FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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JOINT MEETING OF THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE AND DRUG SAFETY & RISK MANAGEMENT ADVISORY COMMITTEE

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OPEN SESSION

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MONDAY,

MAY 5, 2008

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The Committees convened at 9:25 a.m. in the Grand Ballroom of the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland, John T. Farrar, M.D., Chair, presiding.

ANESTHETIC AND LIFE SUPPORT ADVISORY COMMITTEE MEMBERS (voting) PRESENT:

JOHN T. FARRAR, M.D., Chair

KANAWALJEET J.S. ANAND, M.D., Ph.D.
JEFFREY R. KIRSCH, M.D.
NANCY A. NUSSMEIER, M.D.
DONALD S. PROUGH, M.D.
ATHENA F. ZUPPA, M.D.

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBER (voting) PRESENT:

TIMOTHY S. LESAR, Pharm.D.

TEMPORARY VOTING MEMBERS PRESENT:

DIANE ARONSON, B.S., Acting Consumer Representative
WARREN K. BICKEL, Ph.D.
CHARLES CORTINOVIS, M.D.
RUTH S. DAY, Ph.D.

THOMAS R. FLEMING, Ph.D.
JACQUELINE S. GARDNER, Ph.D.
THOMAS KOSTEN, M.D.
SUSAN KRIVACIC, Patient Representative
JANE C. MAXWELL, Ph.D.
LEWIS NELSON, M.D.
STEVEN D. PASSIK, Ph.D.

LEONARD J. PAULOZZI, M.D., M.P.H.
CHRISTINE SANG, M.D., Ph.D.
SULPICIO de GUZMAN SORIANO, III, M.D
FRANK VOCCI, Ph.D.
SIDNEY WOLFE, M.D., Acting Consumer Representative (DsaRM)
MICHAEL YESENKO, Patient Representative

ACTING INDUSTRY REPRESENTATIVES (non-voting) PRESENT:

D. BRUCE BURLINGTON, M.D. (DsaRM)
CHARLES McLESKEY, M.D. (ALSDAC)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH PARTICIPANTS AT THE TABLE (non-voting) PRESENT:

HENRY FRANCIS, M.D.
SHARON HERTZ, M.D

SANDRA KWEDER, M.D.
BOB RAPPAPORT, M.D.
CURTIS ROSEBRAUGH, M.D.

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GUEST SPEAKERS (non-voting) PRESENT:

JOE GFROERER

JUDY K. BALL, Ph.D., M.P.A.

DEBORAH TRUNZO

DESIGNATED FEDERAL OFFICIAL PRESENT:

TERESA WATKINS, Pharm.D.

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A G E N D A

P R O C E E D I N G S

(9:25 a.m.)

CHAIR FARRAR: Good morning. Sorry for the slight delay. I'm sure we can make it up. Everybody's presentation will be short and on time, no doubt.

My name is John Farrar. I'm the Acting Chair of the Committee. I'd like to call this meeting to order, and would like to start with introduction going around the table. Dr. Henry Francis.

DR. FRANCIS: Dr. Henry Francis, Deputy Director, Office of Surveillance and Epidemiology.

DR. KWEDER: Sandra Kweder, the Deputy Director of the Office of New Drugs. Good morning.

DR. ROSEBRAUGH: Curt Rosebraugh, Acting Director, Office of Drug Evaluation II.

DR. RAPPAPORT: Bob Rappaport, Director of Division of Anesthesia, Analgesia, and Rheumatology Products.

DR. HERTZ: Sharon Hertz, Deputy Director, Division of Anesthesia, Analgesia & Rheumatology Products.

MR. YESENKO: Michael Yesenko, Patient Representative.

DR. SANG: Christine Sang, Anesthesiologist and Pain Specialist at the Brigham and Women's Hospital in Boston.

DR. PASSIK: Steve Passik, Psychologist, Memorial Sloan Kettering Cancer Center in New York.

DR. MAXWELL: Jane Maxwell, Addiction Research Institute, the University of Texas at Austin.

DR. GARDNER: Jacqueline Gardner, Professor, University of Washington School of Pharmacy.

DR. FLEMING: Thomas Fleming, Professor of Biostatistics, University of Washington.

DR. CORTINOVIS: Charles Cortinovis, Anesthesiologist, University of

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Pittsburgh, VA Medical Center.

DR. ZUPPA: Athena Zuppa, Pediatric Intensivist and Clinical Pharmacologist at the Children's Hospital, Philadelphia.

DR. LESAR: Timothy Lesar, Director of Clinical Pharmacy Services, Albany Medical Center, Albany, New York.

DR. SORIANO: Sul Soriano, Pediatric Anesthesiologist at Children's Hospital, Boston.

DR. WATKINS: Teresa Watkins, Acting Designated Federal Official for this Committee.

CHAIR FARRAR: John Farrar, Neurologist and Pain Specialist at the University of Pennsylvania.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University.

DR. KIRSCH: Jeff Kirsch, Chair of the Department of Anesthesiology at Oregon

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Health Science University.

DR. PAULOZZI: Len Paulozzi, Medical Epidemiologist at the Centers for Disease Control.

DR. PROUGH: Don Prough, Chair of Anesthesiology, the University of Texas Medical Branch in Galveston, Texas.

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

DR. ANAND: Kanawaljeet Anand, Intesivist and Pain Researcher, University of Arkansas for Medical Sciences.

DR. KOSTEN: Thomas Kosten, Professor of Psychiatry and Neuroscience, Baylor College of Medicine.

DR. NELSON: Lewis Nelson, Emergency Physician and Medical Toxicologist, New York University.

DR. NUSSMEIER: Nancy Nussmeier, Chair of Anesthesiology at SUNY Upstate Medical University in Syracuse.

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DR. VOCCI: Frank Vocci, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse.

MS. KRIVACIC: Susan Krivacic, Patient Representative, Austin, Texas.

MS. ARONSON: Diane Aronson, Consumer Representative.

DR. WOLFE: Sid Wolfe, Health Research Group, a public citizen.

DR. McLESKEY: Charlie McLeskey, Industry Rep from ALSDAC.

DR. BURLINGTON: Bruce Burlington, Industry Rep, retired, formerly with Wyeth.

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

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general reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting, and thank you.

DR. WATKINS: Good morning. I'd like to remind everyone to please silence their cell phones, pagers, and Blackberries, if you've not already done so. I would also like to identify the press contacts for this meeting. It's Ms. Susan Cruzan and Chris Kelly, if you could please stand. Thank you.

Now I'll read into the record the conflict of interest statement. The Food and Drug Administration is convening today's Joint Meeting of the Anesthetic and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and temporary voting members are special government employees, or regular federal employees from

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other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to those found in 18 USC 208 and 712 of the Federal Food, Drug & Cosmetic Act, as being provided to participants in today's meeting, and to the public.

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

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Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees for potential financial conflicts, when necessary, to afford the Committee essential expertise.

Related to today's discussions of today's meeting, members and temporary voting members of these Committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children. And for purposes of 18 USC 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 discussions of new drug application, NDA 22-272, a new formulation of Oxycodone Hydrochloride Controlled-Release Tablets,

trade name OxyContin, Purdue Pharma, L.P., and its safety for the proposed indication of management of moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 USC 208(b)(1), and 712 of the FD&C Act for Dr. Thomas Kosten, for his stock ownership in a competing firm, worth between $25,001 and $50,000. The waivers allow this individual to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver documents, which were posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of

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the Parklawn Building. A copy of this statement will be made available for review at the registration table during this meeting, and will be included as part of the official transcript.

Dr. Charles McLeskey and Dr. Bruce Burlington are serving as industry representatives acting on behalf of regulated industry. Dr. McLeskey is an employee of Baxter Healthcare Corporation, and Dr. Burlington is self-employed by D.B. Burlington of Gaithersburg, Maryland.

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

FDA encourages all other participants to advise the Committee of any

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financial relationships that they may have with any firms at issue. Thank you.

CHAIR FARRAR: I'd now like to ask Bob Rappaport to provide some introductory words.

