some pre-defined point or be scheduled on a product-by-product basis? In addition, how comprehensive should updates be? That is, what level of detail is necessary to detect a shift in the baseline assessment or in abuse levels?

A third issue is a population that is studied. How should high-risk populations be weighted in a baseline abuse assessment? Should traditional high-risk populations always be included, and what about the general population? Addressing these concerns will require careful consideration of when data are available relative to when they are collected and of unrelated events that any affect baseline abuse levels. It may also require the ability to modify or augment currently existing data resources.

In addition to prior population considerations, it is not clear how results from numerator-only sources should be weighed in the national context. Also, what is the value of small, focused, non-epidemiologic studies? How can they contribute to improving or refining the abuse profile and safety issues of a particular product?

In an effort to increase the quality and scope of data available to assess abuse-related outcomes. Several non-traditional data resources are under consideration. These include health care systems such as Kaiser, convenient samples or surveys, and add-ons to

population-based surveys and questionnaires. While these data sources can provide detailed information, data resource validation, as well as sample size and power considerations will still need to be identified and appropriately addressed. It will also be necessary to determine the relative importance of study results. Should they be limited to reporting findings from more commonly-used data resources or are they robust enough to be viewed as an independent study?

A final consideration is somewhat less concrete, but still carries important implications for determining the impact of abuse-deterrence measures. Most studies implicitly assume that less hardcore users means less casual users, but it is not always clear that that is a simple relationship, and, from a public health perspective, is a most effective abuse reduction strategy when the target's new initiates, hardcore users, or individuals who are transitioning from one extreme to the other?

To summarize, this presentation presented several ideas to keep in mind while listening to the upcoming presentations. Has a good baseline picture of

the at-risk population mechanism been established prior to measuring the effect of abuse-deterrent mechanisms? Are the abuse-deterrent mechanisms designed to address major or problematic routes or methods of abuse?

If multiple studies are proposed, will they be completed in sequence or concurrently? How much influence should numerator or sub-national studies have on the overall abuse profile? Have the appropriate comparators been selected? Have timing issues, the time to create a baseline abuse profile, the time to determine appropriate study length, and decide to include time-dependent outcomes been considered and incorporated into the study design? If novel data resources or collection methods are proposed, how will they be validated?

And finally, there were several population-related questions. Is the proposed population similar to the at-risk population? Have demographic, co-morbid, and geographic issues been appropriately incorporated? Should the study target high-risk individuals? Should hardcore users, recreational users, or both be included? Also, what are the implications of performing the study

in a non-traditional data resource?

Thank you.

DR. KIRSCH: Thank you. The next speaker is Dr. Keeton.

Statistical Considerations for Epidemiological Studies of Abuse-Deterrent Formulations

MS. KEETON: Good morning. My name is Stephine Keeton, and I am a statistical safety reviewer in the Office of Biostatistics at FDA. Today, I will present the statistical considerations for epidemiological studies of abuse-deterrent formulations of opioids.

The purpose of this talk is to highlight and discuss generals statistical issues based on the preliminary study proposals submitted by the Sponsors. I will not provide a detailed critique of the proposed statistical analyses, but, instead, will raise general issues for consideration. This talk is in conjunction with Drs. Dormitzer and Kornegay's talks that you've just heard.

Here is an outline of the presentation. I will start by briefly discussing the trend and Cross-

Sectional Approaches described in the proposals. I will then discuss some general modeling issues, followed by issues related to data sources. I will also discuss sample size and power considerations. And finally, I will discuss multiplicity and replication issues before summarizing the statistical considerations.

The overall goal of the Epidemiological Program proposals is to show a reduction in the rates of death, overdose, or abuse by comparing drug products and formulations. One method to compare the rates is the Trend Approach. This is the primary approach used in the OxyContin Program. The Trend Appraoch compares rates before and after the introduction of a new formulation. This approach can also be used to compare rates across time after introduction of a new formulation.

The graphic on the left-hand side illustrates the approach of comparing rates before and after introduction of a new formulation. The X-axis represents time and the Y-axis represents the rate of the outcome. For a product that has been on the market for a considerable time such as OxyContin, the trend

approach compares the rates before and after introduction of the new formulation. The red dash line represents the time of introduction of the new formulation. Two effects on the rate are considered. First, a change in the mean level of the rates before and after introduction of the new formulation, and second, a change in the slope of the rates before and after introduction. It is important to observe what happens to rates for some period of time before and after introduction of a new formulation.

The graphic on the right side illustrates the Trend Approach for other opioid products. Changes in the rates within a population over time may be occurring. These changes may be influenced by other factors such as the introduction of risk, evaluation, and mitigation strategies or changes in cultural behavior related to abuse. These changes in rates from such factors should be accounted for in the analysis.

Another approach proposed is the Cross-Sectional Approach. This is the primary approach used in the Embeda Program. The Cross-Sectional Approach compares rates for a new formulation to other products

at a specific point in time or over a short period of time. The graphics on this page illustrate the Cross-Sectional Approach.

Again, the X-axis represents time, and the Y-axis represents the rates of the outcome. Time 1 on the X-axis denotes some period of time in which a comparison between drug A and other drugs is made. The comparison can also be made at an additional time point, time 2 to evaluate whether the effect remains constant.

In this slide, I will talk about some considerations of the trend and Cross-Sectional Approaches. The Trend Appraoch offers intuitive graphics and analytic summaries. In this approach, it is important to control for changes over time and secular factors related to the outcome of interest. The Trend Approach can also be used to compare rates across time after introduction of a product.

For example, for Embeda, the Trend Approach could be used to look at the effect of the drug over time after introduction of the new formulation. In absence of randomized treatment assignment, other factors may confound association between the product and

the rates. The Cross-Sectional Approach provides a snapshot of abuse in time. However, the effect over time may not be constant and must be considered. Again, in the absence of random treatment assignment, other factors may confound association between a product and the rates.

In the next couple of slides, I will discuss some issues related to modeling of outcomes, death, overdose, and abuse. The analysis should control for potential confounders such as possible patient selection biases. Physicians may preferentially prescribe an abuse-deterrent formulation to patients suspected to abuse opioids, and this may result in higher rates of abuse. Additionally, patient characteristics may differ across time. Techniques such as multivariate analysis and propensity score methods may be used to adjust for differences in patient characteristics across formulations and time.

When considering the model for these studies, it is important to note whether drug availability is included in the model as a covariate or not. For example, in one of the Embeda studies, several models

are proposed to compare rates. The primary model does not adjust for drug availability. Without adjusting for drug availability, the model provides estimates of the proportion of abuse by unlabeled routes of administration among all users. The secondary model does address for drug availability. The model provides rates of abuse by any route of administration among all users. The difference in interpretation of the models should be considered when selecting a model.

I will now discuss some issues related to data sources. The data source should represent the population of interest, for example, abusers versus all users, and enriched population, such as abusers from substance abuse treatment centers, may be easier to study since it will provide more events of interest. I will discuss this topic more later when I discuss power in sample size issues.

Some of the studies propose, such as studies conducted from data using data from substance abuse treatment centers and special populations are based on convenient samples. Caution must be taken when interpreting results from these studies since

generalizing the results to a population that has clinical relevance may be difficult. When interpreting these studies, the results of such studies, one should characterize how the study subjects differ from the population of interest, in particular, pay attention to who might be left out or underrepresented in the data.

The appropriateness and accuracy of denominator information should also be considered to ensure meaningful interpretation of the data. Statistical surveys provide denominator estimates. Well-designed and conducted surveys provide valid denominators. Administrative claims data provide internal denominators. However, these databases may not represent the population of interest. For studies that provide only numerator information, for example, poison control data, the denominator must come from other sources. For such studies, the appropriateness and accuracy of the denominator source should be considered.

Power and sample size determination are necessary if the study is to be used for statistical inference. The sample size impacts the feasibility of conducting the study. The statistical power and sample

size depend on the event rate which I will discuss in more detail in the next slide. As well as the effect size and length of time period for trend analyses. As stated in Dr. Kornegay's talk, defining a significant reduction is a critical component of designing studies to measure change. The required effect size is based on clinical relevance. The smaller the effect size one wants to detect, the larger the sample size required. For trend analysis, the length and number of time periods must be taken into consideration. The longer the time period, the more information, and, therefore, more likely it is to precisely identify patterns of change.

Statistical power depends highly on the number of events captured in a study. More events provide greater statistical power. Studies of enriched population such as studies of patients entering substance abuse treatment centers will likely offer a relatively high number of events, and, thus, easier to study. The choice of outcome also impacts power, as more frequent outcomes are easier to study.

The duration of the study also impacts power

in that the longer the duration, the more events observed. The event rate of the comparator drug or comparative period needs to be considered. Again, more events provide greater statistical power.

Finally, product availability impacts a number of events. If a product is not readily available to use, it may take a considerable amount of time to get events. If any assumptions used to calculate the sample size are incorrect, the study may be underpowered and not capable of demonstrating an effect.

The various studies proposed addressed different populations and questions, but may provide overall information on abuse. However, other sources of data may be required to replicate the results. Testing abuse deterrence over time raises statistical issues. As stated in Dr. Kornegay's talk, the abuse profile of the new formulation may change after some period of time of being on the market. This may require multiple uses of the same data sources and adjustments for multiple testing may be required.

In summary, the Sponsors have proposed two general approaches to measure the abuse-deterrent effect

of new formations. For both the Trend and Cross-Sectional Approaches, there are several important statistical issues to consider when reviewing the abuse-deterrent studies. The analysis should control for potential confounders, such as possible patient selection biases and consider methods to adjust for differences in patient characteristics across formulations and time. The relevance of the data source to the population of interest should be considered, as some studies will be conducted using data based on enriched populations or convenient samples. The appropriateness and accuracy of Denominator information may have an impact on study quality.

The statistical power and sample size depend on the choice of outcome population, duration, and drug availability. These factors does affect the study feasibility.

And lastly, the abuse profile of the new formulation may change after some period of time of being on the market. Multiple uses of the same data over time should be accounted for in the statistical inference.

Thank you for your attention.

DR. KIRSCH: Thank you. Before we break for lunch, I want to ask for any of the morning speakers whether anybody who spoke this morning is not going to be here this afternoon. My preference is to hold the further questions to this afternoon, but if any of the speakers from this morning plans to leave at the lunchtime and not come back, I'd like to direct any questions. There's one. So, we have one speaker who's not coming back, and that's the person from the DAWN Group. So, are there any questions any member of the committee has for that individual speaker before we break for lunch?

Seeing no hands, I'll assume that there will be no questions for that individual, and we will break for lunch now. It's currently 11:55. I will now break for lunch. We will reconvene again in one hour in this room at 12:55. Please take your belongings you may want with you at that time.

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

audience. Thank you.

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

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

(12:55 PM)

DR. KIRSCH: I'd like everybody to take their seats. We're going to reconvene the meeting.

The first session of this afternoon is to address additional clarifying questions. I want to remind the members of the committee that really the purpose that we're here for for these two days is really to help FDA come up with relevant studies to encourage the companies to use in order to look at the outcomes that we think are important. It's really not to necessarily criticize one company or another; it's to really help the FDA come up with studies, which I find it to be a very exciting opportunity.

So, in that context, we're going to go back to our question list, which is--I think, actually, I cut off Dr. Flick when he was talking before. I want to make sure he asked all of his questions.

Clarifying Questions

DR. FLICK: I did have one other question, and the question that wasn't answered was: Do we have the capacity to merge information from one dataset to another? And I don't know which one of the presenters

can address that question. Which of any of the datasets can merge their data to make a more robust dataset?

MR. PAULOZZI: I guess I can try a partial answer to the question. You need, of course, personal identifiers. So, that would mean medical examiner, coroner information, or vital statistics information for deaths, and that information has been, can be merged with--

DR. FLICK: No, I think we're maybe talking about two different things. For example, as I've used before, the National Hospital Discharge Survey, for example, uses the same methodology as the National Survey of Ambulatory Surgery. So, the methodology and the sampling universe can be merged to make an accurate representation of surgical procedures in the U.S., for example. So, I think those are a little bit different things that we're--

MR. PAULOZZI: Yes, yes, and I don't have an answer to that question.

DR. FLICK: Okay.

DR. KIRSCH: Okay, and then Dr. Morrato had a question that she was going to ask during the break and

I cut her off because it wasn't in the public forum, so, I asked her to ask her question in the public forum.

DR. MORRATO: Okay. It was a question related to CDC, and maybe a little bit of what we've discussed before in terms of what can be done before a drug is approved. I know in other areas of public health, they've taken approach of system dynamics modeling. They've used this, for instance, to model national cocaine prevalence, and, most recently, there was a special issue July of the *American Journal on Public Health*, where they were talking about this is a way of looking at tobacco control.

And, so, my question was whether or not anyone has done sort of this theoretical framework that looks at sort of the abuse of prescription opioids as a starting point. So, as we're looking at these different interventions, you might be able to predict which might work better than others.

So, for instance, so, it's a system dynamics modeling, it allows you to model multiple interactions of diseases, risk, delivery systems, populations that we've been talking about, and how it relates to national

and state policy. So, it's more of a modeling exercise, but then it gives guidance for what might be interventions and/or measurements, et cetera. And I don't know the field well enough whether or not CDC folks are aware of it or anyone.

MR. PAULOZZI: I'm sorry; I'm not familiar with that modeling approach. I would think though it depended on the availability of multiple variables about individuals involved, and it seems like the constant problem in this is that you don't have a lot of in-depth information about individuals using the drugs.

DR. MORRATO: Yes, so, it's more of a conceptual framework where it's social sciences create the model, and then you put information in it as you acquire it, but at least you're starting with a framework.

MR. PAULOZZI: Yes.

DR. ANTHONY: The RAND Group probably launched the best starting points for those systems analysis models having to do with cocaine and other drugs. The best work that's been done since then is probably Jonathan Caulkins' work. He works with a group in

Vienna, as well. Jonathan is a Carnegie Mellon.

And then the elaboration with some more sophisticated statistical models is being done by Georgiy Bobashev at Research Triangle Institute. So, there are developments, but it's pretty cartoon-like. You can make some predictions. Validating the assumptions is difficult, but I think it's a very good suggestion and a line to work. They've done some pretty good work on that.

DR. KIRSCH: Okay. Dr. Bickel?

DR. BICKEL: I have two questions. I'll ask them one at a time. And this one is for everybody who has different datasets. So, given that addiction has a strong monotonic association with social economic status that is whether you measure it by educational attainment income or occupational status. The lower your education, the lower of your income, your lower occupational status, the more likely you are to use drugs and to be addicted. Has anyone used these different datasets to model the fact that that is the case and use that to make inferences about who is susceptible?

DR. ANTHONY: I'm sorry. I have to start by challenging your assumption. It depends really heavily on stage of introduction of the drug and the population, and earlier in the stages, there's often an excess among high SES individuals, and in later stages, things straighten out. Tobacco smoking epidemic is an excellent example of that in the United States right now. cocaine, there's someone sitting in this room who's published on this topic in relation to cocaine using the National Surveys on Drug Use and Health and the national household surveys. So, yes, work has been done, but I don't think I'd have as a starting point the assumption that you started with. Okay.

DR. BICKEL: Fair enough. My second point, and, Jim, you started to address this, right? So, who are the early adopters, and should we have a model of them and see whether they're predictive of later use patterns so that we could actually use them as like a canary in the coal mine?

DR. ANTHONY: In my slide on future directions, I planted a little seed, and I'm happy that you've given me a chance to see if it can blossom. If

the regulations allow limited release to subpopulations, there would be some groups that would be useful to try a limited release form of experiment, and those would be hospitals where you know quite a bit of opioid diversion is going on with existing established products. And under fairly carefully controlled conditions, you could release the new product and see what happens in a population where you know there are hospital personnel who will figure out ways to divert new products.

So, I think I'd encourage FDA to think about this as a way of staging the introduction of the product in different subpopulations that might vary in their vulnerability. A long time ago, and this is probably when Dr. Wolfe and I didn't have any gray hair, I recommended FDA randomly assigning regulatory regimes to different states when new products were introduced. I'm pretty sure the Boards of Pharmacy and the like would be open to this, particularly if it would lead us to better evidence about the effect of different regulations and the impact of different compounds.

