



U.S. Food and Drug Administration

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Joint Meeting of the
Anesthetic and Life Support Drugs Advisory Committee
(ALSDAC)
and the
Drug Safety and Risk Management Advisory Committee
(DSaRM)

OPEN SESSION

THURSDAY, SEPTEMBER 24, 2009
9:15 a.m. to 4:15 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

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14 Novo Nordisk, Inc.

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1 **FDA Center for Drug Evaluation and Research**

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4 Director, Office of New Drugs (OND)

5 Center for Drug Evaluation and Research (CDER)

6 Food and Drug Administration (FDA)

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8 **Sharon Hertz, M.D.**

9 Deputy Director

10 DAARP, CDER, FDA

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12 **Ellen Fields, M.D., M.P.H.**

13 Clinical Team Leader

14 DAARP, CDER, FDA

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16 **Robert Rappaport, M.D.**

17 Director, Division of Anesthesia, Analgesia, and

18 Rheumatology Products (DAARP)

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1 **Henry Francis, M.D.**

2 Deputy Director, Office of Surveillance and

3 Epidemiology (OSE)

4 CDER, FDA

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1 P R O C E E D I N G S

2 9:15 a.m.

3 DR. KIRSCH: Good morning. My name is
4 Jeffrey Kirsch. I'm the chair of this committee, and
5 I serve as Chair of the Department of Anesthesiology
6 in Portland, Oregon.

7 Good morning, everybody. I would first
8 like to remind everyone present to please silence
9 your cell phones, if you've not already done so. I'd
10 also like to identify the FDA press contact who's
11 Karen Mahoney -- and if she's here; there she is in
12 the back -- for the press if you have any questions.

13 I'd like to first read a statement, the
14 following. For topics, such as those being discussed
15 at today's meeting, there are often a variety of
16 opinions, some of which are quite strongly held. Our
17 goal is that today's meeting will be a fair and open
18 forum for discussion of these issues and that
19 individuals can express their views without
20 interruption.

21 Thus, as a gentle reminder, individuals
22 will be allowed to speak into the record only if

1 they're recognized by myself, the chair. We look
2 forward to a productive meeting.

3 In the spirit of the Federal Advisory
4 Committee Act and the Government in the Sunshine Act,
5 we ask that the Advisory Committee members take care
6 that their conversations about the topic at hand take
7 place in the open forum of the meeting.

8 We are aware that members of the media are
9 anxious to speak with the FDA about these
10 proceedings. However, FDA will refrain from
11 discussing the details of this meeting with the media
12 until its conclusion.

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

16 I next would like to have the members of
17 the committee introduce themselves and we'll start
18 with the FDA.

19 DR. JENKINS: Good morning. I'm John
20 Jenkins. I'm the Director of the Office of New Drugs
21 at FDA.

22 DR. RAPPAPORT: I'm Bob Rappaport. I'm the

1 Director of the Division of Anesthesia, Analgesia,
2 and Rheumatology Products.

3 DR. HERTZ: Sharon Hertz, Deputy Director,
4 Division of Anesthesia, Analgesia, and Rheumatology
5 Products.

6 DR. FIELDS: Ellen Fields, Clinical Team
7 Leader, Division of Anesthesia, Analgesia, and
8 Rheumatology Products.

9 DR. FRANCIS: Good morning. Henry Francis,
10 Deputy Director, the Office of Surveillance and
11 Epidemiology.

12 DR. PROUGH: Don Prough, Chairman,
13 Anesthesiology, at the University of Texas in
14 Galveston.

15 DR. ZITO: Julie Zito, University of
16 Maryland, Baltimore, pharmacoepidemiologist.

17 DR. COOPER: Bill Cooper. I'm a general
18 pediatrician and a pharmacoepidemiologist at
19 Vanderbilt University in Nashville, Tennessee.

20 DR. CRAWFORD: Good morning. Stephanie
21 Crawford, University of Illinois at Chicago, College
22 of Pharmacy.

1 DR. DESHPANDE: Jayant Deshpande, Pediatric
2 Anesthesia and Critical Care, from Vanderbilt
3 University in Nashville.

4 DR. MARKMAN: John Markman, Neurology and
5 Pain Management, University of Rochester School of
6 Medicine, Rochester, New York.

7 DR. DAY: Ruth Day, Director of The Medical
8 Cognition Laboratory at Duke University.

9 DR. LORENZ: Karl Lorenz. I'm a palliative
10 medicine physician and a primary care internal
11 medicine physician with The Veterans Administration,
12 UCLA, and RAND Health.

13 MS. BHATT: Kalyani Bhatt. I'm the
14 Designated Federal Official, FDA.

15 DR. ZELTERMAN: Dan Zelterman. I'm in the
16 Division of Biostatistics at Yale University.

17 DR. SOLONCHE: Martha Solonche, Patient
18 Representative, from New York City.

19 DR. DENISCO: Richard Denisco, Medical
20 Officer, National Institutes of Health.

21 DR. MORRATO: Elaine Morrato,
22 epidemiologist, from the Colorado School of Public

1 Health, University of Colorado, Denver.

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

5 DR. SHATIN: Deborah Shatin,
6 pharmacoepidemiologist, Shatin Associates, LLC,
7 Minnesota.

8 DR. VAIDA: Allen Vaida, Executive Vice
9 President, at the Institute for Safe Medication
10 Practices. I'm a pharmacist.

11 MR. YESENKO: Michael Yesenko, Patient
12 Representative, Brookeville, Maryland.

13 DR. FLICK: Randall Flick, Chief of
14 Pediatric Anesthesia, Mayo Clinic.

15 DR. TORTELLA: Bartholomew Tortella, Novo
16 Nordisk, Industry Representative.

17 DR. KIRSCH: Thank you. I'd like now to
18 have Kalyani Bhatt read the Conflict of Interest
19 Statement.

20 MS. BHATT: Good morning. Thank you.
21 Before I start, we also have Dr. David Margolis by
22 teleconference.

1 DR. MARGOLIS: Hi. I'm David Margolis.
2 I'm at the University of Pennsylvania. I'm in the
3 Department of Dermatology and Department of
4 Biostatistics and Epidemiology. I'm quarantined in
5 my office because my youngest son had H1N1 a couple
6 days ago.

7 MS. BHATT: Thank you, Dr. Margolis.

8 The Food and Drug Administration, FDA, is
9 convening today's Joint Meeting of the Anesthetic and
10 Life Support Drugs and the Drug Safety and Risk
11 Management Advisory Committees under the authority of
12 the Federal Advisory Committee Act, FACA, of 1972.

13 With the exception of the Industry
14 Representative, all members and temporary voting
15 members of the committees are special government
16 employees, SGEs, or regular federal employees from
17 other agencies and are subject to federal conflict of
18 interest laws and regulations.

19 The following information on the status of
20 this committee's compliance with federal ethics and
21 conflict of interest laws covered by but not limited
22 to those found at 18 USC Section 208 and Section 712

1 of the Federal Food, Drug, and Cosmetic Act, FD&C
2 Act, is being provided to participants in today's
3 meeting and to the public.

4 FDA has determined that members and
5 temporary voting members of these committees are in
6 compliance with federal ethics and conflict of
7 interest laws under the 18 USC Section 208.

8 Congress has authorized FDA to grant
9 waivers to special government employees and regular
10 federal employees who have potential financial
11 conflicts when it is determined that the agency's
12 need for a particular individual's service outweighs
13 his or her potential financial conflict of interest.

14 Under Section 712 of the FD&C Act, Congress
15 has authorized FDA to grant waivers to special
16 government employees and regular federal employees
17 with potential financial conflicts when necessary to
18 afford the committee essential expertise.

19 Related to the discussion of today's
20 meeting, members and temporary voting members of
21 these committees have been screened for potential
22 financial conflicts of interest of their own, as well

1 of their imputed to them, including those of their
2 spouses or minor children, and, for purposes of 18
3 USC Section 208, their employers.

4 These interests may include investments,
5 consulting, expert witness testimony, contracts,
6 grants, gratis, teaching, speaking, writing, patents
7 and royalties and primary employment.

8 Today's agenda involves discussion of New
9 Drug Application NDA-22-272 OxyContin, OxyContin
10 Hydrochloride Controlled-release Tablets, sponsored
11 by Purdue Pharma LP, and its safety for the proposed
12 indication of management, moderate to severe, when
13 continuous around-the-clock analgesic is needed for
14 extended period of time.

15 This formulation was previously reviewed
16 and discussed by these committees on May 5th, 2008,
17 and will be considered again in light of new data.
18 This topic is a particular matter involving specific
19 parties.

20 Based on the agenda for today's meeting and
21 all financial interests reported by the committee
22 members and temporary voting members, no conflict of

1 interest waivers have been issued in connection with
2 this meeting.

3 To ensure transparency, we encourage all
4 standing committee members and temporary voting
5 members to disclose any public statements that they
6 have made concerning the product at issue.

7 With respect to FDA's invited industry
8 representative, we'd like to disclose that Dr.
9 Bartholomew Tortella is participating in this meeting
10 as a non-voting industry representative, acting on
11 behalf of regulated industry.

12 Dr. Tortella's role at this meeting is to
13 represent industry in general and not any particular
14 company. Dr. Tortella is employed by Nova Nordisk,
15 Incorporated.

16 We'd like to remind members and temporary
17 voting members that if the discussion involves any
18 other products or firms not already on the agenda for
19 which an FDA participant has personal or imputed
20 financial interests, the participants need to exclude
21 themselves from such involvement and their exclusion
22 will be noted for the record.

1 FDA encourages all participants, including
2 the sponsor's non-employee presenters, to advise the
3 committee of any financial relationships that they
4 may have with the firm at issue, including consulting
5 fees, travel expenses, honoraria, and interest in the
6 sponsor, including equity interest in those based
7 upon the outcome of the meeting.

8 Thank you.

9 DR. KIRSCH: Thank you. I'd like to ask
10 Ellen Fields from FDA to start our session.

11 DR. FIELDS: Good morning. Dr. Kirsch,
12 members of the Anesthesia and Life Support Drugs and
13 the Drug Safety and Risk Management Advisory
14 Committees, invited guests, thank you for joining us
15 today. To those of you who were not here yesterday,
16 welcome, and to those of you who were here yesterday,
17 we appreciate your returning for a second day of
18 discussion regarding another potent modified release
19 opioid product.

20 As I said in yesterday's opening remarks,
21 we are faced with balancing the risks and benefits of
22 new formulations of opioid drug products related to

1 two important public health concerns: the increase
2 in the misuse, abuse, and diversion of these products
3 and the unmet needs of pain patients living with
4 inadequately-treated pain.

5 We heard yesterday, and we'll hear again
6 today, a great deal of information concerning the
7 abuse and diversion of prescription opioid drug
8 products in the United States. Clearly, as a public
9 health agency, we must find better ways to address
10 this public health crisis.

11 At the same time, we are also responsible
12 for maintaining access to these critically-important
13 drug products for legitimate patients.

14 During the open public session yesterday,
15 we heard the personal stories of patients with
16 inadequately-treated chronic pain and the enormous
17 impact this has on the quality of their lives and the
18 lives of their families.

19 Today, we will be discussing Purdue's
20 reformulation of OxyContin, designed to resist
21 attempts to defeat the physical-chemical properties
22 that make it an extended-release formulation. The

1 same product was presented at the Joint Advisory
2 Committee meeting on May 5th, 2008, which many of you
3 attended and at which time the risks and benefits of
4 this new formulation were discussed.

5 The members of the committees were asked to
6 decide whether there was sufficient evidence to
7 support whether the controlled-release mechanism of
8 the new OxyContin formulation was less likely to be
9 defeated than the earlier formulation and how this
10 might impact the abusability of the product.

11 The members were also asked to discuss what
12 would constitute an adequate degree of abuse
13 resistance to warrant changes to a product's label.

14 The overall consensus of the members at the
15 May 5th meeting was that the available data were not
16 adequate to evaluate whether the new OxyContin
17 formulation would be less likely to reduce its abuse,
18 misuse, or diversion.

19 Purdue's intention at the time of the May
20 5th meeting was to market the reformulated OxyContin
21 only in the 10, 20, 30, and 40 milligram strengths
22 and to maintain the non-reformulated 60 and 80

1 milligram strengths on the market at the same time,
2 reformulating these higher-strength doses in the
3 future.

4 The committee members recommended that the
5 higher non-reformulated strengths of OxyContin should
6 not remain on the market if the lower reformulated
7 strengths were to be approved due to the possibility
8 that prescribers would assume the higher-strength
9 formulations were also an abuse-deterrent,
10 potentially resulting in a number of safety concerns.

11 The committee's opinion on whether the
12 label should include any language regarding the
13 tamper-resistant properties of the product was mixed.
14 The reformulated OxyContin was not approved at that
15 time because the studies of the effects of the
16 physical and chemical manipulation of the new
17 formulation were not conducted with adequate rigor
18 and did not result in information that would allow
19 determination of the actual degree of tamper
20 resistance that exists for the formulation.

21 Purdue has resubmitted the NDA for the
22 reformulated OxyContin with additional data regarding

1 the physical-chemical attributes of the product.
2 They are proposing to market only the reformulated
3 OxyContin as all strengths have now been reformulated
4 and to remove the currently-approved formulation from
5 the market.

6 In contrast to the application reviewed at
7 the advisory committee on May 5th, in the current
8 application, Purdue has not requested labeling to
9 support abuse-resistant claims.

10 Following presentations from Purdue and
11 FDA, you will be asked to discuss whether the studies
12 performed by the sponsor are adequate to provide data
13 on the abuse-deterrent characteristics of the
14 reformulated OxyContin product, whether the change in
15 formulation affects the overall safety profile of
16 OxyContin, and whether this application for
17 reformulated OxyContin should be approved.

18 We hope with your varied expertise and
19 extensive experience will help us answer these
20 important questions. Thank you for assisting us with
21 this challenging task.

22 DR. KIRSCH: Next on the agenda is

1 Anjelina, I can't pronounce the last name. Anjelina
2 P. Dr. Anjelina.

3 DR. POKROVNICHKA: Good morning. That's
4 actually how patients refer to me, as well.

5 My name is Anjelina Pokorvnichka, and I'm a
6 medical reviewer in the Division of Anesthesia,
7 Analgesia, and Rheumatology Products.

8 My presentation will outline the history of
9 OxyContin to date and will include important changes
10 to the product label and a discussion of the risk
11 management activities for OxyContin.

12 OxyContin was approved in December of 1995.
13 The approval occurred during a period of growing
14 recognition that many patients with chronic pain were
15 inadequately treated. However, at the same time the
16 abuse and diversion of prescription drugs was
17 increasing.

18 The initial label indicated that OxyContin
19 is a Schedule II drug. The clinical trials section
20 of the label described the result of several trials
21 in patients with cancer and non-cancer pain, in
22 opioid-naïve patients, and the results of open label

1 and equivalence trials.

2 Initially, OxyContin was indicated for the
3 management of moderate to severe pain when an opioid
4 would be required for more than a few days. The
5 warnings, dosage, and administration section of the
6 label cautioned against destroying the integrity of
7 the tablets and informed that this can lead to the
8 release of a potentially toxic amount of oxycodone.

9 Notably, the drug abuse and dependence
10 section stated that the delayed absorption provided
11 by the controlled-release properties of the drug is
12 believed to reduce the abuse liability of OxyContin.

13 In 1996, the 18 milligrams strength was
14 approved followed in 2000 by the approval of the 160
15 milligram tablet. The label was revised to reflect
16 that this high strength should be used only in
17 opioid-tolerant patients who require a total daily
18 dose of a 160 milligrams or 320 milligrams.

19 Around the time when the 160 milligrams
20 strength was approved and released, Purdue began an
21 aggressive marketing campaign. Through considerable
22 advertising and other strategies, the company

1 promoted the use of OxyContin, mainly among primary
2 care providers as compared to pain specialists.

3 Purdue also promoted the use of OxyContin
4 for non-cancer pain, including pain due to
5 osteoarthritis and postoperative pain. Also,
6 OxyContin was promoted as first-line therapy for
7 chronic pain, which was inconsistent with pain
8 treatment guidelines.

9 In May of 2000, the Division of Direct
10 Marketing, Advertising, and Communications issued an
11 untitled letter to Purdue regarding some of its
12 promotional materials. The letter cited the company
13 for making misleading efficacy claims inconsistent
14 with the label, as well as safety-related text,
15 providing incomplete information for the proper
16 administration of the drug. Following receipt of the
17 letter, Purdue ceased dissemination of these
18 activities.

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

1 result, patients experienced adverse events or
2 effects, including addiction and even fatalities.
3 Also, worse was the fact that teenagers were part of
4 the population abusing OxyContin.

5 There are several possible reasons for why
6 OxyContin became a favored drug of abuse and
7 diversion. A recent study suggests that oxycodone is
8 more reinforcing than morphine. Of note, OxyContin
9 has a higher oxycodone content compared to immediate
10 release oxycodone. Also, in contrast to the initial
11 belief that the pharmacokinetics of the controlled-
12 release formulation would render the drug less
13 abusable, more recent experience has shown that this
14 isn't the case, if the controlled-release properties
15 of the drug are defeated.

16 An additional contributing factor to the
17 increase in OxyContin abuse and diversion is the
18 increased availability of OxyContin. With the
19 emphasis on good pain management, prescribers have
20 been more accepting of the use of opioids to treat
21 pain. That, combined with Purdue's push to promote
22 OxyContin may have led to the increased availability

1 of the drug.

2 Finally, the product labeling could have
3 been a factor. Warnings regarding the release of a
4 high-dose oxycodone with crushing of the pill could
5 have alerted some abusers to how they could misuse
6 the drug. Also, the language about lower abuse
7 potential of OxyContin may have misled patients and
8 prescribers about the actual addictive risks of
9 OxyContin.

10 Both Purdue and FDA took actions to
11 evaluate and attempt to reduce the abuse and
12 diversion of OxyContin. Purdue elected to
13 discontinue marketing of the high-strength 160
14 milligram tablet. FDA experts were focused on
15 reviewing all available data to look at OxyContin-
16 prescribing practices as well as adverse events.

17 As part of the actions to reduce the abuse
18 and diversion of OxyContin, the company and FDA also
19 worked together to develop a risk map that included
20 education and outreach, labeling, surveillance and
21 intervention.

22 As a result of what was learned about abuse

1 and diversion of OxyContin, the agency decided to
2 revise the product label. The revised OxyContin
3 label was approved in July of 2001 and key changes
4 were as follows.

5 First, a boxed warning was added that
6 described the potential for abuse, misuse, and
7 diversion of OxyContin and emphasizes the proper
8 patients for treatment. The clinical trials section
9 was restricted to the sole adequate and well-
10 controlled trial, and the indications section was
11 well written to specify the appropriate treatment
12 population.

13 The indications section now stated that
14 OxyContin is indicated for the management of moderate
15 to severe pain when a continuous around-the-clock
16 analgesic is needed for an extended period of time.
17 The indications section also stated the patients for
18 whom OxyContin is not appropriate, including those
19 who need PRN or as-needed dosing and those in the
20 immediate postoperative period.

21 The warnings section was expanded and
22 rewritten with more prominent and detailed language

1 that cautions against destroying the integrity of the
2 pills and describes the potential for misuse, abuse,
3 and diversion of OxyContin.

4 With respect to the drug abuse and
5 dependence section, the sentence implying reduced
6 abuse liability of OxyContin because of the
7 controlled-release formulation was deleted.

8 The agency held several advisory committee
9 meetings to discuss the use of opioid analgesics in
10 pain patients as well as the potential for abuse and
11 misuse.

12 At the 2002 meeting, the opioid analgesic
13 use, misuse, and abuse, as well as the use of opioids
14 in pediatric patients was discussed. It was
15 concluded that while abuse of opioids is a
16 significant public health problem, these drugs are
17 important for proper pain management. It was also
18 noted that an overly-restrictive risk management plan
19 may limit the proper use of these drugs in legitimate
20 patients.

21 In 2003, the agency held another advisory
22 committee meeting, this time to discuss risk

1 management plans in general and specifically one that
2 had been proposed for Palladone, an extended-release
3 formulation of hydromorphone.

4 I will abbreviate risk management plan as
5 RMP in my talk.

6 At the end of the meeting, it was generally
7 agreed that RMP should have the components of
8 prescriber and patient education and surveillance of
9 the drug misuse, abuse, and diversion, and should
10 also assess the impact of opioid-prescribing
11 practices.