DR. WATKINS: Just as a housekeeping, we do have an overflow room. It's the Montgomery Room located right behind the restaurant, so if seating gets full, there is another room to go to.

DR. RAPPAPORT: Good morning. Dr. Farrar, Members of the Anesthesia and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, invited guests, thank you for your participation in this important meeting.

We are facing many difficult decisions regarding the risks and benefits of new formulations and new indications for opioid drug products. In the last few years, as numerous new formulations of existing opioid drugs have been developed, there has

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also been an increase in the misuse, abuse, and diversion of prescription opioid drug products in the United States.

This, in turn, has led to the significant Public Health burden of innumerable cases of addiction, overdose, and death. Many of those directly affected have been previously healthy people, both young and old.

Together with our colleagues and other government agencies, we at FDA have been working to find better strategies to mitigate this Public Health burden. It is essential that we address how we can balance the real unmet needs of patients living with inadequately treated pain, with the potential for the very treatments for that pain to be diverted, misused, and abused.

Today and tomorrow you will be presented with a great deal of information concerning the abuse and diversion of prescription opioid drug products in the

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United States. This will include, during our Open Public Session, the personal stories of some of the families who have lost loved ones, including even their children, in terrible and unfortunate deaths that all of us wish we could have prevented.

Over the past decade, in collaboration with other federal agencies, academic experts, and the pharmaceutical industry, we at FDA have employed our regulatory authority to limit the abuse and misuse of these products by carefully addressing these problems in risk management plans for the opioid analgesics.

These plans have been meticulously crafted to try to limit the exposure of potent opioid products to legitimate patients, and to provide educational information to prescribers, pharmacists, and patients and their families and caregivers, regarding the potential for misuse and abuse, and the risks of addiction, overdose, and death associated

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with these medications.

In addition to requiring strong warnings in the product labels, we have required the companies who manufacture and distribute opioid analgesics to institute surveillance plans that monitor for diversion and signals of increasing levels of abuse.

When criminal activity or evidence of increasing abuse is discovered through these surveillance programs, we have required that the companies provide reasonable interventions to attempt to resolve the problem. Unfortunately, in spite of our efforts, misuse, abuse, and diversion persist and continue to grow.

On the other hand, the under-treatment of chronic pain in the United States has only been addressed by the medical community since the 1970s. The early work in this critical arena by pioneers in pain management made significant strides in the proper treatment of pain in the last part of

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the 20th century. Yet, millions of Americans with acute and chronic pain still receive inadequate analgesia, even today in the 21st century, often with a devastating impact on their quality of life, sometimes even resulting in suicide. Today and tomorrow you will also hear from these patients and their physicians, caretakers, and families.

The challenge for FDA, and for society is how do we continue to provide adequate availability of these potent opioid products to the patients who truly need them in order to avoid unreasonable suffering, and yet prevent the terrible effects that are occurring in our communities due to diversion and abuse of these products?

There are simply no easy answers to this challenge, but perhaps with your collective advice, we can find reasonable compromises that will have a significant impact on abuse without negatively impacting patients in pain.

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Today we will be discussing an application from Purdue Pharma for a new formulation of OxyContin that have novel physiochemical features. The Applicant contends that these changes in the formulation will provide a significant decrease in the ability of abusers to defeat the controlled-release features of the product; and, thereby, reduce the likelihood that it will be abused, potentially resulting in fewer instances of addiction, overdose, and death.

Following presentations from Purdue and from FDA, we will ask you to address several questions. First, are there tools that can adequately assess the abusability of this type of product, and whether the new features of this specific formulation are likely to result in less abuse of the product.

Second, if you do conclude that there is evidence to support that the controlled-release mechanism of this new

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formulation of OxyContin is less likely to be defeated than the earlier formulation, is this difference of such a degree that it should be included in the product labeling, which would result in an at least implicit claim of reduced abuse liability.

Next, if such a claim were to be included in the product labeling, what potential exists that it might lead to a misconception in the medical and patient communities that the product is safer than other opioids, perhaps resulting in a lower threshold for prescribing, and ultimately resulting in more product available for diversion and abuse.

Also, would the inclusion of the results of the Applicant's studies performed to demonstrate the abuse resistant features of the formulation potentially provide a roadmap to defeat of these features by determined abusers?

The Applicant has chosen to submit

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their NDA before they have been able to successfully reformulate the highest OxyContin dose. If the new formulation is marketed, it will replace the existing OxyContin 10 milligram, 15 milligram, 20, 30, and 40 milligram strength tablets. The 80 milligram strength OxyContin would remain on the market in its current formulation.

We will ask you to consider the potential consequences of this marketing strategy. Specifically, what is the risk that marketing and promotion of the lower dose tablets in a less abusable formulation will result in a misperception by patients and prescribers that the higher strength tablet also includes these characteristics? In particular, would having different formulations for the different dosages result in a potential risk of inadvertent serious medication errors with the higher dosage?

If you do conclude that this new formulation of OxyContin is less likely to be

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abused, we will then ask you to discuss which features of the formulation should be included in the product labeling. We'll ask you to consider not only the value of incorporating this information for patients and prescribers, but also to weight this against the potential for the misconception to occur in patients and prescribers that this product is free of risks of diversion and abuse, and against the possible use of this information by abusers of opioid drug products.

Finally, we will ask you to address which risk mitigation strategies would be useful in preventing further abuse, misuse and diversion of a reformulated, possibly less abusable OxyContin product.

These questions are extremely difficult to answer, and that's why we have asked you to help us to do so. It's also why we have specifically brought together a panel with varied professional expertise to address the challenge. Your responses to our

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questions, and especially your discussions underlying those responses, will be critical to us, as we attempt to make a well-informed, fair, and reasoned decision regarding this application's approvability with as much transparency as possible in the process.

Your advice and our decision will set precedents for future applications for abuse-resistant formulations of opioid drug products. Thank you for undertaking this difficult challenge.

CHAIR FARRAR: Thank you. Dr. Rappaport.

We will now proceed to the Sponsor's presentation for today's meeting. Before Purdue's presentation, I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the Chair.

I'd like to call on Dr. David

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Haddox to begin the session.

DR. HADDOX: Good morning, and thank you. I am David Haddox, Purdue Pharma's Vice President for Risk Management and Health Policy. Prior to joining Purdue, I was a practicing pain physician. I spent most of my clinical career in academic settings teaching pain medicine, anesthesiology, psychiatry, and addiction medicine.

I am certified in psychiatry with a sub-specialty certificate in pain management. I'm also certified by the American Board of Pain Medicine, of which I'm a past president. I am a past president of the American Academy of Pain Medicine, and a former director of the American Pain Society.

Prior to introducing our other speakers, I would like to make an introductory remark, and provide a very brief outline of our presentation.

As Dr. Rappaport indicated, the FDA has convened this meeting for specific

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purposes that have been communicated to you. If we step back for a moment, we are all here today because of one phenomenon, the intersection of two epidemics; the epidemic of persistent pain, and the epidemic of unprecedented non-medical use of opioid analgesics.

It will come as no surprise to you that we, at Purdue, have given a great deal of thought to these epidemics. We welcome the opportunity to share our views on those inter-related Public Health issues, provide you with information on our newly formulated OxyContin, and to present our position on the importance of clear and accurate labeling for modified release, opioid analgesic products that are specifically designed to impede intentional or accidental misuse by physical or chemical tampering.

I will provide a very brief overview of the use and abuse of OxyContin, present some high-level information on the

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newly formulated product, and introduce our position on the importance of approved labeling language to form the basis of our communications with the community of healthcare professionals.

Dr. Jack Henningfield, Vice President for Research and Health Policy at Pinney Associates, and an Adjunct Professor in the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine, and former Chief of Clinical Pharmacology at NIDA will follow me with a brief review of information on abuse of, and addiction to OxyContin, specifically, which will augment the information to be presented later by the officials from the Federal Substance Abuse and Mental Services Administration.