DR. KIRSCH: Dr. Denisco?

MR. DENISCO: Thank you. A couple of comments

along with a question to possibly Dr. Paulozzi and anybody else.

One is we looked at populations. We briefly discussed subpopulations that we needed to pay attention to in pediatric populations were mentioned. Another population that I think needs to be mentioned is the prisoner population. We have almost 1 percent of the population is incarcerated, and especially with the NSDUH study, that doesn't sound like 1 percent would affect the statistics very much, but a little back of the napkin calculation, when you look at the high prevalence rate of addiction in that population, it can really throw things. So, I was wondering if there was any way better than the back of the napkin to sort of address that. That was one thing.

The second thing is --

DR. KIRSCH: Well, let's hold off for the first question first. Was the question pointed at Dr. Paulozzi?

MR. PAULOZZI: So, you're asking whether or not the surveys can be affected by not including incarcerated populations and how that can be affected?

Yes, I can see your point, 1 percent with a tenfold great prevalence of addiction might really make a difference in the statistics. I don't have an answer though in terms of how to address that particular problem since that would be an issue really for the SAMHSA people to try to address how to involve that population. They do have surveys of drug use of perpetrators who were arrested, ADAMS System, which gets at drug use and screens people at intake after arrest, which gives you some sense of drug prevalence or use of drugs in that population.

DR. KIRSCH: Dr. Anthony?

DR. ANTHONY: So, if you live long enough, you get to make many sins. We actually did what you're proposing that we should do. In the NMIH Epidemiologic Catchment Area studies in the early 1980s where we had coordinated samples of household, institutional, and homeless individuals, and institutions included prisons and jails and nursing homes and the like, mental institutions. We really didn't find much variation in the estimates, although, of course, there are concentrations of the cases where you would predict.

But it turns out the relative proportions in those subpopulations are small enough that they don't really perturb the estimates when you take the confidence intervals of the estimates into account. Because any single point estimate is not going to be all that helpful, but if you put a confidence interval around it and then ask how often are you moving the estimate around outside of the confidence interval, it didn't really happen very much.

Subsequently, I don't believe any of the investments, and we're talking about more than $1 billion in the early 1980s in these surveys. I don't think any of the subsequent studies have included coordinated household, non-household populations as we did there. Perhaps because we didn't find that it made all that much difference, but, as Len pointed out, there are special studies of prisoners and special studies of the homeless and so on.

DR. KIRSCH: Okay. Go to your second question.

MR. DENISCO: Yes, the second question is: Since the prescription drug problem is closely

intertwined with the pain medicine treatment and under treatment of pain. Certainly, there's going to be unintended consequences, and I would do an almost proposed. It's not really a question, more a comment, that any time these issues of prescription drugs are studied, there should be some attention paid to what it does to the availability of legal prescriptions to appropriately screen patients.

DR. KIRSCH: I would bet that our open public hearing tomorrow, we'll hear a lot about that.

Dr. Bilker?

DR. BILKER: Yes, I was wondering whether it would be important and if any of the databases are capable of assessing abuse by new or previously naïve abusers of illicit drug versus continuing abuses. If possible, that would allow estimation of barriers to abuse as a deterrent to initiation of new abusers versus continuing users.

I had one more question after that.

DR. KIRSCH: Dr. Anthony, did you want to--

DR. ANTHONY: You'll be happy to know it's been done. So, within the limits of the assessment, you

can restrict your estimates to people who have used no other drug before the one of interest and people who've started with tobacco or alcohol and people who have used cocaine and so on. So, that routinely is being done, and the context of new products is a new one, and it hasn't been done there because usually these surveys are contracted out in five-year increments. The assessment plans are laid out fairly well in advance, and the capacity of the survey team to move quickly when a new product is introduced is slow. I mean, it's there, but it's slow and expensive.

Now, if you had asked me is it worth it to make the expense of putting a piggyback assessment on a standardized assessment in order to learn something of value for the public's health, I'd say in many cases we're going to find that it's worth the cost. But that hasn't been done yet. Not to my knowledge.

DR. BILKER: Are any of the databases that we're talking about capable of doing this? Making this assessment?

DR. ANTHONY: In the existing data, you have a trace for each individual of the age of onset of each

drug, and you also, for people who've used and started to use in the past 24 months or so, you have month of first use. So, you can actually get some pretty fine-grained, temporal sequences for each individual, and that would allow you to study these variations that you're pointing toward.

DR. BILKER: Okay. Great.

DR. KIRSCH: Did you have a second question?

DR. BILKER: Yes. Just one point I wanted to make about the Trend Approach, in looking at the trends over time. It might be very important early on after introduction of the drug to consider nonlinear effects. You're looking at linear effects, but there might be bumps as people figure out how to get the drug out. You'll see bumps in the road. So, it'll be important not to just look at linear effects.

DR. KIRSCH: Thank you.

Dr. Wolfe?

DR. WOLFE: This is for my gray-haired colleague, Dr. Anthony, which was I'd just like to hear a little bit more about your interesting concept of processed phenotypes both in terms of how that could be

incorporated into post-approval surveillance or even arguably into pre-approval looks. I mean, we obviously are using amongst others as subjects for studies people who are beyond that, who are clearly addicted or at the other end of the spectrum who are new, but here's the halfway, and it would seem that this is a sensitive group to be able to assess whether or not X is going to more rapidly move them towards the other end of the spectrum.

Could you just comment on that, please?

DR. ANTHONY: Thanks for the opportunity. So, let's think about the patient who's given one of the opioids that has a relatively high side effect profile for a dysphoric response. So, for pharmacokinetic reasons or other reasons is generating dysphoria.

In that patient for that product, you wouldn't expect more than one pill or so to disappear from the dispensed container. And by doing a pill count study, you might find a population that's very low susceptible to the repeated use of the drug that would lead to a dependent syndrome or subsequent problems. And then you've got people who are given prescriptions say for

dental surgery, maybe a run for 14 days or something, but after 2 days, the pain has subsided and the rest of the product sits in the medicine cabinet. Those, again, are going to be individuals who you'd suspect to be less likely to develop dependence.

Now, what that leads me to then is to suggest that very early monitoring of the dispensed prescriptions to do pill count studies and to see how often people are ramping them up, whether they ramp them up more quickly for an established product versus a new product, that's the kind of thing that I don't think has been done, but could be done. Now, maybe we'll learn from industry that it has been done, but I haven't seen the published studies. But those are the very early steps that you'd think that are leading toward this outcome of dependence that would give us some early clues about what might happen next.

And then time from the first use of the drug to the second use of the drug is not routinely assessed in any of these studies, but it would seem to me that that interval is a very informative interval with respect to the likelihood that someone's going to become

a repetitive user.

DR. WOLFE: Thank you.

DR. KIRSCH: Okay. We don't have any more people who want to ask questions, so, we're going to go on to the presentation by the Sponsor.

MS. BHATT: Dr. Walsh. I'm sorry.

DR. KIRSCH: I'm sorry. Dr. Walsh?

DR. WALSH: Thank you. Yes, actually my question in part, I have two questions, but it falls on from what Dr. Wolfe was just asking about. It seems like we're being asked to be creative in thinking about what needs to be captured in advance, but we're asking a question that hasn't been answered before: How do we detect a signal that's a change either historically or to some kind of comparator? And my questions are directed to Dr. Anthony. I was intrigued by your creativity, and in the processed phenotype, thinking about intent.

You said that you were asking about what have you done and then what do you intend to do? And we have heard from people about changes over time that may take place, where people either determine that they can

compensate for the deterrent properties and you would see an increase in use or alternatively, they may decide that it really isn't worth the time and effort, and then it really does have abuse-deterrent properties because it's not popular among the abusers. And I'm wondering, trying to get at the questions of why, what can we learn about the motives between first and second use and strategies for misuse, what can we incorporate into these kinds of studies to ask the questions about why and actually get valid information about that that could help us for future drug design questions.

DR. ANTHONY: Thanks for the question, but I think there I might have been misunderstood because for reasons you probably know, I don't usually ask people why they do things because I don't usually believe the answer.

DR. WALSH: Well, that's why I'm asking because I think it's important to know why here because there's a lot to be learned from it.

DR. ANTHONY: Yes.

DR. WALSH: So, how do we construct that to--

DR. ANTHONY: No, I think it's a great

question, but this isn't the guy to answer that question because I don't study things like that, but there are people who do in the social psychology realm, ethnography, anthropology, and so on.

DR. WALSH: Well, I mean, the question is not the existential why, it's really why with this medication, why would you continue to use the original product of OxyContin and why did you not determine that you would use it a second time? What were the barriers?

DR. ANTHONY: You're asking great questions, but you're looking at a large sample, shallow, quantitative epidemiologist. And you need someone who has a little bit more depth in terms of what's going to be probed into the answer to that question. And there may be someone in the room, but it's not going to be me.

DR. WALSH: Well, let me ask you the second question because I think that this one you probably have thought about. So, it wasn't until, I think, the last presentation from Dr. Keeton that someone raised the fact that we really need to be thinking about the relative risk or abuse, misuse versus exposure, and one measure of exposure is sales, and it's very possible

that as a new product rolls out that is abuse-deterrent that the sales are going to fluctuate, and that's a changing background, and I'm wondering if you could just say a few things about how to control for those changing things.

And then the other thing that I started thinking about was how would sales change? Let's say that something really is successfully abuse-deterrent, if you just in a very simplistic model think that there's two categories of sales, and there's more than that, obviously, but one is for legitimate patients and then one is for the pseudo patients who are getting legitimate prescriptions, but then are misusing it or selling it.

You'd expect that those two pockets of sales would really be differentially affected once it was determined that the drug was abuse-deterrent and had a lower street value, for instance. So, how do you control for those factors in the background as we go forward?

DR. ANTHONY: Okay, so, I think I have to introduce three ideas.

One of them is that with respect to the last point about the heterogeneity and the consumer population, econometricians and economists have great models for that heterogeneity. And whether someone is buying the Volvo for safety considerations or because of its looks or because it used to be from Sweden, I mean, those are human behavioral economic modeling of the type that Dr. Bickel was mentioning is really appropriate there, but I don't think it's ever been applied in the context of do FDA-type regulation of drug products.

Working backward toward the sales, I've always really been a critic of using the sales as a denominator when gauging event outcomes like the number of overdoses and so on because the sales, as you just pointed out, are a manifestation of demand of the drug. Again, what you really require here is a multivariate model, not a simple ablative ratio that is going to destroy information that's contained in the sales and in the event rate values.

So, I think the answer there is a multivariate model where you're modeling sales; at the same time, you're modeling outcomes sometimes with a lag that will

take into account that some of the outcomes are being determined by a product that's been sitting in that medicine cabinet for 6 to 12 months or more, and then finally is getting out into a consumer pool that it otherwise shouldn't get into.

And then back to the exposure question, you know I love to ask people about if they've had a chance to try a drug, and I would think with these new products, knowing transition probabilities from having a chance to try, and you could actually show them a picture of the pill and whether they've actually used, that transition probability is a really important one. one might expect that a product that's favorable, that's protective will have a longer lag time between chance to try and actual use as compared to one that has a reputation on the street as being the greatest thing since sliced bread.

Okay, thanks.

DR. KIRSCH: Okay, so, next, we're going to get to the presentation of the Sponsor.

Both the Food and Drug Administration and the public believe in a transparent process for information

gathering and decision making. To ensure such transparency at the Advisory Committee Meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the Sponsor's non-employee presenters, to advise the Committee of any financial relationship that you may have with the firm at issue, such as consulting fees, travel expenses, honaria, and interest in the sponsor, including equity interests and those based upon the outcome of today's meeting. Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

There's been in a change in the organization of the presentation by Purdue. So, I'll announce each speaker as they come up. The first speaker is Dr. Landau.

Industry Presentation: Purdue

Introduction

DR. LANDAU: Thank you. Good afternoon. I'm Craig Landau, Purdue's chief medical officer. On behalf of our company, I want to thank the Agency and the combined advisory committees for the opportunity to present and share with the group our Epidemiologic Study Program. We believe and hope we'll shed light on whether or not we've been successful and to what degree we've been successful on effecting abuse and it's consequences with the reformulation.

We've used reformulation science to lessen OxyContin's attractiveness to abusers, while retaining the benefits intended for patients. We reformulated OxyContin in such a way that we view it as a risk mitigation tool to deter its abuse. And we certainly recognize the role OxyContin has played. It's a vulnerability in the ease with which it could be crushed and how attractive that feature has made it to abusers. So, we're very happy to be here today to attempt to learn how to do something about that and measure it. The reformulation was approved earlier this year, and we're actually in the midst of transitioning to the new

formulation as we speak.

Following my introduction, we'll provide an overview and sort of a description for our rationale in designing this eight-study program. We'll then move into a presentation of individual studies, a detailed presentation. The Chairman, Dr. Kirsch, has done me a favor by notifying everyone that the agenda, the sequence of the presentations is different from the original agenda, but the slides that have been provided to you are in the correct order. So, following the individual study presentations, we'll conclude by summarizing and offering some closing remarks.

Before the scientific presentations begin, I'll speak to four topics: our rationale for reformulating the product, the transition to the new formulation, our thoughts on how formulations intended to deter abuse should be characterized, and our position on label claims for abuse deterrence.

Millions of patients have been treated with OxyContin since it was approved in 1995. And while safe and effective when used appropriately by legitimate patients, we recognize the original formulations

controlled-release delivery system could be easily crushed, easily defeated. Within seconds, an abuser with no more than two spoons or a bottom of a beer bottle could defeat the controlled-release delivery system and convert a controlled-release, twice-daily product to an immediate-release dose form of oxycodone. The result in material could then be swallowed, snorted, or even injected. So, we reformulated the product for the purpose of reducing or addressing this vulnerability and reducing its abuse.

The next few slides provide a visual impression and highlight some of the features between the original formulation and the reformulated medicine. And, as you can see here, the two formulations are similar in appearance, but not identical. The most obvious difference is in the indicia. The original tablet on the top of the slide, displaying an OC indicia, and the reformulated product on the bottom displaying OP.

And, like most strengths of the formulation, including the 40 mg tablet represented here, most of them are slightly larger and slightly thicker than the

original formulation.

But, despite their similar visual appearance, the formulations have very different physical chemical characteristics. The original formulation on the top half of the slide can be converted to a fine powder in a matter of seconds, as I've mentioned. The reformulated tablets require much more effort, much more time, and, in some cases, specific tools and energy to reduce the tablets into smaller particle sizes. We understand from our experience that inadvertent misuse by patients and intentional abuse by abusers often, but not always, starts with attempts to manipulate the tablet.

Of course, the image on top is the original formulation, crushed between two spoons. You can see a final powder. On the bottom half of the slide, a reformulated tablet that contains the same tablet strength after five minutes of vigorous manipulation in a mortar and pestle. And you can see large tablet fragments there.

When mixed with a volume of water-soluble for intravenous injection through a tuberculin or an insulin syringe, the original tablet, when hydrated, is easily

drawn up and easily injected. It's what makes it so very attractive to those who seek to abuse it via the intravenous route. The reformulated tablet, on the other hand, becomes quite viscous, difficult to syringe or draw up into a syringe, if not impossible to draw up and inject using commonly-available syringes, 27 or higher gauge needles.

These are the properties we introduced into the tablet to make them more difficult to manipulate and less attractive to abusers. It was specifically designed to deter crushing, snorting, and intravenous injection. It's bioequivalent to the original formulation, and, therefore, it's considered therapeutically interchangeable for patients. The Agency approved the reformulated product on April 5 of this year, and we're in the midst, as I mentioned a moment ago, of the transition to the reformulation. Our goal is to do this as quickly as possible to reduce confusion, reduce overlap of the two formulations, but to do it not at the expense of patient access. We understand the concept of physical dependence, and want to avoid a condition where a patient would go to a

pharmacy to fill their prescription and not be in a position to receive one. This could become a safety issue. So, with over 1.2 million patients treated annually, this transition is quite significant.