12 The initial NDA application for the new
13 OxyContin formulation was discussed at an advisory
14 committee meeting held in May 2008. The committee
15 concluded that tamper-resistant claims were not
16 adequately supported by the available data. Also, a
17 concern was expressed that inclusion of the new
18 physiochemical properties in the label may result in
19 false security and adversely impact the already-
20 existing addiction and overdose problems. With
21 regards to the RMP, it was recommended that it be
22 directed to the entire opioid class.

1 In November of 2008, a meeting of the
2 advisory committee was held to discuss another
3 extended-release oxycodone formulation, Remoxy XRT.
4 The inadequacy of data to support tamper resistance
5 and false security from including the new properties
6 in the label were discussed again. The committee
7 also emphasized on the need to define minimum
8 standards for assessment of tamper-resistant
9 qualities.

10 According to Section 501 of the FDA
11 Amendments Act, the agency has been granted authority
12 to require risk evaluation and mitigation strategies,
13 or REMS, for products when it is necessary to ensure
14 that the benefits of the drug outweigh the risks.

15 FDA's working on a class-wide REMS strength
16 to include all extended-release and long-acting
17 opioids. Until the class-wide opioid REMS is
18 implemented, the agency has determined that extended-
19 release opioids may be approved as long as the risk-
20 benefit ratio is at least as good as already approved
21 extended-release opioids.

22 As with the recent approval of an extended-

1 release morphine product, OxyContin would have an
2 interim REMS should it be approved. The proposed
3 interim REMS OxyContin will consist of a medication
4 guide and a communication plan that includes Dear
5 Healthcare Provider and Dear Pharmacist letters and a
6 timetable for submission of assessments.

7 To summarize, the agency and Purdue have
8 worked to strengthen OxyContin's product label and
9 develop a risk management plan. Nevertheless, abuse
10 and diversion of OxyContin continue to be a
11 considerable public health problem. While it is
12 desirable to have a less abusable controlled-release
13 oxycodone on the market, the actual impact of this
14 product abuse is unknown. Epidemiologic studies of
15 abuse will be required to assess the impact of
16 reported abuse-resistant formulations.

17 Thank you.

18 DR. KIRSCH: Thank you. Next will be Dr.
19 Katherine Dormitzer.

20 DR. DORMITZER: Good morning. My name is
21 Katherine Dormitzer. I'm an epidemiologist in the
22 Division of Epidemiology in the Office of

1 Surveillance and Epidemiology.

2 Today, I'm going to present a brief summary
3 of the presentations that were previously presented
4 at the AC meeting that was held on May 5th. This
5 presentation will include presentations that included
6 data from SAMHSA, which is the Substance Abuse Mental
7 Health Services, which would be TEDS, which is the
8 Treatment Episode Dataset, NSDUH, which is the
9 National Survey on Drug Use and Health, and DAWN, the
10 Drug Abuse Warning Network, as well as previously-
11 presented analysis on drug abuse ratios associated
12 with OxyContin.

13 TEDS, otherwise which is the Treatment
14 Episode Dataset, is a data system that provides
15 descriptive information about the admissions from
16 alcohol or treatment facilities that were publicly-
17 funded. It collects annual data on the number and
18 characteristics of persons admitted to these
19 programs. And although information is available on
20 the drug substance or class that was responsible for
21 these admissions, only 16 states report on the
22 specific opioid that was involved in this admission.

1 This slide shows that opioid analgesics
2 were the primary substance responsible for admissions
3 to a treatment program in 2006. It's 4 percent. And
4 based on the 16 states that provided data on the
5 specific opioid involved in this treatment admission,
6 oxycodone was mentioned 15,000 times. And as you can
7 see, the number of admissions for opioid analgesics
8 began to increase after OxyContin was approved.

9 Now I'm going to just summarize the
10 National Survey on Drug Use and Health. It's called
11 NSDUH, and it was formerly titled the National
12 Household Survey on Drug Abuse. And it provides
13 reports on quarterly and annual estimates on the
14 abuse of illegal drugs, alcohol, tobacco, as well as
15 benign medical use of prescription drugs. And that's
16 where this -- the question that they ask is, you
17 know, did you take this drug that was not prescribed
18 for you or you took the drug only for the experience
19 or feeling it caused?

20 Here's a pill show card that respondents
21 used to identify the pain reliever that they
22 responded was used non-medically. and as you can

1 see, we have oxycodone products up there and
2 then -- where are the OxyContins? Okay. Well, I
3 lost them, but they're on this pill show card.

4 These are the estimates in millions of the
5 non-medical use of pain relievers by type. This is a
6 lifetime use estimate. So respondents may not have
7 necessarily have used a substance in the past year.
8 And as you can see, there were 4.1 million lifetime
9 users of OxyContin specifically.

10 This slide presents past year use of
11 OxyContin. And as you can see, there were more than
12 500,000 people in the United States that used
13 OxyContin non-medically for the first time. That's
14 the past year initiates. There were more than a
15 million people who used OxyContin non-medically in
16 the past year and this is by year, 2004 to 2006. And
17 more than 300,000 people endorsed DSM criteria for
18 dependence. Again, you can see it, 2004 to 2006.

19 This slide displays the percentage of
20 people with drug dependence among past year users of
21 each drug type. So for OxyContin, 5 percent of past
22 year users responded with symptoms of DSM criteria

1 for drug abuse and 23 percent of past year users
2 responded with symptoms of DSM criteria for drug
3 dependence.

4 The Drug Abuse Warning Network, DAWN, is
5 administered by SAMHSA and it's a public health
6 surveillance system of emergency room visits and will
7 provide national estimates on these visits.

8 Okay. I'm going to be providing estimates
9 on the non-medical use of pharmaceuticals, which
10 would be over here. And here, the confidence
11 intervals help because when the confidence intervals
12 overlap, then they're not statistically significant.
13 And what you can see here is that the DAWN estimates
14 for 2006 related to hydrocodone and to oxycodone
15 overlap a great deal.

16 This is a presentation of the national
17 estimates in DAWN on the extended-release
18 formulations and the immediate release formulations.
19 And again, you can see a fair amount of overlap in
20 the estimates. These are visits in thousands, so
21 22,000 visits, 18,000 visits in 2004.

22 So now I'm going to be presenting on the

1 drug abuse ratios. So for the numerator data, I will
2 be using DAWN, and for denominator data, I will be
3 using drug utilization data and calculate estimates
4 per 10,000 retail prescriptions.

5 Again, the numerator, these were the
6 estimates that we saw for hydrocodone and oxycodone,
7 and we saw that they were basically the same. And
8 denominator, that's not what's shown. What's shown
9 is that the number of hydrocodone prescriptions are
10 significantly higher than they are for all oxycodone
11 products.

12 Therefore, when you look at the ratios of
13 ED visits per 10,000 prescriptions, the numbers for
14 hydrocodone are remarkably lower than for oxycodone.
15 But now what we're looking at is extended-release
16 oxycodone products and immediate release oxycodone
17 products and this is the numerator. As you can see,
18 they're very similar, but the denominator, immediate
19 release oxycodone products, is again significantly
20 higher than the extended-release. And so, what we're
21 seeing again is that the immediate release products
22 here, the numbers of non-medical use per 10,000

1 prescriptions, is considerably lower than for the
2 extended-release oxycodone products.

3 So there are limitations with these when
4 we're calculating these estimates because they are
5 different sampling methodologies, they are different
6 populations, and the data are in no way linked. What
7 this means is that DAWN does not have information on
8 did the patient have a prescription to the drug that
9 brought them to the ED.

10 So what we are seeing from TEDS, NSDUH and
11 DAWN is that there is a significant public health
12 burden on the non-medical use of opioids and
13 specifically for OxyContin, and that even though the
14 ratios appear to be stable, in other words the
15 numbers per 10,000 retail visits appears to be fairly
16 flat, the numbers of users are actually increasing
17 because the numbers of prescriptions are also
18 increasing.

19 Thank you.

20 DR. KIRSCH: Thank you.

21 We're now scheduled to take a break. The
22 break will be 10 minutes in duration. Committee

1 members, please remember that there should be no
2 discussion of the meeting topic during the break
3 amongst yourselves or with any member of the
4 audience. We will resume at 10:05.

5 (Whereupon, a recess is taken.)

6 DR. KIRSCH: I'd like to have everyone
7 please take their seats.

8 I'd like to welcome the sponsor to the
9 podium for their presentation. First for the sponsor
10 is John Stewart.

11 DR. LANDAU: Good morning. I am Craig
12 Landau. I'll be introducing John Stewart. But I
13 wanted to thank everyone in attendance for inviting
14 us here to participate. I'll be facilitating this
15 morning's public session. I'll also be presenting
16 some of the segments on the agenda.

17 Our president and chief executive officer,
18 Mr. John Stewart, has some introductory remarks to
19 make.

20 DR. STEWART: Thank you, Craig, and good
21 morning, ladies and gentlemen. We appreciate the
22 opportunity to speak with you today.

1 As Craig has said, I'm John Stewart,
2 president and CEO of Purdue Pharma, and I assumed
3 this role 15 months ago, but my experience with the
4 organization goes back for many years.

5 I was previously head of Purdue Pharma in
6 Canada, and prior to that, led the research and
7 development activities in that country where I was
8 closely involved with the development and
9 registration of controlled-release formulations of
10 morphine, codeine, hydromorphone, as well as
11 oxycodone.

12 The majority of our presentation today will
13 be led by our chief medical officer, Craig Landau,
14 and Craig will call on several of our colleagues and
15 two external experts who worked with us on the
16 development of this new formulation. But prior to
17 that, I'd like to just take a few minutes to give you
18 some background on Purdue Pharma, the development of
19 OxyContin, and our involvement in many activities
20 that are designed to reduce abuse, misuse, and
21 diversion.

22 Purdue Pharma is a research-based

1 pharmaceutical company and for the past 25 years has
2 been one of the leading companies in the area of pain
3 research. By far, our best-known pain products are
4 MS Contin, a controlled-release formulation of
5 morphine, and OxyContin.

6 Introduced in 1984, MS Contin was the first
7 controlled-release opioid marketed in the United
8 States, and it was widely recognized as a significant
9 advance for the treatment of cancer pain. OxyContin
10 itself was developed in the late 1980s and early
11 1990s, and since being approved in 1995 has been
12 prescribed to millions of patients, providing relief
13 from pain and improving the quality of many lives.

14 As we know from the history of the past
15 years, unfortunately, OxyContin's delivery system can
16 relatively easily be compromised and when that
17 happens, overdose can occur.

18 As you know, OxyContin has also become a
19 target of abuse by both educated addicts and
20 recreational abusers, sometimes with fatal
21 consequences. Accidental misuse by patients or
22 caregivers has also been a real, if less frequent,

1 problem. And for these reasons, we are here to talk
2 to you today about our efforts to reformulate
3 OxyContin. These efforts reflect our appreciation of
4 the deep sorrow that is caused by the loss of loved
5 ones to drug abuse and at the same time the
6 importance of providing therapeutic options for
7 patients suffering from chronic pain.

8 Our aim is to introduce a new formulation
9 of OxyContin, a formulation that has all the same
10 efficacy as the existing product but with additional
11 physiochemical properties to make it more difficult
12 to certain routes of abuse.

13 We fully recognize, however, that a new
14 formulation is not going to be possible to address
15 all forms of abuse, and a new formulation, for
16 example, cannot impact individuals who simply take a
17 quantity of tablets and wait for the contents to be
18 released over time. And for this reason, we see the
19 introduction of this new formulation as only one
20 element, albeit an important element, of the many
21 activities to reduce abuse, diversion, and misuse.

22 It is our belief that through a variety of

1 activities, we can make a significant impact on the
2 abuse of prescription opioids while at the same time
3 not overly restricting the availability of these
4 needed drugs for patients in pain.

5 As such, we are committed to pursuing a
6 wide variety of actions to reduce abuse, including
7 working with the FDA, key stakeholders, and other
8 members of the pharmaceutical industry to develop a
9 class risk evaluation and mitigation strategy to be
10 applied to all long-acting opioids.

11 We'll also continue our long-standing
12 support of community partnerships and anti-abuse
13 campaigns and investments in activities to support
14 law enforcement and crime reduction. We also have a
15 number of other programs that Pamela Bennett will
16 describe more fully in her presentation.

17 In closing, we've learned a great deal from
18 our experience with OxyContin. We understand that
19 while we manufacture and develop products to bring
20 important therapeutic benefits to patients, those
21 products carry real risks. Across our entire
22 organization, it is our responsibility and commitment

1 to take actions to see that those products are
2 appropriately prescribed and used as directed while
3 at the same time mitigating against their risks of
4 abuse, diversion, and misuse.

5 Thank you very much for your attention and
6 now let me turn the meeting back over to Craig.

7 DR. LANDAU: Thank you, John. So here's
8 how our public session is laid out for the rest of
9 the morning. After some introductory remarks of my
10 own, Pamela Bennett will provide a summary of some of
11 the efforts Purdue's taking to address the abuse of
12 our product and other opioids. We'll speak to
13 polyethylene oxide, the primary excipient in the new
14 formulation. We'll present data demonstrating
15 bioequivalence of the reformulation to the current
16 product, and we'll hear from one of our external
17 experts, Dr. Ed Cone.

18 Dr. Ed Cone will describe the approach we
19 took with his assistance and other experts in
20 designing our in vitro testing program. One of my
21 colleagues from Purdue will present representative
22 and properly-redacted summary methods and results,

1 and another one of our external experts, Dr. Ed
2 Sellers, will provide his interpretation of the
3 results of these in vitro studies and his view of the
4 potential impact the reformulation can make in
5 multiple settings.

6 I'll conclude with some remarks on what we
7 understand about the reformulation and why we believe
8 we should be transitioning to the new formulation in
9 the marketplace just as soon as possible.

10 Now, it's important to start with what's
11 relevant for our development path here. As John
12 mentioned, this product, the original formulation and
13 the reformulation, are developed for patients. Over
14 one million patients every year are treated with
15 OxyContin and they use it to effectively manage their
16 pain and maintain a certain quality of life.

17 The current product has a specific
18 vulnerability and it's well understood by all of us.
19 It can be easily crushed within a matter of seconds
20 with no more than a bottom of a glass or two spoons,
21 rendering all of its oxycodone immediately available,
22 whether this is an intentional act or an inadvertent

1 one.

2 This is what makes it attractive to abusers
3 who seek to manipulate the tablets for a rapid or
4 fast high or what makes it dangerous for experimental
5 abusers, including teenagers who might receive the
6 product in a schoolyard and be told to crush it or
7 chew it. This is why we reformulated the product and
8 this is why we're here today to speak about it.

9 Now to understand the potential value of
10 the reformulation through the in vitro experiments
11 we've conducted, it's important to understand how the
12 current product performs when taken as directed into
13 an intact form. And we can see this in results of
14 standard dissolution testing.

15 What I have here plotted on the vertical
16 axis is percentage of oxycodone released from a
17 current intact OxyContin tablet. It's plotted over
18 time on the horizontal axis, and what's obvious is
19 that over 12 hours, all the oxycodone is released.
20 This is how it becomes therapeutic for patients.

21 Now this picture changes dramatically when
22 the tablet's crushed. Something I mentioned a moment

1 ago, it happens quickly and easily in a matter of
2 seconds. And here you have a picture of a crushed
3 OxyContin current tablet. If you can't make out the
4 resolution in the back, it resembles bleached flour.
5 It's a fine series of particles. This is all
6 oxycodone and excipient.

7 Here are the corresponding dissolution
8 profiles for tablets manipulated with a pill crusher,
9 a mortar and pestle, or even two spoons from a
10 kitchen cabinet. What's obvious here through
11 analysis of the first 60 minutes is that all of the
12 oxycodone in a given tablet is available within 5 to
13 10 minutes. Again, this is why we reformulated and
14 this is why we're here to discuss it.

15 We understand that with the exception of
16 swallowing, which is another substantial route of
17 abuse, swallowing of intact tablets, crushing
18 underlies the abuse and misuse of OxyContin through
19 many routes of administration, oral administration,
20 snorting, rectal administration, smoking and, of
21 course, intravenous injection, a very dangerous
22 practice. It's also a precursor to further chemical

1 manipulation for the purposes of extracting drug from
2 the tablet.

3 But the importance of crushing, where the
4 relevance is not lost simply on abusers, it's also
5 relevant for patients in the context of medication
6 errors. We understand this occurs. We have reports
7 of this in our database and FDA has reports of it in
8 their reporting system.

9 Inadvertent crushing or chewing by a
10 patient or administration of a crushed tablet by a
11 well-intended caregiver is something that occurs.
12 And although it doesn't involve crushing or
13 manipulation, another important question to ask
14 ourselves is, is this new formulation sensitive to
15 the effects of alcohol? Does it dose dump in alcohol
16 when a patient might inadvertently administer, self-
17 administer the tablet along with a beer, wine, or
18 even a cough suppressant at night.

19 So we started to address these issues
20 through reformulation as far back as 2000. We used
21 multiple technologies and formulation platforms. We
22 conducted multiple in vitro experiments, non-clinical

1 experiments, and even in vivo studies to assess a
2 variety of formulations that could help to address
3 the problem I just presented.

4 Ultimately in 2004, we began focusing on
5 the formulation we're talking about today. It's a
6 single entity, controlled-release formulation of
7 oxycodone that utilizes a different primary
8 excipient, polyethylene oxide. We'll speak about it
9 in a little while.

10 In November 2007, after discussing the
11 elements of the development plan with FDA, the Review
12 Division, we filed the initial NDA. The NDA included
13 data supporting the bioequivalence of a subset of the
14 tablet strengths, 10 through 40 milligrams.

15 In May of 2008, we participated in our
16 first advisory committee meeting for this
17 formulation, and later that year, in October, we
18 received a complete response letter. The formulation
19 was not approved.

20 In March of this year, we resubmitted the
21 NDA, this time with data supporting bioequivalence of
22 the remaining strengths, the 60 and 80 milligram

1 tablets, and also data from a comprehensive in vitro
2 testing program that very clearly demonstrate the
3 physiochemical differences between the reformulated
4 product and the product it's intended to replace. Of
5 course, we're here today in our second advisory
6 committee and we're looking forward to a productive
7 discussion.

8 Now to make certain we designed and
9 conducted experiments that were sensitive to the
10 comments and the suggestions received from the
11 advisory committees and from FDA, we consulted
12 experts in abuse and tablet manipulation.

13 Two of these experts are here with us
14 today. They'll be presenting a little later on in
15 the public session. These are Dr. Ed Cone and Dr. Ed
16 Sellers.

17 Based on their input, the input of the
18 combined advisory committees, and specific guidance
19 from FDA, we've modified our approach in three very
20 important ways and it's very important everyone
21 understands this.

22 Of course, we've submitted results from a

1 comprehensive in vitro testing program demonstrating
2 a clear incremental improvement upon the current
3 formulation.

4 Since we've reformulated the remaining
5 strengths, we're now in a position to introduce all
6 of them at the same time. And, most importantly, our
7 proposed package insert includes no reference to
8 tamper testing, in vitro data, tamper resistance,
9 abuse resistance, or abuse deterrence.

10 I'd like to pause for a moment before
11 moving on with the next portion of our agenda, as I
12 think it's very important that we're clear.

13 Unless and until post-marketing
14 epidemiology data support it, Purdue will not and
15 cannot assume and promote that the reformulation
16 carries any less abuse liability than the current
17 formulation.

18 Our next speaker is Pamela Bennett. She'll
19 be speaking to some of the efforts Purdue has
20 undertaken to address the opioid abuse problem of
21 OxyContin and other drugs.

22 Pamela.

1 MS. BENNETT: Thank you, Craig.

2 Good morning. My name is Pamela Bennett.
3 I'm a registered nurse and the past president for the
4 American Society of Pain Management Nursing. I've
5 spent my career caring for people with pain, be it at
6 the bedside, in management, as an advocate, or in my
7 current role with the company. This is my life's
8 work.

9 Shortly after joining Purdue in 2001, I
10 became involved with several of our company's efforts
11 to address prescription drug abuse. We recognize,
12 both as individuals and as a company, the tragic
13 consequences that can result from the abuse and
14 misuse of prescription medications.