Following Dr. Henningfield will be my colleague, Dr. Richard Mannion, a Pharmacist Scientist who will describe in some detail the tamper resistance test battery, and

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the performance of the new formulation.

I will then return to the podium and review the epidemiology study being conducted for the new formulation as part of the revised risk map, provide a summation of our remarks, and moderate for Purdue during the question and answer period.

In addition to the speakers listed, we are also joined by another expert in addiction, Dr. Edward Cone. He is a scientific consultant with Pinney Associates. He is an Associate Professor Adjunct status in the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University School of Medicine, and is formerly the Chief of Chemistry and Drug Metabolism at NIDA, and he will be available to answer questions you may have relative to behaviors employed by drug abusers, his particular area of expertise.

Almost everyone has experienced acute pain from trauma or disease, a broken bone, a dental abscess, a bad sprain, a

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surgical procedure. Acute pain, even if intense, significantly tends to improve with the resolution of the inciting event. However, for approximately 50 million Americans, the pain doesn't go away. It persists around the clock, and if moderate to severe in intensity, significantly impacts the quality of life.

This is a brief overview of the treatment of persistent pain. It begins with identifying the underlying cause of pain, and correcting it, if possible. However, as many of the clinicians here know in experiences similar to mine, sometimes we can make a definitive diagnosis, but we can't correct the problem.

Identifying and addressing the co-morbidities are key to effective treatment. Non-pharmacological approaches, such as physical and occupational therapy, are often utilized to aid in the achievement of specific treatment objectives. Psychological therapies

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can be extremely helpful to many patients with persistent pain, and complement the biomedical therapies. Pharmacological approaches begin in a stepwise fashion, starting with non-steroidal anti-inflammatory drugs, if they are appropriate, and if the patient can tolerate them. The addition of adjuvant analgesics, such as anti-depressants or anti-convulsants that have their own unique analgesic properties are also utilized. And then, when appropriate, the use of opioid analgesics.

Opioid analgesics comprise two classes, immediate release, and long-acting opioid. The immediate release opioids are further classified as combination products; that is, combined with aspirin, acetaminophen, or ibuprofen, or as single entity products containing the opioid as the only pharmaceutical ingredient.

In some patients with persistent pain, the clinical utility of the combination agents is limited because of the dose-limiting

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toxicity from the non-opioid analgesic component. The long-acting opioids are all a single entity, but they also have two classes, those that are pharmaceutically long-acting - excuse me - inherently long-acting, such as Levorphanol and Methadone, and those that are pharmaceutically long-acting, that is created to be long-acting, such as Fentanyl, Oxycodone, Oxymorphone, and Morphine.

The importance of these long-acting opioid analgesics in the treatment of persistent pain has been recognized by a number of organizations, including the American Medical Association, the American Geriatric Society, and the Department of Defense, Division of Veteran Health Affairs in their clinical practice guideline for the use of opioid analgesics in the treatment of chronic pain.

The intersection of these two co-occurring epidemics, persistent pain and non-medical use of opioid analgesics, the very

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drugs that are often used to treat persistent pain, led us to develop the research objectives that gave rise to the drug product being considered today. You will note that from time to time we refer to this product by its internal product designation, OTR, so you'll hear that term periodically.

The objectives of our research were two-fold. First and foremost, maintain the benefits to patients, and introduce impediments that would reduce the desirability of the drug to abusers. We have developed a new formulation that has met the statistical standards for bioequivalence to the original formulation, and, as Dr. Mannion will point out in some detail, with in vitro testing compared to the original formulation introduces demonstrable barriers to physical manipulation and extraction of Oxycodone, collectively referred to as tampering with the formulation.

We submitted an NDA for the 10-40

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milligram tablet strengths of the new formulation. We are completing an SNDA for the 60 and 80 milligram tablets of the new formulation, and will be prepared to submit that shortly after approval of the 10 through 40 milligram.

It was our original intention to have all tablet strengths approved at the same time. However, development of the 60 and 80 milligram formulations with the required product attributes took longer. The potential public health benefit of the newly formulated lower strength tablets that comprise approximately 83 percent of the current prescriptions for controlled-release OxyCodone products warrant their introduction prior to the approval of the 60 and 80 milligram tablets.

Regarding the abuse of OxyContin, the 12-hour dose of Oxycodone in each tablet that contributes to OxyContin being an effective pain reliever unfortunately makes it

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a target for drug abusers. Abusers often crush, break, or chew the tablets to destroy the controlled-release delivery system rendering a 12-hour dose of Oxycodone immediately available for abuse. Crushing the tablets results in a powder that can be readily swallowed, snorted, or dissolved for injection.

The dangers of this type of abuse and misuse following tampering with the controlled-release delivery system are great enough to warrant the following in the current box warning for OxyContin. "Taking broken, chewed, or crushed OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of Oxycodone."

This new formulation represents a meaningful incremental improvement over the original formulation. It provides improvement in creating impediments to some forms of compromising OxyContin's controlled-release delivery system. The in vitro studies

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indicate the reformulated tablet is substantially more difficult than the original formulation to crush and inject, and also suggests that it will be more difficult to chew or snort. An epidemiological study to assess the correlation between in vitro tamper testing results and any abuse resistance will be conducted following introduction of the new formulation.

We share FDA's concern that information about the new formulation be clear and accurate. There are already misconceptions and confusion about the new formulation. It is being mischaracterized in public discussions, including some stories in the media, and posts on blogs, as abuse-proof, which it is certainly not.

Some of this discussion has also falsely suggested that the statements arose from comments made by Purdue to the press. Purdue has made no such statements about this new drug to the press. Our approach is to add

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clear and accurate information about the in vitro tests to the description section of the full prescribing information or FPI, and to make no claims of abuse reduction until they are proven.

Providing in vitro information in the FPI will reduce misconceptions and confusion. Including, rather than excluding, accurate information provides clarity. Having a summary of in vitro information included will maintain the FPI as the definitive source of product information for healthcare professionals, a source upon which we rely for facts about any drug product. And, very importantly, including such language provides uniform, approved language to facilitate clear and consistent communication about the medication.

I reiterate, we will make no claim that the new formulation reduces abuse unless and until we submit the results from an appropriately designed study, and FDA approves

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the language of any claims based upon those results.

The 10-40 milligram tablets would be available before the 60 and 80 milligram tablets because of some technical difficulties I alluded to we initially encountered in formulating the higher strengths, which were successfully resolved, but which delayed our ability to complete an approval package for those strengths within the time frame for the submission of the 10-40 milligram strengths. The sooner any tamper resistant tablet strengths are available, the sooner there may be a significant Public Health benefit.

FDA is concerned that the availability of the newly formulated 10-40 milligram tablets before the 60 and 80 milligram tablets are available in the new OTR formulation could lead prescribers and patients to mistakenly assume that all strengths have the same features. Our approach to resolving this is to include in

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the FPI a precise description of the in vitro tests, making clear that the description applies only to the 10-40 milligram tablets, until such time at the 60 and 80 milligram tablets are approved in the new formulation. Including precise information in the FPI is better than providing no information, which, itself, as we've seen already, can lead to misconceptions and confusion.

In summary, adding appropriate and precise language to the FPI regarding the in vitro studies of the new formulation as each tablet strength is approved would provide healthcare professionals accurate information about the medicine, and minimize misconceptions.

In my overview, I made reference to the abuse of OxyContin. It is now my pleasure to introduce Dr. Jack Henningfield, a leading expert in addiction, to go into more detail about this phenomenon, which will be further augmented later today by

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representatives from SAMHSA. Dr. Henningfield.

DR. HENNINGFIELD: Good morning. It's a pleasure to have the opportunity to help you understand OxyContin abuse, and implications of the new formulation.

Today you are considering a technology that I believe has the potential to effectively treat pain, while simultaneously reducing certain avenues to abuse. A few terms and concepts are important to understand in my presentation, and throughout the day.