Here on this slide, we see a plot of weekly prescriptions dispensed for OxyContin at retail pharmacies. In the yellow color, we see the original formulation over time starting in June of this year, and in the orange color, the reformulated OxyContin product.

A few things to point out here. We stopped shipping the original formulation on Thursday, August 5, and we began to ship exclusively to wholesalers the reformulated product on Monday, August 9. As of October 1, the only formulation a retail outlet could obtain from a wholesaler was the reformulated product. So, at the wholesaler level, the supply chain was saturated with only reformulation.

For the week ending October 1, 65 percent of all OxyContin prescriptions dispensed were for the reformulation, and, in fact, at the break, I just learned that within the week ending October 8, that number is now 70 percent. By the end of this month, we

expect it to approximate 90 percent, and sometime before or at or about the end of the year, we expect the transition to be nearly complete at the patient level.

So, in order to characterize its potential abuse, we worked with the Agency, Abuse Surveillance, and drug safety experts to develop what we think is a very rational, four-step plan, much like the plan or approach described earlier today included in certain guidance documents and referred to by Dr. Rappaport in his memorandum to the combined advisory committees.

The first step is *in vitro* testing in a laboratory, and where we look to define the physical chemical properties of the formulation and go further to define its failure limits. Now, we've done that, of course, and the data was the subject of discussion at the September 2009 meeting of these combined advisory committees.

Our experiments were designed by external experts in abuse and extraction, and the experiments were designed to reflect methods that abusers currently and could use to defeat a controlled-release delivery system. The large majority of the experiments were done

on the outside through third-party CROs to reduce potential bias. The data were QAed and then interpreted on the outside, as well, by experts.

The results of the studies, for those not familiar, suggest the reformulation to be more difficult to purposefully or inadvertently crush. Certainly more difficult to insufflate if one does to abuse by intravenous injection. That it doesn't dose dump in the presence of alcohol, and that it's inefficient to abuse by smoking.

The second level of testing, pharmacokinetic testing, is fairly straight forward. We looked to determine the bioavailability of the intact tablet and tampered tablets along with relevant controls in the volunteer setting.

Studies on the third level, abuse liability, go one step further, and looked to introduce subjective measures or an evaluation of subjective measures. Again, alongside pharmacokinetics, studying intact and tampered reformulated OxyContin and relevant controls.

So, the *in vitro* data were submitted to the NDA. They were discussed and reviewed by the Agency,

discussed at the Advisory Committee in September of last year. The testing on levels two and three were recently completed and submitted to the division for review. Each of the levels, the first, second, and third level, as mentioned earlier this morning, are informative for sure, but they're insufficient to predict what will happen when a product is introduced in a real-world setting. To do this, post-marketing outcome data are needed, and these studies comprised the fourth level of testing, epidemiologic testing.

Purdue believes all newly-approved opioid products should possess some degree of abuse-deterrent features, whether they be pharmacologic or physical chemical. And all such products should undergo testing on each one of these four axes at the relevant time in their development.

The testing performed to date with the reformulated OxyContin product tells us it’s an incremental improvement over the original formulation with respect to its resistance to manipulation. But new formulations are not a complete solution. We understand that prescription drug abuse is complex, it’s a multi-

factorial problem, and it can't be solved simply by addressing a defect in a single formulation, that is the ease with which OxyContin product could be crushed and its controlled-release delivery system defeated. Or by introducing a new product. Our reformulation will still be abused whether by swallowing intact tablets or after tampering, after an abuser looks to spend the required time and effort to manipulate the tablet.

Nonetheless, transitioning to the reformulation as we did, or as we begun in August, represents an opportunity to make a positive impact, and that's what we're here to do. Understanding the impact of the formulation requires diverse approaches, and that's what this meeting is about.

The transition and the unprecedented challenge of designing the studies we're discussing provides us a unique opportunity. It's an opportunity to research and to measure if and how a change in a formulation can impact a clinical outcome. I don't know that we've had this opportunity before.

We've also learned that no single epidemiologic study can adequately assess the impact a

formulation can make. We're hopeful that the eight studies, the multi-study program we've proposed will give us a lens and help us to understand if and how one can be successful; we or other Sponsors.

We're pursuing the studies to meet a post-marketing requirement issued to Purdue as an approval requirement, and, of course, to learn what impact, if any, a formulation could have on abuse and its consequences. We did not design these studies with the goal of pursuing a label claim, and we're not currently seeking one.

Given the complexities of the studies and the context in which we're discussing them, we feel a conservative approach to both interpretation and communicating the results of the study is warranted. We start with an assumption that within the class or within a given schedule of drug, the abuse liability of all the products should be considered the same or similar. Any claim of reduced abuse liability must be based on substantial, sustained, and consistent effects measured over time in a real-world setting on a number or axes of evaluation. We understand the complexities and the

interrelationships of some of the outcomes we're going to be presenting in a few minutes.

Even if the evidence is deemed sufficient to support a label claim at some point going forward, there were risks to making one. We heard some of the speakers this morning talk about them. For one thing, and members of this panel and previous meeting have surfaced, creating a false sense of security in the minds of prescribers, dispensers, and patients is something we'd look to avoid. It could introduce or cause reduced vigilance. Reduced vigilance could eliminate or at least reduce any of the potential benefits of formulation like our reformulation could introduce, and it could certainly undermine the goals of the class REMS currently under consideration within FDA.

I said more plainly reduced vigilance could worsen the already significant public health crisis we spoke about this morning, that of prescription opioid abuse and prescription drug abuse, something we wish to avoid. If we, in the future, or any sponsor does generate a level of convincing evidence substantial and sustained and consistent across axes, I think at that

point, we would hope that we press pause and a benefit risk assessment be made. We'd want to be as certain as we can that the benefits of introducing language in a product's label offset the risk we talked about in the context of the larger public health.

To help us design and understand the results of the studies we'll be presenting in a moment, we've enlisted the help of outside experts. A couple are here with us today, and you'll from Dr. Richard Dart in a moment. The experts are listed here, Dr. Elizabeth Andrews, Dr. Greg Burkhart, and Dr. Richard Dart, Dr. Ken Rothman, and Dr. Ed Sellers.

In a moment, we'll move forward with the agenda. You'll hear from Dr. Paul Coplan next. He's Purdue's new head of Risk Management in Epidemiology. He's also an adjunct assistant professor at the University of Pennsylvania School of Medicine in the Department of Clinical Biostatistics in Epidemiology.

Paul will provide the overview and the rational for the eight-study program.

Following Paul, five external experts and one internal expert, Dr. Howard Chilcoat, who's new to

Purdue, will go through each of the individual studies in more detail. Prior to joining Purdue, Howard was an associate professor at Johns Hopkins Bloomberg School of Public Health, and was also chief of the epidemiology research branch at the National Institute on Drug Abuse. And when we conclude the study presentations, Paul will come back with some concluding remarks and direct responses to any questions the committee or anyone has on our work.

Thank you.

Overview and Rationale of Study Program

DR. COPLAN: Thank you, Dr. Landau. Good afternoon. Thank you for the opportunity to address this committee. The purpose of this presentation is to provide an overview and rationale for the Epidemiologic Study Program that Purdue plans to conduct to assess the effect of the new formulation on abuse. This program is designed to meet FDA's requirements for post-marketing studies. We very much appreciate the insight of the FDA, members of the Advisory Committee, and other experts to ensure that the studies answer the most important public health questions about the new

formulation, particularly in the light of the limitations of each of the available data sources that we heard about earlier today.

In order to evaluate the effects of a new formulation on the epidemiology of prescription opioid abuse, it is important to first characterize the background epidemiology of prescription opioid abuse and its adverse consequences. For each of the upcoming presentations, we have worked to provide the relevant background epidemiology so that you can evaluate the relevance of the study designs, the study populations, and the outcome measures. This background epidemiology, including baseline data, may also assist in predicting the hypothesized effect of the new formulation.

OxyContin is the extended-release formulation of oxycodone. The extended-release system of the original formulation was easily circumvented by crushing, breaking, or dissolving. And to address an earlier question by Dr. Omoigui, this is crushing the tablet and dissolving it for purpose of snorting or injecting.

A characteristic of oxycodone in general, and

extended-released oxycodone in particular, is the diversity of routes by which it is popularly abused. We get a baseline picture of these routes of abuse from the National Surveillance System of 500 abuse treatment centers around the U.S. In the past 3.5 years, more than 7,000 people who enter treatment in one of the 2 centers of the network reported abusing OxyContin during the intake clinical examination by at least 1 of 4 routes. Snorting was the most common route of abuse, and 34 percent reported abuse by injecting. These numbers don't add up to 100 percent because subjects could endorse more than one route of abuse, as Dr. Paulozzi referred to earlier.

Other frequently-abused opioid drugs have fewer primary routes of abuse. For example, people primarily abuse hydrocodone via the oral route and abuse morphine through injecting, as we'll see in a later presentation by Ms. Cassidy.

Oxycodone's diversity of route of abuse may have increased its popularity among people who initiate abuse via the oral route and who progress to more frequent abuse via injecting and snorting.

This pattern is reflected in data from a study of people abusing OxyContin in Kentucky. Located in the Appalachian region that has one of the highest rates of death from opioid overdoses in the U.S. It looks at people entering a treatment program of an average of 19.7 months of abusing the drug. The left bar shows the initial route of administration when they started abusing OxyContin and is based on the medical chart information.

The right bar shows the stated routes of administration upon admission to the treatment center. There were substantial shifts in the routes of abuse after 19 months of abusing. Snorting increased from 16 percent to 58 percent and injecting increased from 1 percent when initiating abuse to 21 percent upon treatment admission. These data provide one example of how routes of abuse can change as the stages of abuse progress and suggest the likely benefits the reformulation may provide.

For legitimate users, the hypothesized benefit is to provide bioequivalent delivery of oxycodone to treat moderate to severe pain while reducing the

inadvertent areas in usage that the patients and nursing staff sometimes commit through breaking, crushing, or chewing of OxyContin, which was previously referred to by the FDA definitions as misuse. To date, 155 cases of OxyContin overdose associated with such areas have been reported to the Purdue Case Report Database.

For abusers of OxyContin, the hypothesized benefits if the physical chemical properties of the reformulation impede tampering are reduction in abuse through breaking, crushing, or chewing due to the tablet's hardness. Injecting will be reduced due to the hydro-gelling of the tablet when dissolved in water, as Dr. Landau mentioned earlier, snorting will reduced due to properties of the new formulation tablet that, when crushed, they crumble into large chunks rather than a fine powder created by crushing the old formulation, and the large chunks form a gel in the nasal passages. FDA is requiring measurable endpoints for the epidemiology studies. The hypothesized benefits need to be mapped to these endpoints.

In FDA's background document for this meeting, FDA stated future studies need to address abuse and

misuse and its consequences, overdose, addiction, and death. To measure the impact on abuse and misuse, the potential impact of the new formulation can be studied by assisting changes in the prevalence of abuse, demand for purposes of abuse, and abuse via routes of administration that require tampering.

It is possible that reducing abuse via routes that require tampering may have a downstream benefit of reducing the clinical outcomes of abuse, including overdose, addiction, and death. These are what FDA has referred to as the consequences of abuse. We have been tasked with designing epidemiology studies that will measure the effects of the new formulation.

Because of the multifaceted nature of the prescription opioid abuse problem in the overall community, no single study could assess all the aspects of the problem, such as the subpopulations affected, the influence of routes of administration, and the stages of addiction that we heard in the discussion by Dr. Anthony earlier. Each of the studies have specific strengths and limitations relating in part to the strengths and limitations of available data sources. As a result, we

engaged a panel of experts to help us design multiple studies to measure the different aspects of the problem. based on the input, we've developed a program of studies designed to comprehensively measure the effects of the new formation. The individual studies will provide collaborating evidence of the real-world effects across studies and multiple data sources. Taken together, the totality of the program is designed to leverage the strengths and address the limitations of the individual studies.

The key questions that we will be seeking to address in these eight studies will be based on these design principles. The first question is, and this could be phrased as a question or a hypothesis, is: Will the methods for tampering and extraction become widespread? We know that certain routes of abuse will be developed, but if they require too much effort and are too burdensome, they're unlikely to become widespread.

Is the reduction in abuse via routes that require tampering? Is there a reduction in abuse in the community? Is the reduction in demand for purposes of

abuse? And, lastly, and most importantly, is there a reduction in clinical endpoints, including in specific subpopulations of pain patients, the general population, and the people entering treatment for addiction? These questions will then be matched to specific studies to address the questions.

The Internet discussion will be conducted to address the first question. A study of an abuser cohort in Kentucky and surveillance of addiction treatment will be conducted to address the second question. Surveys, such as the NSDUH, and other surveys will be conducted to assess the third question. Law enforcement in the RADARS System and doctor shopping and Prescription Monitoring Programs will be conducted to assist the fifth question.

And lastly, the Kaiser Overdose Study and the Poison Center Program--the Kaiser Overdose Study will be conducted to assist outcomes in pain patients. To assist outcomes in the general population, the Poison Center Program, and, in addition, the Kaiser Overdose Study will be used. And, lastly, to monitor changes in routes of abuse and types of abuse in people entering

treatment for addiction, we'll be using a study of surveillance of addiction treatment centers.

A table showing the eight studies and the outcomes they're designed to measure would be helpful for summarizing the program. This helps to see that the eight studies cover the outcomes that FDA is requesting to be addressed. I should mention that in produced background document for this meeting, only seven studies were listed. We added an eighth study, a study of law enforcement event in the RADARS System. This study was added because when we were preparing for this meeting, some external experts told us that a study of law enforcement events would be helpful. Since Purdue was already conducting such a study as part of an ongoing risk management activity, we added this to the study program.

The duration of baseline data for each of these studies will be relevant to the ability of the studies to measure changes over time, and we'll be coming back to this slide repeatedly and using it as a structure for organizing each of the eight studies so that the eight studies don't seem like a morass of

diffused studies, but that their purpose in measuring specific outcomes is apparent or hopefully apparent.

The duration of the baseline varies from 6 months for the abuser cohort in Kentucky to 7 to 8 years in the Drug Diversion Study, and the Poison Center Study, in 10 years in the Kaiser Overdose Study. All of the studies already collecting the data needed for validating the effect of the new formulation.

For the Poison Center and Drug Diversion Programs, Purdue has been receiving quarterly reports from the Rocky Mountain Poison Center and will continue to get these in an ongoing fashion, and Dr. Rick Dart will present more on that in a moment.

The Kaiser data is an Electronic Medical Record System that collects data on patients using OxyContin in an ongoing way. So, as we speak, the endpoints for the study are being collected.

The time to see an effect for the new formulation, we estimate, will vary depending on the nature of the endpoint that the study's designed to detect. It'll take six to nine months for studies that measure routes of abuse, according to our best estimate,

one to two years to see an effect for studies that measure changes in usage and demand, and one to two years, probably closer to two years, to see an effect for studies that measure changes in clinical outcomes. The planned analysis must take into account the baseline trend, the pre post changes, and compared to comparator drugs, as was mentioned earlier by the FDA speaker.

The planned analyses will use an interrupted time series approach where baseline trend is identified, a change shortly after the introduction of the new formulation is evaluated, and, secondly, the trend over time after the introduction of the new formulation is evaluated. The changes in trends will be assessed for OxyContin as well as for comparator opioids.

The depiction on this slide is one of the ways in which we hypothesize success will look. A change in the trend for OxyContin, but not for other comparator opioids. It is important to select comparator prescription opioids that can capture background trends in abuse of prescription opioids.

Immediate-release oxycodone provides a close comparison to OxyContin since they share a common active

drug substance and only different extended-release mechanism versus the immediate-release formulation. Hydrocodone combinations are one of the most frequently prescribed and abused types of opioids in the U.S., and, therefore, provides a relevant comparator.

Extended-release opioids, such as extended-release morphine sulfate, excluding naltrexone-containing formulations, and the fentanyl transdermal patch provide a useful comparator since they are indicated for the same indication as OxyContin. In addition, these comparators are also included with class REMS for longer-acting opioids. So, they provide a control for the background effects of the class REMS.