15 While we are here today to discuss the new
16 formulation of OxyContin, we recognize that there's
17 not one single solution to combat the problem of
18 prescription drug abuse. And that is why we are
19 partnering with numerous stakeholders, including
20 industry, government, law enforcement, healthcare
21 professionals, patients and communities to address
22 this problem.

1 We recognize these efforts cannot be
2 fleeting and they will require sustained attention
3 and commitment on the part of all people involved,
4 and Purdue is committed. And today I'm going to
5 highlight just a few areas in which we've been active
6 in this area.

7 Our efforts have encompassed national
8 initiatives to detect abuse and diversion,
9 encouraging states to enact effective prescription
10 monitoring programs, as well as efforts to educate
11 local law enforcement, healthcare professionals, and
12 communities.

13 One of our major efforts was the creation
14 of the RADARS System. In direct response to the
15 abuse problem in 2001, Purdue convened an advisory
16 panel of external experts to develop a timely and
17 geographically-specific monitoring program to detect
18 abuse and diversion of opioid analgesics.

19 The RADARS System draws together the
20 broadest range of early warning systems, providing
21 stakeholders with a first alert for significant
22 changes in abuse trends. As you know, in 2006 Purdue

1 transferred ownership of the system to the not-for-
2 profit Denver Health and Hospital Authority, which
3 now owns and operates it independently.

4 Supporting appropriately-designed state
5 prescription monitoring programs is another one of
6 our national efforts. The goal of these programs is
7 to identify, deter, and prevent drug abuse and
8 diversion while supporting access to the legitimate
9 use of these medicines.

10 One example of what a PMP can do is it can
11 help identify those individuals who are doctor
12 shopping or are going to multiple prescribers to
13 obtain multiple prescriptions.

14 Again, early on, since October of 2001,
15 Purdue has supported the development and passage of
16 state legislation to adopt appropriately-designed
17 PMPs. We continue to partner with state health
18 departments, licensing boards, and professional
19 societies to promote the use of this program. To
20 date, 40 states have enacted legislation in this
21 area. We also recognize the importance of education
22 at the community level and we're engaged with a

1 variety of efforts with law enforcement, healthcare
2 professionals, and the public.

3 Purdue's law enforcement education and
4 liaison program, which is staffed by drug diversion
5 experts, provides education and technical assistance
6 to law enforcement agencies to help them effectively
7 combat drug diversion. The program also helps
8 healthcare professionals recognize and prevent
9 attempts by diverters to inappropriately obtain
10 controlled substances.

11 This effort is in addition to our ongoing
12 commitment to healthcare professionals in their
13 education. We make unrestricted educational grants
14 to accredited providers of medical education, such as
15 hospitals and academic institutions. The funded
16 programs have reached over 1.2 million healthcare
17 professionals.

18 We have also engaged with community
19 organizations and individuals across the country to
20 raise awareness about the dangers of prescription
21 drug abuse, and I'd like to just share two brief
22 examples.

1 Since 2001, we've been working with
2 national drug abuse organizations, such as the
3 Partnership for Drug-Free America, and with local
4 community coalitions to raise public awareness of the
5 problem.

6 In 2002, Purdue created the Medicine
7 Cabinet Public Service Campaign to educate the public
8 and communities where abuse was a particular problem
9 about the importance of safeguarding medications in
10 the home. The picture seen here is what is present
11 in the newspaper ad that we run.

12 Prescription drug abuse is a serious
13 problem. And as I can tell you as a mother, I worry
14 about the welfare of my daughter, and I would do
15 anything I could to protect her and to keep her safe.
16 I've spoken to parents who have lost a loved one to
17 overdose and I can't even begin to imagine the depths
18 of the grief and loss that they experience.

19 We are committed to combat this problem, to
20 help prevent needless tragedies that result from the
21 misuse and abuse of these prescription drugs.

22 As a nurse and a caregiver, I also know the

1 burden that pain has on our society and the impact it
2 has on patients and their families, the day-to-day
3 moment-by-moment struggles that many of these people
4 suffer. Many lose their ability to enjoy life or to
5 work. Most become isolated. Several lose their
6 families and, unfortunately and tragically, some lose
7 their lives.

8 Managing people's pain provides an
9 opportunity for people to have their life back. And
10 I can tell you there's nothing more rewarding than to
11 help someone go back to work or to be able to hold
12 their child or to be able to find joy in the simple
13 things that make life meaningful for all of us.

14 I believe that as a society we must do
15 whatever it takes to ensure that people with pain
16 have effective access to appropriate and effective
17 care.

18 My hope is that, as you consider the
19 science of what is being presented today and the very
20 real and significant problem of prescription drug
21 abuse, that you will not forget and that you will
22 remember the needs of the very patients that we

1 strive to serve.

2 Thank you.

3 DR. LANDAU: Okay. Before we move on to
4 present data demonstrating bioequivalence of the
5 reformulated product to the current formulation, I
6 thought I'd speak just a few minutes, short minutes,
7 a bit on the formulation's primary excipients, since
8 it's new, to the formulation, polyethylene oxide.

9 Polyethylene oxide is inert and it's found
10 in a great many foods and pharmaceutical agents.
11 It's an ideal excipient for us in this formulation
12 because when subject to a specific manufacturing
13 process, it confers hardness to the tablets. And
14 based upon its underlying properties, it hydrogels in
15 small volumes of water, and you'll see this in a few
16 minutes. It was this absorption of water that
17 allowed us to create this bioequivalent formulation
18 to the current product.

19 So here's the structure of polyethylene.
20 Polymers, containing multiple subunits of this
21 structure, are distinguished from one another based
22 upon the number of times the subunit repeats and,

1 hence, its molecular weight. Polymers with less than
2 roughly 2,300 repeats of this structure or a
3 corresponding molecular weight of less than 100,000
4 are generally considered polyethylene glycols or PEG,
5 very common component of many medications that are
6 currently marketed. They exist as liquids to waxes.

7 Polymers that have more than 2,300 repeats
8 of the structure are considered polyethylene oxides.
9 They exist as waxes, waxes to powders. You can see a
10 white dot on this arrow represents the specific
11 molecular weight of the polyethylene oxide used in
12 this formulation.

13 I mentioned polyethylene oxide is not new.
14 It's found in many pharmaceutical products. We've
15 listed just a few of them, a handful here. These are
16 over-the-counter medications, some of which are
17 indicated for the treatment of children. They're
18 mostly cough suppressants or cough/cold medications
19 here, but it's also a well-known component of a
20 variety of prescription medications, including some
21 that have been marketed for 20 years or more and used
22 in the treatment of millions of patients.

1 So there are three important components or
2 factors to keep in mind throughout the public
3 presentations and the discussions that follow
4 regarding polyethylene oxide.

5 Its slow uptake of water makes it an ideal
6 excipient to be used in controlled-release
7 formulations like OxyContin. Its hydrogelling
8 properties in small volumes and the hardness it
9 confers when subjected to a specific manufacturing
10 process make it an excellent choice to make tablets
11 harder and more difficult to manipulate. And,
12 finally, as I mentioned just a moment ago, its
13 longstanding track record of use in multiple
14 pharmaceutical products and foods assures us that
15 it's a safe excipient to use.

16 With this, we'll begin our presentation of
17 data. These are data demonstrating bioequivalence of
18 the reformulation to the current product, and for
19 this I'll call on Dr. Stephen Harris, who heads up
20 our Clinical Pharmacology Department at Purdue.

21 DR. HARRIS: Thanks, Craig. Before briefly
22 reviewing the design of our bioequivalence and dose

1 proportionality pivotal studies, I'd like to spend
2 just a moment reviewing some of the terms that
3 provide a context for the conduct of these studies.

4 Bioequivalence is the demonstration of the
5 absence of a major difference, in this case, of
6 oxycodone exposure. And bioequivalence is assessed
7 statistically by standardized FDA methodology that's
8 been promulgated in various guidance documents and
9 has been in successful use for over 20 years.

10 The essence of this statistical testing is
11 establishing 90 percent confidence intervals for the
12 relevant pharmacokinetic comparisons and
13 demonstrating that those 90 percent confidence
14 intervals lie within the defined acceptance range of
15 80 to 125 percent.

16 Therapeutic equivalence, as Craig mentioned
17 earlier, was the goal of our reformulated product in
18 order to ensure that it will deliver the same safe
19 and effective treatment to patients when taken as
20 directed, and bioequivalence provides the support for
21 that through the determination that in fact oxycodone
22 exposures are similar.

1 Bioequivalence testing involves a test
2 formulation. In today's case our reformulated
3 OxyContin product is the test formulation and a
4 reference comparator, in this case the current
5 OxyContin formulation.

6 Bioequivalence determinations are commonly
7 used in drug development. They underwrite the
8 approval of generic drugs. They are also used in new
9 drug application contexts. For example, when a
10 sponsor changes a formulation slightly between Phase
11 III pivotal studies and the introduction of a
12 commercializable dosage form, demonstration of
13 bioequivalence allows therapeutic equivalence between
14 those two related formulations to be established.

15 In addition, bioequivalence studies are
16 used in a post-approval setting, such as the one
17 before us today, where a formulation change, a
18 manufacturing site change, an excipient change, or
19 other change requires a demonstration in human beings
20 of the comparability of exposure to the active
21 pharmaceutical ingredient.

22 We have conducted six pivotal

1 bioequivalence studies and two pivotal studies to
2 assess dose proportionality. I'd like to begin to
3 explain the bioequivalence studies by showing the
4 three tablet strengths at which these studies were
5 conducted. We have the 10 and 80 milligram
6 strengths, which are respectively the lowest and
7 highest tablet strengths for both the current
8 OxyContin formulation and the reformulated product,
9 and we also studied the intermediate strength of 40
10 milligrams.

11 At each of these three tablet strengths, we
12 conducted paired studies under fasted conditions as
13 well as under fed conditions. And this is consistent
14 with FDA guidance regarding modified-release products
15 where one needs to study them -- in addition to the
16 fasted state, to study them in the fed state where
17 administration of a standardized high-fat meal
18 stimulates the various physiological and chemical
19 changes in the gastrointestinal tract that may
20 produce a lack of comparability.

21 In the middle we have features that are in
22 common to all of the studies we've conducted. They

1 were randomized open label single-dose comparisons
2 using healthy male and female subjects under
3 naltrexone blockade.

4 The design of the BE studies in particular
5 is the standard design two-way crossover studies with
6 the reformulated OxyContin as the test product,
7 current OxyContin as the reference product.

8 On the lower portion of the slide we see
9 the two dose proportionality studies. These are
10 studies of the reformulated product intended to
11 demonstrate that the exposure to oxycodone that
12 results is proportional to the amount of oxycodone
13 contained in the tablets, and the design of these
14 studies was as appropriate to the number of tablet
15 strengths that were studied in each of those.

16 Now I'd briefly like to review the results,
17 and I don't expect anyone to look at all these
18 numbers, but this table is of the six bioequivalence
19 studies, one study per row in the data section. And
20 I'd like to draw attention to the critical
21 statistical evaluation.

22 These are the 90 percent confidence

1 intervals for the key pharmacokinetic comparisons of
2 C_{max}, the maximum exposure to oxycodone, and AUC
3 infinity, a measure of total exposure to oxycodone.
4 And the regulatory standard for bioequivalence is
5 that these 90 percent confidence intervals lie within
6 the 80 to 125 acceptance region. And as you can see
7 in each case for all six studies and for both
8 metrics, the confidence intervals are well within
9 that acceptance region.

10 Shown below, briefly, are the results of
11 the two bioequivalence studies. There's an analogous
12 statistical procedure to establish dose
13 proportionality. And these two studies have
14 demonstrated that for the reformulated OxyContin
15 product, the exposure to oxycodone is proportional to
16 the tablet strength.

17 I'd now like to show the mean concentration
18 versus time profiles from some of these studies. In
19 particular, this is the 10 milligram tablet strength
20 in the fasted state. The curve here is following
21 single doses administered at time zero with a 72-hour
22 X axis; on the Y, or the vertical axis, concentration

1 of oxycodone. The blue line with the hollow circles
2 is the current formulation. The red line is the
3 reformulated product, and you can see they're
4 performing similarly.

5 These are the same plots now for 10
6 milligrams in the fed state. And then at our top
7 tablet strength of 80 milligrams for the two
8 products, here are the comparative mean concentration
9 versus time profiles for 80 milligrams in the fasted
10 state and, finally, for 80 milligrams in the fed
11 state.

12 So taken together, these studies
13 demonstrate the therapeutic equivalence of current
14 OxyContin and the reformulated OxyContin demonstrated
15 by fed and fasted bioequivalence at 10, 40 and 80
16 milligram tablet strengths and also demonstrate dose
17 proportional oxycodone exposure for the reformulated
18 product over the full range of tablet strengths from
19 80 down to 10 milligrams.

20 Thank you.

21 DR. LANDAU: Okay. I had mentioned earlier
22 on when we reviewed the agenda that we'd be joined by

1 two external consultants, the first of whom is Dr. Ed
2 Cone, who advised us specifically on how best to
3 design our in vitro studies so that they would
4 reflect real-world tablet manipulation scenarios that
5 exist today and might exist in the future.

6 So Dr. Cone.

7 DR. CONE: Well, good morning to all of
8 you. I'm Ed Cone. I'd like to start out by just
9 saying thank you for your time that you're investing
10 here and the opportunity to speak to you.

11 I'm going to try to briefly explain my role
12 in helping Purdue Pharma develop laboratory methods
13 for the tamper assessment of their new reformulated
14 product.

15 We basically had two missions in mind that
16 we had to do and one was to look and identify what
17 people were doing to current OxyContin, but not only
18 OxyContin, other opioid formulations, in terms of
19 manipulating and changing the formulation from a
20 controlled-release-type formulation to an immediate-
21 release formulation, and then to translate, and it's
22 not always easy to do, those real-world scenarios

1 into systematic rigorous scientific studies.

2 Before I go into any basic detail, though,
3 I just want to give you a little bit of background on
4 who I am and how I fit into the picture.

5 I obtained my Ph.D. in organic chemistry
6 from the University of Alabama, my home state. I'm
7 always proud to get that in. But I did postdoc at
8 the University of Kentucky studying tobacco alkaloid
9 chemistry.

10 I then joined the Addiction Research Center
11 in Lexington, Kentucky, which ultimately was
12 assimilated into the National Institute on Drug
13 Abuse, NIDA. And that was an extremely rewarding
14 experience to be a researcher in the clinical program
15 at the Addiction Research Center, which ultimately
16 then I spent 12 years there. And then ultimately
17 they moved the center to Baltimore and I started up
18 the clinical research program in Baltimore at that
19 point. And I spent another 14 years in Baltimore.

20 It was quite an unusual experience for a
21 research chemist to be able to work in the clinical
22 program. I worked for the entire 26 years almost on

1 a daily basis in being able to talk to and interact
2 with drug addicts. These were volunteers in the
3 program and I was always very conscious to show them
4 all the respect. These were just people like you and
5 I but had taken a different course in life in terms
6 of their drug use, but they were making an incredible
7 contribution to the program as well.

8 But in those conversations, those many,
9 many, many hours that I spent in conversation with
10 them, I was very interested in understanding the whys
11 and wherefores and hows of their drug abuse behavior
12 and habits. Why was it important? To me it was
13 important to understand because that was the real-
14 world thing, and I could take all of that knowledge
15 back to the laboratory and try to translate that into
16 reproducible laboratory assessments of the
17 pharmacology and the chemistry of drugs of abuse. So
18 it was an incredibly rewarding experience and, of
19 course, over the years I've published extensively on
20 my studies.

21 I retired from NIDA as a commissioned
22 officer in 1998 and joined Pinney Associates as a

1 consultant and have worked since then with Pinney
2 Associates.

3 Just very briefly, Pinney Associates is a
4 consulting firm in Bethesda, Maryland, and they
5 specialize in pharmaceutical risk management, issues
6 management. They also have a very strong expertise
7 in abuse liability assessment.

8 So with that as background, I also should
9 provide you with some disclosure of my status, my
10 relationship with Purdue. I appear today and have
11 worked with Purdue as a consultant from Pinney
12 Associates. Pinney Associates gets paid for my time
13 and I should also mention that the opinions I express
14 are my opinions, and not those of Purdue and not
15 those of Pinney Associates.

16 So our basic job in developing laboratory
17 experiments was to first identify what is happening
18 in the real world with OxyContin and other opioids,
19 and I thought the place to start was to understand at
20 least some of the information that was available on
21 routes of administration.

22 So the next slide I'll show you -- oh, I'm

1 sorry. Before I go on, I wanted to briefly outline
2 the work I've done over the past year or so with
3 Purdue just to give you a little bit better feel.

4 I've served on any number of their
5 committees in identifying routes of administration
6 and types of abuser behavior that are pertinent to
7 manipulation. I've served on all of the three
8 committees. The goal of these committees, of course,
9 was to develop laboratory assessment methods based on
10 real-world scenarios.

11 I'm the one that went out to the third
12 party laboratories that were performing most of these
13 studies under blind conditions and checked them out
14 and looked over their shoulder and to see how they
15 were doing it.

16 I also wrote sort of a chapter as part of
17 Purdue's NDA filing on tamper assessment, and I think
18 I was asked to do that basically because I had
19 published a review way back before I started work
20 with Purdue, back in 2006, on tamper assessment
21 methodologies across many, many different types of
22 pharmaceutical drugs and that was published in *Drug*

1 *and Alcohol Dependence*. So I've been heavily
2 involved since 2008 in this reformulated project.

3 Now to get back to the theme in mind, how
4 did we develop these laboratory tests. And as I
5 said, the route of administration was the place I
6 thought we should start. So we started with looking
7 at what was known and this is one study. There are
8 three or four studies now that tell us some detailed
9 information about OxyContin and its relationship to
10 some other drugs, as well, but primarily OxyContin
11 and how it's abused in the real world.

12 This is a study by Katz, et al., in 2008,
13 where he surveyed people on the Internet who were
14 primarily recreational drug abusers about their mode
15 and behavior and use of OxyContin. And this
16 illustrates the most prevalent routes of
17 administration. And, as you'll see, insufflation, or
18 snorting, came up as extremely high prevalence. It's
19 the highest one there, followed by oral.

20 This is intact drug use of OxyContin. But
21 chewing came in third, smaller numbers of injection,
22 and occasionally a few people would mention smoking,

1 but certainly snorting, insufflation, and chewing
2 were very prominent in this study.

3 A second study or series of studies for
4 additional information on OxyContin is shown in this
5 slide. And what you see here, this is a little study
6 that I did back in early 2009, another Internet study
7 to get an update on what people were reporting on
8 OxyContin. And again, we saw insufflation and
9 snorting is the primary route that we're seeing or
10 hearing from recreational users. But we also hear --
11 they reported in this case, this is primarily or all
12 the oral route, is all chewing, and occasionally that
13 chewing is combined with making an oral solution and
14 drinking it. And again, IV use is relatively low in
15 this population, but it is there, and we even see
16 occasional weird routes, like rectal administration.

17 Now, if you look at the study on the right-
18 hand side, this is a bigger study by Carise, et al.
19 in 2007. And this is a different population, very
20 distinctly different population. These are hard-core
21 drug addicts who are entering drug treatment. And
22 you see a very different-looking pattern, but it's

1 primarily now in addition to other opioids that they
2 use. They report using OxyContin by the oral route.

3 Unfortunately, she didn't
4 differentiate whether it was chewed or intact. Most
5 likely, it's a very healthy combination of both. But
6 you see also IV use now has virtually doubled in this
7 population and insufflation is also used but
8 considerably less than in recreational.

9 But what these studies and some other data
10 told us was clearly there's three important routes.
11 And it's insufflation or snorting, it's oral,
12 frequently chewing or oral solution, and, to a lesser
13 extent, IV use. So that sort of characterizes the
14 problem.

15 From there, we had to, I thought, go to,
16 okay, so we know a little bit more about the problem,
17 how do we translate that into solid science.

18 So the first thing we started out with was
19 looking at manipulations; what's reported, how is the
20 tablet done, various things. And certainly, the
21 first one is physical manipulation, physiochemical
22 processes that you can reduce the formulation into

1 something, and that's illustrated here. And this
2 comes from a huge amount of my reading the Internet
3 and talking with subjects and so forth. But,
4 basically, they like simple tools. They like simple
5 formulations to be able to crush a tablet by various
6 means. And they report use of all sorts of little
7 simple household items, like scrapers, grinders,
8 cutters. Some of them also mentioned mortar and
9 pestle. Okay. That's getting a little bit more in
10 the chemistry area that I'm more familiar with, but
11 they certainly are very familiar with the use of the
12 mortar and pestle, and they're very familiar with the
13 use of pill crushers, and you can buy a variety of
14 them off the Internet or even from your pharmacy. So
15 they've gotten that far and those are the simple
16 tools. Very few go on to more sophisticated methods
17 but occasionally you'll see a little bit of that.