First, tamper resistance is the performance of a drug product in bench testing that has been designed to simulate methods of formulation tampering that are commonly employed by drug abusers. Abuse-resistance is the ability of a tamper resistant drug product to present sufficient barriers to non-labeled use of the formulation in such a way that a meaningful decrease in one or more methods of abuse can be scientifically demonstrated.

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Epidemiological studies would be needed, however, to determine if this has actually been achieved. Abuse-proof is a term used to describe a therapeutic drug product that cannot be abused in any manner. This is a theoretical ideal. By abuse, I mean the use of prescription opioids motivated, in part, by the psychoactive effects of the drug, and not for the purposes of pain treatment.

Now, let me turn to the prevalence of opioid abuse, in general, and OxyContin abuse, in particular. Later this morning, Dr. Gfroerer from SAMHSA will provide a much more extensive analysis of prescription drug abuse, but I want to highlight a couple of points.

Federal surveys show that opioid analgesics have the highest rate of non-medical use of all prescription drugs. This slide summarizes data from the National Survey on Drug Use and Health. It shows that the highest rates of non-medical use are reported for 18 to 25 year olds. This is male and

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females, and the rates are higher in males than females, by the way.

As you can see, 4.9 percent reported pain reliever use in the past month, .4 percent had used OxyContin in the last month, two percent reported tranquilizer use, 1.3 stimulant use, and .2 percent sedative use. Although the percentage for OxyContin may appear small, it is a very serious problem, and the reason we're here today.

Well, what put OxyContin on the radar screen of drug abuse, drug abusers and Public Health professionals alike? Undoubtedly, there were many contributing factors, but a major one was the fact that the controlled-release technology could be readily defeated by crushing. In fact, as we have seen over the past decade, many drug abusers did chew and crush OxyContin tablets to obtain stronger, faster effects.

The ability to readily pulverize the tablet and extract the drug made it

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possible to obtain still faster effects by nasal insufflation, often referred to as "snorting", or intravenous injection. These routes, in turn, are associated with an even higher risk of serious adverse effects because of the explosively high levels of drug that can be quickly absorbed.

The proportion of people using various routes varies across study. Crushing, chewing, injecting, and nasally insufflating are especially attractive to many drug abusers, however, because these methods produce the rapid delivery of high doses that many of them seek. Unfortunately, these are also the most dangerous methods of use.

The category of oral use, which you will hear discussed today, also includes people who crush, then use orally. Oral use can include people who put the tablet in their mouth and chew it, and oral use can also include use by swallowing an intact tablet.

Now, how drug abusers in the real

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world actually use OxyContin is important to know in considering the potential benefits and the limitations of the new formulation.

This slide shows rates of abuse by various routes of administration. You can see that 17 percent were injecting, 11 percent intra-nasally. That's about 28 percent by those two routes; 72 percent were using orally. However, these data do not tell us what percentage of the oral users were crushing and chewing.

Another thing we know is that some OxyContin users began by swallowing in-tact tablets, began by some form of oral use, and then progressed to nasal use, or intravenous injection.

This slide shows the results of one study that examined the progression of OxyContin use and abuse among drug abusers who registered for treatment at a facility in Kentucky. The red bars show how OxyContin users reported that they were actually using

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the drug at the time of their admission to treatment. About 20 percent reported that they were using it orally, about 60 percent reported nasally, and about 20 percent were intravenous injectors. This is how they reported they were using at their admission to treatment. However, they were asked how they initially used the drug, and that's shown in the green bars. About 80 percent reported that they began use of OxyContin orally, about 17 percent by the nasal route, and about one percent only by the intravenous route.

This study begins to help us understand the progression that has occurred with OxyContin. One of the things that we learn, however, is that abuse usually starts with oral ingestion. It may lead to other forms of abuse. It may lead to addiction. I believe that the new OxyContin formulation will impede this progression, because it will make OxyContin more difficult to crush, powder, inject, or nasally insufflate. The

original formulation could be easily and quickly crushed; the new formulation is tougher. I believe that the appropriate label for such a formulation is tamper resistant.

Now, in considering the potential contribution of a tamper resistant formulation, we can look to laboratory studies. Some of this research is similar to the kind of research I have done over the years with other drugs. And this kind of research has led us to a number of identification of the kinds of factors that appear more attractive to drug abusers.

In general, rapid onset of drug effects is more attractive, and some of these studies have been done with various drugs in animals and people. High-intensity of effects, that is, high brain levels, or what we often refer to as the dose response relationship. Rapid offset of drugs. The new OxyContin formulation, I think is an important step in applying drug formulation technology

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to deterring such effects, while retaining the desirable therapeutic profile.

Now, as you have heard and will see in greater detail in the next presentation, the new formulation does not make tampering or abuse impossible. I am convinced, however, by the data that I have seen that the new formulation will make tampering and abuse by several routes more difficult.

Let me summarize, in conclusion, some implications for the new OxyContin formulation. First, laboratory studies of humans and animals indicate that intake and adverse effects can also be reduced when the effort or cost per dose is increased. In my specialty area of behavioral pharmacology, we refer to this as response cost.

Second, at high levels of effort requirement, self-administration effects often cease. We often refer to this as a break point. I think I skipped the first point,

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which is that decreased intake is generally directly related to the increase in effort or the response cost. And, finally, individuals differ in the break points. It's not that animals and humans are different, as this slide suggests, but it's that individuals are different in what level of effort it takes to cease their use, or extinguish the behavior of drug self-administration.

Taken together, these findings suggest that the impediments to tampering posed by the new formulation may reduce self-administration. However, real-world experience will be necessary to confirm this. Thank you.

DR. HADDOX: Thank you, Dr. Henningfield.

FDA has discussed with Purdue its views concerning what the full prescribing information should state concerning the tamper resistant qualities of the new formulation. Based on these discussions, Purdue proposed an

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addition to the description section of the FPI applicable only to the 10-40 milligram tablets of the new formulation, which has been provided in your background information from FDA, and reads, in part, as follows:

"During in vitro testing, tablets were manipulated to recover Oxycodone by crushing, milling, heating, and crushing followed by boiling and filtering fragments, and crushing followed by extracting with various solvents, including ethanol. The tablets either did not break, or broke into fragments that retained some of the controlled-release characteristics. When in contact with aqueous media, the tablets or the fragments formed a gelatinous mass."

As our next speaker will demonstrate, this proposed wording accurately describes the data from our in vitro tamper-testing protocol; that is, OTR has some degree of tamper resistance, as defined by Dr. Henningfield, but this language does not make

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any claim about abuse resistance, the impact these attributes may have on abuse, as that cannot be studied systematically until OTR is available.

Just before I introduce our next speaker from Purdue's Pharmaceutics Group, let me review the charge we gave to our formulators. We took information from the literature and from other sources about how abusers compromise, or might attempt to compromise a controlled-release Oxycodone-containing formulation.

We know that some of the most lethal methods of abuse involve crushing the tablet as a preparatory step. We also know that IV drug abusers typically crush a tablet and dissolve it in a small amount of hot water for injection.

We charged the formulators with the following; make an OxyContin that will meet the research objectives of maintaining the current clinical benefits to patients,

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while introducing impediments to these known methods of tampering with OxyContin.

It is now my pleasure to introduce my colleague, Dr. Richard Mannion.

DR. MANNION: Hello. I will briefly review the development and technological basis of the new formulation. I will then describe the extensive range of testing to which the new formulation was subjected in order to evaluate the resistance to defeat of the controlled-release mechanism, and show the results obtained for these tests. The objectives and challenges in developing this product from a pharmaceutical perspective can be divided into two categories.

Developing a product with tamper resistant properties, but also developing a product with the properties required to be an effective medication, the product needs to have resistance to physical and chemical methods of tampering. We placed on an emphasis on the resistance to breaking of the

dosage form, and the barrier this difficulty presents to subsequent extraction of the active ingredient.

There is also a requirement that, like the original OxyContin product, drug release not be accelerated by the presence of ethanol. Just being tamper resistant is not enough. In addition, the product must meet the requirements of any reformulation. It must be bioequivalent to the original formulation. It must be possible to manufacture the product reproducibly at commercial scale, and it must be stable.