Lastly, methadone will be used as a comparator because in many mortality studies, methadone, at least in the past, did appear as the number one cause of opioid overdose deaths.

As an example of why it is important to measure background trends and comparator opioids, changes in immediate release or I'll call them IR, and extended releases, or ER oxycodone are relevant.

Over the past 10 years, there have been large

shifts in prescribing practices for extended-release oxycodone and immediate-release, single entity oxycodone that must be considered when utilizing immediate-release, single entity oxycodone as a comparator. This data from SDI looking at retail prescriptions shows that there's been a 40 percent rise in the number of prescriptions for extended-release oxycodone from 5.5 million prescriptions in 2000 to 7.7 million prescriptions in 2009.

In the same time period, there's been a 660 percent rise in the number of prescriptions for IR single entity oxycodone from 1.2 million prescriptions in 2000 to 9.2 million prescriptions in 2009. The source of the data is the FDA's Advisory Committee Briefing Document from the last advisory committee of this group.

In selecting a comparator, it is also important to differentiate between immediate-release single entity oxycodone and immediate-release combination oxycodone. Ninety-nine percent of the immediate-release combination of oxycodone prescribed in the U.S. is for oxycodone-acetaminophen combinations.

Data from the DAWN study that the FDA presented to this advisory committee on April 22 show that the risk of emergency department visits for non-medical use using a denominator of 10,000 prescriptions that was obtained from the SDI data show that there's substantially different risk of ED visits for immediate-release single entity oxycodone, which is shown in the violet line and immediate-release oxycodone in combination shown in the green line.

In 2008, the risk of overdose at adverse events was substantially higher for immediate-release single entity oxycodone than for IR oxycodone combination. Forty-five versus thirteen per ten thousand prescriptions respectively. And between 2004 and 2008, the risk of overdose adverse events was 20 percent for ER oxycodone, 62 percent for IR oxycodone combined, and 150 percent for IR oxycodone single entity. It would be important to take these background trends into account when designing studies and interpreting the results. Data systems that do not differentiate whether the cause of overdose or death is due to IR or ER oxycodone could thus mass-effect with

tamper-deterrent formulation.

This overview and rationale provides a context for the presentation of the individual studies. The first study utilizes the existing Electronic Medical Records System of the Kaiser Permanente Health System that records overdoses and poisonings due to opioids. If the new formulation is successful, this study will demonstrate reductions in the instance rate of OxyContin overdoses and poisonings per prescriptions for OxyContin amongst the membership of the Kaiser population. The first study will be presented by Dr. Nancy Perrin, who's a senior investigator at Kaiser Permanente Northwest in Portland, Oregon.

Overdose Rates in OxyContin Patients and Non-Patients at Kaiser Permanente

DR. PERRIN: Good afternoon. I'm Nancy Perrin, a senior investigator at the Center for Health Research at Kaiser Permanente Northwest. My area of expertise is biostatistics and research design.

Prior to coming to the Center, I was professor and director of the Statistical Corps in the School of Nursing at Oregon Health and Science University. I have

no personal financial interests in the outcome of this meeting, and I have been paid by Purdue for my time.

I am leading this study, exploring the rates of adverse events in OxyContin patients and non-patients at Kaiser Permanente. The study is particularly relevant because it focused on clinical outcomes in a broad population. We have 10 years of Electronic Medical Records to establish the trend and adverse events prior to the introduction of the new formulation. The study will provide data on the impact of the new formulation on opioid-related adverse events reported within the Kaiser Permanente System.

We have already gathered data to determine the baseline trend. This is our initial estimate of opioid-related poisonings in Kaiser Permanente Northwest from 1998 to 2009. We identified poisonings and linked those with opioid dispensings in the six months prior to the event.

The graph shows the number of poisonings among people with various dispensings of opioids. OxyContin and extended-release oxycodone are shown in orange, immediate-release oxycodone in pink, and other Schedule

II opioids in yellow.

The trend in the poisonings is increasing over time for all the groups, which increases our power to detect a change with a new formulation. Interestingly, many of the opioid-related poisonings are among patients that did not have a dispensing of any opioid in the six months prior to the adverse event, as shown in the blue line here at the top of the graph. These are likely people who are intentionally misusing opioids.

As Dr. Coplan mentioned, we are continuing to assess adverse events since the introduction of the new formulation. The objective of our study is to assess if the rate of overdose adverse events associated with OxyContin decreases with the new formulation. The population for this study are Kaiser Permanente Health Plan members, both with and without dispensing of opioids. Using a cohort study, we'll examine poisoning and overdose adverse events derived from Electronic Medical Records. We have 10 years of baseline data, and it will take 2 years after the introduction of the new formulation of OxyContin to determine its effect.

Kaiser Permanente, or KP, as we like to call

it, has multiple regions, many of which will be included in our study. The pilot work is being conducted at the KP Northwest, which has over 475,000 members annually and will guide the scale of the full study.

For the full study, we have access to data from over 8 million members across the regions of KP. The regions are linked by the Virtual Data Warehouse, which is a unique data resource that combined comprehensive membership, demographic, in-patient utilization, outpatient utilization, dispensed prescriptions, laboratory tests, and imaging data dating back to 1996 from multiple health plans. It's derived from Electronic Medical Records, not insurance claims.

The KP population and the Virtual Data Warehouse provide us with an opportunity to also examine adverse events among family members of patients dispensed opioids. We will identify family members of individuals with dispensings of opioids and conduct separate analyses for this sub-sample. This is a unique opportunity to examine accidental use and misuse of OxyContin.

As I mentioned, we are studying the trend in

adverse events over time. We plan to compare cohorts with dispensings of different opioids, as Dr. Coplan mentioned, with an interrupted time series approach. The interrupted time series design is an optimal method for conducting naturalistic studies of the effect of system level changes, such as the introduction of the new formulation of OxyContin. This approach compares the trend over time and the rate of adverse events before and after the introduction of the new formulation. As we begin to observe the trend forward, we can test if it follows the same path as the baseline trend or if there has been a significant change in the trend.

Critical to the validity of the study is the proper identification of adverse events in the Electronic Medical Records. Adverse events can be derived from ICD-9 and 10 codes. These events can be classified as poisonings or overdoses. To be sure that we are capturing changes in the use of the ICD codes over time, we are currently conducting chart audits to examine patterns of codes used to document opioid-related adverse events in the KP Northwest System.

Additional audits are being used to validate our algorithms to extract adverse events from the Electronic Medical Records.

The analysis is based on rates of adverse events. We will actually look at multiple rates. The first is the rate of OxyContin-related adverse events for which the numerator is the number of adverse events among patients prescribed OxyContin and the denominator reflects the extent of the use of OxyContin. The rate will be calculated for each time period in the time series and compared to rates of adverse events among patients prescribed other opioids. We will compute comparator rates for OxyContin immediate release and other Schedule II opioids, and we can vary these denominators to capture different subpopulations such as people with new prescriptions of opioids.

Comparing the rates allows us to control for changes in the number of members and prescribing patterns across time. Regression will be used for the statistical analyses. The model we will use yields unbiased estimates of the level and slope of the trend in the adverse events prior to the introduction of the

new formulation to the left of the dotted line here and estimates of the change in the level and slope after the introduction of the new formulation.

The change in level provides an estimate of the immediate effect. The change in slope provides an estimate of the difference in the trends between the two time periods.

The main comparison is between the slope of the trend prior to and post the new formulation. This means that statistical power of the study is a function of the change in slope. Long, stable baseline periods provide greater statistical power to detect changes after the implementation of the new formulation. And rates based on large sample sizes and the same populations over time improve stability. The multiple regions of KP provide very large populations to estimate these trends.

In our pilot work, we have observed in KP Northwest over 580 opioid-related poisonings per year in recent years, and estimate there will be approximately 125 to 150 additional overdose events per year. We have calculated preliminary estimates of power based on the

pilot data for poisonings in KP Northwest.

We are still working on our algorithms to extract overdose events. Approximately 1 percent of patients in KP Northwest with dispensings of OxyContin has a poisoning event. We calculated the number of patients needed to detect various degrees of change from the two years prior to the new formulation to the year after the introduction of the new formulation. Approximately 3,600 patients are needed to detect a 50 percent reduction in the rate of poisonings and with 80 percent power, and approximately 4,800 patients with 90 percent power. These are preliminary, conservative estimates of power as they were based on comparisons of two rates, not the differences in the slope of the trends over time, and they were based on poisonings only.

The main power analysis will be conducted when we conclude our pilot work, and we'll use simulations approaches to determine the sample size needed to detect various changes in slopes. Based on these power estimates, we'll determine which KP regions to include in the main study to assure an ample sample size.

One strength of our design is our ability to statistically compare trends over time for different opioids. Including comparator groups improves the internal validity of our study. Differences in the changes and trends over time between OxyContin and comparator opioids can be tested by incorporating interaction terms into the regression analyses. We might find that there's no change in the trend of adverse events pre and post the introduction of the new formulation for either OxyContin or the comparator opioid, as illustrated here. Or we may see a decline in the rate of adverse events for OxyContin after the new formulation is introduced, but not the comparator opioid, as illustrated on the left.

Alternatively, there could be a decline in the rate of adverse events for OxyContin and an increase in the rate of adverse events for other opioids. The study I have described today has its strengths and limitations. The limitations of the design include the fact that not everyone fills their prescriptions at KP. However, we do know from previous work that less than 10 percent of prescriptions are filled outside of the KP

System. We may not always be able to identify the opioid uniquely associated with an adverse event since people can be prescribed more than one type of opioid, especially to manage pain within the observation window. The study does have a limited socioeconomic profile as it is conducted in an insured population.

The strengths of the study include the ability to incorporate a comparator time series of other opioids, improving the internal validity of the research. We have a 10-year baseline period from which to detect changes in trends after the new formulation. Use of data derived from Electronic Medical Records and access to geographically diverse regions of KP through the Virtual Data Warehouse are additional strengths of the study.

Thank you.

DR. COPLAN: Thank you, Dr. Perrin.

Our next study, the second study, utilizes the existing network of poison centers in the U.S. if the new formulation is successful, this study will demonstrate reductions in the number of OxyContin exposures reported to poison centers over time. This

study will also assess whether the number of deaths from OxyContin reported to poison centers declines as a ratio of the number of reported exposures.

The presenter for this is Professor Rick Dart.

Exposures Reported to Poison Centers

DR. DART: Good afternoon, and thanks for the opportunity to present to the committee and describe how RADARS can be used to assess the new formulation of OxyContin.

First, my disclaimer. I have no personal financial interest in the outcomes of this meeting, however, my travel expenses only were paid for by Purdue for this trip.

I'd like to start with an overview of the RADARS system. The idea here, of course, is we're trying to understand prescription medication abuse and misuse, and, as several speakers have said today, you need to look at it from multiple perspectives because these people rarely present themselves. So, the principle behind RADARS is to do exactly that, is to create a mosaic by looking at prescription medication abuse from several different perspectives. We currently

have six different programs, and in response to one of the comments made this morning, we actually have just created the methodology and tested it to look at street price of prescription opioids, as well, and we'll be adding that program to the RADARS System.

Purdue and most of the manufacturers of opioids use RADARS for their post-marketing commitments and to perform risk management. Specifically for the evaluation of OxyContin though, we're focusing on three programs, and I'm going to talk about two of those today. The first two you see here, which is the criminal justice system through drug diversion and acute events through the poison center.

First, the poison centers. The U.S. is very fortunate, at least I think so, in that we have a system of 60 poison centers across the country that cover every part of the United States, and you can reach them through a single toll-free number, the poison help number, and that leads the caller to initial triage and care advice for their poisoning or their exposure I should say because not all of these are true poisonings. That information, they're helped by a health care

professional, either a nurse of a pharmacist, and that information is entered into a single database from all poison centers. We all use the same fields, and that software has certain data-checking elements to it to make sure we don't enter pregnant males and that type of issue.

Eventually, the patient receives a disposition, they're followed throughout their hospital course by the poison center by telephone, and that leads to reporting on QA and QC. Now, 49 of these 60 poison centers in the United States currently participate in the RADARS System, and if you take their coverage areas, their jurisdictions, if you will, that's 240 million or almost 85 percent of the U.S. population.

One nice thing about poison centers is you really get 100 percent reporting rate every quarter because we can bug them until they do it.

Now, an exposure is defined as an individual taking a drug leading to a call to the poison center, some type of event. Often, there are medical symptoms and signs. Sometimes it is I took an extra dose of medication. Will that lead to an adverse event? For

just the opioids and RADARS' participating poison centers, there were over 42,000 exposures reported in 2009.

So, we have quite a bit of baseline data on these medications. This shows the reported intentional exposures using the denominator of population. We also can use the denominator of individuals filling a prescription for the drug, but for simplicity's sake, I'm showing this as the population denominator.

You can see in the purple line, which is immediate-release oxycodone, that there has been a relentless increase in the amount of just a single entity immediate-release oxycodone over the past seven years. The orange line is OxyContin. OxyContin has been more stable, but has a slight increase in 2008 and 2009. the yellow line is generic extended-release oxycodone, which was introduced in 2004, and has subsequently been largely withdrawn from the market. So, it came, was detected by the Poison Center Program, but then has gone back down as the drug was decreased.

If we focus just on OxyContin in this slide, we have the Poison Center data just for OxyContin with

the rate of intentional exposures again. The orange line is the combination actually of OxyContin and the ER oxycodone. The light blue lines are the 95 percent confidence intervals around that number, and then, as you'll see, and these data, I should point out, go through June of 2010.

So, in RADARS, we report out our data three months after the close of each quarter. So, we have data through June. That's all real data up to that dotted line. And then after the dotted line are the potential effects of the introduction of a new formulation of OxyContin. And, as you can see, the hypothesis would be that it could continue unchanged. In theory, it could even increase, but, for some reason, the new formulation was more attractive and used more. Or it could decrease, as shown by the orange triangles.

We're also going to look at the case fatality rate for OxyContin. This slide is just a sample to compare OxyContin to methadone. Methadone was chosen because it has the highest case fatality rate in the RADARS' Poison Center Program. I've broken the ages into greater than 12 and less than 12-years-of-age, but

we get the patient's age in each case. So, we can analyze this by any age group that you would like.

For methadone, if you take the younger patients, you can see that there are still some deaths, but over the period of 2003 to 2009, there were only 7, although, in my world, 7 is a lot. And then as people get older, you can see the rate goes up to 241 deaths. So, really 1.5 percent of cases coming to a poison center involving methadone end up as a fatality.

For OxyContin, the rates are lower. I'd say there's relatively high, but lower than methadone. For greater than 12, it was .58 percent.

If we plot the trends of these over the years, this shows methadone, fentanyl, OxyContin, and hydrocodone. You can see that fentanyl and methadone group in the top two lines and OxyContin and hydrocodone in the bottom two lines. And the baseline data here is relatively stable, which will help us see a difference if one occurs after the introduction of OxyContin.

To summarize that study, what we'll be looking at will the incidence rate, the first slides I showed, change after the introduction of the new formulation,

and will the case fatality rate change after the introduction of the new OxyContin?

These calls come from the general population. In fact, all poison centers have to solicit calls from the entire population of their service area. It's an observational time series. And the primary outcome will be the case fatality rate, but also the incidence rate, as I mentioned. We have seven years of baseline data, and we think that we will see an effect in six to nine months if there is an effect.

I mentioned that a case is an intentional exposure, and an incidence rate will be calculated simply by taking the cases per quarter for a specific medication and dividing it by the population that was actually covered by the poison centers covering that. That's the 85 percent I was describing earlier.

Case fatality rate is a measure of toxicity, and this is exposures resulting in death divided by the total exposures. The idea is that a change in toxicity of OxyContin could result in a decreased case fatality rate. We can use any opioid comparator that you would like because we collect this information on all of the

opioid medications.

For our analytic approach, the case fatality rate is an interrupted time series. We have to realize that event rates are relatively low, and, so, the data will be analyzed using a Poisson distribution.