18 So the yellow line is where I put about 90
19 to 95 percent of the entire population of people that
20 tamper with opioids and specifically with OxyContin,
21 they fall into this group of fairly simple tools.
22 And the primary aim, of course, is to get it reduced

1 down to a powder, and from a powder they can do a lot
2 more things with.

3 They can extract it for oral consumption.
4 They can extract it for IV use or if they've got a
5 fine powder, they can snort it, which is all three of
6 those routes are important. And if they snort it,
7 they generally like nice fine powder.

8 So what are the most prevalent things that
9 people do? It's simple things. It's simple aqueous
10 extractions again as illustrated here. This is where
11 again 90-95 percent of the people are reporting what
12 they do, both on the Internet and talking with them,
13 but you do see some detailed recipes. They're pretty
14 sophisticated, even from a chem standpoint.

15 I don't put those as being very prevalent,
16 but they are there. Some people do them, and they
17 involve some degree of training, resources, and
18 skill. You see all sorts of recipes that involve use
19 of alcohols or acids, somewhat advanced solvents, all
20 sorts of interesting discussions on the Internet
21 about effects of pH, what's the best solvent, all
22 sorts of things, and how to purify it and isolate it.

1 Again, you see that. My thought is that that's in
2 the very small percentage but it's there. So we have
3 to evaluate those things.

4 Putting those physical-chemical processes
5 together, I think then we get a much better
6 assessment of what people are doing in terms of
7 crushing, swallowing, insufflation, and injection,
8 and occasionally a little bit more bizarre routes,
9 like smoking which is rarely reported, and occasional
10 rectal use.

11 So with this thought process in mind, I
12 also wanted to at least talk to Purdue and tell them
13 about
14 -- and fortunately we had a formulation that had some
15 of these characteristics. But I, over the years in
16 talking and learning about tampering practices, came
17 up with at least three processes that really affect
18 tamperability.

19 This is a snippet, but I've seen these
20 hundreds and hundreds of examples of these types of
21 reports. The average tamperer, if there is such a
22 thing, the person who wants to manipulate a product

1 to get it reduced down to a powder, really hates
2 those formulations when they come out that are
3 extremely hard to crush.

4 This is just an example. This guy, he's
5 pretty frustrated. He's talking about the tablet
6 that's definitely not in any crushable form, and he
7 goes on to say what else you can do with it. But
8 he's really frustrated. He says put it in a glass of
9 water and wait for it all to be released, but it'll
10 take you about as long as if you just swallow it. So
11 he's really frustrated with the hardness of the
12 tablet. That's a good thing. That's what I've been
13 telling every drug company I've talked to over the
14 years. This is a good thing.

15 Another commonly-recurring theme that's
16 reported over and over again is those formulations
17 that, if they try to hydrate them, they turn into a
18 sticky viscous mass. And you'll hear some discussion
19 of the current formulation involves a lot of these
20 things as a reason for discussing it. But these are
21 good things to have.

22 Here, you'll see another snippet from this

1 person who says, "Don't snort this stuff. You'll be
2 pulling massive amounts of thick sticky gel out of
3 your nasal cavity." So he'd successfully reduced it
4 to powder, and he had snorted it, but he didn't like
5 the effect.

6 And finally, a more subtle concept that's
7 important, though, I think in consideration of
8 designing a good formulation, is the idea of work.
9 How much work does it take the person to get from
10 point A to point B a crushed or extracted product,
11 and that involves time, resources, skill and so
12 forth. So the concept of work is there. And just to
13 illustrate it, a little snippet here says, "I don't
14 know, man. Seems to gel more. Waiting two to four
15 hours for it to seep into solution on a hot plate
16 stove might work. This is a lot of work."

17 So those three concepts in mind are part of
18 the milieu of thinking in how to approach a
19 formulation.

20 So with those in mind, this comes almost
21 exactly out of my review back in 2006, and I think
22 these principles still hold true today. This is what

1 I enunciated in this review that I had sort of gained
2 from this knowledge of reading and reviewing and
3 talking with so many drug abusers who were tampering
4 with the products.

5 What it basically says is that although
6 there will be a few of these people who take these
7 detailed recipes and work and work and work on them,
8 that's going to be in the very small minority of
9 folks that are tampering with these products. Most
10 people want fast, easy methods. And why? Because
11 they want a bigger dose and a faster high and they
12 don't want to spend a lot of time doing it.

13 So if you can put that barrier, that
14 resistance barrier, or could call it work function
15 into your formulation, so much the better, and as the
16 work requirements go up, in my opinion, the frequency
17 of tampering will go down.

18 So with all that in mind, here's how I
19 advised Purdue. We had to take all of this knowledge
20 base that we had about tampering methodologies and
21 identify them. And something incredibly important
22 and challenging was that not only do we have to look

1 at the way OxyContin is currently abused -- because
2 it's easy. I could abuse it; anybody can abuse it,
3 can crush it down to a powder in a matter of seconds
4 with anything you got on the table in front of you.

5 So we couldn't limit our scope to those
6 easy things. We had to reach out to other opioids
7 and to other possible things that haven't even been
8 described yet, and that's a pretty important and
9 difficult challenge.

10 So when Purdue asked me did I have any
11 ideas about all of that stuff, I said, oh, man, do I
12 have ideas. We went over them and our goal was to
13 translate those ideas and knowledge into systematic
14 rigorous scientific studies. And along the way it
15 was fun for me because I had input on virtually all
16 of the methodological details, the number of
17 replicates that needed to be done and so forth. But
18 the best thing that I had going for me was I got to
19 challenge the product in the lab myself, and I got to
20 think up all these weird things that people might do,
21 and then they had to test them out. And it was kind
22 of neat.

1 When we put all this together, I think
2 you'll see that Purdue designed a whole series of
3 rigorous scientific studies that are representative
4 of real-world scenarios. And I've listed the things
5 that I was interested in making sure they did and
6 they were in total agreement with all of these
7 things, that we didn't just test one dose strength,
8 we tested all dose strengths in virtually almost all
9 of the experiments. If we didn't test them all, we
10 bracketed them. Most of them involved testing all
11 dose strengths.

12 I didn't want to stop testing at 10 minutes
13 or 60 minutes or even an hour. One of my
14 philosophies in helping them and working with them,
15 and they listened, was we want to make it fail. We
16 want to see where it fails. If we don't, you're
17 going to be asking those questions; if you kept on
18 doing this, what would have happened? So my
19 philosophy was we keep on doing it. And if we can
20 make it fail, we will make it fail and then define
21 those conditions.

22 So to make it fail, we had to involve a lot

1 of different things. We didn't always -- we weren't
2 very successful in many cases. But to make it fail,
3 we had to cover environmental things, like high
4 temperature, low temperature, the possibility of
5 freezing, what happens in a microwave, all sorts of
6 things.

7 We extended the time frame way out beyond
8 12 hours. Virtually all the experiments went almost
9 to 24 hours or more. We had to have appropriate
10 controls so that once we got a result, what do we
11 compare it to. Our primary control was OxyContin,
12 but we had to use other controls, as well. We had to
13 do a sufficient number of replicates to make it a
14 valid experiment and assess what's the variability in
15 this process. Validated methods, of course, are
16 required. And finally, independent laboratories
17 under blind conditions and those folks at the
18 laboratory were working with coded samples.

19 So to sum it all up, this incredible
20 resource of information does have real-world
21 significance in looking at how people actually do it
22 on the in vivo side. It has aspects that describe

1 all sorts of things, like powdering, what happens
2 when you swallow it, effects of alcohol, from simple
3 to complex extraction methods, can it be pulled up in
4 a syringe, all sorts of things.

5 When you hear the next speaker, I think
6 you'll be relatively impressed by the incredible
7 amount of work and hopefully the quality of the data
8 that's available.

9 Thank you.

10 DR. LANDAU: Thank you, Dr. Cone. Our next
11 speaker is Dr. Judy Lee. She's a colleague of mine
12 from our Analytics and Preformulation Development
13 Area. She's going to present to you appropriately-
14 redacted summary information on the methods and
15 resulting data from our testing program.

16 DR. LEE: Thank you, Craig.

17 Good morning. Underlining our tamper-
18 testing protocol, we have three important goals in
19 mind. First, we want to characterize physical-
20 chemical properties of the reformulation. We want to
21 compare the performance of the reformulation to
22 current formulation, and we also want to test both

1 formulations to complete failure.

2 In designing, we got input from experts for
3 real-world extraction of oxycodone for abuse. We
4 also tested different lengths of time, effort, and
5 special equipment required in order to reduce the
6 particle size. We want to ensure all our studies are
7 scientifically robust.

8 In designing, we have to consider all
9 routes of real-world manipulation. As is shown here
10 that you have seen before, here is a list of real-
11 world tablet manipulation scenarios. We take each
12 scenario and convert them into a specific laboratory
13 procedure. It becomes our Studies 1 through 5.

14 Now before we start testing in the
15 laboratory, we need to make sure the data we generate
16 are meaningful and robust. We want to determine the
17 number of replicates that are needed to conduct each
18 test. So guided by our internal experimental data,
19 we want to produce results with observed mean within
20 10 percent of the true mean at 95 percent confidence.

21 Guided by this statistical approach, we
22 determined the appropriate number of replicates for

1 reformulated OxyContin. For example, N should be 5
2 for a small volume extraction. For current
3 OxyContin, on the other hand, it's reduced to fine
4 powder quickly, therefore N equals 3 is appropriate.

5 Now I want to show you a schematic design
6 of one of our small volume extractions to illustrate
7 our approach. Here is an example using a simple
8 solvent one. First, we start with a whole tablet, in
9 this case showing you here is a 10 milligram
10 reformulated OxyContin.

11 Each test we conduct at two temperatures to
12 understand the heating effect. With each
13 temperature, we study six particle sizes from largest
14 to smallest. With each particle size, we generated
15 extraction kinetics at various time points. What we
16 show you here is from 10 minutes to 24 hours. This
17 is a study for all seven strengths and each test was
18 conducted five times. This one design is
19 encompassing more than 2,500 data points.

20 Now we also want to make sure the data
21 generated is independent and unbiased, so all the
22 studies were outsourced to contract research

1 laboratories. We conduct the development and
2 validation internally. Once that's completed, we
3 transfer the testing methods to CRO. The analysts at
4 CRO were blinded to samples to the extent possible.

5 We have also external experts that conduct
6 a site visit to make sure the procedures were
7 conducted properly. Then at the end we have
8 externally conducting the quality assurance and
9 statistical analysis with all the data generated.

10 Now let me discuss Study 1. We have two
11 goals we want to achieve for Study 1. First, we want
12 to simulate expected abuser approach intentionally to
13 crush a tablet for further abuse. Secondly, we want
14 to understand the likelihood that a tablet can be
15 accidentally crushed by patient or intentionally
16 crushed by well-meaning caregivers.

17 Here is how we approached the Study 1.
18 First, we need to identify tools to be used to crush
19 hard substances. This is because reformulated
20 OxyContin tablets are hard. We identified 16 common
21 household tools that broadly represent all possible
22 ways to reduce tablet sizes.

1 We evaluated different amount of effort and
2 time with all the 16 tools. We identified a broad
3 range of particle sizes from largest to the smallest.
4 Then we divided this whole range of particle sizes
5 into six distinct particle size bands. Then we used
6 the standard laboratory equipment to reproduce those
7 bands for further testing.

8 As I said, the reformulated OxyContin are
9 hard. Let me show you the results generated with
10 those household tools. On the left-hand side I'm
11 showing you the 16 tools we used. When you apply
12 these tools to current OxyContin, you get only one
13 form; only fine powder was produced.

14 When you use the same 16 tools for
15 reformulated OxyContin, here is what you will see.
16 Indicated by the axis, most of the tools does not
17 have any effect on OxyContin reformulated. The few
18 that does work, it creates fragment, slices, or
19 granulated particles, never fine powder. So we can
20 conclude from our study current OxyContin tablets are
21 crushable. It has a binary effect, either whole
22 tablet or fine powder.

1 Reformulated tablets are hard. It takes
2 time and effort in order to reduce their size. Even
3 if you find a special tool, it has a graded response.
4 Many household tools do not work on crushed
5 reformulated OxyContin.

6 Now let me discuss Studies 2 and 4. Our
7 goal for Studies 2 and 4 is to simulate a scenario of
8 an abuser attempting to extract oxycodone from intact
9 or crushed tablets in small volume of liquid.

10 Here is how we approached these two
11 studies. First, we need to perform extraction. We
12 choose 30 ml because it's equivalent to an ounce, bar
13 shot that can be easily drinkable. We have three
14 type of solvents we investigated. Each solvent was
15 conducted at two temperatures. As I said, we want to
16 understand the heating effect. And every study is
17 conducted with constant agitation at 100 rpm. At the
18 end, we determined the amount of oxycodone can be
19 extracted at various time points, including those
20 listed here.

21 It's very important to make sure our
22 selection of solvents are proper. We want to cover a

1 wide range of chemical properties. Here, we consider
2 three most important characteristics that define
3 solvents. They are polarity, ionic strength, and pH.
4 We cover the widest range of these three
5 characteristics. With the help of experts, we came
6 up with the list of solvents shown here. They
7 include six simple solvents that's ingestible, three
8 advanced solvents that's non-ingestible, and we have
9 four buffers that cover a range of pH.

10 Let me show you some of our study results
11 here. This is a complicated slide. Please allow me
12 a moment to explain. On the left-hand side is
13 showing you the three classifications of the solvents
14 we discussed and the list of solvents within each
15 classification. Across the top is showing you
16 extraction time from 10 minutes to 18 hours. Right
17 below that is particle size band covering large,
18 medium, and small that we used.

19 The number in the slide is a percentage.
20 It's the amount of oxycodone that's released on
21 reformulated OxyContin related to current OxyContin.
22 So these are percentage numbers. So you can see 100

1 meaning the same quantity is released. When it's
2 less than 100, as we show here, 53, for instance, for
3 simple solvent 1, medium particles at 10 minutes,
4 that means 53 percent oxycodone released from
5 reformulated as compared to current.

6 Now let me first discuss the data generated
7 under 18 hours. You see a lot of high ratios. This
8 is understandable. This is 12-hour product. At 18
9 hours you expect everything should have been
10 released. Therefore, we did not conduct statistics
11 on data generated at 18 hours.

12 We evaluated data generated at 10 minutes
13 and 60 minutes since these time points are more
14 relevant to the abusers. We conduct statistical
15 analysis on all the data generated here. Let me
16 first show you those two data points here, 100 for
17 simple solvent 3, 99 for advanced solvent 1. These
18 are the two data points with showing no significant
19 difference between the amount of oxycodone released
20 from reformulated versus current, which means the
21 rest of the data points, they are statistically
22 significant.

1 Let me highlight for you the two data
2 points that's in the bottom of the slide here for
3 advanced solvent 3. These two data points are shown
4 statistically significant that more oxycodone was
5 released from reformulated OxyContin. That means the
6 rest of the data points, the vast majority here, are
7 significantly different than oxycodone released from
8 reformulated OxyContin are lower, slower than current
9 OxyContin.

10 Now let me explain these two data points,
11 123 and 127, why we are not concerned. This is
12 because advanced solvent 3 is not a very efficient
13 solvent. Let me show you the data we generated.
14 There's only 16 percent that was extracted from
15 reformulated OxyContin compared to 13 percent for
16 current OxyContin. This very small 3 percent
17 difference creates a number 123. You can see similar
18 results that generated data 127.

19 So we can conclude that the small particles
20 release oxycodone faster than larger particles and at
21 the time points tested that's relevant to abusers.
22 As I mentioned, 10 minutes and 60 minutes, the

1 reformulation released oxycodone significantly slower
2 in all effective solvents tested.

3 Now let me discuss Study 3. The goal for
4 Study 3 is to assess whether reformulated OxyContin
5 will dose dump in ethanol. This is to simulate a
6 scenario of patients taking tablets together with
7 alcoholic beverage inadvertently. Also, in some
8 cases for abusers, they might also try to take it
9 with alcohol in an effort to get high.

10 Here is how we approached this study. We
11 used the solution, which is the standard USP basket
12 apparatus, 900 ml, using simulated gastric fluid
13 and/or ethanol in simulated gastric fluid, performing
14 the test at body temperature with constant agitation
15 at 100 rpm. At the end, we generated the amount of
16 oxycodone that can be released at the time points
17 shown here.

18 Our results indicated reformulated
19 OxyContin does not dose dump in any of the particle
20 sizes we have studied. Similarly, you have no from
21 current OxyContin.

22 Let me show you the results here. Across

1 the top is the particle size we studied from small,
2 medium, to large. On the left-hand side showing you
3 all seven strengths of reformulated OxyContin we
4 studied. We used F2 similarity factor to do the data
5 evaluation. F2 similarity factor is a standard
6 statistical methodology that's published by FDA to
7 evaluate the similarity of two dissolution profiles.

8 Across the particle size, there's no dose
9 dump. It also goes across the strengths. So we can
10 conclude here reformulated OxyContin does not dose
11 dump in alcohol and this holds true across all
12 particle sizes and the strengths.

13 Now let me discuss Study 5. There are two
14 parts to Study 5. This first part, our goal is to
15 assess whether reformulated OxyContin can be injected
16 using an insulin syringe.

17 To study if reformulated OxyContin can be
18 abused intravenously, you have to evaluate both
19 syringability and injectability. Here is our
20 approach to conduct the study. For syringability, we
21 look at different temperature, time, and volume of
22 water. We use 27 and 28 gauge needles. Twenty-eight

1 gauge, as you are aware, is the most commonly used by
2 the abusers because it's readily available.

3 We do use 27 gauge in our studies because
4 we conduct our study more than just 2 ml extraction
5 and we need to have a needle that can be attached to
6 a larger syringe. We use a constant drawing up to
7 one minute. At the end we determine the amount of
8 oxycodone that can be syringed and the volume of
9 solution that can be syringed.

10 Now let me discuss how we approach
11 injectability. In this case, we had to pour the
12 solution in the back of the syringe and then see how
13 much we can expel. Again, we studied different
14 temperatures, time, and volume of water. Here, we
15 used 27 gauge because we need larger volume and water
16 to pour the solution to. You cannot pour into a 28
17 gauge insulin syringe.

18 Again, the same constant, expel up to one
19 minute and we determined at the end the amount of
20 oxycodone that can be injected and the volume of the
21 solution that can be injected. Through our study, we
22 have found that reformulated OxyContin cannot be

1 easily injected or syringed using an insulin type of
2 syringe.

3 Here, let me show you data for
4 syringability first using a 27 gauge. Showing here
5 is a 2 ml preparation. The number on top is
6 milligram oxycodone. On the left-hand side showing
7 you across the strengths of reformulated OxyContin;
8 to the right showing you the crushed current
9 OxyContin bracket with 10 through 80 milligrams.

10 As you can see, most of the numbers here
11 are zero, except 40 milligram strengths reformulated
12 OxyContin, a small 2 milligram was syringed. This is
13 because of the excipient for reformulated OxyContin
14 polyethylene oxide hydrogel in small volume. When
15 the hydrogel's in small volume, oxycodone does not
16 dissolve or extract. Also, the solution that's
17 produced is very viscous. It cannot be syringed with
18 this preparation with this size of insulin type of
19 syringes.

20 We wanted to see if we increased the
21 volume, could we potentially get more oxycodone being
22 syringed. So we used ten 5 ml preparation, same set-

1 up. You can see we get a little more, but still the
2 maximum amount is only 6 milligrams from a 30
3 milligram reformulated. And compared to current, you
4 get 71 milligrams from an 80 milligram tablet. Even
5 upping the volume to 5 ml, the solution is still
6 viscous.

7 Now let me show you the results of
8 injectability. Here, as I have discussed, 2 ml is
9 just too thick. You cannot pour. So we used a 5 ml.
10 With injecting through the back of a syringe, we got
11 a little bit more, but worse case still is 40
12 milligrams from 80 milligram tablet compared to what
13 you can see, 60 out of 80 from current OxyContin.