New formulation OxyContin tablets have a similar, but not identical, appearance to the original formulation. The dimensions of the reformulated tablets are slightly different to those of the original formulation. The reformulated tablet is thicker. For some strengths, but not the 40 milligram shown, there will be a change in tablet diameter. Also, the indicia on one

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face has been changed to OP on the renewed formulation, instead of OC on the original. There is no change in the color of any of the tablets. All, except the 60 milligram, will use the same cosmetic coating material as the equivalent strength of the original formulation. The 60 milligram will continue to be red, but a different dye will be used in the coat, resulting in this strength being a different shade. The differences in appearance between the new formulation and original tablets are apparent.

The development of a tamper resistant dosage form is something Purdue have been working on for many years. Purdue developed and evaluated multiple technology platforms prior to selecting the compositions containing the specific polymer which are the basis for the new formulation. It is this polymer, that when subjected to a novel manufacturing process, makes the tablets difficult to break or crush. If breaking the

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tablets is achieved, tablet fragments retain some controlled-release properties, and by this, I mean that they continue to release Oxycodone over an extended time period. They don't become immediate release. Also, on hydration of tablet fragments, the polymer becomes a viscous gel that inhibits extraction of active ingredient for injection.

So how difficult is it to break these tablets? During the development of this product, one of the tests which we used is a rapid evaluation of whether the product have the desired tamper resistant properties, was to strike the tablet several times with a hammer. This wasn't part of the standardized testing protocol, but it gave a good high-level indication of the properties of the tablet. It is a simulation of a real-life situation where a blunt instrument of some kind is used to defeat the controlled-release mechanism.

The photograph on the left shows

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the results of striking one of the 40 milligram reformulated tablets several times with a hammer. The one on the right shows that the tablet is not broken into pieces. A conventional tablet would be reduced to a fine powder if treated in the same way.

One common method of tampering with the original formulation of OxyContin is to crush the tablets between two spoons. In contrast to the original formulation on the right, the new formulation on the left cannot be crushed in this manner.

As I move between the images, the difference is apparent. The original formulation is reduced to a fine powder; whereas the new formulation is only slightly deformed, and has one small crack.

There are no industry-wide standards for testing to assess tamper resistance properties. Purdue has published and presented strategies for tamper testing. The protocol used for the new formulation

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includes a series of internally standardized tests. The protocol was submitted to FDA for review several months prior to the NDA submission, and FDA comments were incorporated into the protocol.

Our strategy was to perform a series of tests in the laboratory that simulate methods used to defeat the medication's controlled-release mechanism. These include simulations of methods known to be used by those abusing controlled-release tablets, but also go beyond this to evaluate tampering by more complex methods, which require significant knowledge of chemistry.

The testing employed increasingly aggressive methods of tampering. The levels of physical manipulation to break the tablets start with manual crushing using a tool designed to crush or break items, and then progressed to a mechanical mill.

Each manipulation was followed by a dissolution test and an extraction test on

the resultant material. The chemical extraction studies are classified as either simple, moderate, or advanced. The classification is driven by the availability of the solvents, the toxicity of the solvents, the time, and the temperature used for this extraction.

Simple extraction is at room temperature with readily available non-toxic solvents, and involves shorter durations. Moderate extraction is also at room temperature, but with less readily available and more harmful solvents. Advanced extraction utilize higher temperature, longer duration or organic solvents which are more toxic, some of which need a secondary extraction. The protocol also includes a simulated preparation for IV abuse.

The initial level of physical manipulation used in the protocol is manual crushing using a significantly more aggressive tool than many real-world techniques, such as

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spoons. Even then, the new formulation remains in large pieces, as illustrated in the image on the left. In contrast, the original formulation on the right can be crushed easily into a fine powder.

We subjected tablets treated in this way to a dissolution test to measure the amount of Oxycodone released. The dissolution test is the industry recognized way of measuring drug release from a dosage form. Testing in this way is an approximate simulation of drug release if the tablets were crushed or swallowed.

The table shows the range for the amounts released from the original and new formulations. In this and subsequent slides the range is low to high, are the lowest to highest values obtained, and the low value does not, necessarily, correspond to the 10 milligram strength, and the high value to the 80 milligram.

The data show that the original

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formulation releases essentially all of the Oxycodone in the specific time period, indicating that the controlled-release mechanism has been defeated by manual crushing. In contrast, the new formulation released between 20 and 49 percent of the Oxycodone, at the product was not rendered immediate release. The large pieces generated by manual crushing retained some of the controlled-release properties of the intact tablets.

The extraction studies conducted on the materials obtained after manual crushing are classified internally as simple extraction. They used readily available non-toxic solvents at room temperature, and do not continue for extended time periods. The data presented show the range for the amounts extracted from the new and original formulations.

The original formulation tablets released essentially all of the Oxycodone in

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the effective solvents. The amounts of Oxycodone released in the effective solvents from the new formulation were much lower, indicating that manual crushing, followed by simple extraction, did not defeat the controlled-release mechanism of the tablets.

The next level of physical manipulation evaluated was the use of a mechanical mill. The difference in convenience and potential for spontaneity between this and something equivalent to the equipment used for manual crushing is large. Greater planning and effort are required, compared to crushing by a non-mechanical method, and it places restrictions on where the tampering can take place.

However, even with this more aggressive technique, we only managed to break the new formulation tablets into pieces that are visibly larger than those achieved by manually crushing the original formulation, as shown in the contrast between the two images.

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Because the original formulation of OxyContin could be manually crushed effectively, material from tablets manipulated by this method was used for subsequent tests. Using a more complex procedure was not necessary.

The data in this table show the range of amounts released from the milled new formulation and crushed original formulation. The data for the crushed original formulation are the same data shown earlier in the presentation, and show that essentially all of the Oxycodone has been released. This contrasts with the new formulation, where amounts released were only approximately 20 to 30 percent higher than from intact tablets tested in the same way. However, the table does not show the whole story. In order to obtain a greater understanding of what was happening, a separate test was done on the 10 milligram tablets, where samples were taken every five minutes.

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This plot shows time from zero to 50 minutes on the X-axis, and percent released on the Y-axis. The crushed original formulation tablet released all of its drug load after five minutes, or less. Crushing has reduced the original controlled-release tablet to being extremely immediate release. Contrast this result with the milled new formulation tablet. It's not turned into an immediate release product. The large pieces retain some of the controlled-release properties of the intact tablet, and the active ingredient is released gradually throughout the duration of the test.

The single data points on the lower right of the graph represent the percent released from intact tablets of the original and new formulation when tested in the same way. In fact, the amount released after 40 minutes from the milled new formulation is only a few percent higher than the amount released from the intact original formulation

tablets when subjected to the same dissolution test.

The gelling of the polymer, which causes pieces of tablets to retain some controlled-release properties, also acts to inhibit tampering to obtain something which can be injected.

In order to evaluate tampering for IV abuse, the tablets were first milled in the case of the new formulation, or crushed in the case of the original formulation. Water was added to enable extraction of the active ingredient for injection. The picture on the left shows the results of executing this procedure in a 40 milligram new formulation tablet. The addition of water to the milled tablet has caused the formation of a gelatinous mass, which could not be drawn into a syringe. The syringe is empty.

This contrasts with the image on the right, showing the results of conducting this procedure on an original formulation 40

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milligram tablet. The syringe is full of the liquid used to extract the drug.

The results of testing are shown in the table. The values obtained for the new formulation reflect the difficulty in extracting the drug by this method. In contrast, the data obtained for the original formulation show that 49 to 58 percent of the Oxycodone is made available for IV abuse.

We also evaluated whether thermal treatment could be used to extract the drug from the original and new formulation. Milled new formulation and crushed original formulation were added to a solvent and boiled for a preset time. The milled new formulation tablets released 21 to 48 percent less Oxycodone than the corresponding strength of the crushed original formulation.

Additional extraction studies were conducted on the milled new formulation and crushed original formulation. The solvents used for these studies and the manipulation of

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the tablets using the mill instead of manual crushing resulted in these being classified internally as moderate extraction studies.