The time series data tend to be auto correlated. So, data will be modeled to allow the current inferences. Separate trend lines will be fit before and after the formulation change. All of this is accommodated by using a generalized linear mixed model.

The main limitation to poison center data is that calling a poison center is not mandatory. It's a voluntary act by someone or their friends or family who feel a need after an exposure to call the poison center. However, it's a large system, and it seems unlikely that systematic changes will occur across all 49 centers simultaneously, and our long track record of baseline data will help us show that.

The main strength is that it has large national coverage of the general population, and we have consistent data collection. All centers use the same data fields, as I mentioned, but RADARS has a specific

change unique to RADARS.

If you think about NPDS, the National Poison Data System of the AAPCC, American Association of Poison Control Centers, all these centers participate in both systems. In fact, the data feed for RADARS is identical to NPDS. The difference is that we collect more fields, and, in particular, we collect what's called the case notes for each case. These are notes that the specialist fills out during the case. We use that information to check fields like product coding and route of administration to make sure that that data is accurate and internally valid.

As I mentioned, the data are available within three months of the close of each quarter, and another advantage that's my particular favorite is that cases involving children can be analyzed separately to see if there's any unintended effects of the introduction.

DR. COPLAN: Thank you.

So, the first two studies addressed the outcomes of overdose and death. The third study, now we'll move on to studies that will address the first three outcomes. The next study will address routes of

abuse and usage and demand. And Ms. Theresa Cassidy from Inflexxion, director of Epidemiology at Inflexxion will present the next study.

Thank you, Theresa.

OxyContin Abuse Among Entrants to Substance Abuse Treatment Programs

MS. CASSIDY: Thank you, Dr. Coplan.

Good afternoon. I am Theresa Cassidy, director of Epidemiology at Inflexxion. Inflexxion is a private public health research and technology company with expertise in substance abuse research. We provide risk management and post-marketing surveillance services to pharmaceutical companies through the NAVIPRO System. I have no personal financial interest in the outcome of this meeting, but I have been paid by Purdue for my time.

We will be conducting the study of abuse of the reformulated OxyContin among adults entering substance abuse treatment programs. Through NAVIPPRO's ASI-MV Connect data, we have over three years of baseline on abuse of OxyContin. This graph shows baseline route of administration data for three drugs

from the ASI-MV Connect Treatment Center Network since 2007. For OxyContin, shown farthest to the left, a variety of routes of administration are reported by adults in treatment, with the most frequently being snorting at 58 percent, followed by oral administration, and then injection.

In contrast, injection is reported most frequently from morphine extended release products, while snorting is a little bit lower in frequency. And the most common route of abuse reported for hydrocodone is oral administration at 92 percent.

Monitoring changes in the route of administration profile will be a key element to evaluating the question of tamper-resistance for the reformulated OxyContin. As observed from the baseline data just shown, specific route of administration profiles exist for different prescription opioid products.

From our data, we have observed that these profiles can be used to characterize a drug's pattern of abuse because the profiles are distinct, they can be differentiated from one product to another, and they

tend to be stable over time.

For example, these baseline data show the different routes of administration reported for OxyContin by adults entering substance abuse treatment are generally consistent and have been stable since 2007.

The objective of our study is to assess both the route and frequency of abuse for the reformulated OxyContin pre and post launch in comparison to other prescription opioids. The study population includes adults entering treatment programs from a defined network of centers using data from ASI-MV Connect. This observational surveillance study will measure recent or past 30-day abuse and specific routes of administration reported by abusers of OxyContin and other opioid products.

The ASI-MV Connect has more than three years of baseline data to use for comparison, and we anticipate being able to observe a change within six to nine months after the full introduction of the reformulated OxyContin.

To provide a little background on our data

source, the ASI-MV Connect collects information in near real-time from a network of about 500 treatment programs across the United States located in 36 states. The data are collected using a computerized interview, which is a standardized and validated instrument required during clinical intake to treatment. Individuals identified drugs that they've abused through pictures, drug names, and street names, and the data are self-reported and identified so that they are HIPAA-compliant.

This study will use statistical modeling approaches that apply regression analysis to assess both the frequency of abuse and the routes of administration over time. We will compare the difference in the proportion of patients reporting past 30 day abuse of OxyContin pre and post reformulation. We will also compare the difference in the continued rate of abuse by measuring the number of days that a patient has reported abuse within the past 30 days prior to treatment.

The modeling approach will take into consideration adjustment for factors such as prescription volume and geographic location. For route of administration, we will compare the differences in

the proportion of patients reporting abuse through different routes with specific breakdowns for the oral category that includes swallowing whole, chewing, and other oral routes of administration.

One limitation to the study is that the sample is now representative of all those entering substance abuse treatment nationally, but rather are collected from the 500 centers located in 36 different states. Also, the ASI-MV Connect Network does not necessarily collect data from individuals who do not seek treatment.

The study does, however, exhibit strengths, and these include the use of consistent measurements over time that allow for reliable detection of differences in the route of administration profile for the reformulated OxyContin, and this among a sentinel population that is at high risk of abuse for prescription opioids.

Additionally, the online data collection methodology that we use allows for timely analysis and for prospective outcome monitoring with a high level of specificity.

DR. COPLAN: Thank you, Ms. Cassidy.

The next study, we'll use surveys, in particular, the NSDUH survey, and we'll be looking at routes of abuse, usage and demand, and addiction in the study, and it'll be presented by Dr. Howard Chilcoat, director of Epidemiology at Purdue.

Using Surveys to Assess the Impact of a New Formulation of OxyContin

DR. CHILCOAT: Thank you, Dr. Coplan.

Data from national surveys on drug use will be a valuable tool to help us understand the impact of the reformulation of OxyContin on non-medical use in the U.S. population. One survey that you've seen presented earlier in several presentations is the National Survey on Drug Use and Health, or NSDUH, which is often used to examine trends in drug use. We can use NSDUH data to provide baseline data on non-medical OxyContin use.

As shown on this slide, these NSDUH data show the percentage of the U.S. population that used OxyContin non-medically from 2004 to 2009. There's been a slight increase in non-medical use of OxyContin during this period. In particular, the recently-released 2009 data show an uptick to 0.7 percent from levels of around

.5 percent from 2004 to 2006. We'll have to wait for the 2010 data become available to see if the increase in 2009 represents a trend. Then we will look to see what happens to this trend after the introduction of the reformulation.

Our plan is to use data from NSDUH and three other national cross-sectional surveys to compare trends in the prevalence of non-medical use of OxyContin and other prescription opioids. These surveys are measured in a systematic way year by year and cover the vast majority of the population. Because these surveys have assessed non-medical OxyContin use for up to six years prior to the introduction of the reformulation, they provide a useful baseline.

However, due to the time needed to collect the data each year and prepare datasets for public use, it will be at least two years before we see an effect from these studies.

We plan to use data from four different national surveys, as outlined on this slide. These surveys include the NSDUH, as well as the Monitoring the Future Study, Partnership Attitude Tracking Survey, and

the RADAR System College Survey.

As you can see on this table, the studies have different age ranges and sample sizes. The MTF, PATS, and RADARS enroll school-based samples ranging from middle school to college. In the interest of time today, I will focus on our strategy for using NSDUH data because it covers the broadest scope of the U.S. population and has more extensive measures of OxyContin than other surveys.

The NSDUH started in 1971, and has been conducted annually since 1990 by the Substance Abuse and Mental Health Services Administration. It interviews over 60,000 respondents each year, and the survey methods have not changed since 2002, allowing trend comparisons for years since then. The NSDUH has collected data specific to OxyContin since 2004.

Our strategy for using NSDUH data will be to examine trends for several outcomes of non-medical use of OxyContin and other prescription opioids. We will look at the period prevalence, frequency of use, recency of use, and the presence of DSM-IV dependence diagnosis. We will depict prevalence used trends graphically and

then we will compare trends across the time periods before and after the introduction of the reformulation.

The most commonly used measure in surveys such as NSDUH is period prevalence, which captures the percentage of the U.S. population who use a drug in a specified timeframe such as in the year prior to survey, as I showed earlier.

The orange line represents the population of past year OxyContin users. However, it combines all users from experimenters who have used the drug just once orally all the way to daily injectors who are addicted. And as Dr. Coplan described earlier, it's possible that the reformulation of OxyContin might have varying effects on abuse and different populations, depending on route of administration and stage of use.

To get a better understanding of the different populations this orange line represents, we have divided OxyContin users by frequency of use. Frequency of use is associated with route of administration and stage of drug use, and we expect that the formulation would have a greater impact on more versus less-frequent users.

The blue line shows the trends for low

frequency use, defined here as less than once a month. And the yellow line shows a trend for high frequency users, those who use monthly or more on average. By disaggregating by frequency of use, we begin to see different trends emerge. Existing data through 2008 indicates that the overall increase in the overall prevalence is accounted for by increases in frequent use, whereas low frequency uses remain relatively stable.

We'll extend this analysis by using future NSDUH data. We will start by comparing trends in any OxyContin use before and after the introduction of the reformulation. The dotted lines on the right-hand side of the slide represent hypothesized changes following the introduction of the reformulation. We'll examine whether there's an overall decrease in non-medical use, and then explore whether the changes are specific to frequent users or occasional users.

I've highlighted frequency of use in the presentation, but we will look at several other indicators of abuse. We will explore whether the impact of the reformulation is greater for persistent versus

recent onset use, as well as by history of prior other drugs. We will see whether the occurrence of DSM-IV dependence changes among those using OxyContin non-medically, and we can even possibly explore whether there's a switch to heroin once the reformulation is available by assessing the occurrence of heroin use among former OxyContin users.

In this way, we can gain greater insight into the pathways through which the reformulation might affect abuse at the level of the population. We understand it is possible that the changes that we observe in OxyContin use after the introduction of the reformulation could be caused by overall trends in non-medical use of prescription opioids that are unrelated to OxyContin. It will be necessary for us to do a parallel set of analyses for all prescription opioids to see if the changes are specific to OxyContin.

As we looked at all the national surveys, we noted that while they have a number of strengths that will assist our works, they also have some limitations.

The limitations of large-scale survey data are well-known. It's been discussed today. Retrospective

self reports are subject to underreporting and under reliability.

However, because these surveys use consistent methods each year, it is unlikely that the changes in trends would be due to differential underreporting over time. With the exception of the RADARS College Survey, the surveys did not measure different routes of administration of OxyContin. However, the available data will allow us to look at frequency of use, as well as other indicators of abuse that might be related to route of administration.

In addition, the surveys did not capture certain populations. For instance, it's been discussed earlier the NSDUH doesn't include those in institutional settings. The school-based surveys don't include students who have dropped out or not attending school. But we don't expect this limitation to affect trends.

Among strengths, these surveys capture patterns of non-medical use in the general population rather than specialized samples, such as those entering treatment. Only about 10 percent of those with opioid dependence ever receive treatment, and, so, we need to

go beyond this group.

The surveys also ask OxyContin-specific questions, which will be vital for our work. It will give us a well-established baseline upon which to compare trends following the introduction of the reformulation. So, until the data from the new formulation come in, we will analyze existing data to better understand how OxyContin and other opioids are used and develop a baseline against which we will compare findings found in the introduction of the reformulation.

So, although it may take awhile, we believe that the data from national surveys will significantly contribute to our understanding of the impact of a formulation designed to make it more difficult to manipulate OxyContin for the purpose of abuse.

Thank you.

DR. COPLAN: Thank you, Dr. Chilcoat. The next study of law enforcement in the RADARS System, it'll be measuring demand for purposes of abuse, and will be presented by Professor Rick Dart.

Law Enforcement Events in the Drug Diversion Program of

RADARS System

DR. DART: Thank you.

The Drug Diversion System in RADARS is a network of about 300 reporters in 50 states that are either in local law enforcement agencies or in some statewide taskforces that report each quarter about the new cases in their area. So, for new case of diversion, the investigator in that area submits a report using a standard report tool into the database, and that's reported out quarterly in terms of incidence rates for that jurisdictional area.

This program is run by the Center for Drug and Alcohol Studies from the University of Delaware, and it currently covers 658 of the 3-digit zip codes in the country, and there are about 960 or 70 of those. It's about 68 percent of the total population, and for the first 8 years, reported over 77,000 events of diversion.

So, this system has a lot of baseline data, as well. This is the same structure as my previous slide which shows the incidence rate on the right per 100,000 population. The purple line is immediate-release oxycodone, the orange line is OxyContin, and the yellow

is the generic extended-release form of oxycodone.

As you can see, it's a very similar trend in both of the RADARS' programs. We've experienced dramatic increases in immediate-release oxycodone over the last few years, and some increase in OxyContin, as well. These in general have been quite related to the number of people filling a prescription for those medications.

What we will study here is the question will diversion of OxyContin and comparators change after the introduction of the new formulation? The population is unique; it's drug dealers and diverters. It's standardized surveillance from a long-established network of centers, and the outcome really is the number of new drug diversion events in that jurisdiction each quarter. We have eight years of baseline data, and we think we will see an effect in the system in six to nine months.

Just to clarify a little bit about what a case is, specifically, it involves a new written report investigated during the prior three months. This has to be documented in the legal records and their arrest

records. And this is based on attempt or actual diversion based on legal prescriptions, physician or pharmacy reports of prescriptions, empty prescription bottles, or actual drugs seized, such as in a buy.

The incidence rate for drug diversion events is just simply the number of cases reported divided by the population for that jurisdiction, and we add all those together to get the total. This system also collects street price. I hadn't planned on including that in the presentation, but if there's questions, I can answer them during the Q and A.

For our analytical approach, this is very similar to what I presented for poison centers, an interrupted time series with low rates. We're going to have to model that to allow correct inferences and we're going to include covariates, such as local prescription availability and geographic location.

This shows a slide of reported diversion events from 2004. The data through mid-2010 is actual data from the system, showing OxyContin, and it's 95 percent confidence intervals. The orange lines to the right of the dotted line labeled "New Formulation" are

the potential outcomes here. And, as I described before, we'll be looking for either no change or a substantial decrease in the diversion of OxyContin.

As I mentioned, we can also look for a change in the price on the street of OxyContin. If demand decreases, we should see a decrease in the price.

The primary limitation of law enforcement data is potential for reporting bias, and intensity of enforcement focus can vary somewhat. These professionals are responding to the needs of their community, and sometimes prescription drug abuse is primary, and sometimes it isn't. However, you can see from the baseline that we have long-term data over eight years, and we don't think that that will change substantially, with over 300 investigators simultaneously.

Another point I want to make is that the data don't represent pain patients, and a previous speaker mentioned this, but it's really important to understand that we may think they're pain patients, but, in reality, most of these are not pain patients. They're dealers who are making a profit, entrepreneurs, if you

will, trying to make a profit.

The strength of our RADARS System is that we create a mosaic by reporting from multiple stakeholders and perspectives on the same phenomenon, and a positive strength of the Drug Diversion System is that the product is available usually for accurate identification because they seized it in the arrest. And, as with our other systems, the data available within three months of the close.

Doctor Shopping for OxyContin as Measured by Prescription Monitoring Programs

DR. COPLAN: The next study is a measure of Doctor Shopping Prescription Monitoring Programs and this is a measure of usage and demand.

Doctor shopping occurs when individuals visit numerous physicians to obtain multiple prescriptions. The excess drug can be abused or diverted. Prescription Monitoring Programs were developed to track abuse and diversion of prescription drugs at a state level. Thirty-four states have operational PMPs. Delaware has recently been added. The slide by Dr. Dormitzer was correct. To date, two state PMPs have agreed to share

data for analyses, Ohio and Connecticut. We've also been in discussions with other PMPs, such as Massachusetts, Maine, North Carolina, and Utah to participate in sharing data for an analysis.

The objective of the study is to assess whether the number of people who doctor shop for OxyContin decreases with the new formulation. The study population of people receiving opioid prescriptions in the states covered by the PMPs. The design is an open cohort study comparing changes in doctor shopping for OxyContin and compared to opioids using data collected by the PMPs. And the outcome measure for the studies, the number of individuals who doctor shop.