14 So reformulated OxyContin really cannot be
15 easily injected or syringed, even with upping the
16 volume to 5 ml.

17 In order to abuse a product through
18 intravenously, you first have to take an intact
19 tablet. You have to crush it. You have to dissolve
20 the active, and then you can syringe and inject.
21 Current OxyContin is quite easily crushed. Oxycodone
22 can be dissolved and then successfully syringed and

1 injected. For reformulated OxyContin, it's very
2 difficult to crush and the oxycodone does not
3 dissolve because of the hydrogelling property of
4 polyethylene oxide. And because the resulting
5 solution is viscous, it cannot be syringed or
6 injected using an insulin type of syringe.

7 Now let me discuss the second part of Study
8 5. The goal for this study is to simulate smoking of
9 reformulated OxyContin and compare that to known
10 controls that are efficient for smoking.

11 Here is how we approached this study.
12 First, we had to perform vaporization. We used
13 heating block to hold the constant temperature with
14 constant air flow to simulate inhalation of a smoke,
15 and we collected vaporized oxycodone using a solid
16 face cartridge.

17 Now for this study, it's very important to
18 determine the proper temperature that can maximize
19 the vaporization and minimize burning. We did a lot
20 of studies in our laboratory to find out what is this
21 optimized temperature and we determined it's a very
22 narrow range. So we did this for reformulated

1 OxyContin and current OxyContin. We also included in
2 our study two appropriate controls, a negative and a
3 positive, to demonstrate the validity of our
4 procedure. At the end, we determined the amount of
5 oxycodone that can be vaporized.

6 Through our study, we found both
7 reformulated and current OxyContin cannot be
8 efficiently smoked. Let me show you the data here.
9 On the left-hand side from the top first are the
10 seven strengths of reformulated OxyContin. In the
11 middle here is current OxyContin bracketed with 10 to
12 80 milligrams, then the two controls I just
13 discussed.

14 What I also included here are three
15 references. These are the illicit drugs that is
16 known to be abused through smoking. As you see the
17 data on the right-hand side, X is meaning the yield
18 we can vaporize from reformulated OxyContin all the
19 way down to including current OxyContin or low, which
20 is supported by our negative control.

21 The positive control here is showing 68
22 percent that demonstrated the validity of our

1 procedure. And this compared to the three references
2 I just mentioned has very high efficiency from 80 to
3 98 percent. So we can conclude that our procedure
4 does demonstrate a positive control showing the
5 material can be vaporized. And the current
6 OxyContin, although it can be crushed, it cannot be
7 efficiently vaporized. For reformulated OxyContin,
8 it cannot be easily crushed and also it does not
9 vaporize efficiently.

10 Now let me summarize the findings from all
11 our studies. Reformulated OxyContin tablets are
12 difficult to crush. They release oxycodone slower
13 than current OxyContin tablets in a range of
14 solvents, even when the tablets are reduced to
15 particles.

16 They do not dose dump in ethanol, even when
17 reduced to particles. They are difficult to syringe
18 or inject using an insulin type of syringe, and they
19 are inefficient to release oxycodone through
20 vaporization.

21 Thank you.

22 DR. LANDAU: Thank you.

1 Our next speaker will be Dr. Ed Sellers.
2 Dr. Sellers will provide his interpretation of the in
3 vitro program and its results and also provide his
4 views on the potential impact this formulation may
5 have on multiple subpopulations.

6 DR. SELLERS: Thank you, Craig.

7 Good morning, everyone. My name is Dr. Ed
8 Sellers. I've been asked by Purdue to provide an
9 independent evaluation of the preclinical studies and
10 to forecast what I think the public health
11 consequences of their change in formulation are
12 likely to be.

13 First, I'd like to give the committee some
14 background on myself, so you can place my comments in
15 perspective.

16 I'm a medical graduate of the University of
17 Toronto and have a Ph.D. from Harvard University, and
18 I'm board-certified in Internal Medicine, both in the
19 United States and Canada.

20 I'm currently a Professor Emeritus at the
21 University of Toronto. For the past almost 40 years
22 I've been deeply engaged in research in clinical care

1 with respect to therapeutic drugs that have
2 dependence and abuse potential.

3 My work has covered the full range of
4 preclinical to clinical to post-marketing studies.
5 My colleagues and I have published over 600 peer-
6 reviewed scientific papers and a number of these have
7 been in leading journals, such as *Nature*, the *Journal*
8 *of Pharmacology and Experimental Therapeutics*,
9 *Clinical Pharmacology and Therapeutics*, and *Drugs and*
10 *Alcohol Dependence*. I've frequently been asked to
11 write chapters and reviews.

12 I'm currently a member of the World Health
13 Organization, Expert Committee on Problems of Drug
14 Dependence. I'm a past president of the American
15 Society of Clinical Pharmacology and Therapeutics,
16 foremost society of clinical pharmacologists, and a
17 past president also of the College of Problems of
18 Drug Dependence, the leading organization that
19 considers issues of abuse liability.

20 In my past, I was also former vice
21 president and medical director of the Addiction
22 Research Foundation in Toronto, Ontario, a leading

1 research organization in the field.

2 At present, I'm Vice President, Kendle
3 International, for their early-stage part of their
4 business. Kendle is one of the world's leading
5 contract research organizations, provides services to
6 the biopharmaceutical industry. Kendle's early-stage
7 unit in Toronto is particularly well known because it
8 is the foremost research center for the conduct of
9 human abuse liability studies and tampering studies,
10 and that group has conducted more than 200 such
11 studies.

12 Before I continue, I want to tell the
13 committee about my relationship with Purdue and that
14 of Kendle with Purdue.

15 First, the opinions that I'm going to share
16 with you are entirely my own and based on our
17 research and my understanding of the scientific
18 database that tells us about what abusers do and why
19 they do it.

20 I'm appearing today as an independent
21 consultant. Kendle will be paid for my time by
22 Purdue Pharma.

1 In addition to providing services to
2 Purdue, I've worked with virtually all of the other
3 leading pharmaceutical companies to either advise
4 them on drug development issues as related to abuse
5 liability and tampering and in a number of cases have
6 actually performed such studies for them.

7 I should probably note, give as a footnote,
8 that Kendle was not among the CROs that performed the
9 in vitro testing.

10 Like Dr. Cone, I've done previous work with
11 Purdue, started in October 2008, where I was a member
12 of an expert panel that advised Purdue on what
13 abusers do and what kind of in vitro testing systems
14 and programs they should implement.

15 In January of this year, I attended a
16 closed FDA meeting with Purdue where the Purdue
17 approach to in vitro testing was discussed. In
18 February of this year, I reviewed the in vitro data
19 that you've just had presented. And since April
20 2009, I've been working with Purdue on the
21 development of a number of post-marketing studies.

22 From this interaction with Purdue and with

1 many other companies, my evaluation of this in vitro
2 program that's been developed and executed by Purdue
3 is that this program is the largest and most
4 carefully-conducted such program that I've
5 encountered anywhere in the industry. There may be
6 something else out there that's bigger and better,
7 but I haven't seen it yet.

8 Now, in the course of our research work,
9 we've conducted a number of indepth surveys and
10 interviews with abusers, so we're very familiar about
11 what they like and what they don't like. The
12 Internet in particular is a particularly rich source
13 of information about what abusers are thinking about,
14 what they're going to do, and what they are doing at
15 the moment. And I'd like to share with you some of
16 the kinds of things -- you've seen some of these from
17 Dr. Cone, but I want to share with you a few that are
18 particularly pertinent to the new formulation.

19 The place to start is perhaps what do
20 abusers say about preparations that gel and contain
21 polyethylene oxide. There is one such product on the
22 market at present. It's methylphenidate. It has a

1 trade name of Concerta. It's a controlled-release
2 dose form. The drug is used for the treatment of
3 ADHD. It was developed in part to address the
4 problem of the abuse of methylphenidate, which exists
5 in an immediate-release form. And one trade product
6 name you might be familiar with would be Ritalin.

7 So here's a representative quote. I don't
8 have obviously time to share all this information,
9 but I can assure you that these quotes are exactly
10 what you will see repeated again and again on the
11 Internet.

12 "Concerta, when crushed up and snorted, has
13 been known to completely clog up the nostrils as it
14 turns into a slime. I wouldn't inject it unless, of
15 course, you want your blood to become the consistency
16 of maple syrup. Concerta is only good for eating, no
17 matter what you do with it." And then there's sort
18 of a little editorial comment from this individual,
19 "and even eating it is pointless."

20 Now, there are other products out there
21 that have some hydrogelling types of properties and
22 here's another kind of quote. "In terms of

1 potency," -- and this is relative to oxycodone-
2 containing product, "In terms of potency, they should
3 be no different in any brand. However, some brands
4 are a pain to crush and if you want to sniff them,
5 they turn to gel." So this is kind of an echo of
6 what Dr. Cone was telling you about.

7 Finally, you've heard some data about
8 vaporization and models of smoking oxycodone, and the
9 first point is that this is not a very common or very
10 successful kind of thing for people to do with the
11 existing product and here's some quote that bears on
12 that.

13 "I've heard of people smoking OxyContin
14 with success, but I don't get how that works with all
15 the binders and fillers that's in Oxy. I tried it
16 once and it was very disgusting. I didn't feel
17 anything from it. I even tried it with the instant-
18 released oxycodone, and that was just as bad as
19 smoking 40 milligrams of OxyContin."

20 The reason that it's disgusting to them is
21 that the product contains excipients that when you
22 start to vaporize them, it produces basically a glop

1 and it's very inefficient. It's very hard to
2 vaporize oxycodone right off. And I would anticipate
3 when you mix it all up with the polyethylene oxide
4 that you're certainly not going to see an increase in
5 this behavior, and I would expect it to be even less
6 smoking.

7 Now, over the past 15 years, we've learned
8 a lot about tampering, determinants of abuse
9 liability and abuser behavior, and I'd like to review
10 what we have learned.

11 In the upper two panels of this figure,
12 I've summarized pictorially the observation that has
13 been seen across a wide range of different drugs and
14 different formulations, that the in vitro dissolution
15 pattern matches to what we then find with in vivo
16 kinetics of the drug and so this is kind of a cartoon
17 version of an immediate-release drug and a
18 controlled-release drug and the profiles. You can
19 see the similarity.

20 The third panel summarizes what we have
21 learned about the relationship of kinetics and
22 liking. And what it shows is that abusers like the

1 IR type of dose form because they've got greater
2 liking and have greater preference for it. And this
3 is something that happens in the first hour or so
4 when the drug is taken.

5 If you take a controlled-release dose form
6 and spread out the kinetics, what you find is you get
7 much, much lower kinds of reports of liking and
8 preference. And in fact with some of the controlled-
9 release dose forms, what you find is later, after
10 they've received the drug, they don't like the drug
11 at all; they report disliking it. And that's because
12 a number of the adverse effects start to kick in.

13 So this is a pattern that we see again and
14 again with different classes of drugs, not only
15 opioids. You see it with stimulants. You see it
16 with a variety of sedatives and so forth.

17 In the past 15 years, we've learned that
18 abusers will tamper and we've learned that abusers
19 don't like gels. They don't like excipients. They
20 don't like hardness. They don't like additives, and
21 they do a lot of things to avoid them.

22 They like fast and easily-powdered, and they

1 like to be able to get it into a solution that is
2 clear. I'm describing basically the currently-
3 marketed formulation of OxyContin. When it gets
4 hard, they go looking for something that's easier.
5 So they will gravitate to use immediate-release dose
6 forms or other drugs that are more easily tampered
7 with.

8 Now, based on what we've learned about
9 abuser behavior over the last while, I think we can
10 be pretty confident that we can anticipate that the
11 changes in formulation are going to move the safety
12 and the public health implications sort of in the
13 positive direction.

14 Now, what we can't predict is exactly how
15 far this positive change is going to occur. Now, in
16 that context, Purdue asked me if they should do in
17 vivo studies, liking studies or something of that
18 sort, in order to bring greater certainty to the
19 prediction about the direction and the size of the
20 change that one would expect with this formulation.
21 And it was my opinion that for an approved product,
22 for which there was a recognized public health

1 problem, that yes, you'd generate more data, but you
2 actually wouldn't be able to predict any more
3 precisely the size of the change. And, therefore, I
4 advised them that they wouldn't learn anything that
5 would give them any greater precision or anybody
6 else. And I think you've already heard that there
7 are going to have to be epidemiologic studies to
8 answer that question precisely.

9 But from the data at hand, I think that the
10 direction of change is clear. What's at debate is,
11 is this a 20, 30, 40, 50, 60, 80 percent improvement?
12 We can't answer that quite yet.

13 Now, when a controlled-release dose form is
14 prepared, the first thing is you're obviously
15 directing it at patients for benefit. There's no
16 point in producing a dose form that doesn't release
17 drug. So you're balancing the benefit to the patient
18 against safety and risk. That's for the intended
19 population.

20 Then there's some issues with non-patients,
21 people who abuse. And then there are some conditions
22 of use that you never intended but you have to be

1 concerned about, and you've heard a number of the
2 attempts that Purdue has made to try and understand
3 some of those unusual kinds of behaviors.

4 So let me tell you what I think is the
5 implication of the in vitro testing you've heard
6 about with respect to patients. With patients, of
7 course, we have examples of them accidentally or
8 intentionally modifying the existing formulation by
9 crushing it between two spoons. It's trivial to do
10 this, and then it can be sprinkled, and things that
11 were never intended could be done. And this has
12 resulted in misadventure, and I think it's clear that
13 patients and caregivers are not particularly
14 motivated to go and do this. And so I would
15 categorize what goes on now as sort of accidental or
16 misadventure. I think that it's quite clear that the
17 new formulation is going to change that.

18 The next group to consider, I guess, would
19 be the non-patient group. So these are the abusers,
20 and you've heard several times that the harder the
21 tablet is, the less likely is that tampering is going
22 to occur. If it's more difficult to crush or

1 dissolve, it's less likely that it's going to be
2 abused.

3 I think because of the gelling properties
4 of this product, whether it's something you're
5 thinking about injecting or putting in your nose, the
6 gelling properties are going to be a pretty big
7 deterrent to those behaviors.

8 Now, there is one situation which has
9 already been alluded to, and that is there is some
10 abuse of the intact existing formulation of OxyContin
11 not particularly common, and hard-core abusers tamper
12 with it. So some people do take the controlled-
13 release because of a long-term kind of effect.
14 Obviously this new formulation is not going to do
15 anything about that. That will be basically an
16 enduring issue with all controlled-release tamper-
17 resistant-like products.

18 So let me now summarize, using the kind of
19 template that you've seen before, what I think is
20 going to happen with respect to safety and public
21 health advantage.

22 First of all, I already mentioned that

1 there's going to be no impact of the new formulation
2 on the abuse of the intact product, but I think that
3 we can be pretty confident that there will be a
4 directional positive change with respect to crushing,
5 crushing and extracting, nasal crushing and snorting,
6 rectal use of the drug. Smoking might not be too big
7 an effect there; injection, crushing, extracting, and
8 so forth, again, I think we'll see that will be an
9 improvement. And then I've already mentioned that I
10 think for patients, that there's not going to be any
11 casual or accidental kind of crushing occurring.

12 This tablet is simply just too hard for that.

13 Finally, I suppose we should look at sort
14 of populations of people who we might regard at risk
15 and look at what might happen to the safety profile
16 there. There are some situations of accidental
17 misuse. I suppose one example would be maybe a child
18 that got ahold of prescription drugs that weren't
19 under proper control by the person who had the
20 prescription. And here, you know, it's very easy for
21 a child to disrupt the existing formulation because
22 it's very, very soft, and that kind of conversion of

1 a potentially high-dose-containing dose unit into an
2 IR form could be lethal.

3 So I think that that will be much, much improved.

4 There's another group of individuals who
5 are kind of a composite of experimenters,
6 opportunistic use, peer-driven use, incidental use at
7 a party. I think again here, they're going to see
8 fewer problems than have been already recognized with
9 the existing formulation.

10 With recreational abusers, that would be
11 individuals who are using more consistently, I think
12 what you'll see here is that they're a group that
13 generally don't want to put much work into finding a
14 drug to abuse and you'll see them either stopping,
15 reducing, or they're going to gravitate to use some
16 other immediate-release dose form.

17 The final group, I suppose, would be the
18 sophisticated or hard-core kind of addicts. There
19 are a few of these individuals who take pride in
20 being able to defeat any technology. They consider
21 it to be an intellectual game, but, of course, there
22 are very few of them. This group will also shift

1 their patterns of use, and I think what you'll see is
2 that, again, there will be a positive impact on this
3 group, but it's going to be the more resistant group.
4 But remember, when we think about abusers, the vast
5 majority of them, at least 70 percent, are not in
6 this kind of hard-core group, and so they're a group
7 that are going to be -- you know, the vast majority
8 are going to be affected by this new formulation.

9 So in conclusion, I guess I'd share with
10 you that abusers prefer immediate-release dose forms.
11 Eighty percent of abuse of opiates is already with
12 immediate-release dose forms or dose forms that are
13 easily converted to IR. I think that the new
14 formulation is better from a patient and a public
15 health point of view. The in vitro studies you've
16 heard about are the most comprehensive I'm aware of,
17 and it is my opinion that if this new formulation is
18 approved, that it should have a positive public
19 health impact.

20 Thank you for your attention.

21 DR. LANDAU: So I'd like to conclude with a
22 few remarks on what we know about the reformulation.

1 We presented earlier data demonstrating the fact that
2 it's bioequivalent to the current product, and on
3 this basis should be considered therapeutically
4 equivalent for the million or more patients each year
5 treated with it to manage their pain and maintain a
6 quality of life.

7 Based on its physical-chemical properties
8 demonstrated through the in vitro program, it's an
9 important advancement from a formulation perspective.
10 It'll be more difficult to prepare for abuse via
11 multiple routes, and on the patient side, it'll make
12 it less likely that patients will be exposed to
13 oxycodone through inadvertent chewing or
14 intentionally through an otherwise well-intended
15 caregiver.

16 It's our intention, if approved, to
17 introduce all strengths of the new reformulated
18 product simultaneously and transition to this new
19 formulation just as soon as we can.

20 Thank you. This concludes our
21 presentation, Mr. Chairman.

22 DR. KIRSCH: Thank you. Thanks to all the

1 speakers on behalf of the sponsor.

2 We will now take a break for lunch. We
3 will reconvene in this room one hour from now, which
4 will be at 12:45 p.m. Please take any personal
5 belongings you may want with you at this time.
6 Committee members, please remember that there should
7 be no discussion of the meeting during lunch amongst
8 yourselves, with the press, or with any members of
9 the audience. Thank you.

10 (Whereupon, at 11:44 a.m., a lunch recess
11 was taken.)

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

13 DR. KIRSCH: Welcome, everybody, back from
14 lunch. Both the Food and Drug Administration, FDA,
15 and the public believe in a transparent process for
16 information-gathering and decision-making. To ensure
17 such transparency at the open public hearing session
18 of the Advisory Committee meeting, FDA believes that
19 it is important to understand the context of an
20 individual's presentation.

21 For this reason, FDA encourages you, the
22 open public hearing speaker, at the beginning of your

1 written or oral statement to advise the committee of
2 any financial relationship that you may have with the
3 sponsor, its product, and, if known, its direct
4 competitors.

5 For example, this financial information may
6 include the sponsor's payment of your travel,
7 lodging, or other expenses in connection with your
8 attendance at the meeting.

9 Likewise, FDA encourages you at the
10 beginning of your statement to advise the committee
11 if you do not have any such financial relationships.
12 If you choose not to address this issue of financial
13 relationships at the beginning of your statement, it
14 will not preclude you from speaking.

15 The FDA and this committee place great
16 importance in the open public hearing process. The
17 insights and comments provided can help the agency
18 and this committee in their consideration of the
19 issues before them.

20 That said, in many instances and for many
21 topics, there will be a variety of opinions. One of
22 our goals today is for this open public hearing to be

1 conducted in a fair and open way, where every
2 participant is listened to carefully and treated with
3 dignity, courtesy, and respect.

4 Therefore, please speak only when
5 recognized by the chair. Thank you for your
6 cooperation.

7 For the speakers, there will be a green
8 light on when you begin to speak. It will turn
9 yellow when you're near the end, and then it will
10 turn red. After your time allotted, the speaker will
11 turn off and we'll ask you to step aside. Thank you.