The table shows the range of data obtained in each solvent for the new and original formulation. Release from the new formulation in medium solvents I and II was lower than release from the original formulation. Medium solvent III was not a good solvent for extracting out Oxycodone.

Longer extraction times were evaluated with a broader range of solvents. The degree of complexity and time combined with the toxicity of some of the solvents caused these tests to be classified internally as advanced extraction. The range of results for the new and original products in each solvent are presented. The results obtained for the new formulation are an incremental improvement than those of the original formulation. The data show that with some solvents and an extended time period,

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significant amounts of Oxycodone can be extracted from the formulation. The best solvent for extracting Oxycodone from the new formulation, Complex Solvent I, is not something which can be ingested. And because of the toxic nature of this solvent, a secondary extraction or equivalent would be needed to obtain the drug in a usable form.

When assessing the meaning of data, such as that obtained for Complex Solvent I, the activities required to extract the drug need to be taken into consideration. The tablets have been milled and shaken with a toxic organic solvent for an extended time. In order to get the drug into an ingestible or injectable form, a secondary extraction would be required. This is a complicated and lengthy procedure.

This table shows the impact of a higher temperature on these advanced extraction studies. The data show that release is generally not accelerated by

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heating the samples.

In summary, the in vitro testing was rigorous and extensive. It simulated increasingly aggressive methods for defeating the controlled-release mechanism. The tablets are difficult to break. If they break, they break into fragments which retain controlled-release characteristics. A gelatinous mass forms when tablets or fragments are in contact with aqueous media, and the active ingredient is difficult to extract. Thank you.

DR. HADDOX: Thank you, Dr. Mannion. Dr. Mannion has provided you with the laboratory evidence of the new formulation's performance on our tamper resistant protocol, and supports the labeling language we proposed to FDA that applies specifically to the 10 to 40 milligram tablets of the new formulation. The wording is consistent with our understanding of discussion with FDA, and meets the dual goals of not making claims for abuse-resistance, nor

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providing clear instructions on how to tamper with the product.

The proposed FPI for the new formulation includes the same boxed warning, all other warnings, all precautions, and all the information about drug abuse as the current OxyContin FPI.

Healthcare professionals should know that there is a difference between the new and the original formulations, and make their prescribing decisions based on full information. As with any product safety concern, healthcare professionals should be warned about potential issues, and advised of the product characteristics that may effect those issues. In this case, adding appropriate language to the FPI regarding the tamper resistant qualities of the new formulation would provide healthcare professionals accurate information about the medication, and minimize misconceptions.

As you know, as Dr. Rappaport

pointed out, many drugs now have RiskMAPs associated with them, especially those drugs that have abuse potential. We've had a risk management program for OxyContin for some time, even predating the RiskMAP guidance. The history of our RiskMAP will be reviewed in detail by FDA later this morning.

The goals of the RiskMAP for OxyContin's new formulation are three; to minimize the abuse of OxyContin, to minimize the diversion of OxyContin, and to minimize exposure to OxyContin among those under the age of 18.

As you know from the RiskMAP guidance, each goal must have at least one objective supporting it, employ one or more tools aimed at achieving the objective, and have an evaluation plan using one or more tools or methods of evaluation, if possible, to determine if the objective has been reached, or to inform subsequent efforts to achieve that objective.

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Our new RiskMAP incorporates the new formulation itself as a key risk management tool. Our RiskMAP also insures accurate and clear information about the appropriate use of the product through education of healthcare professionals about OxyContin. It also evaluates the impact of the new formulation on the abuse of OxyContin through a long-term epidemiological study. I'd like to take a few moments to talk about that in some detail.

We planned this study to assess the impact of the new formulation on abuse. We will compare the prevalence of OxyContin abuse by participating site among enrollees to one of 68 opioid treatment programs or OTPs, that use Methadone maintenance to treat addiction. We will gather data before and after the availability of the new formulation.

The OTP study is a component of the RADARS system that is owned and operated by Denver Health, the not-for-profit that

operates Denver's Public Safety Net Hospital and the Rocky Mountain Poison and Drug Center. Our study will involve a secondary analysis of data collected in the ongoing OTP study.

The primary objective will be to assess the impact of the launch of OTR on the proportion of OTP study participants reporting past month use of OxyContin to get high. The design is a pre/post method. The pre period will be four quarters prior to the availability of the 10 through 40 milligram new formulation tablets data collection which is ongoing now. The post period will be four quarters following the availability of all strengths of the new formulation. The unit of analysis will be at the opioid treatment program level.

The data collection instrument used by the RADARS system is a one-page self-administered questionnaire. It is conducted at the point of intake to the program. The data are anonymous with the exception of the

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ZIP code of the reporter. The participants receive a token reward to enhance their participation. The items assess the demographics of the individual, record the site, of course, since that's a unit of analysis, and include a checklist of drugs used to get high in the past month, including Heroin, OxyContin, and 13 other opioid analgesic products. The survey also asks the primary drug of abuse before seeking admission to the opioid treatment program.

The analysis will include a two-sample Z-test to test the null hypothesis that the proportion of study participants in each OTP who report the use of OxyContin within the past month to get high has stayed the same or increased in the post period, versus the alternative hypothesis, that the proportion has decreased. The null hypothesis will be tested at the level of each participating opioid treatment program. The reason for this is that we know from RADARS and other data

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that there are geographic variations in trends around the country in terms of drug abuse. The P-values from each of these two sample tests will be pooled according to Fisher's rule for combining significant probabilities, and the analysis results will be declared statistically significant if the overall P-value is less than 0.025.

In conclusion, the introduction of the new OxyContin formulation has the potential for meaningful public health benefits. The new formulation of OxyContin is intended to be every bit as effective for patients as the original, with a potential to reduce abuse. The new formulation resists crushing and other common methods of tampering. We hope this will translate into reduced abuse, but agree with FDA that post-approval study is required to determine if this goal is achieved. The new formulation will not eliminate abuse. The inclusion in labeling of descriptive information will help

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clarify understanding, and minimize misconceptions. Thank you.

CHAIR FARRAR: Thank you very much. We'll move right into the FDA presentation, and I'd like to ask Mwango Kashoki to come and give the first presentation.

DR. KASHOKI: Good morning. My name is Mwango Kashoki, and I'm a Medical Team Leader in the Division of Anesthesia, Analgesia and Rheumatology Products. My presentation will outline the history of OxyContin to date, and will include events relating to the product label, and the risk management plan.

OxyContin was approved in December of 1995, and the approval occurred during a period of growing recognition that many patients with pain are inadequately treated. And, also, that there was an increase in abuse and diversion of prescription drugs.

The `95 label indicated that

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OxyContin is a Schedule II drug. And the clinical trial section of the label describe the results of several studies, including trials in both cancer and non-cancer pain. The non-cancer pain trials were in patients with arthritis and post-operative pain. The use of OxyContin in opioid-naive patients was also described in the clinical trial section, and the results of open label and equivalence trials were also reported in that section.

Initially, OxyContin was indicated for the management of moderate to severe pain when an opioid would be required for more than a few days. The warnings and drug abuse and dependence sections of the label cautioned against crushing, or breaking, or otherwise destroying the integrity of the tablets due to the release of a potentially toxic amount of Oxycodone. Notably, the drug abuse and dependence section stated that delayed absorption of the OxyContin that resulted from the controlled-release properties of the drug

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was believed to reduce the abuse liability of OxyContin.

At that time, the thinking was that the pharmacokinetics of a delayed or controlled release formulation, namely, the slower and lower Cmax or p-concentration, as well as fewer peaks and troughs would reduce the reinforcing effects of the drug. And this is what led to the inclusion of such language about reduced abuse liability in the label.

In 1996, the 80 milligram strength was approved. The label was modified to reflect that this highest dose was to be used only in opioid tolerant patients who would require minimum daily dose of 160 milligrams, but the label language otherwise remained the same.