The baseline data is approximately two to three years. It has been collected in the existing PMPs, and we predict a time to see an effect of approximately 12 months.

There are two phases of the study. The first phase of the study will develop and validate an algorithm to measure doctor shopping by combining the data elements in the PMP databases to measure doctor shopping. And the second phase in the analysis will

analyze changes in rates of doctor shopping using the identified data.

The data elements that are available to detect doctor shopping in the database are the number of prescribers per time and the number of pharmacies per time. These have been used in the published literature, for example, by Dr. Ned Katz, to look at whether there's a change in the rate of measures of doctor shopping over time.

Other researchers, primarily in Europe, in France, have used overlapping dispensing periods of repeated prescriptions or fills for opioids as a measure of doctor shopping.

The measure of quantity and dose of prescriptions can sometimes be indicative of a doctor shopping. In addition, cash payments can be indicative because people who are doctor shopping tend not to use insurance since the insurance can pick up the multiple prescriptions. In addition, if the patient is receiving benzodiazepine prescriptions, that also can be indicative and would also be captured by the PMP. We will calculate a rate of doctor shopping, which is the

number of doctor shoppers divided by either the number of prescriptions or the Census population in that area.

One limitation of the study is that there is no gold standard to measure doctor shopping. This could lead to a high false positive rate of doctor shoppers. However, the false positive rate should be relatively consistent over time when measuring trends.

And also, this could be addressed by varying the sensitivity and specificity of the doctor shopping measures, as was indicated by Dr. Paulozzi in his presentation and seeing how that changes the trends.

In addition, the study is somewhat limited by the geographic coverage of the PMPs who participate in the study. One strength of the study is that it provides an assessment of the desirability of OxyContin for purposes of abuse, and it complements a study of substance abuse treatment centers because the PMP study population is not limited to those who seek treatment.

The next study will look at Internet discussions, and this is a measure of routes of abuse and usage and demand.

Internet Discussion About Reformulated OxyContin Abuse

MS. CASSIDY: Thank you.

This study also uses data from the NAVIPPRO System to study Internet discussion about abuse of the reformulated OxyContin.

A number of Web Sites exist that support active discussion forums solely devoted to recreational illicit drug use. Drug users who frequent these Web Sites freely offer their ideas and beliefs, discuss trends and preferences, and they offer information and warnings about prescription medications. Many of them provide suggestions and instructions in the form of recipes for the physical and chemical extraction of active ingredients. We can examine these conversations on Web Sites for a discussion related to a number of different topics, including routes of administration for specific products, product comparisons, pill identification, and methods for obtaining drugs for illicit use.

Monitoring these Internet discussions allows review of unfiltered opinions on various prescription drugs among a sentinel population of abusers. These discussions provide early indications on whether abusers

attempt to tamper with a product for abuse by alternate routes of administration. And, more importantly, these discussions are available for wider dissemination among non-participants who view the information, but do not actively participate in these discussions.

The objective of this study is to assess differences in the pattern of Internet discussion among drug abusers regarding the new formulation of OxyContin. The population for this study are drug abusers on the Internet and the study uses an observational surveillance approach. Using NAVIPPRO Internet Monitoring Data from a number of drug discussion Web Sites, we will examine the proportion of discussion related to conversations about tampering, routes of administration, and overall sentiment by drug abusers regarding the new formulation.

This approach is currently being used by a number of companies as part of their FDA post-marketing surveillance requirements. We have been monitoring Internet discussion for the original OxyContin, and have over three years of baseline data. Given the nature of this type of surveillance, the data are available in a

quick timeframe, and we estimate that it would take approximately three to six months after the introduction of the new formulation to determine an effect of whether there is a change among abusers in the nature of their discussion in their interest in abusing this drug.

Although, it is not possible to quantify all of the Internet discussion regarding the new formulation, we are able to gain an understanding of the types and the level of conversation occurring among drug abusers within a stable community of individuals who are on these selected Web Sites. This study is designed to characterize differences in online discussion between the old and the new formulation of OxyContin by quantifying the proportion of posts, threads, and unique authors that contribute to the conversation about the drug.

One example of quantifying the level of discussion is to calculate the proportion of posts pertaining to a particular product over the total number of posts on a selected Web Site. We can use this approach to evaluate the number of individuals that contribute to the conversation and to quantify the level

of discussion for specific topics.

To characterize Internet discussion by topic area, we will obtain and review a random sample of drug-specific posts. The posts are then reviewed and rated by research staff using standardized coding procedures to assess the sentiment of the message, including whether the author endorses, discourages, or has mixed comments about abusing the drug.

For example, if an author would post that they enjoyed getting high from OxyContin, this would be coded as endorsing the product for abuse. But, alternatively, if an individual references being addicted, which is typically referenced in a negative connotation, or warns against using OxyContin, this would coded as discouraging the product for abuse.

To ensure consistency between coders and over time, inter-rater reliability is assessed using blinded co-samples. And these methods are used to code posts by topic area including the routes of administration and recipes for tampering with the drug.

These baseline data shows sentiment in Internet discussion for three categories from a sample

of posts for the original OxyContin and hydrocodone products since 2007. The data indicate that OxyContin, shown here in the orange bars, is more frequently discussed in an endorsing manner among drug abusers online at 38 percent of the sample of posts. In contrast, sentiment towards abuse of hydrocodone products shown here in the blue bars is ambivalent, with an equal percentage of posts endorsing and both discouraging the product.

We have observed some early Internet discussion on the reformulation, and, in general, the early discussion indicates dislike and frustration with the reformulation by abusers. The question was asked here by the committee earlier if we are aware of any information about the street price of the drug, and we have seen some evidence of increases in the street price of the original OxyContin, as shown in this example. We've also seen intention by abusers to switch to other opioid products preferred for abuse.

Like any data source, there are certain limitations to the study of Internet discussion, and the nature and size of the Internet make it impossible to

quantify and report on all discussions specific to the new formulation. In addition, the extent to which these data may relate to increase or decreases in population-based trends of abuse is uncertain. Other factors, such as the availability of a drug in any particular location may also influence what is being abused there, and then subsequently discussed online.

Study of Internet discussions, however, have a number of strengths. Analyses from the Internet discussion can act as a rapid sentinel surveillance system among sentinel population of abusers who are motivated to tamper with the product for abuse. Monitoring these discussions over time allows to detect changes in how, why, who, and sometimes even where diversion in formulation tampering can occur. Another strength is that we have more than three years of baseline data to use as a comparison and that the data collection and analytic procedures that we are using are consistent over time to allow for changing patterns.

DR. COPLAN: Thank you.

The next study is abuser cohort in Kentucky. This study will follow-up individuals over time and will

assess the measures of routes of abuse, demand for reasons of abuse, and also the outcome measure of addiction.

Professor Carl Leukefeld from the University of Kentucky will present.

Changes in Abuse Patterns in a Cohort of People Abusing OxyContin in Rural Kentucky

MR. LEUKEFELD: Thank you.

I'd like to start by saying I have no personal financial interest in the outcome of this meeting. I have been paid by Purdue for my time, and I have no interest in the outcome of the study.

Our research team has been studying drug abuse for prescription drug abuse as well as illegal drug abuse in rural Kentucky for several years. As a result, we have a good understanding of the baseline of OxyContin abuse in this population.

Let me fist give you some background on this region and the cohort, and then I'll discuss the study's objectives and methods.

Research indicates that prescription opioid abuse and dependence is more prevalent in some rural

areas, thus, we believe we have been working with a sentinel population for this type of research.

In addition, government and media reports have pronounced that prescription opioid misuse is at epidemic levels in the Appalachian regions of Kentucky, Virginia, and West Virginia, where it is thought that long and labor-intensive work, such as mining and logging, has helped to create what has been called a pain culture. This supposition is supported by 2004 to 2008 national data.

In our own 2007 study, more than 40 percent of those indicating past 30-day prescription opioid abuse that also injected during their lifetime, and our cohort every OxyContin abuser reported injecting OxyContin, which was surprising, and this is in the same study, same county that we focused our current study on. In contrast, significant and a number of injectors who had said they had Hepatitis C was significantly greater than those who did not inject.

Another study described the routes of administration for prescription opioids. We have previously studied these 101 opioid abusers in Perry

County. What we found was a high rate of snorting behavior across all drugs, and a high rate of injection behavior with OxyContin specifically. With this in mind, I will now move on to the overview of the study we are about to undertake.

The objective of our study is to describe changes in use and abuse patterns of OxyContin following the introduction of the reformulation. We will interview and follow 200 OxyContin abusers to examiner self-reported changes in routes of administration and preparation methods.

Let me say something about Perry County, Kentucky. It has been popularized in the media. There are about 30,000 folks who live there. The main city is Hazard, of about 5,000 people, with a population that is 30 percent below the poverty line, and there are limited economic opportunities there after the coal mining industry collapsed. We're going to collect both qualitative and quantitative data. We'll recruit people who have been abusing OxyContin from a variety of sources. More than half will likely have been participants in an ongoing study of a current study of

prescription opioid abusers in Perry County. We expect baseline enrollment to be completed by early next year. We'll also use qualitative extensive face-to-face interviews with 15 randomly-selected participants about the impact of the new formulation in their own drug use, about the patterns of their drug use, and about what drug use means to their family, friends, as well as others in the community. The follow-up structured interviews will be about three to six months after the baseline to assess any changes.

These interviews will be conducted by a trained interviewer, and will be quite detailed to gain a picture of how these people abuse drugs.

Our structured interviews will assess what you see here across and within individuals, preparation, administration, abuse, opioid abuse. We'll use the addiction severity measures to look at symptoms and look at symptoms of abuse and dependence, rates at which people change their use of OxyContin, other prescription opioids, and other drugs after the reformulation.

Our particular interest will be determining the extent to which OxyContin abusers switched to other

opioids, such as IR oxycodone methadone tablets or heroin. As with any study, this one has certain limitations, and our findings will need to be considered in light of these, including the single geographic area, some limited generalized ability, reliance on self-reports.

Along with these limitations are: the extensive qualitative and quantitative data will provide an opportunity to conduct exploratory data analysis, as well as to apply more complex statistical approaches. We believe we will be able to examine changes in the abuse of other opioids as a sentinel population. Our follow-up with individuals who are abusing OxyContin when the reformulation is introduced provides a way to directly assess changes in abuse behavior.

Finally, this study represents an extraordinarily opportunity for us to examine the abuse of opioids. We can now hypothesize at a reformulation an abused drug might make a measurable impact in drug abuse behaviors which we have not been able to do in our studies for the last 20 years.

Thank you.

DR. COPLAN: Thank you, Professor Leukefeld.

Summary and Conclusions

Taken together, the eight studies are designed to make the most of the existing data sources to piece together a clear picture of changes in patterns of abuse. The mosaic of studies that we've assembled to address FDA's request help to disaggregate the drivers of abuse and its outcomes. We have a particular focus on studies routes of administration to assess the impact of the new formulation, and we've attempted to incorporate wherever possible different geographies and populations. The results will inform us and FDA of the impact, if any, of the reformulation in the real world.

Interpretation of the eight studies will be focused on answering the five key questions that we introduced earlier. There are one or two studies that address each question. Our goal is to describe and estimate effects rather than test formal, statistical hypothesis. We'll be looking for substantial effect that is sustained and consistent across the studies.

The data collection has already begun within most of the data sources, and it's estimated to take

between 6 to 9 months and 24 months to see an effect. These timeframes are our best guess. We will remain diligent in continuing to monitor the effects in case a way to circumvent the new formulation is developed after the two-year horizon, or if additional cases are required for study precision and power, particularly in the Kaiser study.

The estimated time to see an effect can be used to determine a proposed duration of the studies for a post-licensure commitment. It is anticipated within two years we'll be able to see an effect. However, for select data, it make take two years to become available, such as the NSDUH data, two years after the observational period. Therefore, the proposed observational period is for two years to be initiated, and we have initiated data collection beginning in August 2010. However, the duration may be lengthened if event rates are lower than expected to increase study power.

Purdue will submit annual reports to the FDA, and investigators will independently report their results of their studies. The overall interpretation of

the results will consist of an internal assessment by Purdue staff and an independent evaluation by the expert panel that Dr. Landau mentioned in the introduction.

The Epidemiologic Study Program is designed to address the five outcomes of interest using eight studies, and this mosaic of studies will provide an opportunity to address the impact of the new formulation.

In conclusion, the new formulation is expected to reduce injecting, snorting, and smoking routes of administration of OxyContin by impeding the ease of tampering with OxyContin. These are the routes that are associated with more frequent and independent abuse. Multiple studies are required to demonstrate an effect of the new formulation on various populations, stages of abuse, and outcome measures. We've designed eight studies to provide a comprehensive picture of the impact of the new formulation.

If the approach of the tamper-deterrent formulation is demonstrated to be effective for OxyContin, the approach may be generalizable to other prescription opioids. Our goal today is to develop the

best possible studies to address the questions about the potential impact of the new formulation, and we welcome the input of the panel in designing these studies.

Thank you for your attention to this rather long presentation.

DR. KIRSCH: Thank you.

We will now take a 15-minute break. Committee 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 at 3:15.

(Break.)

Clarifying Questions

DR. KIRSCH: All right, we're going to restart the last part of the session for today. And this is a session, if everyone could take their seats, for clarifying questions to the Sponsor. So, if you have a question, raise your hand, and we will recognize you.

Dr. Fletcher?

DR. FLETCHER: Thank you. I'd like to congratulate the Sponsor and also FDA for kind of laying out the various databases and the information about

prior exposure and information about existing and stability of some of the measures that are proposed going forward prospectively to see changes in, but I wondered if particularly the Sponsors the individual speakers could address the issue of effect size in these various databases and changes.

Being a clinician, I'm interested in that, and while FDA's questions don't specifically address effect size, they imply that that's an important aspect of it in our deliberation tomorrow, and I'm wondering, for example, given the baseline levels of data and variability known, what kind of an effect size would be able to be seen in the timeframe of the one to two years for these various programs?

I'm particularly interested for Dr. Perrin from the Kaiser Permanente, and, perhaps, Dr. Cassidy and Inflexxion if they could comment about what size of an effect in their measures could they be able to see a difference in based on the information they have already. Just to put in perspective the question about what's clinically important difference for the group tomorrow. So, if anyone would want to address that.

DR. COPLAN: Okay. We'll present our three outcomes studies looking at the effect size of each of those. Could we have backup slide 45 for the Kaiser Study, please? Forty-five.

And, so, the power calculation for the Kaiser addressed the effect size somewhat. We've tried to avoid setting a mechanistic threshold above which we would call an observed effect a success because we don't really have an evidence base on which to evaluate what would be a priority, what would be a success. So, we've tried to focus more on estimation, and look at the precision to estimate trends or changes.

So, in this slide, to detect a 50 percent reduction in the Kaiser Study that Dr. Perrin showed, we would need 4,800 patients for 90 percent power or 3,600 patients for 80 percent power, which we're easily able to get, especially if we combined Kaiser Northwest with Kaiser in Southern California and Kaiser in Northern California. They're approximately 6,000 to 7,000 patients a year if we combine those 6.6 million roughly from a guess.

Dr. Perrin, do you want to add anything?

DR. PERRIN: (Off microphone.)

DR. COPLAN: Yes, so, to detect an effect size of 75 percent, we would be very well powered. However, below 50 percent, we're really starting to run into an inability to detect effect within one year. So, if it was 40 percent, we probably would be okay with 80 percent power, but below that in one year, we wouldn't be able to detect. If we went out two or three years, then, obviously, we would be getting three times that amount of patients, and power would increase.

Could we have backup slide 54, please? Fifty-four.

So, if we look, another system would be the Poison Control Center, which is another way of measuring outcomes, and, as Professor Dart showed, these are the 95 percent confidence intervals around the poison control reports over time for OxyContin, so, it provides an estimate of the precision. The confidence intervals and fairly tight, so, if we saw a 50 percent reduction or a 30 percent reduction, I think that we'd have adequate power to detect that.