12 So the first speaker that's recognized is
13 Mary Bennett.

14 MS. BENNETT: In terms of your request, I
15 have no financial disclosures.

16 My name is Mary Bennett, the Director of
17 Grassroots Advocacy for the American Pain Foundation,
18 which is a non-profit organization whose mission is
19 to improve the quality of life for people with pain
20 by raising public awareness, providing practical
21 information, and advocating to remove barriers,
22 increase access to effective pain management.

1 Pain affects more than 76.5 million
2 Americans. It is the number one reason people seek
3 medical attention. There are more Americans affected
4 by pain than cancer, diabetes, and heart disease
5 combined.

6 Whether pain is a result of a disease, a
7 car accident, or injury sustained in combat, the lack
8 of pain care can make life a living hell. Some have
9 described their pain as a form of torture.

10 The lack of access to effective treatments
11 has a tremendous impact on every part of one's life
12 and can rob a person of dignity, the ability to
13 function, the capacity to contribute to one's family.
14 The under-treatment of pain costs approximately \$100
15 billion annually.

16 We recognize the need for a broad range of
17 pain treatment options. Opioid analgesics, when
18 taken as directed, have effectively provided life-
19 saving relief for millions of Americans with moderate
20 to severe pain. Do not abandon those who benefit
21 from round-the-clock, long-acting opioids and the new
22 abuse deterrent.

1 We share your commitment to protect public
2 health. We recognize the serious problem of
3 prescription drug abuse and illegal use and the need
4 for strong and effective measures.

5 A fundamental question is should illegal
6 and criminal activity dictate the care for others?
7 Should people with pain who are using medications as
8 directed be victimized by illegal use and accidental
9 overdose?

10 It is critically important to aggressively
11 address prescription drug abuse and its tragic impact
12 with effective strategies but not at the expense of
13 millions of people with persistent pain. Policies
14 and public health strategies that curb drug abuse
15 without undermining relief for patients in pain are
16 possible and are in the best interests of society.

17 The development and approval of extended-
18 release opioid medicines, which are intended to
19 reduce the risk of abuse and diversion, is a welcomed
20 advance. Many people living with pain do not have
21 access to these medicines because far too many
22 healthcare providers fear that these medicines might

1 get into the wrong hands.

2 DR. KIRSCH: Thank you.

3 MS. BENNETT: Thank you very much.

4 DR. KIRSCH: The next speaker will be Don
5 Bivins.

6 DR. BIVINS: Thank you, sir. I have no
7 financial disclosures to make.

8 I am Dr. Don Bivins, and I am a patient.
9 My career was interrupted in 2006 when I developed
10 pain and weakness in both legs. I did not have pain
11 control because the physicians prescribed short-
12 acting opiates. I had to lie on my stomach 24 hours
13 every day because the pain was terrible. I slept
14 less than three hours each day.

15 Four months into my illness, I achieved
16 significant pain relief because long-acting opiates
17 were initiated. I then could feed myself but
18 required assistance for dressing. Five months into
19 the illness, the doses of the long-acting opiates
20 were adjusted and I could walk into other rooms and
21 begin to dress myself.

22 I am also a physician, having practiced or

1 taught pain management from 2001 until the present.

2 I live and work in Southwestern Virginia, an area
3 well known for the misuse of prescription pain
4 medications.

5 A colleague of mine researched many deaths
6 related to OxyContin misuse in Southwest Virginia.
7 The demographics separated into two groups. The
8 largest group was depressed middle-aged women on
9 multiple medications from multiple physicians and who
10 died of accidental overdose. The second largest
11 category was young people who used a variety of
12 prescription drugs with alcohol and marijuana. They
13 unknowingly but dangerously mixed these street drugs
14 and prescription analgesics. They also died of
15 accidental overdose.

16 When I had an active clinical practice,
17 using long-acting opiates was a necessity for more
18 than 50 percent of my patients. Long-acting pain
19 medicines allowed patients to return to work or to
20 gain independence in activities of daily living.
21 Several of my patients were able to leave retirement
22 and medical disability to return to gainful

1 employment.

2 I am well aware of the usefulness and the
3 difficulty associated with long-acting opiates.
4 There is a potential danger in using the long-acting
5 opiates. It must be emphasized, however, that the
6 danger occurs when the drugs are misused or
7 prescribed incorrectly.

8 I sincerely regret that families have lost
9 a loved one to the misuse of these medicines. Making
10 the drugs more difficult to misuse is the logical
11 next step. The appropriate training of healthcare
12 providers is vital.

13 I commend Purdue for the new formulation
14 and urge this committee to expedite its approval.
15 Your approval will protect patients with legitimate
16 pain disorders and will protect families whose
17 children or siblings misuse long-acting opiates out
18 of ignorance or out of innocence.

19 Thank you.

20 DR. KIRSCH: Thank you.

21 The next speaker is Dr. Gregory Bogdan.

22 DR. BOGDAN: I'll disclose that Purdue

1 Pharma is a subscriber to the RADAR System.

2 Good afternoon. My name is Greg Bogdan,
3 and I am the Research Director for the RADAR System,
4 which is owned and operated independently by the
5 Denver Health and Hospital Authority. I'll be
6 presenting on the RADAR system and its ability to
7 evaluate changes in prescription drug abuse,
8 especially as it may relate to the reformulation of
9 OxyContin.

10 The strategy behind the RADAR System is
11 simple: to provide multiple perspectives on the
12 misuse, abuse, and diversion of prescription
13 medications.

14 The RADAR System provides that perspective
15 from six signal detection systems representing the
16 criminal justice system, treatment professionals,
17 acute health events caused by abuse, the perspective
18 of patients under treatment, impaired nurses,
19 pharmacists, and physicians, and college students.

20 These six signal detection systems
21 identified a specific product and formulation that is
22 being misused, abused, and diverted, coded to a

1 three-digit zip code. This gives us the ability to
2 address every part of the pathway of addiction from
3 initial experimentation to relapse after remission.

4 What the RADAR System may see after the
5 introduction of a reformulated OxyContin is that the
6 reduced rates could either stay the same, increase,
7 or decrease, and this would be compared to abuse
8 rates for other oxycodone and opioid drugs. No
9 matter what the outcome, we would have the ability to
10 monitor changes in abuse rates. Previously the RADAR
11 System has shown the ability to detect changes after
12 a community intervention.

13 I'm going to talk to you now about Kentucky
14 UNITE. Kentucky UNITE's first activities were
15 initiated in 2004 in a 29-county region of Eastern
16 Kentucky. These interventions included but were not
17 limited to undercover narcotics investigations, 800
18 numbers for substance abuse and treatment support for
19 family members and friends, and education efforts.

20 Using RADAR System Poison Center data, one
21 of our six systems, the three-digit zip codes in
22 Kentucky were classified into the Eastern or UNITE

1 region and then the Central Western region.

2 Average regional intentional exposure rates
3 per 1,000 unique recipients of dispensed drug were
4 calculated for all oxycodone drugs, as depicted on
5 that slide there.

6 Our data indicated that the intentional
7 exposure calls were more common in the UNITE region
8 than the Central Western region before the initiation
9 of Kentucky UNITE. Rates for oxycodone drugs then
10 decreased after implementation while they seemed to
11 increase in the other part of the state. Recently,
12 the rates are starting to go up again. It will be
13 interesting to see what effect a reformulated
14 OxyContin will have on these trends.

15 In conclusion, OxyContin's reformulation
16 offers a great opportunity to evaluate the impact on
17 prescription drug abuse, misuse, and diversion.
18 There are many perspectives to drug abuse and each
19 represents a different population. And the RADAR
20 System can provide data related to these different
21 perspectives and has experience in evaluating
22 interventions.

1 Thank you for your time.

2 DR. KIRSCH: Thank you.

3 The next speaker is Jennifer Bolen.

4 Is Ms. Bolen here?

5 [No response.]

6 DR. KIRSCH: Okay. We'll go to the next
7 one. Fred Wells Brasen.

8 MR. BRASEN: Good afternoon. I represent
9 Wilkes County, North Carolina. I'm Project Director
10 for our Chronic Pain Initiative as well as chairing
11 the Substance Abuse Task Force for Wilkes County and
12 the Western North Carolina Region.

13 In that, we're the first county and
14 actually the first state to begin a naloxone-
15 dispensing program called Project Lazarus in order to
16 hopefully stem the overdoses that are occurring in
17 our region of North Carolina. And I do have to state
18 I'm here at my own expense. There's no financial
19 disclosure regarding what I'm sharing.

20 In Western North Carolina, the average
21 death rate per 100,000 from opiate drugs is 16.
22 Wilkes County, it's 41. The state average is 11, and

1 in the United States, it's about between eight and
2 nine per 100,000.

3 So we took a community coalition approach.
4 We took the rescue medication approach. We took a
5 physician education approach, CMEs, on proper
6 prescribing. So we've looked at the whole scope.

7 Another responsibility that I've had is
8 director of our local hospice and I'm also the
9 hospice chaplain. So I've been working on both ends,
10 working with the individual who was abusing or
11 misusing and dying from the opiate drugs, and then
12 I've also been working with those patients, those
13 pain patients who desperately need the opiate
14 narcotic in order to have a comfortable functional
15 lifestyle.

16 So in saying that, such a formulation as
17 this to make it safer, less abusable, I have to say
18 we want that in the individual's -- well, not
19 medicine cabinet. We have to say lockbox because
20 that's preferred because of the stealing that's going
21 on. But in so doing, we have to look at the whole
22 community aspect regarding opiate-prescribing.

1 The community needs greater and more
2 education because the abuser is going to do what they
3 feel that they need to do to try and get the drugs,
4 so we have doctor-shopping. We're addressing that
5 with law enforcement. But then the other side of
6 that is we're educating the abusing population and
7 we're educating the misusing population, because the
8 abuser needs to know that if they do this to this
9 medication, crush it, snort it, inject it, they are
10 at greater risk because they've changed the dynamics
11 of the drug.

12 So if the pharmaceutical companies, such as
13 Purdue Pharma, is changing the formulation to make it
14 where that does not work, does not meet the abuser's
15 intent, then we have stepped into that arena of the
16 community that needs to be addressed and making it
17 safer, because, as I work with chronic pain patients
18 every single week, I head up a support group, they
19 need the medication in order to function, and we
20 can't -- you know, just because somebody speeds in
21 their vehicle doesn't mean that all of us have to
22 lose our cars.

1 So it's the same thing with the abuser.
2 Just because somebody is doing something illegal, we
3 can't take it away from the individual that needs
4 that narcotic prescription. So we are working with
5 the physicians, and I encourage you and the other
6 pharmaceutical companies to do the formulations that
7 are necessary to make it safe because I've got 41
8 people in my county who died last year.

9 Some of those were abusers, some of those
10 were misusers. And it's probably right now about the
11 number one county in the United States, and I thank
12 you for your time and appreciate it.

13 DR. KIRSCH: Thank you.

14 The next speaker is Maggie Buckley.

15 MS. BUCKLEY: Thank you. I have no
16 financial disclosure.

17 My name is Maggie Buckley. I'm a wife,
18 daughter, sister, friend, aunt, neighbor, and
19 photographer. I live with Ehler-Danlos Syndrome or
20 EDS, a painful genetic connective tissue disorder
21 that causes joint dislocations and excessive
22 bruising.

1 Living with EDS is like trying to move
2 through the world during an earthquake, never knowing
3 if the next footstep will land flat on the floor or
4 if I will fall and dislocate something else. Pain
5 has been my constant companion since childhood. The
6 pain levels range from mild to so excruciating I find
7 myself unable to form words, let alone speak.

8 I'm here today to discuss why long-acting
9 opioids are as important a part of my pain management
10 arsenal as my assistive devices. Long-acting opioids
11 are just one of many tools that I use to manage my
12 pain. Though I don't use all of them all the time, I
13 do use them for extended periods of time as part of a
14 recovery process from the frequent dislocations and
15 injuries.

16 Each tool is a key to my overall health.
17 When there's a spike in pain or injury levels, the
18 controlled-release medications have been the best
19 intervention to get me back on track.

20 I've been prescribed these types of
21 medications successfully at different points in my
22 life for varying lengths of time. I have lived

1 without long-acting pain medications but that life
2 left me looking for a way out and feeling that I was
3 a burden to others.

4 In my teens, I was prescribed NSAIDs, which
5 left me with GI irritation. In my twenties, exercise
6 and working through the pain were recommended in
7 spite of poor muscle tone due to EDS and an increase
8 in injuries from the increase in exercise. In my
9 thirties, I was lucky if a short-acting opioid was
10 offered.

11 Eleven years ago, I suffered a horrendous
12 hip dislocation and was forced to leave the workforce
13 for rehabilitation and recovery. Rest, ice, heat,
14 physical therapy, short-acting opioids, anti-nausea
15 medications and laxatives were the only tools
16 available to me. I would get a little better, push a
17 little harder, and then injure something else.

18 By 2000, I had reconciled myself to being
19 depressed and dependent upon others. I primarily
20 used a power wheelchair to get around. Some days I
21 couldn't get out of bed or even eat because the pain
22 was so bad. Emotionally, I felt defeated and I felt

1 like dying.

2 The cycle of untreated pain, depression,
3 re-injury and hoping for a lifeline continued until
4 2003 when a physician prescribed a long-acting opioid
5 after I had concurrent shoulder and ankle
6 dislocations. I felt like I was freed from prison.
7 Taking the prescription as directed for a period of
8 three months allowed me to fully participate in my
9 own care, actively exercise, enjoy the company of
10 friends and family, and be engaged fully in my own
11 treatment plan.

12 The nature of the long-acting pain
13 medication minimized the wild fluctuations in my pain
14 levels that had previously prevented me from living
15 my life. Long-acting opioid medication has saved my
16 life. This medication choice has come to my rescue
17 more than once, and I hope it will be there again
18 when I need it as I continue to live with EDS and the
19 pain it exerts on me. The responsible use of long-
20 acting opioids makes it possible for me to recover.

21 DR. KIRSCH: Thank you.

22 Our next speaker is John Carney.

1 MR. CARNEY: Thank you. I'm John Carney
2 from the Center for Practical Bioethics.

3 The center has, during its 25-year history,
4 received at times unrestricted gifts from the
5 sponsor, as from a number of other pharmaceutical
6 companies, to improve access to quality end-of-life
7 care.

8 We owe a particular obligation to those who
9 are traditionally underserved, including some of our
10 most vulnerable patients, our long-term care
11 residents, and those living in nursing homes and
12 others, including those of ethnicities and
13 disenfranchised populations.

14 New American Geriatric Society guidelines
15 call for the treatment of pain, for chronic pain for
16 elderly people, to be opioids as opposed to NSAIDs.
17 And placing additional scrutiny in this already over-
18 conservative area of long-term care poses significant
19 risks for those patients and a return to the world of
20 the 1980s in which baby aspirins were really all that
21 was dispensed in long-term care settings for chronic
22 pain.

1 The principle of respect for autonomy is a
2 fundamental tenet of healthcare. The Center for
3 Practical Bioethics has for more than 15 years worked
4 with the National Associations of Attorneys General,
5 the Federation of State Medical Boards, the DEA, and
6 pain policy advocates from across the country in
7 developing balanced pain policy strategies familiar
8 to many in this room.

9 Dignity is an essential component of
10 personhood. Informing and maintaining a sense of who
11 we are, we become self-directed. When you are robbed
12 of the ability to be self-directing, our dignity and
13 personhood is jeopardized. When that loss of sense
14 of self is preventable and treatable, as it is with
15 pain, healthcare providers have an obligation to act.

16 Pain steals from its victims and punishes
17 them unnecessarily and our collective professional
18 responsibility to protect those persons is something
19 that cannot be restricted. We must remember above
20 all else that pain is subjective.

21 Our under-treatment should be subject to as
22 much scrutiny as our concern for the legitimate risks

1 associated with misappropriation, and the principle
2 of justice cannot be subjected to over-
3 simplification.

4 Do we treat pain the same or do we treat
5 people according to their need? When the
6 consequences are minor and the inconvenience is a
7 nuisance, then all can be asked to make adjustments.
8 However, the pain patients require more from us
9 because of the price that they have to pay because
10 then they become victims twice over, once because of
11 their health condition and once because they need
12 treatment and seek drugs.

13 There is no question that what we need is a
14 balanced policy and thoughtful consideration and
15 restraint and dutiful attention for both the policy
16 formulation and the treatment that patients need.

17 The preponderance of literature in this
18 area deals with misappropriation and treating
19 patients as addicts and subversive activities. These
20 characterizations get amplified when policies get
21 implemented, especially in relation to race,
22 ethnicity, and cultural language barriers.

1 The ominous tone will only grow more dark
2 if we are not vigilant and work to implement balanced
3 pain policy.

4 Thank you.

5 DR. KIRSCH: Thank you.

6 The next speaker is Charles Cichon.

7 MR. CICHON: Good afternoon. I'm Charlie
8 Cichon. I'm the Executive Director of the National
9 Association of Drug Diversion Investigators.

10 DR. KIRSCH: Sorry.

11 MR. CICHON: That's fine. Nobody ever gets
12 it right. NADDI.

13 I have nothing to declare, but I will
14 discuss some sponsorships and unrestricted grants
15 that NADDI has received from Purdue Pharma, as well
16 as other pharmaceutical companies.

17 NADDI is a non-profit organization
18 dedicated to providing education to its members and
19 the public on the issues surrounding prescription
20 drug abuse and diversion. The majority of our
21 members are law enforcement, but also included is a
22 considerable population of regulatory agents,

1 healthcare professionals, and healthcare fraud
2 investigators.

3 Due to the ongoing problems with drug
4 diversion in the United States, NADDI is a strong
5 proponent of new controlled substances that make it
6 more difficult for an abuser and more helpful for law
7 enforcement, yet still provide quality relief to the
8 patient.

9 NADDI has a strong belief that the
10 diversion of prescription medication can many times
11 ultimately negatively affect legitimate patients, the
12 vast majority of those who use controlled substances.

13 NADDI has provided grants to law
14 enforcement agencies across the country, most
15 recently to the Kentucky Office of the Attorney
16 General, Drug Diversion Task Force, a statewide task
17 force originally formed to focus on stopping
18 prescription drug abuse and diversion in Eastern
19 Kentucky.

20 NADDI's Seed grant is sponsored by Abbott
21 Labs and is designed to encourage local and state law
22 enforcement to dedicate at least one full-time law

1 enforcement officer to investigate prescription drug
2 abuse.

3 Sponsorship by Purdue Pharma supports our
4 Abused Pharmaceutical Substance Brochure. This
5 brochure is designed to be a field reference for law
6 enforcement officers across the country. NADDI has
7 dispensed over 400,000 of these brochures free to law
8 enforcement officers throughout the United States.

9 NADDI's law enforcement grant was developed
10 through sponsorship provided by Purdue Pharma to help
11 address the complex problem of prescription abuse and
12 diversion and put more resources in the hands of
13 local law enforcement entities engaged in combating
14 the abuse and diversion of scheduled prescription
15 drugs. The LE Grant Program is designed to recognize
16 law enforcement agencies that have achieved
17 excellence in the investigation of pharmaceutical
18 diversion.

19 NADDI's 20th anniversary conference in
20 November is in Annapolis, Maryland, and one of the
21 highlights of that conference will be a program
22 entitled Teens in Crisis. This session will involve

1 a group of teenagers that have had a severe addiction
2 to prescription drugs and are traveling around the
3 country to tell their story. The Teens in Crisis
4 presentation is sponsored by King Pharmaceuticals.

5 Purdue Pharma is a leader in the industry
6 with its collaborative efforts with the public and
7 law enforcement and here are several examples.
8 Painfully Obvious is a public service campaign
9 designed to educate parents, teachers, and students
10 about the dangers of prescription drugs. Prior to
11 Painfully Obvious, there was no national program to
12 address the growing issue of prescription drug abuse
13 among young people.

14 DR. KIRSCH: Thank you.

15 MR. CICHON: Thank you very much for your
16 time and attention.

17 DR. KIRSCH: Thank you.

18 Next is Michael Clark.

19 DR. CLARK: Good afternoon. I'm Dr.
20 Michael Clark. I have no financial disclosures.

21 I'm a psychiatrist, pain specialist, and
22 member of the Board of Directors of the American

1 Society of Pain Educators. This is the only
2 organization in the United States focused solely on
3 pain education. We have been actively involved in
4 the risk evaluation and mitigation strategies
5 hearings, writing to the docket with regard to REMS
6 and acetaminophen.