In 2000, an even higher strength tablet, 160 milligrams, was approved. Again, the label was revised to reflect that this high strength should also be used in opioid tolerant patients who needed daily doses of at

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least 320 milligrams. But, otherwise, no new modifications to the label.

Now, around the time that the 160 milligram strength was approved and released, Purdue began a fairly aggressive marketing campaign for OxyContin. Through considerable advertising and other strategies directed at physicians, the company promoted the use of OxyContin primarily among primary care providers, as compared to pain specialists. And Purdue also promoted the use of OxyContin for non-cancer pain, including pain due to arthritis or post-operative pain. And, also, OxyContin was promoted as first line therapy for chronic pain, which was inconsistent with pain treatment guidelines.

In May of 2000, the Division of Drug Marketing, Advertising, and Communications, also known as DDMAC, issued an untitled letter to Purdue regarding some of its promotional materials. The letter cited the company for making misleading efficacy

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claims. For example, some of the materials described the use of the 160 milligram strength in a manner that was inconsistent with the label, and also described prompt effect, which was inconsistent with the data, and made claims about effects on other patient symptoms, such as improved sleep and mood, which was not substantiated by the data.

With regard to the safety information, some of the materials had safety-related text that was presented in such a way that either reduced its readability or prominence in the materials. And, also, there was incomplete information regarding proper administration of the drug. Following receipt of the letter, Purdue ceased dissemination of these advertisements.

In that same year, the media in certain states began to report cases of abuse and diversion of OxyContin. The drug was being crushed and administered by non-oral routes. As a result, patients experienced

adverse events or effects, including addiction and even fatalities. And some states were more effective than others, including the Appalachian states, New England states, and Ohio. Also worrisome was the fact that teenagers were amongst the populations that were abusing OxyContin.

There are several possible reasons why OxyContin became a favored drug of abuse and diversion. A recent study suggests that Oxycodone is more reinforcing than Morphine. And with respect to the drug formulation, OxyContin has a higher Oxycodone content compared to immediate release Oxycodone. And even those initially believed that the pharmacokinetics of a controlled-release formulation would render a drug less abusable, more recent experience has shown that this isn't the case if the controlled-release properties of the drug are defeated.

Additionally, there's more drug available, in general, with the emphasis on

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good pain management, prescribers are probably becoming more comfortable in terms of prescribing opioid analgesics. There's also Purdue's push to promote OxyContin that could have led to increased availability of the drug. And, finally, the product labeling could have been a factor. The language about the release of a high dose of Oxycodone with crushing of the pill could have alerted some abusers as to how they could misuse the drug. And, also, the language about lower abuse potential of OxyContin may have misled patients and prescribers about the actual addictive risks of OxyContin.

Now, initially in response to the reports of OxyContin abuse and diversion, Purdue contacted the Agency to discuss these issues. Also, formed a response team to look at the problems developing in Maine. That was a hotspot area. And the company also elected to discontinue marketing of the highest strength 160 milligram tablet.

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The Agency requested additional information from various sources, and we reviewed all available data to look at OxyContin prescribing practices, as well as adverse events. And we met with Purdue to discuss these problems.

As a result of what was learned about abuse and diversion of OxyContin, the Agency decided to revise the product label for the drug. A labeling supplement proposing other revisions to the label had previously been submitted, and so we used this as an opportunity to reconsider the language of the entire label.

The revised OxyContin label was approved in July of 2001, and key changes were as follows. First, a boxed warning was added that describes the potential for abuse, misuse, and diversion of OxyContin, and emphasizes the proper patients for treatment. The clinical trial section was restricted to the sole adequate and well-controlled study,

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and the indications section was rewritten to specify the appropriate treatment population.

The indications section now states that OxyContin is indicated for patients with moderate to severe pain who require around-the-clock analgesia for an extended period of time. The indications section also states the patients for whom OxyContin is not appropriate, including those who need PRN, or as-needed dosing, and those in the immediate post-operative period.

The warning section cautions against destroying the integrity of the pills, and there is now more prominently under the warning section, detailed language that describes the potential for misuse, abuse, and diversion of OxyContin. The previous label just had a few sentences about these risks under the drug abuse and dependence section.

With respect to the drug abuse and dependence section, the sentence implying reduced abuse liability of OxyContin because

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of the controlled-release formulation has been deleted.

In addition to rewriting the product label, the Agency specified to Purdue that all material that was to promote OxyContin had to be based on the revised product label, and if any new risk information was added to the package insert or to the product label, the promotional materials had to be revised to reflect this.

Now, while negotiations about the revised product label were underway, the Agency and Purdue began discussions regarding the implementation of a risk management plan. I'll abbreviate that, RMP, in my talk. You've also heard it referred to as a RiskMAP.

The ideal components of an RMP were considered, and clearly, prevention of abuse, misuse, and diversion was important. And adequate product labeling, patient and prescriber education, and the development of an abuse deterrent or an abuse-resistant

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formulation were considered important prevention strategies.

Surveillance was another important component of the RMP, and risk management involving assessment of the scope of the problem, and the effectiveness of any interventions that were taking place in response to a signal were also employed, should be employed in an RMP.

So the initial draft of the OxyContin RMP was submitted to the Agency in August of 2001, and the RMP had multiple features, including education and surveillance, as well as strategies for intervention should a signal be detected about abuse, misuse, or diversion.

The surveillance component of the RMP makes use of existing data collection systems, and also established a new one known as RADARS that was previously described. You'll be hearing about some of these other data collection systems in other talks to be

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presented.

In addition, in 2002, product labeling in the form of a patient package insert was approved, and the patient package insert, or PPI, describes the patients who are supposed to be treated with OxyContin, how to take the drug properly, and also describes OxyContin as a highly favored drug for abuse and diversion, and what strategies patients can take in order to minimize these risks.

Later in 2002, the Agency held an Advisory Committee meeting to discuss the use of opioid analgesics in pain patients, as well as their potential for abuse and misuse. And at this meeting, it was concluded that while abuse of opioids is a significant Public Health problem, these drugs are important for proper pain management. And an overly restrictive risk management plan may limit the proper use of these drugs in legitimate patients.

Following the 2002 Advisory

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Committee meetings, Purdue and the FDA began discussions regarding development of a reformulated OxyContin product that was potentially less abusable. And over the years, many ways of reformulating the product have been discussed.

Meanwhile, in 2003, DDMAC issued a warning letter to Purdue regarding certain advertisements that appeared in medical journals. As presented, DDMAC stated that the ads minimized the risks of OxyContin, and promoted broader use of the drug than as described in the product label. Following receipt of the letter, Purdue stopped disseminating those ads.

In addition to the warning letter, the Agency has issued other untitled letters to Purdue regarding some of its promotional materials. These issues have basically been that the ads minimize risk, imply broader use than is actually approved, and did not completely state how OxyContin is to be

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administered appropriately.

In 2003, the Agency held another Advisory Committee meeting, this time to discuss risk management plans, in general, and specifically one that had been proposed for Palladone. At the end of the meeting, it was generally agreed that the RMP should have the components of prescriber and patient education, and surveillance of drug use, and should also assess the impact of opioid prescribing practices.

The following year, in 2004, the first generic extended release Oxycodone products were approved, and each of those had a risk management plan. While the generic applications were still under review, Purdue filed suit against the generics for patient infringement. The initial ruling was made by the District Court in 2004, and was in favor of the generic companies. And the District Court's ruling was affirmed the following year by the Federal Circuit.

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In February 2006, however, the Federal Circuit withdrew its affirmance, and also vacated the District Court decision. And in October of 2006, Purdue settled with the generic companies, and the final agreement was that the generic versions of extended release Oxycodone would be discontinued, but only after a certain time after the settlement agreement.

So with regard to the generic extended release Oxycodone products, the current status is as follows. Teva and Impax remain approved, but are no longer marketed. The final approved for Endo's Oxycodone extended release generic was rescinded, and is now in tentative approval status. Watson has the only generic extended Oxycodone on the market. The Watson product is actually Purdue's generic OxyContin, and Watson is Purdue's authorized distributor for this drug.