Professor Dart, did you want to add? I think

the power calculation that you did, you had 80 percent power to detect a 24 percent reduction.

Theresa, did you want to address the Inflexxion?

Did you have anything to add? Sure.

DR. DART: I just wanted to mention that I think this question goes both ways because with a high number of events being reported, I think we'll be able to report a change, but whether that's a change that you would recognize as important or the panel or society is one of the issues I have is because we have so many events that if we show a 5 percent decrease, but it's statistically significant, is that really a meaningful change and what that conclusion might be from the advisory committee.

DR. FLETCHER: Yes, I greatly appreciate that. It's not your role to necessarily say what are clinically-important differences. I just wanted the committee, because they're the experts here.

DR. DART: Right.

DR. FLETCHER: To say what the power is to see what kind of a change, and then the deliberation might

be informed tomorrow about what the size of these effects are clinically-valid.

DR. DART: Sounds good.

DR. FLETCHER: So, I completely agree with your conclusion there.

DR. COPLAN: Also, could we have back up slide 65 to address the Inflexxion System? Sixty-five.

So, one of the slides shown by Ms. Cassidy was looking at the baseline data of OxyContin route of administration over time by various rates. We didn't put the Confidence Intervals on this graph because it would be too busy. But they're very small because this is approximately 7,000 patients who are reporting OxyContin abuse. So, again, I think we would have the ability to detect a statistically-significant difference quite easily, but whether that would be clinically-significant would be a different story.

DR. FLETCHER: Thank you very much. I think, to me, that's quite helpful for our discussion tomorrow after we've heard all of the presentations. Thanks.

DR. KIRSCH: Dr. Walsh?

DR. KEETON: My question is for Dr. Landau.

So, I'm just asking for a point of clarification. In the early part of your initial presentation, you said that the company is not seeking any claims, and in addition, on the slide, it says that any claims for abuse liability should require substantial evidence to support the claim. So, is it your position that you are never seeking any claims for this new formulation or is it your hope that maybe these studies will yield the substantial data that are needed to support a claim?

DR. LANDAU: So, we'd be very happy, obviously, if the studies we proposed were able or provided us a look and we're able to detect a significant change that we in the Agency would agree is meaningful. It's our current position, and not that we're not pursuing a claim, if on the other hand the studies bear out and the Agency believes it's in the best interest of the public health to have this type of information in a package insert, we'd certainly be willing to have the discussion. This is unchartered territory for us, and it's not a path we're ready to pursue at this time.

DR. KIRSCH: I'm going to ask the next

question, and it's for Dr. Coplan and Dr. Perrin. You've chosen to use the database from Kaiser, and one of the weaknesses of that database, as was pointed out by Dr. Perrin, is that it's an insured population. Two questions related to that.

There are many organizations now that have Electronic Health Records similar or identical to the one that's used at Kaiser. Why go to their population which is not representative of most of the United States? And, second, what does one do within that system to pick up patients who are cared for primarily in that system, but who go to other institutions when they have an overdose or have a complication from the treatment that's given to them at Kaiser?

DR. PERRIN: I think one of the reasons for the selection of the Kaiser System is because we have 10 years of Electronic Medical Records to establish that baseline. A lot of the newer community health centers that we actually work on with other studies do not have a long enough baseline period with Electronic Medical Records. It's a more recent event for them.

So, then I think to address your second

question, Kaiser does record outside claims. So, if somebody goes to an emergency room that is not Kaiser-run, those are registered into our databases if the health plan is billed. So, we can already see trends in the differences from our initial looks at the data of outside claims that come in, claims of poisonings from outside of the system versus inside of the system. So, that's a key variable that we'll be looking at. If they go outside the system and they ask for Kaiser not to be billed, we will not be able to pick them up.

DR. KIRSCH: Dr. Wolfe?

DR. WOLFE: I have two questions. You asked the second one, except I'll just add a little piece for Dr. Perrin again. Deaths that occur outside the system, someone is found at home or someone goes to an emergency room or whatever, how do you capture those deaths?

DR. PERRIN: We do have death data with codes, Death ICD-10 codes, actually, in our system. So, if their primary care physician was the person who signed the death certificate, they also register that into our--we have an Internal Death Database.

DR. WOLFE: But that, again, assumes it

happens within the system. If they die outside the system, go somewhere other, not necessarily getting billed, they just are found dead at home, go there, how do you capture that?

DR. PERRIN: We only can capture those deaths through the state death records, which we do check regularly. Now, to be honest, the extent to which the cause of death is easily ascertained on those records is going to be difficult.

DR. WOLFE: Right. It’s a problem.

The other question was for Dr. Dart, and has to do with his slide 53, if you could put that up.

My memory is that during the period before the generic prescribing stopped that a significant proportion, 10, 20, 30 percent or more of all prescriptions for oxycodone extended-release were generic, and yet, this slide makes it appear that consistently during this time, the last few dots are probably with almost no prescriptions. That's understandable, but consistently during this time, the rate of intentional exposures per 100,000 population is much less, much lower per 100,000 than with the

OxyContin.

And the question is: Why is that? I mean, I've heard previously, and it may have nothing to do with this, that on the street or other places, the OC is recognized as OxyContin, and people pick it up, they use it, they sell it, whatever, that might not be true for the generic, but I'm just really curious as to why there are these huge differences between the generic extended-release oxycodone and OxyContin, if you have any ideas about that.

DR. DART: I don't have a lot of ideas. I think yours is a reasonable one. Those products were harder to identify. We have a program where we actually orient and educate the poison centers, in other words, new coming products, what they look like and that type of thing, but because it didn't have a clear indicia on it, a lot of times, it's harder to identify those.

So, I would say that that's part of it. Part of it was they have somewhat lower sales, although, like you said, they had substantial sales before they started--

DR. WOLFE: Yes, I think sometime in the last

2 to 3 years, it was 20, 30, 40 percent.

DR. DART: Yes, yes. It got up that high, and I think the main reason is that. The other is that Dr. Jim Inciardi, who has passed away, but worked with RADARS, has pointed out many times about the brand loyalty and has published some papers on brand loyalty, and that's a very strong phenomenon among drug abusers. It takes time for them to switch. In fact, he even did some work to show that it takes about three years for them to kind of get the idea that the generic is the same as the branded product and switch to it. So, I think one of the problems there is that they never actually totally became convinced that abusing the generic form was as good as abusing OxyContin itself.

DR. WOLFE: Maybe the OC or an OP should be removed from the pill so that it could back to the--

DR. KIRSCH: Dr. Flick, next question.

MR. WOLFE: That's all. Thank you.

DR. COPLAN: Actually, could I just add a quick note to that? We did look at the overdose rates in the Kaiser System generic extended-release oxycodone and branded OxyContin, and during the time period, that

actually was in an earlier version on the slide deck. We took it out in order to cut down time. And I don't have it in the backup, but I can show you that at the break. And what is shows is that the overdoes adverse event rate went up slightly at the time of the extended-release oxycodone introduction.

DR. WOLFE: The generic?

DR. COPLAN: The generic, yes. Yes. I'll show you at the break.

DR. KIRSCH: Dr. Flick?

DR. FLICK: Just a couple of questions to better understand the databases. On slide 53, with regard to the poison center data, Dr. Dart, these are incidence rates per 100,000.

DR. DART: That's right.

DR. FLICK: Now, the poison centers, you don't have all poison centers participating.

DR. DART: That's correct.

DR. FLICK: And poison centers overlap in their coverage areas. Is that right?

DR. DART: No. The state has to designate the coverage area for a poison center. So, each one will

have a discreet coverage area.

DR. FLICK: So, you clearly know the population?

DR. DART: That's true.

DR. FLICK: Okay. And on slide 83, a similar question with regard to RADARS. Again, these are described as "incidence rates," but based on I think it was ZIP codes or jurisdictions--

DR. DART: Right, we match the jurisdiction of the investigator two or three-digit ZIP codes.

DR. FLICK: So, do jurisdictions match ZIP codes?

DR. DART: They don't match perfectly, so, we have to proportionalize the data sometimes. That's correct.

DR. FLICK: Okay. And one brief last question.

Ms. Perrin, I think the death certificate data is critical to your results, but you don't sound like you have a very clear and absolute link to death certificate data in your population.

DR. PERRIN: We can get access to the national

death certificates and the state death certificates. We also have in our own database cause of death for those who have died.

DR. FLICK: Well, but certainly there are a significant number of these deaths that occur out of hospital. Those deaths never enter a hospital.

DR. PERRIN: Yes.

DR. FLICK: And, so, they would only be captured in death certificate data, and I would think that you would not answer by saying we can get access to that. I think you must have access to that, and it must be part of the study.

DR. PERRIN: Right, and that makes sense, yes.

DR. KIRSCH: Dr. Nelson?

DR. NELSON: Thank you. I actually have two questions.

Like Rick Dart, I'm intimately involved with a poison center at the New York City Poison Control Center, and we don't contribute. We're 1 of the 20 percent of centers that don't actually contribute data to RADARS. But one of the things in Dr. Perrin's slides that she discussed, and I think this is going to be a

semantic issue, are that for most of the day, we've been talking about abuse and misuse, and she spent a lot of time talking about adverse events and poisoning and overdose. The problem with that is that when we think about overdose, we usually think about suicidality or some other intent, which I guess my question really is: How do we reconcile that as you try to figure out the data? How do you integrate the terminology?

DR. COPLAN: So, as Dr. Perrin showed in her slide, the adverse events really refer to overdoses and poisonings associated with prescription opioids. Specific ICD-9 codes 965.0 and EA-50, which is very specific for poisoning and overdose. So, yes, when we refer to adverse events, we're really referring to those specific ICD-9 codes.

DR. NELSON: Right, but I guess my question is when you look up an ICD-9 code for an overdose, you might not be looking at an abuse or a misuse. You might be looking at a suicidal patient, and when you look up poisoning, it's a very vague term. Adverse event usually generally means therapeutic misadventure, a therapeutic problem.

DR. COPLAN: Yes, yes.

DR. NELSON: It could also mean a medical error. I mean, these are terms that don't match very well. And I guess since we're really talking about misuse and abuse as a construct, I'm not sure how these terms are going to easily equate to the terms that we're interested in hearing about.

DR. COPLAN: Well, we categorized our outcomes into measures of abuse, measures of routes of administration, and changes in the overdose rates and poisoning rates over time in essentially a cohort study of the Kaiser membership population. So, what we're looking at is changes over time. So, if there is some misclassification, that should be consistent over time, and, therefore, the trends in OxyContin versus a trend in comparator opioids should be reasonably meaningful.

I agree with you that if that was as foolproof, as bulletproof as a randomized, clinical trial, where you specifically look for these endpoints then we wouldn't have to do eight studies, we would just do that one study.

DR. NELSON: Yes, I don't want to belabor it,

but I guess my question is: Why don't you look at misuse and abuse as concepts within the KP data instead of looking at these codes because they're not really reconcilable? At least I don't think they're easily reconcilable.

My other question--

DR. COPLAN: That is something we will consider.

DR. NELSON: Yes. My other issue is, and I want to second the comments about medical examiner data, about death data because, I mean, clearly, one of the big issues that we see with abuse and misuse as a very defined endpoint is death. I've commented in the past, and I'll comment at another time about the use of medical examiner data to define abuse and misuse because there are a lot of issues with that.

One of my concerns is that the two systems you're going to use to look at death, one of them involves the KP data. The other one involves the poison center data, and as Rick Dart will elaborate on, if you'd like, most deaths are not called into poison centers. Right?

I mean, when we compared our data to medical examiner data, we have only a fraction of the poisoning-related deaths. And since many, if not most opioid overdose-related deaths occur outside of a hospital, we're going to miss the vast majority of overdoses. So, without looking at some other database, meaning the medical examiner database or some vital statistics database, I think we're going to miss a lot of deaths. Just looking at the two that you have, as some people have already pointed out, is going to be very limiting.

DR. COPLAN: I fully agree with you. That's one of the reasons why we use this case fatality rate top of metric in the Poison Control Center, which hasn't been used for an analytic type of study before, precisely to address this concern because the case fatality rate looks at the number of deaths per exposures, and looking at whether it's changed in the time of fatalities per exposures as one way of getting at that. I don't think it's a perfect way.

DR. NELSON: Yes, my strong recommendation would be to look at medical examiner data. With all its limitations, it still will account for the majority of

the deaths, which I think you'll miss in this system.

DR. COPLAN: Yes. Nab, do you want to address this? We're calling on someone from the other bullpen.

(Laughter.)

MR. DASGUPTA: My name is Nabarun Dasgupta. I am with the University of North Carolina and Chapel Hill, and I have no financial interest in this meeting, but my way here has been paid for King.

The reason I'm up here is that we've been in talks with Paul and the other folks at Purdue to do exactly the study that you proposed, Dr. Nelson, and what Dr. Paulozzi has proposed before, where we can link the Prescription Monitoring Program to the medical examiner data. We passed legislation in our state earlier this year to allow for that linkage to happen. The State Health Department has done a pilot study doing the linkages between the Prescription Monitoring Program and the medical examiner data in three counties. We have a methodology for it, and we have agreement within that state health government structure to go forward with it.

That study is not presented here because it's

not formalized and hasn't been advanced enough at this point to warrant full scientific scrutiny, but it is something that we are looking at and have some experience with, and are confident that we can do.

DR. COPLAN: So, essentially, what we're planning to do is a repetition of the study Aaron Hall and colleagues from the CDC that looked at linking state medical coroner's reports for deaths in West Virginia in the year of 2006 with Prescription Monitoring Programs and state toxicology reports, and we would look at that by looking at changes over time.

As Nab pointed out, we haven't presented that yet today. We did actually mention it when first submitted something to the FDA that that was a study that we would like to do, but because of the feasibility of integrating multiple state agencies and third-party groups to do the statistical analysis, it would take some time, particularly when working as a for-profit company, a drug sponsor trying to get this study to happen, it would take some careful negotiations to bring together various state parties. But that is something that we are actively pursuing, and we do seem to have an

avenue that's opening for that.

DR. KIRSCH: Before I call on the next person, I want to remind the members of the committee we're calling on people in order from when they raised their hand. So, if you think we're ignoring you, we're not. We'll get to you.

For the FDA, I actually have a question. With a number of people who we have on the list to ask questions, I think it's very likely we'll run over our 4:00 time, which, for me, as long as I get done by 9:00 to watch Oregon beat UCLA, I'll be okay.

(Laughter.)

DR. KIRSCH: But if we run a little bit over, will that be a problem?

DR. RAPPAPORT: Well, I have a show on earlier than that.

(Laughter.)

DR. RAPPAPORT: But I think it's your discretion when to end the meeting.

DR. KIRSCH: Okay.

Ms. Krivacic?

MS. KRIVACIC: Thank you. I have a couple of

short questions. One is for Chilcoat. The question is there was reference made to the materials that we receive about the PRIDE Survey, the acronym PRIDE, and if that is part of the surveys that will be utilized here.

DR. COPLAN: Dr. Chilcoat?

DR. CHILCOAT: No, it's not. It actually only grants one question about OxyContin. So, I think a lot of the prevalence for that study is much higher than what you see in other surveys, and, so, we decided not to use it, even though we originally considered it.

MS. KRIVACIC: Thank you. My second question refers back to slide 56, the case fatality rate, and I was wondering if Dr. Dart can speak to teasing that data out by way of age range, adolescence. Is that something that you have access to? And then, also, can you tease it out by even socioeconomic status?

Thank you.

DR. DART: That's a yes and a no. So, for age, we can bring it out really of any single year you want, any age range grouping you want, that can be done. So, if we want to look at adolescence for new initiates

or into your 20s, we can do that. But when it comes to socioeconomic status, we don't gather that information. The reason is that this is an acute health care event. So, the real reason of a poison center, of course, is to give some advice to the caller or to the health care provider who's calling, and, so, we don't ask a lot of demographic questions since we're basically taking care of the patient. So, yes.

DR. KIRSCH: Dr. Zelterman?

DR. COPLAN: I'm sorry, could we have backup 55? Just to add to that response, if you wouldn't mind.