7 We well understand that effective education
8 is the best approach for improving treatment
9 adherence and compliance, assuring safe use and
10 helping patients to raise their function and quality
11 of life.

12 Today, on behalf of the American Society of
13 Pain Educators, I come to support continued access to
14 controlled-release opioid analgesics. These vital
15 medications are life-affirming for people with
16 around-the-clock moderate to severe pain. They
17 afford continuous pain relief and stabilize blood
18 levels to minimize side effects and enhance their
19 established efficacy.

20 Consistent with the ASPE's previous
21 statements, we believe that access to controlled-
22 release opioids, such as OxyContin, is necessary to

1 maintain excellence in pain management for legitimate
2 patients.

3 We support any and all efforts made to make
4 these medications resistant to tampering by people
5 who would misuse them. We recognize that there may
6 never be 100 percent tamper-proof medications because
7 such forms would likely not relieve pain. However,
8 we do believe that efforts to minimize conversion
9 from controlled-release to immediate-release by
10 matrix destruction will improve the safety of these
11 medications and lessen their desirability for
12 purposes of recreational use or intoxication.

13 The ASPE respectfully calls upon the
14 members of this advisory board to answer the
15 questions posed by the FDA. Today's meeting is about
16 a formulation change for a single medication. It is
17 not the time nor appropriate forum to address all of
18 the concerns related to REMS or other product
19 technologies.

20 OxyContin has been an effective medication,
21 able to help those with chronic disabling pain live
22 more satisfying lives. We ask that you review the

1 data with proper deliberation and allow practitioners
2 to prescribe OxyContin in the new and safer
3 formulation.

4 Thank you for your attention to these
5 important issues and the opportunity to speak to you
6 today.

7 DR. KIRSCH: Thank you.

8 Next is Eliot Cole.

9 Is Dr. Cole here?

10 [No response.]

11 DR. KIRSCH: No. Then we'll go on to the
12 next one then. Penny Cowan.

13 MS. COWAN: Cowan. Thank you.

14 My name is Penny Cowan. I'm the Founder
15 and Executive Director for the American Chronic Pain
16 Association, and I have nothing to declare. I've no
17 financial obligations.

18 For almost 30 years, the American Chronic
19 Pain Association has daily contact through phone
20 support, e-mails and our support groups across the
21 country with real people living with real pain. Many
22 of these people use strong medications to enable them

1 to live a productive near-normal life.

2 People with pain did not ask for the pain,
3 they did nothing to deserve it, and they would gladly
4 trade it in for a life as it was before it began.
5 However, they cannot. They must depend on their
6 healthcare providers to help them manage a life
7 filled with pain and with fear.

8 While we understand that safety is the
9 number one concern, access to care and personal
10 dignity must be preserved while helping to establish
11 a clear understanding of the risks and safety issues.

12 People with pain fear increasing the stigma
13 already attached to the use of opioids. Establishing
14 a national registry for those who need opioids to
15 function violates the HIPAA and personal privacy. We
16 all know that there's little these days that is safe
17 from intrusion, be it cyber crime or other means.

18 Entering every person who takes pain
19 medications into a registry can threaten their
20 employment, insurance, and access to future care.
21 There is no evidence that a registry would reduce the
22 intentional abuse and diversion of these medications.

1 It only makes life more difficult for the person with
2 pain.

3 Education is the heart of the appropriate
4 prescribing, dispensing, taking, storing, and
5 disposal of all opioids. This is an issue of both
6 healthcare providers and consumers. Ideally, every
7 healthcare provider should understand pain and have
8 the knowledge and skill to help their patients manage
9 their pain.

10 Reality is most do not have the training nor would
11 they be willing to obtain it.

12 A system that requires physicians to
13 register would result in severely-limited access to
14 care for people with pain. To avoid this,
15 certification of prescribers and dispensers should be
16 tied to the existing DEA registration process. In
17 addition, limiting where opioids are dispensed would
18 be of great harm to those living with pain in rural
19 areas and inner cities.

20 Creating such obstacles for people with
21 pain will not deter those who misuse opioids
22 intentionally. It will only further stigmatize and

1 punish people with pain who obtain the medications
2 legitimately and who need them to function more
3 fully. Limiting access to care and treating people
4 with pain like criminals does not really address the
5 drug problem facing the nation today.

6 Thank you very much.

7 DR. KIRSCH: Thank you.

8 Our next speaker is Lennie Duensing.

9 MS. DUENSING: Right.

10 DR. KIRSCH: Got one right.

11 MS. DUENSING: Very unusual.

12 Well, my name is Lennie Duensing, and I'm
13 the Director of the American Academy of Pain
14 Management. We're the nation's largest professional
15 organization serving clinicians who treat people with
16 pain, and we're the only organization that educates
17 clinicians about pain from an integrative
18 perspective. This means that we support a model of
19 care that is patient-centered and brings together all
20 appropriate therapeutic approaches to reduce pain and
21 achieve optimal health and healing.

22 The Academy recognizes, however, that for

1 millions of people with persistent pain, this
2 comprehensive treatment absolutely must include
3 opioid analgesics because they remain one of the most
4 effective treatment options for relieving both cancer
5 and non-cancer pain, restoring function, and
6 restoring life.

7 For those suffering with pain around the
8 clock, the advent of extended-release opioids has
9 brought relief for millions and they've been used
10 safely and effectively and in a variety of treatment
11 settings. But just how extensive is the pain
12 problem?

13 Consider this astounding fact. There are
14 approximately 33 million Americans who have lived
15 with moderate to severe pain for more than one year.
16 Think about it. If they all lived in one state, and
17 let's call that the state of pain, it would be the
18 second largest state in population in the country,
19 second only to California and larger than Texas.

20 If the state of pain were a reality,
21 there'd be two U.S. senators and over 30 members of
22 the House of Representatives speaking out with

1 passion to guarantee that these long-acting opioids
2 be made readily available to their constituents.

3 I have another fact. There are
4 approximately 4 million Americans who are using long-
5 acting opioids to relieve their pain. This is over
6 five times the population of the District of
7 Columbia. So think about that while you're driving
8 home tonight.

9 But what does it mean to live with pain?
10 We know that persistent pain robs people of their
11 lives, of their families, of their work, and even
12 simple pleasures. And we know that pain also robs
13 people of their bodies. And I'm not going to go
14 through all of the various ways, except to let you
15 know that a study came out this last week that showed
16 that the physical abilities of people who had ongoing
17 pain who were 50 to 59 were comparable to people who
18 were 80 to 89 who did not have pain.

19 Over the last 12 years, working both with
20 the American Pain Foundation and the Academy, I've
21 taken many suicide calls, too many suicide calls,
22 from people who said that they could not live another

1 moment.

2 Just this last month at the Academy, we
3 heard from a woman who said that her husband had his
4 pain medications reduced because his doctor was
5 afraid of prescribing. His pain became unbearable
6 and he shot himself in the head.

7 You at the FDA have been charged with the
8 task of ensuring that the benefits of these drugs
9 continue to outweigh the risks. On March 3rd, Dr.
10 Rappaport said, "We expect companies marketing these
11 products to work with us to get this done
12 expeditiously."

13 DR. KIRSCH: Thank you.

14 The next speaker is Lisa Fowler.

15 DR. FOWLER: I have no financial
16 disclosure.

17 Good afternoon, and thank you for the
18 opportunity to share a community pharmacy perspective
19 on the approval of a long-acting opioid medication.

20 I am Lisa Fowler, Director of Management
21 and Professional Affairs at the National Community
22 Pharmacists Association. NCPA represents America's

1 community pharmacists, including the owners of more
2 than 23,000 community pharmacies, pharmacy
3 franchises, and chains. These stores dispense nearly
4 half of the nation's retail prescription medications.

5 I am a pharmacist, and up until just about
6 a year ago, I spent my days behind the counter of one
7 of NCPA's member pharmacies. I know that OxyContin
8 and medications like it, when used as indicated, ease
9 the suffering in the lives of patients with prolonged
10 moderate to severe and chronic pain.

11 It is important to note that in the
12 provision of care process, pharmacists have standard
13 workflow procedures that ensure prescription
14 medications are delivered safely to their patients.
15 Face to face counseling with the pharmacist at point
16 of dispensing reinforces proper medication use and
17 detects non-compliance, which can be immediately
18 addressed.

19 Related to activity at FDA regarding class-
20 wide REMS for long-acting opioid products, NCPA
21 asserts that an automated standardized REMS process
22 that can be integrated within existing pharmacy

1 workflow is critical to the successful execution of
2 the program.

3 I also want to stress that community
4 pharmacies are highly regulated in each state by
5 boards of pharmacy, in addition to being regulated by
6 the DEA. It is therefore NCPA's position that any
7 state and DEA-licensed pharmacy should be eligible to
8 dispense opioid products.

9 Finally, NCPA supports regulation changes
10 that will allow for a simpler take-back process of
11 controlled substances. Typically, patients must wait
12 for a take-back event that is staffed with law
13 enforcement and are allowed only to return products
14 which were prescribed to them.

15 NCPA supports NCPA efforts to encourage
16 disposal of expired and unwanted medications through
17 appropriately-designed drug take-back programs. When
18 there are fewer unwanted doses of controlled
19 substances in the kitchen cupboards and medicine
20 cabinets of our neighbors and relatives, there will
21 be fewer diverted and abused prescription drugs.

22 Thank you for your time.

1 DR. KIRSCH: Thank you.

2 The next speaker is Larry Golbom.

3 MR. GOLBOM: Does this -- can I move this
4 forward to the first slide?

5 DR. KIRSCH: One second. It's loading.

6 MR. GOLBOM: While you're doing that, I'm
7 Larry Golbom. Okay.

8 Can all the committee members please see
9 that slide?

10 I am Larry Golbom, and I do a local radio
11 show in the Tampa Bay market of Florida called The
12 Prescription Addiction Radio Show, Breaking the
13 Silence.

14 For those who have missed the past
15 meetings, this first slide is another reminder of why
16 Purdue is here today. For Purdue, it's all about
17 narcotics distribution and Purdue has ingeniously
18 repackaged and marketed the opium plant to become a
19 major drug cartel in our country. The media and the
20 American public are beginning to understand the opium
21 epidemic that Purdue has started.

22 You know, America is here with us today.

1 The petition to ban OxyContin is growing every day.
2 The thousands who have signed the petition and the
3 comments in the handout before you reflect a dramatic
4 difference. Excuse me. I couldn't get that handout
5 to you, but please do ask for it.

6 There's a reality of death and addiction in
7 every community in America because of OxyContin.
8 Thousands continue to die with OxyContin in their
9 bodies.

10 The petition has grown by word of mouth.
11 There's no telling how large this movement is going
12 to become. Bracelets are printed. College students
13 are getting involved. Parents and families are
14 uniting.

15 You know, heroin was on the market for 14
16 years. We wait for the FDA to make the decision to
17 pull OxyContin. Why does the most dangerous drug in
18 history since heroin continue to remain on the
19 market?

20 In my hand is the formulation. It can be
21 gotten off the Internet. Dr. Jenkins, Dr. Rappaport,
22 did Mr. Stewart or Mr. Landau tell you that this

1 product can probably be put in the oven to separate
2 out the active ingredient?

3 The formulation before you is a product
4 that is probably more dangerous, more dangerous than
5 your original OxyContin, just by simply putting it in
6 the oven.

7 Dr. Stewart and Dr. Landau, did you tell
8 the committee members that few, if any, heating
9 studies have been done on this product? Which member
10 is going to vote for this product knowing that
11 putting it in the oven may make it more dangerous
12 than the original formulation?

13 I didn't hear Dr. Cone mention the oven
14 when he gave his presentation. Smoking it could be
15 more deadly, more deadly, than the original
16 OxyContin.

17 Purdue has continually misled America. I
18 hope today we find out who is running the FDA: a
19 drug company that continually brings embarrassment to
20 the thousands of employees who are dedicated to the
21 FDA or a privately-held legal drug cartel.

22 After thousands of deaths attached to

1 OxyContin, I ask the Advisory Committee to help bring
2 sense to the OxyContin fiasco. Recently, we lost a
3 10-year-old child to this drug swallowing it whole.
4 I hope you're outraged by this news that you can
5 possibly put this product in an oven or smoke it and
6 bring more death to our communities.

7 Thank you for your time.

8 DR. KIRSCH: Thank you.

9 The next speaker is Steve Hayes.

10 MR. HAYES: Hi. I have no financial
11 disclosure to make to you, except that I paid my own
12 way, as we've been doing, because I'm the director of
13 a medical detox center. I get to treat and try to
14 help the people that this drug company has mostly
15 sent to us because many of the people that come to us
16 are taking OxyContin.

17 Now one of the things that I was really
18 excited about when I heard that they were going to
19 have a tamper-proof formulation was that they were
20 going to do what they told the FDA, in fact their
21 convicted felon medical director told the FDA in
22 2002, which was in a few years in a press release

1 they were going to be making OxyContin with naloxone.

2 Now I can tell you that addicts and people
3 that abuse it are scared to death of suboxone because
4 of the additive of naloxone.

5 Did they do that? No. They didn't make an
6 effective blocker. They made something that made it
7 more difficult, but you're going to have a situation
8 where you're being asked to trust a company that
9 Judge Stein said so misrepresented their patent that
10 he was going to invalidate it, a company that in 2007
11 pled guilty to a felony of lying.

12 How do you know that their representatives
13 aren't going to spread the word to everybody this is
14 tamper-proof? Oh, the label doesn't say it, but it's
15 tamper-proof because this is what they have done
16 before.

17 Basically, I think there's another
18 unintended consequence for many of the public that I
19 deal with. That unintended consequence is you are
20 going to have people who are addicts, who are first-
21 time users, who are going to take this pill. And
22 they're going to be told, this new formulation,

1 you're going to get a buzz. They don't feel
2 anything, so they take another one. They don't feel
3 anything, they take another one, and pretty soon
4 you've got a situation, particularly with more
5 opioid-naïve people, you've got an overdose.

6 So you've got an unintended consequence of
7 this drug and you've got a situation where what
8 you're being asked to do is put a drug on the market
9 that will be marketed, I guarantee you, as tamper-
10 resistant no matter what you say on the label.

11 Is it time to do this? Is it time for more
12 people to die because they take this drug? I'm one
13 of the co-sponsors of the Ban OxyContin Petition. I
14 believe this is a drug that should have been off the
15 market. This is a company, except for a miscarriage
16 of justice in 2007, should have been banned from
17 dealing with the government and should have been
18 banned from dealing with the FDA.

19 So as far as I am saying to you is take a
20 good look because every one of those kids that I find
21 out about that overdosed is going to be on your
22 conscience.

1 I deal with people dying. It's not myth to me.

2 Thank you very much.

3 DR. KIRSCH: Thank you.

4 MS. HAYES: Hi. My name is Paula Hayes.

5 I'm here representing Sandra Kresser who was going to
6 be here from Salt Lake City, Utah, today, in memory
7 of her son Josh who passed away three years ago next
8 week from a lethal combination of prescription drugs.

9 These drugs were all prescribed to him by a
10 doctor who knew his complete history of opiate
11 addiction, multiple overdoses, relapses, and rehab
12 treatment episodes, but chose to ignore all of this
13 and prescribe it to him anyway. None of the levels
14 were toxic, but it was the combination of these
15 prescribed drugs taken as directed that killed her
16 son.

17 During the last two and a half years of
18 Josh's life, he suffered and was held captive by a
19 very dangerous addiction to prescription drugs.
20 Josh's plunge into opiate addiction began on April
21 13th, 2004, when his doctor first prescribed
22 OxyContin to him for two herniated disks in his back

1 that he sustained in a work-related injury.

2 OxyContin grabbed hold of Josh by the throat and
3 wouldn't let him go, no matter how hard he tried.

4 Josh spent over 404 days in active
5 treatment, trying to break the change of this very
6 powerful addiction that was fueled by his back pain,
7 by clueless doctors on addiction who continued
8 prescribing the opiates to him, and by the lies and
9 deceit of Purdue Pharma and OxyContin.

10 Josh had the love and support of his family
11 and friends. And each time he completed the
12 treatment program, they became cautiously optimistic
13 that he was finally going to get his miracle and go
14 on to live a long, healthy, happy, and drug-free
15 life. This miracle was unfortunately not to be.

16 Many would have you believe that those who
17 have become addicted and tragically died were to
18 blame for choosing to misuse or abuse these powerful
19 narcotics. I assure you that no one would ever
20 choose to become an addict. The life of an addict is
21 one of untold pain and suffering.

22 "The only thing my son chose was to seek

1 help from a doctor that he trusted." This doctor
2 believed the lies that he was told by the Purdue reps
3 about the safety of OxyContin and prescribed it to
4 her son. Both were dead wrong.

5 Everyone who has become addicted or
6 tragically died from OxyContin are the real victims.
7 It doesn't matter if they were patients with
8 legitimate pain taking it as prescribed, patients
9 who, like her son, became addicted after being
10 prescribed it for a legitimate injury, those who used
11 it for non-medical reasons or those who naively tried
12 it only once, the results are the same: addiction
13 and death. All of those people are the real victims
14 of OxyContin.

15 We are here today for the proposed approval
16 of a new formulation of OxyContin that is supposed to
17 be a somehow safer alternative to the current poison
18 pill on the market. Purdue Pharma, a criminally-
19 convicted company, lied to the FDA, medical
20 communities, and public before about the safety and
21 low addiction risk of the current formulation.

22 The mounting toll of addiction and death as

1 a result of these lies and deceit is horrendous. Why
2 should we believe that anything is different now with
3 this new formulation? Why would we believe a
4 criminally-convicted company whose only motivation is
5 to continue lining their pockets with more blood
6 money?

7 Thank you.

8 DR. KIRSCH: Before you leave the podium,
9 could you state your name?

10 MS. HAYES: Paula Hayes.

11 DR. KIRSCH: Thank you.

12 The next speaker is Ed Vanicky.

13 MR. VANICKY: Vanicky. Happens all the
14 time.

15 Good afternoon. I have no disclosures.
16 Misbranding, illegal promotion, misleading doctors
17 and patients, lying about the abuse potential,
18 misleading advertising and fraud, and that's just
19 what they would admit to.

20 All of the criminal actions of Purdue
21 Pharma resulted in billions of dollars in sales and
22 thousands of deaths. The crimes began in meetings

1 such as this with the new drug application for
2 OxyContin and with FDA approval.

3 Now years later and with deaths, abuse and
4 crimes associated with OxyContin skyrocketing,
5 they're asking you for your permission to allow them
6 to commit these same crimes again.

7 Sixteen months ago, they stood before the
8 panel and presented the usual brand of junk science
9 and stated their claim that they had finally
10 discovered an abuse-resistant form of OxyContin. The
11 panel was wise enough to recognize this junk science
12 and Purdue went home embarrassed and empty-handed.

13 Purdue claims to have been working on a new
14 formulation since 2000. Other companies have created
15 versions in as little as six months. Why has it
16 taken Purdue so long? Given the severe problems with
17 OxyContin, you would think the company with a
18 conscience that supposedly puts patient safety first
19 would have worked night and day to correct the
20 problems with their drug or pulled it all together,
21 for that matter.

22 They could have worked with other companies

1 that were developing abuse-resistant technology and
2 shared ideas. Not this company, though. They would
3 rather sue those very companies for patent
4 infringement rather than invest the time, money, and
5 energy in finding a solution to the problem.

6 So after all these years, they claim to
7 have the correct version of it. That was not so in
8 May of '08 when even the company's Vice President of
9 Risk Management and Health Policy was quoted as
10 saying that "We can argue that we have met some
11 degree of tamper-resistance, but the abuse-resistance
12 is yet to be determined."

13 Are they now saying that in a scant 16
14 months that they have solved both of those clearing
15 issues? The motivation here today, and it's their
16 only motivation, is to get this approved and begin to
17 market it before the patent on OxyContin expires.
18 Money drives the motivation, not a safe product for
19 patient safety.

20 The national call to action to once and for
21 all ban OxyContin and expose the real truth about
22 this company is underway. Thousands have signed up

1 and thousands more will, as well. Activities are
2 being planned around the country in an effort to
3 educate people on the dangers of this drug.