Another notable event in the history of OxyContin is the guilty plea that

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Purdue and three of its executives made to charges that they misled the public about the risks of OxyContin. The charges were regarding promotional activities that occurred prior to mid-2001, which is when the product label was revised.

Last year, the new drug application for the tamper resistant reformulation of OxyContin was submitted, and all but the 80 milligram strength, which is currently the highest marketed strength, have been reformulated. And the reformulated tablets are purportedly more resistant to physical and chemical manipulation. And testing, as we have heard, for tamper resistance was based on known methods of abuse.

Purdue proposes inclusion in the product label language that describes the effects of physical manipulation on the reformulated product. Additionally, there'll be other surveillance components that have

been proposed for the risk management plan or program. The surveillance will include assessment of OxyContin abuse patterns after approval of the reformulation, and a comparison of abuse methods and adverse effects of the reformulated versus non-reformulated OxyContin products.

So the status is today that the Agency and Purdue have worked to strength OxyContin's product label and the risk management plan. Nevertheless, abuse and diversion of OxyContin continue to be considerable health problems. And while it's desirable to have less abusable controlled-release Oxycodone on the market, we don't know what the actual impact of such a drug will be. Thank you.

CHAIR FARRAR: Thank you for that presentation. We're going to move on to Lieutenant Commander Kendra Worthy's presentation. I'd advise the Board that the questions and answers for this section will

come after lunch.

DR. WORTHY: Good morning. My name is Kendra Worthy, and I am a Drug Utilization Analyst in the Division of Epidemiology in the Office of Surveillance and Epidemiology, and I will be discussing out-patient drug utilization trends for Oxycodone products.

Outlining my talk this morning, I will be discussing sales distribution data that was provided by IMS Health, IMS National Sales Perspectives, Retail and non-Retail. We will be looking at retail prescription data, specifically trends within the opioid market, state level data, and prescriber specialty data from Verispan's Vector One National, otherwise known as VONA.

Please note that VONA does not include data from mail-order pharmacies, out-patient clinics, long-term care facilities, or same-day surgery centers. An age distribution of patient-level data from Verispan's total

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patient tracker is also included. Lastly, I will summarize with conclusions.

We will now take a look at sales distribution data from year 2007, with a brief description of the database. The IMS Health, IMS National Sales Perspectives Database measures volume information and unit sales of a given product from the manufacturer to various channels of distribution. The units measured in these databases are extended units, which are, for example, individual tablets and capsules.

The retail perspective measures chain, independent, mass merchandisers, food stores with pharmacies, and mail-order pharmacies. The non-retail perspective measures federal facilities, non-federal hospitals, clinics, long-term care facilities, home healthcare, HMOs, and miscellaneous channels, such as prisons and universities.

This pie chart shows the number of combined OxyContin and generic Oxycodone ER

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tablets sold from the manufacturer to retail and non-retail pharmacies in the year 2007. Approximately 87 percent of sales were to retail channels of distribution; therefore, this presentation will focus on retail data.

Moving on to prescription and patient-level data with a brief description of the database. Verispan's Vector One National, VONA, is a national-level projected prescription and patient-centric tracking service. They receive over two billion prescription claims per year, representing over 160 million unique patients. The number of dispensed prescriptions is obtained from a sample of approximately 59,000 pharmacies throughout the United States, accounting for nearly all retail pharmacies, and represent nearly half of retail prescriptions dispensed nationwide.

Retail pharmacies include national retail chains, mass merchandisers, pharmacy benefit managers and their data systems, and

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provider groups. Data on prescribing specialty and patient age and gender are available, as well as state-level data.

This graph shows the utilization trend of frequently dispensed opioids since 1997. Hydrocodone products dominate the opioid market. For the past 10 years, Hydrocodone, shown here in red, has been the number one dispensed product out of all prescription drug products. Oxycodone products, shown here in gold, come in at a distant second to Hydrocodone, with approximately 42 million prescriptions dispensed in 2007.

This graph removes Hydrocodone and takes a closer look at the dispensing trends of other leading opioid products since 1997. Of the 42 million Oxycodone prescriptions dispensed in year 2007 that were mentioned on the previous slide, 7.5 million of those were extended-release Oxycodone, shown here in red. Of those, approximately 5.5 million were

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generic Oxycodone ER prescriptions, and two million were OxyContin prescriptions.

Fentanyl, which is represented by the gold line, and Morphine in the green, tied for third among opioid prescriptions dispensed in 2007, with approximately 5.5 retail prescriptions each. Approximately four million Methadone prescriptions, and 1.6 million Hydromorphone prescriptions were dispensed in 2007.

This bar graph shows the trend for Oxycodone products immediate-release versus extended-release since 1997. The extended-release Oxycodone market, which is represented by the blue bars, has held constant at approximately 6 to 8 million prescriptions, while prescriptions for the immediate-release formulations, which are represented by the green bars, have continued to increase since the late 1990s. Just under 35 million immediate-release Oxycodone prescriptions were dispensed in year 2007.

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The following shows a distribution of retail prescriptions dispensed for extended-release Oxycodone products by state for year 2007. The top five states with the highest volume of extended-release Oxycodone prescriptions are Florida, California, Pennsylvania, Ohio, New York, and New Jersey.

This graph takes a look at extended-release Oxycodone by company. The Teva brand, which is shown in red, led the market share in 2007, accounting for approximately 2.8 million retail prescriptions representing 37 percent of the extended-release Oxycodone market. Purdue, which is shown in orange, was second with 27 percent of market share at approximately two million retail prescriptions. Watson, which is shown in the green, is Purdue's authorized distributor for generic Oxycodone ER. In 2007, approximately 1.4 million prescriptions for Watson's extended-release Oxycodone ER were dispensed, representing 18 percent of the

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extended release Oxycodone market. As previously mentioned, most of the generic extended-release Oxycodones have discontinued marketing in late 2007, and early 2008.

This slide shows the number of OxyContin and generic Oxycodone ER retail prescriptions dispensed since 1998. Between years 2003 and 2004, retail prescriptions dispensed for OxyContin, shown here as the green line, decreased approximately nine percent, from 6.6 million to 6.1 million prescriptions. With the introduction of generic Oxycodone ER, shown in red, to the market in 2004, OxyContin prescriptions continued to drop approximately 77 percent, and please update your handout to this. They dropped approximately 77 percent, from 6.1 million during year 2004, to 1.4 million prescriptions during year 2006, when Oxycodone ER prescription volume peaked at 5.5 million prescriptions.

This graph shows the trend of

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extended-release Oxycodone products by strength. The 20 milligram strength has led the market share with 2.4 million prescriptions dispensed in year 2007. The 40 milligram strength has been second since 2002, with 2.3 million prescriptions dispensed in year 2007. Both the 10 milligram and 80 milligram strength had 1.4 million prescriptions dispensed in year 2007.

This graph is of the number of retail OxyContin and generic Oxycodone ER prescriptions dispensed by prescribing physician specialties since 1998. General practitioners, which are represented by the family medicine, osteopathic medicine, and general practice specialties, and is shown here in red, are leading prescribing specialties, followed by internal medicine, which is shown in gold.

General practitioners prescribed approximately 2.1 million or 28 percent of retail extended-release Oxycodone

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prescriptions dispensed in year 2007. Internal medicine physicians prescribed 1.3 million, or 18 percent.

This slide shows a comparison of retail prescriptions on the left, and unique patients on the right, for extended-release Oxycodones stratified by age. As you can see, the trend is very similar between prescriptions and patients. Approximately 1.3 million patients filled a retail prescription for generic Oxycodone ER in 2007, and approximately 400,000 patients filled a prescription for OxyContin during the same time period. Collectively, patients aged 41 to 65 years filled the majority of long-acting Oxycodone prescriptions. Pediatric patients age zero to 16 years account for less than 1 percent of patients that fill prescriptions for these products.

In summary, Hydrocodone products are the number one dispensed prescription product, with 119 million prescriptions

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