This is data broken down by, as Professor Dart mentioned, this was somewhat arbitrary. We broke it down into less than 12 and greater than 12 to see if we could detect an effect specifically in the pediatric population with the assumption that if a new formulation didn't allow the extended-release mechanism to be so easily broken by a kid, an infant or a child, they would have more time to get into emergency department and get a shot of naloxone and be able to save the kid. But, unfortunately, there are only three deaths of--not unfortunately. Sorry.

(Laughter.)

DR. COPLAN: For the purpose of this study, there are rather few deaths to be able to make any determination of that.

DR. KIRSCH: Dr. Zelterman?

DR. ZELTERMAN: A comment about the Internet study and then the Kaiser Permanente Study.

My mother told me not to believe what I read, and that's especially true of the Internet.

(Laughter.)

DR. ZELTERMAN: If you really want it, I mean, by Monday morning, we could have 100,000 posts of what you can do with OxyContin that defy your imagination. What you can get out of the Internet is if somebody really finds a way using common household methods of extracting the slow release, and that's what you can get. That's, I think, the only thing the Internet is going to teach you that is if somebody figures that out.

As for the Kaiser Permanente, could I see slide 42? Slide 42, these are the comparisons that are going to be made, and Dr. Kirsch already pointed out that the Kaiser Permanente data is not a random sample

from the population; it's a very biased sample. It's subscribers of this health insurance. It's not clear whether over a period of time the patients are changing, the coverage is changing. It's not clear.

And then if I can go to slide 45, while you address that. On slide 45, Dr. Perrin commented that there are many different regions and different groups that could be included, and if you want to get the point 0.05 significance in front of the FDA, I think you usually have to specify your population before rather than hunt around and find the ones that support your hypothesis.

DR. PERRIN: Okay, so, we'll start with the first issue. So, which slide were we on?

DR. COPLAN: Slide 42.

DR. PERRIN: Forty-two.

DR. COPLAN: Can you go back to 42?

DR. PERRIN: So, yes, there are changes in membership over time, and there are also changes in prescribing patterns over time. And that's why we feel that using a time series design with a comparator is so important. And, also, looking at this in different

subgroups where we know that there have been some changes.

We can also add into our time series, and I didn't go into this in detail, but we can add time varying covariates into the model that will adjust for these different trends over time, if necessary.

And, so, for the second one, I promise you I won't hunt around for which regions are the right regions, but what we do plan to do is, based on the size of the region, figure out how many more regions we need to bring in. So, we are not looking at data from any of the other regions, we're only looking at the size of the membership, and then we would begin to figure out which ones to collaborate with and share our codes. So, we're extracting records in exactly the same way.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: Yes, my question relates to your interest in demonstrating sustainability and how you're defining sustainability and duration of observation. So, I understand and appreciate the rationale for the time series, but it wasn't clear to me always what was the unit of time that's being done in some of the

studies and how that might differ. And, therefore, how many points you're actually looking at when you're assessing trends. So, for instance, in the Kaiser study, it looked like there's annual rates based on what I saw, so, that would give you two time points. The NSDUH survey, again, I think is annual. That gives you two time points, and it's a two-year lag for the data. So, it's actually four years out for that. and, so, that's one question.

And related to that is, on the other hand, you have some opportunity to get very discreet data, let's say the Internet discussions or the abuser cohort in Kentucky, and you only carry those studies out for six to nine months. One might anticipate that that's going to be an evolving market in which what you learn and adapt to in the first few months is going to be very different than how people might adapt a year later. So, I don't know how that's supporting sustainability.

DR. COPLAN: Yes, that's something we've discussed a lot. It's obviously a key issue.

Could I have back up slide 35?

So, this is the Kaiser data. So, one of the

questions was: What are the units? Is this annual? This is actually in a six-month period. So, in two years, we would have four periods. Some of the quotes we've been seeing on the Internet, there's a real aversion to the new formulation. We have seen methods of tampering being posted by abusers on the Web Site, but, as Dr. Zelterman referred to, they are not widespread.

So, definitely, we're going to see very determined abusers finding ways to get around the formulation. The question is whether 50 or 60 other abusers say wow, this works for me, this is great, we found a way, and we haven't see that. Other people say well, I tried it and I spent two hours heating and freezing and I didn't really get much of a high.

So, based on that, we would expect to see a relatively quick change. And then the sustainability then becomes what do we see over the four halves of the year? As we mentioned, if it's a very clear trend, then that would be evidence of sustainability. That does mean, as we mentioned, that we would no longer monitor. We have been monitoring adverse event rates for

OxyContin since 2002, created a system to do that since the database didn't exist to do that, and we're continuing to evolve new systems of surveillance that use more complex geographic information systems to do that, which we haven't discussed today.

We also have some collaborating evidence. Could I have slide 573?

We have some collaborating evidence of changes in prescribing. That suggest we would see a relatively quick effect.

This is some data looking at change in prescriptions of the new formulation and generic ER oxycodone in the past eight weeks in health care providers with questionable prescribing or medical practices. Purdue keeps a database of prescribers who through various sources of information, primarily the field sales force, who has a very good handle on which prescribers are problematic. So, we keep a list of those prescribers to make sure that we do not call on them. The field sales force does not them.

We've been tracking using the SDI data that has been referred to earlier to look at changes in

prescriptions amongst these health care providers, and we have some very preliminary data. I think it needs to be further worked out, but for OxyContin, in the current 4 weeks, there were 10,700 prescriptions compared to the previous 4 weeks of 16,000 prescriptions for a reduction of 5,000 prescription or minus 34 percent.

For ER generic oxycodone, they were smaller in absolute numbers, but there was a increase in prescriptions in the 8-week period for a net increase of 24 percent. And for the total ER oxycodone brand and generic, we've seen a reduction of 27 percent. Now this, obviously, has many flaws in it.

We need to compare these with 1,300 prescribers on the do-not-call list, we need to look at comparing prescribers who are not on the do-not-call list, but this suggests that we're likely to see a relatively quick effect, and that four subsequent measures would be reasonable. If it's not, we are perfectly willing to continue to survey this as long as it's needed.

DR. KIRSCH: Dr. Omoigui?

DR. OMOIGUI: I am wondering, bring back the

slide 35 again. And ask if the others can do two opioids. Were those short-acting, long-acting, or both?

DR. COPLAN: That's a mixture. The hierarchy in determining this was first OxyContin or ER oxycodone, then other oxycodone, which would be the immediate-release oxycodone single and combination, and then other Schedule IIs would be hydrocodone, methadone, fentanyl patch.

PARTICIPANT: Not hydrocodone.

DR. COPLAN: Sorry, not hydrocodone. Thank you. Hydrocodone would be Schedule III. So, yes.

DR. OMOIGUI: Okay, if we look again at this slide 53 and 83, it looks like in the last few years there's an increasing trend in the greater abuse and diversion of the immediate-release oxycodone as compared to the OxyContin, and I believe during those few years was when we've had increased dose trends of some of the immediate-release oxycodone. I think the 30 mgs came out in the last few years.

So, the question is this then: Are we already seeing a trend away from OxyContin into the immediate-release oxycodone, and if we are doing that, are we

going to be proactive in the fact that if this new reformulated OxyContin is successful, you're going to see a shift, an even greater shift into the immediate-release because the drug abuse problem is not going to go away quietly into the night.

It's going to try and shift, and we have to be proactive in checking that out. And I noticed that some of your studies, you are assessing the impact of the new formulation on the abuse of the immediate-release.

Is there a way you can do that in all your studies so that that way if you're seeing a reduction in the abuse of the OxyContin you can tie it into any changes in abuse of the immediate-release formulations?

DR. COPLAN: Good, thank you for that question. So, we'll look at it in two ways. First, we will look at the data to estimate is there a shift occurring, and, secondly, Dr. Landau will address the issue of a potential shifting.

Nelson, could I have backup slide 30? Thank you.

So, as mentioned earlier, even before the new formulation of OxyContin came out. This is data going

up to 2009, and this is data that was presented by the FDA at the last adcom that this group had. If you look at the single ingredient oxycodone, it has increased 660 percent, whereas extended-release oxycodone has increased by 40 percent in the last 10 years. So, we have been seeing a dramatic shift already occurring independent of any new formulation of extended-release oxycodone.

There was also a discussion at the last advisory committee around what was the predominant drug that was being dispensed in the Florida pill mills which, as we all know, is one of the worst sources of opioids for the purposes of abuse. And some people said well, it was OxyContin that was the most prescribed in the Florida pill mills. And then someone who's on the board of directors of the Florida pill mills said no, it's shifted. It's now immediate-release single ingredients oxycodone, and we don't actually have data on that.

We're trying to look to see if we can actually get data on that, but, based on that discussion, there has been some evidence of the Florida pill mills

reducing their prescription. Not that they stopped prescribing OxyContin, but there's a reduction in the overall patent, and that's largely because the DEA was using certain prescribing metrics to determine who to arrest.

And so, if you look back in Google, you can get the information of which providers were arrested by DEA. Initially, they were arrested because the major flag was that they were prescribing most 60 and 80 mg OxyContin and for cash payments. So, once a couple of people got arrested for that, then people adapted.

So, we're already seeing a shift occurring, and now we'll talk about the second part of the problem is how we do address the public health impact of this formulation potentially adding to that shift?

DR. LANDAU: Thank you Paul. I would only add that it's an unfortunate reality, but it is our expectation that if we're successful with the formulation, that abusers will shift either to other routes of abuse that are more practical to them or to other drugs. We've seen evidence that this is occurring already in close to real time through Internet

monitoring. We expect to see a significant reduction in intravenous abuse and intranasal abuse. I think it speaks to the complexity and the limited role one pharmaceutical company can play in a multi-factorial problem. And I think it's an excellent question.

Thank you.

DR. COPLAN: If I could add one thing, as we mentioned--

DR. KIRSCH: Well, if it's critical. We are out of time.

DR. COPLAN: Sorry.

DR. KIRSCH: So, I'm going to go through a couple more of these.

Dr. Bickel?

DR. BICKEL: First, I want to commend the FDA and the Sponsor for presenting very interesting and important sets of presentations today.

For the Sponsor, and I guess Dr. Landau, I'd like to understand what the company's response would be under two sets of circumstances. One, the set of eight studies produced results that are inconsistent, or, alternatively, the set of eight studies suggests that

the problem is actually getting worse or staying the same?

DR. LANDAU: Well, in either scenario, we'd be interpreting and discussing the results of the studies, as Dr. Coplan mentioned, on a periodic basis, reviewing them internally with our expert panel, and sharing the results with the Agency. It's hard to predict how we would respond, given the complex nature of the problem and the complex interrelationship with some of the behaviors and the outcomes these studies are intended to measure.

What I can tell you is that we're very interested in measuring and monitoring, and we have been and will continue to be very proactive in our actions, and they're be appropriate and shared with the regulators.

Thank you.

DR. COPLAN: We think that the cornerstone of determining whether these studies are demonstrating an effect will ultimately be expert judgment that will involve clinical, statistical, and epidemiological expertise.

DR. KIRSCH: Dr. Morris-Kukoski?

DR. MORRIS-KUKOSKI: I have two questions. One is since you said you're already collecting data as of August, but you realize that the market is still going to continue to have the old formulation of the OxyContin through the first of the year. Are you not going to then shift your data that you're actually looking at so you actually have this slight overlap so you can continue past that period of time when we know the regular OxyContin or the old formula is still out there? That's my first question.

DR. COPLAN: We thought a lot about how to do that because that is a key issue. For trends, for determining a pre-post change between two incidence rates, we would need to take that mixed time out, perhaps that one quarter. For trends, that reduction over time becomes important for us to include.

DR. MORRIS-KUKOSKI: And my second question is: Is you definition for more difficult to manipulate only crushing with spoons and dissolving with water?

DR. LANDAU: I'm going to call up a slide in a moment. The short answer to the question is no. In

March of 2009, we submitted along with our resubmission to a complete response letter to the division the results from seven separate and comprehensive in vitro studies, and I mentioned earlier very briefly they were designed with the assistance of experts and abuse in tablet tampering and extraction techniques and even drug enforcement. The results tell us a great number of things, and the interpretation goes well beyond more difficult to crush and inject.

May I have slide--

DR. KIRSCH: Is the slide different than what you've just said?

DR. LANDAU: Slide 481, please. Yes.

Okay, so, shown here, the experiments replicated proceed replicated techniques of tablet tampering that are relevant both to the abuse and the patient error context, and I don't have a pointer here, but under "Route," what's common to each one of these circumstances or settings is, in many cases, all, with the exception, frankly, of swallowing intact tablets, is some degree of physical or chemical manipulation. So, the seven separate experiments were designed, as

represented here, to inform a prediction for how difficult or what incremental change would exist for this formulation relative to the original formulation in both the patient and the abuser setting.

On the right margin, you see are sort of the results broadly characterized for a public setting like this, and in each scenario of testing or each access of testing, the new formulation, the reformulation was, well, in most all, more robust or more difficult to manipulate or convert to a dose form that was necessary to abuse via one or more of these routes and never worse.

DR. KIRSCH: Thank you.

Dr. Mendelson?

DR. MENDELSON: Yes, hi. Just a couple of quick points.

First, the one thing that does seem to be missing is the economic data again, and I think you could collect this through Kaiser. How much do people pay as a co-payment for their prescriptions? I think that would be very useful information. If it costs twice and much to get one and people prefer that, that's

actual news, that it's the Dr. Bickel's behavioral economics.

Second, I think it's ironic that the FDA requires suicide assessments for almost all new drug evaluations right now, yet, suicide is not explicitly parsed out or separated in this analysis. I think you guys have an inconsistency with your other drug programs by not making suicide explicitly separated in the overdose data. And if a lot of these overdose deaths are suicides either intentional with drug intoxication or during withdrawal because they can't obtain the drug, that would be big news.

And finally, I would note that Purdue does make immediate-release oxycodone. It sells two brands of that. We just looked it up on Epocrates here. And, so, you guys might be back here with more trouble in the future. You may want to address that now and actually ask what's going on with your IR oxycodone products as they move up the ladder of acceptability and preferability in addicts.

DR. LANDAU: Sure. I'd like to address I guess the latter part of your series of questions, the

last one. We no longer manufacturer and market immediate release oxycodone, just for a point of clarity.

DR. KIRSCH: Thank you.

Could you pull up slide 119, please?

DR. COPLAN: We had some data on prospect.

DR. KIRSCH: The question that I have about 119 is it was unclear to me how the data is going to be delivered to the FDA. Will it be delivered from these individual studies after being filtered through the company or will they investigate individual groups doing the investigation, report directly to the FDA?

DR. COPLAN: The nature of FDA's reporting mechanism is that the sponsors were responsible for providing an annual report on whatever timeframe the FDA deems is appropriate. Generally, it's annually.

What we have stated here is that we would include a PDF that's obtained from the investigators of the study, Dr. Perrin, Dr. Dart, Dr. Cassidy, and submit those as part of the report with an overall integration by the expert panel and by Purdue. It's two separate.

DR. KIRSCH: That is--

DR. RAPPAPORT: Jeff?

DR. KIRSCH: Yes.

DR. RAPPAPORT: Can I clarify something about that? I mean, everything that comes into the agency comes in through the sponsors. Occasionally, we do get citizen's petitions and things like that, but in regard to an application, it comes from a sponsor. But we have a long history of investigating data integrity, and we get all of the data and the raw data, as well. So, we look at that very carefully to make sure that what they've synopsized for us is consistent with the raw data and we go out and investigate their sites and all of that.

DR. KIRSCH: Thank you.

Dr. Denisco?

MR. DENISCO: Asked and answered.

DR. KIRSCH: Asked and answered.

Dr. Flick?

DR. FLICK: That was my question.

DR. KIRSCH: Dr. Kerns? Last question.

DR. KERNS: I'll wait until tomorrow.

DR. KIRSCH: Okay. With that, we'll adjourn

the meeting. Thanks, everybody for their attention.

DR. COPLAN: Thank you.

(Whereupon, at 4:07 p.m., the meeting was adjourned.)