4 Although it should be the responsibility of
5 the FDA to do that, the gross lack of action by the
6 FDA in regard to the dangers of OxyContin is forcing
7 people to do the FDA's job themselves.

8 My wife Mary Jo was prescribed OxyContin
9 for a herniated disk. A drug as powerful as
10 OxyContin should never have been prescribed for that
11 type of injury. Through Purdue's criminal activity,
12 she is one of the untold numbers of legitimately-
13 prescribed patients to die from OxyContin.

14 It is because of her death and all the
15 others due to this dangerous drug that I stand before
16 you today and remind you that although this company
17 deceived you in 1995 when they launched the OxyContin
18 epidemic, please do not let them deceive you today.

19 Thank you.

20 DR. KIRSCH: Thank you.

21 Next is Pete Jackson.

22 MR. JACKSON: Good afternoon. I'm Pete

1 Jackson. I have no financial disclosures.

2 The smiling girl on the screen is my
3 daughter Emily, a friendly 18-year-old girl who died
4 from an overdose of OxyContin in August of 2006,
5 after she had taken one OxyContin pill offered to her
6 by her cousin.

7 This was her only encounter with OxyContin. One pill
8 swallowed whole.

9 What other drug can kill you like that with
10 one pill?

11 I have appeared before your committees
12 several times, as has my wife. We've begged FDA to
13 help stem the tide of death and addiction from the
14 non-selective widespread use of OxyContin. We are
15 still waiting.

16 OxyContin is responsible for more deaths
17 than any other drug. How many more people must die
18 before the FDA will finally do something to stop this
19 epidemic? I wonder how many people have died on
20 FDA's watch since I first asked that question at one
21 of your committee meetings two and a half years ago.

22 Of course, the official purpose of today's

1 meeting is to review once again the new drug
2 application for OxyContin that is purportedly tamper-
3 resistant.

4 Well, what about the many people like my
5 daughter who swallowed the pill whole and then died?
6 There are a large percentage of the total deaths from
7 OxyContin that follow this avenue, as did my
8 daughter. Is the new formulation somehow less risky
9 for these individuals who swallow the pill whole? We
10 heard this morning the answer is clearly no.

11 Do you even know what percentage of
12 OxyContin victims' misuse involves tampering? Any
13 new formulation of OxyContin will be perceived as
14 tamper-resistant and will lead to doctors to a false
15 sense of security, and the resulting surge in sales
16 will lead to more deaths, not fewer. Remember,
17 deaths track sales, period. I urge you not to
18 endorse this NDA for OxyContin.

19 But today your joint committee has much
20 more important business to conduct. FDA's mission is
21 to promote and protect the public health. FDA has
22 failed in this mission insofar as OxyContin is

1 concerned. The problem with OxyContin has existed
2 for some time, well before this NDA. Because of this
3 drug's continued legacy of death and addiction,
4 Purdue's long history of unethical and illegal
5 marketing and the company's felony record for
6 misbranding, you must strongly recommend today that
7 the FDA remove OxyContin from all U.S. markets.

8 The risk-benefit ratio of OxyContin can no
9 longer be evaluated without considering the felony
10 record of this company. This company should no
11 longer be allowed to sell a drug that resulted in the
12 deaths of thousands of Americans due to the over-
13 prescribing that resulted from Purdue's acknowledged
14 lies to doctors. The harm from this drug is far
15 greater than any perceived benefits since OxyContin
16 offers no efficacy or safety benefits over other
17 previously-available opioid medications.

18 It's too late to save my daughter, but
19 there are many other people whose lives could be
20 saved with your voice without sacrificing access to
21 other available opioid medications. It's time for
22 you to stand up and do the right thing. Stop the

1 deaths, ban OxyContin now.

2 DR. KIRSCH: Thank you.

3 The open public hearing portion of this
4 meeting has now concluded and we will no longer take
5 comments from the audience.

6 The committee will now turn its attention
7 to address the task at hand, the careful
8 consideration --

9 MS. PAUKSTIS: Excuse me. I'm Beverly
10 Paukstis. I represent the Hospice and Palliative
11 Nurses Association.

12 DR. KIRSCH: Okay. Could you --

13 MS. PAUKSTIS: I'll be quick.

14 DR. KIRSCH: No. You get your full time.
15 Give us your name on the microphone, please.

16 MS. PAUKSTIS: Sure. My name is Beverly
17 Paukstis, and I'm a member of the Board of Directors
18 of the Hospice and Palliative Nurses Association, and
19 I've been a nurse since 1964 and doing hospice work
20 since 1985. I have no financial disclosure.

21 I represent nearly 10,000 hospice and
22 palliative nurses who are at any given moment today

1 providing care to 30 to 50,000 patients in their
2 homes who are dying, dying with pain that these
3 nurses are seeking in partnership with physicians and
4 pharmacists to relieve.

5 We in HPNA strongly and favorably support
6 the FDA REMS process because we know that abuse and
7 misuse occur. We are in favor of all efforts to
8 curtail this. However, we are deeply concerned about
9 some unintended consequences that may occur.

10 Specifically, we are concerned about the
11 unintended consequences of restriction to access for
12 the very patients that Purdue had in mind when
13 OxyContin was developed, and that is our population
14 of patients who are dying in severe pain.

15 One could argue that there are other drugs
16 to use. The reality is, though, that we frequently
17 see patients with allergies and patients who have
18 such fear and anxiety over anything that mentions the
19 word "morphine," that they won't take anything at
20 all. And, as well, many of them have poor response
21 to many of the traditionally-used opiates. It's
22 often necessary for us to try four or five opiates

1 before we find the right one.

2 Access to a full complement of opiates
3 assures our ability to relieve the pain of dying
4 patients. Eliminating OxyContin from that menu
5 significantly harms access.

6 We recognize our unique role and
7 participation with the REMS process at the time of
8 death or discharge. We in HPNA strongly promote and
9 vigorously teach policies for drug disposal in the
10 home when the drug is no longer needed.

11 We believe it is absolutely possible to
12 curtail inappropriate access while retaining
13 necessary and vital access for people in pain.

14 Thank you.

15 DR. KIRSCH: Thank you. I'm going to read
16 this again. The open public hearing portion of the
17 meeting has now concluded and we will no longer taken
18 comments from the audience.

19 The committee will now turn its attention
20 to address the task at hand, the careful
21 consideration of the data before the committee as
22 well as the public comments.

1 We are now going to open the floor for
2 questions from members of the committee to either the
3 sponsor or FDA. Like yesterday or like usual, if you
4 have something to say, please raise your hand. We'll
5 write your name down here and then call you in turn.

6 Dr. Crawford.

7 DR. CRAWFORD: Thank you, Mr. Chairman.
8 May I please ask one question to the sponsor and one
9 to the agency?

10 DR. KIRSCH: Sure.

11 DR. CRAWFORD: Thank you. First -- well,
12 I'll present both and whichever representative wishes
13 to go first. One regards from the agency, Dr. P's
14 presentation. I'm sorry. I don't want to
15 mispronounce it.

16 Based on the OxyContin risk management plan
17 and the thoughts about the class-wide risk management
18 plan for long-acting opiates, I'm not sure what is
19 meant with respect to the interim REMS, either for
20 this part or in the general class-wide, what the
21 medication guide, a little briefly, what it would
22 entail. And you talk about a time table for

1 submission of assessments, because part of what I'm
2 grappling with, with this particular product, might
3 be any recommendations about other studies, so I need
4 to know more about assessments.

5 Now for the sponsor, my question's a little
6 different. So we've heard interesting data today
7 from the in vitro studies and anticipated outcomes
8 deemed likely, largely based on opinions of expert
9 consultants and others, and very carefully-worded
10 ways throughout this briefing document and in the
11 presentation. And I say this in sensitivity to some
12 of the open comments we just heard.

13 The words that we heard kept making sure we
14 knew the message that you did not want to convey but
15 it still made sure to promote in some way -- that
16 might not be the correct word, but this reformulation
17 suggests the reformulated tablets will be safer, the
18 reformulation is an incremental improvement. And
19 also we see that -- it was actually stated, the
20 message we are trying to avoid, but to let us know
21 that message is a new and improved formulation.

22 So if this product were approved, it would

1 be on the market, health professionals, including
2 pharmacists, physicians, others, consumers would want
3 to know what's going on. So I ask the sponsor
4 exactly what is that message that would be promoted
5 if this is on the market with a brand new formulation
6 and lots of new questions?

7 DR. KIRSCH: Could I ask the sponsor to
8 address that, please?

9 DR. LANDAU: Thank you for your question.
10 It's a very important question. And before I provide
11 a direct answer, I'll say that we're not making --
12 it's very clear what our motivation is to reformulate
13 the product.

14 Okay. Our motivation is to address the
15 specific vulnerability that contributes to its
16 overall abuse liability and danger when used in
17 various subpopulations. So we want to make that
18 clear.

19 I also want to make it clear that we have
20 no intention whatsoever of promoting the product
21 based upon these characteristics. It's a reality
22 that these discussions happen in an open environment.

1 The specific question regarding what we
2 will say is something we have to speak very, very
3 closely with the division and with DDMAC. We
4 recognize we're likely to be asked these questions by
5 pharmacists, patients are going to ask, physicians
6 who are prescribing. And physicians might call the
7 company through our Medical Information or Medical
8 Services area, and we want to be certain that we
9 don't give anyone a false sense of security that this
10 formulation is anything it's not.

11 I spoke earlier to our intention to promote
12 this product just the same way we're promoting the
13 current product. Until post-marketing data support
14 it, we can't assume that there's any reduction of
15 abuse liability.

16 I don't know if Dr. Rappaport wants to
17 respond to that, to the first part of the question.
18 Sorry.

19 DR. RAPPAPORT: Yes, thank you. I
20 definitely don't want to respond to the last part.

21 Okay. So going back, just to remind
22 people, I think you were asking about the interim

1 REMS and what that is going to be.

2 To clarify, we're working on the class REMS
3 for the extended-release, long-acting opioid products
4 and we have a lot of information to go through and
5 that's going to take us some more time. So in the
6 meantime, we have an issue that we had to address of
7 products that are coming up for approval that would
8 fall into this class and what do we do with them
9 since we don't have a REMS in place that we could
10 implement.

11 What we decided, based on the fact that
12 there are already products out there that have risk
13 management programs that are similar to these
14 products, such as Embeda and OxyContin in this
15 reformulation, that it would be unfair to not approve
16 these products with a similar risk management
17 program, or in this case REMS for the newer products,
18 and with an agreement in place that they would
19 implement the new class-wide REMS as soon as it
20 becomes available. And for the one product we
21 approved with that, which is Embeda, the company did
22 give us written agreement that they will implement

1 the new REMS as soon as we make it available.

2 Now the interim REMS consists of a
3 communication plan and a med guide, and an
4 implementation time table, but that's all. There are
5 no elements to assure safe use. The communication
6 plan is a Dear Healthcare Provider letter and that
7 sort of thing, and then the medication guide is for
8 the patients.

9 DR. KIRSCH: Dr. Lorenz.

10 DR. LORENZ: Thank you. I would like to
11 focus for a moment on the narrow question of how this
12 formulation might represent a benefit in terms of its
13 advance and ability to tamper with it.

14 I'm wondering if we could look at slide 50
15 for starters. That was slide 50 on the packet that
16 we received.

17 DR. LANDAU: Slide 50, please.

18 DR. LORENZ: It shows a list of tools and
19 it was very impressive for its length, but I guess
20 one of the questions that impressed me is that
21 regardless of the length of tools that do or do not
22 work, at least 4 out of 16 do, and I wondered if

1 those are common tools or if in fact they were
2 somehow difficult to obtain.

3 Do you think they're common tools, common
4 household tools?

5 DR. LANDAU: The tools selected or
6 evaluated of these 16 were all commonly available.

7 DR. LORENZ: So they're commonly-available
8 tools.

9 Could we go to slide 56? So at least two
10 of those tools produced something called particles,
11 and on slide 56, --

12 DR. LANDAU: Slide 56, please.

13 DR. LORENZ: -- slide 56, we look at simple
14 solvents. So I understand that the sponsor looked at
15 the ability to manipulate the drug using common
16 solvents, and those also are commonly available in
17 households.

18 For example, at least simple solvent 6,
19 particle size Band 6, notes that in -- that, if I
20 understand it correctly, would show that using a
21 simple solvent and a small particle band, which is
22 achievable using normal household tools, right, using

1 a normal household solvent, that in fact the
2 bioavailability -- well, not bioavailability, but the
3 availability in solution of this formulation of
4 oxycodone would be 100 percent, then, of currently-
5 available oxycodone.

6 Is that a correct assumption?

7 DR. LANDAU: Jennifer, would you respond,
8 please?

9 MS. GIORDANO: Thank you. Just to clarify
10 how this table is set up, it's actually the amount of
11 oxycodone that's released from the reformulated
12 tablet divided by the amount released from the
13 current formulation.

14 So what 100 represents is that the number
15 is equivalent. However, in this situation for simple
16 solvent 6, it's an inefficient solvent, so both
17 numbers are low and therefore the ratio is 100.

18 DR. LORENZ: So using solvents that are
19 readily available, what is in fact -- I don't know if
20 it's correct to ask this, so you can tell me if I'm
21 not supposed to ask it or no one needs to answer it.

22 But what would be -- if we were going to be

1 skeptics about the ability of this medication to
2 represent an advance, what would be the largest ratio
3 that one might achieve in common and otherwise
4 effective solvents usually used for abuse?

5 MS. GIORDANO: I'm sorry. If you could
6 clarify, I'd appreciate it.

7 DR. LORENZ: Solvents that are normally
8 used by abusers trying to achieve a solution of
9 something like oxycodone, what kinds of ratios might
10 one expect to achieve, say, within the maximum --

11 MS. GIORDANO: Oh, I see.

12 DR. LORENZ: -- of the time frames you
13 looked at, where not only the ratio but the amount of
14 drug would reflect sort of common goals of an abuser?

15 MS. GIORDANO: We fully characterized the
16 rate of release of oxycodone from the reformulation.
17 I don't know how to name a number that would be
18 considered defeat of the controlled-released
19 mechanism. What we do know is the difference between
20 the reformulation and the current formulation and
21 that delta is what we set out to find.

22 DR. LORENZ: Okay. Well, I guess using

1 this slide that's present here, at least some of
2 those comparisons would suggest that there wouldn't
3 be a difference in terms of what an abuser might
4 achieve, is that right? Fair to say?

5 MS. GIORDANO: I guess if you're speaking
6 of numbers that are close to 100 or over 100
7 here -- and many of the cases, the numbers are very
8 low and therefore the numbers are a little bit
9 misleading.

10 DR. LORENZ: Okay.

11 MS. GIORDANO: In cases where the numbers
12 might be high, advanced solvent number 1, these
13 numbers, 78 and 88, those are higher numbers and more
14 efficient extraction of the oxycodone.

15 DR. LORENZ: Okay.

16 MS. GIORDANO: But that's still a relative
17 between one to the other.

18 DR. LORENZ: Okay. Well, for me, it begs a
19 bit of a question. And I don't know that there's a
20 good answer to this. But since we're talking about
21 extraction rates instead of amounts, what extraction
22 rate is clinically relevant to abuse? How much

1 trouble is too much trouble? Do we have any idea?

2 DR. LANDAU: Perhaps we can have Dr.

3 Sellers respond to this question, please. While Dr.

4 Sellers is coming -- oh, you have a mike. Sorry.

5 DR. SELLERS: The simple answer to that

6 question is that, you know, any effort that's more

7 than what you have to do with the existing

8 formulation is going to have some impact. I mean,

9 the fact of the matter is the existing formulation

10 takes absolutely trivial maneuvers to reduce it to a

11 powder, put it in a solution. You can snort it. You

12 can inject it. It's a solution that isn't offensive.

13 It isn't viscous or anything like that.

14 So, you know, the bar is very, very low

15 here, and what we see in abuser behavior is that the

16 harder it gets, the less likely it is to happen. And

17 as I tried to indicate in my presentation, that all

18 of these data are directional.

19 It is conceivable that there is some

20 situation where the improvement will be small, but in

21 some of these other areas, you can appreciate that

22 the likely impact is going to be quite large on

1 certain behaviors by abusers.

2 I don't know. Does that help?

3 DR. LORENZ: It certainly does help. And I
4 don't mean to be antagonistic about this, but it's an
5 honest question in the sense that, you know,
6 sometimes I like to make lentils. I'll put a pot of
7 lentils on the stove with water and leave it
8 overnight and it doesn't seem like too troublesome of
9 a maneuver to make.

10 I'm not implying that that in fact is any
11 maneuver that you might have tried here, and I'm not
12 planning to put OxyContin in with my lentils. But it
13 does beg the question of exactly how much trouble
14 should be too much trouble; what kind of ratios,
15 extraction ratios really matter.

16 I actually am very encouraged by the fact
17 that you as the sponsoring company have agreed not to
18 market on the basis of that benefit and in fact that
19 there were epidemiologic studies on that to affirm a
20 clinical impact on abuse. But it also for me begs
21 the question of how this data should be interpreted
22 and so I'm wondering what guidance you can provide

1 beyond the fact that indeed it is an incremental
2 advance.

3 DR. LANDAU: I'll take that.

4 Well, that is really all we're proposing.
5 We're learning from this reformulation and from the
6 in vitro data that it is substantially better than
7 the current formulation, which is so easily reduced
8 to a fine particle size where all this oxycodone is
9 accessed.

10 I'd like to return back to slide 56, if I
11 can, to address another issue that I don't know was
12 addressed successfully.

13 The 18-hour time point for these
14 experiments is included for reference and it's part
15 of our approach to define the failure limits of the
16 formulation. One has to appreciate that this is a
17 product intended for dosing every 12 hours.

18 So you're correct. Should one elect to lay
19 a tablet in a glass of water for 12 hours, to be
20 therapeutic, the oxycodone needs to be released from
21 the formulation. So I don't know the relevance for
22 consideration here in regard to a barrier for

1 manipulation the 18-hour time point confers.

2 One other point I'd make is that for the
3 overwhelming majority of the time points for all of
4 the solvents tested, the reformulated product
5 releases oxycodone more slowly and requires more time
6 than the current formulation.

7 When there are -- when release is enhanced
8 relative to the current formulation, it's reflecting
9 a ratio of a very small percentage difference.

10 DR. KIRSCH: Dr. Denisco.

11 DR. DENISCO: Thank you, Dr. Kirsch. I'd
12 like to ask a question more as a point of
13 information.

14 What we're talking about today is not the
15 active ingredient but the excipient, the polyethylene
16 oxide. And when I look up some of the prior
17 formulations that I guess were generic but other
18 extended-release oxycodone products that were on the
19 market, they all had different excipients. One of
20 them even had polyethylene glycol, which was shown
21 that it was even on the same continuum as the
22 polyethylene oxide.

1 So I guess I'm wondering why is this a new
2 drug application since it's the same active
3 ingredient. Forgive my -- I'm really -- I don't
4 understand that, and forgive my lack of knowledge.
5 But we're looking at the excipient, and it's been
6 used a hundred other times before.

7 DR. KIRSCH: Will the FDA address that
8 question, please?

9 DR. RAPPAPORT: Any changes to excipients
10 with very few exceptions becomes a new drug product.
11 There are exceptions, such as preservatives and
12 antioxidants and things such as those, but that's not
13 what that is in there for. The fact that it's been
14 used in other drug products is not an issue in terms
15 of making determination here. If the excipients were
16 the same, it would be a generic.

17 DR. KIRSCH: Mr. Yesenko.

18 MR. YESENKO: This is for the sponsor.

19 Did you mention anything about REMS, and
20 will that be something that will be part of your
21 roll-out for this product? That's the first
22 question.

1 The second part of that question is will
2 there be any training online or otherwise for
3 prescribers for the reformulated OxyContin?

4 I have a couple more questions after you
5 answer those, if you can.

6 DR. LANDAU: Sure. Of course. Thank you
7 for your question.

8 Yes, the answer to your first question is
9 yes, we will be rolling out a REMS. It's under
10 active discussion with the division. We've been
11 communicating a number of times. The composition of
12 the REMS includes communication plan aimed at
13 providing educational materials, both to individual
14 prescribers based on the types of prescriptions they
15 write and also to various and sundry medical
16 societies that are maybe an effective vehicle for
17 getting this type of information out to their
18 members.

19 Maybe perhaps a little follow-up. In
20 addition to the work we're doing on our product-
21 specific REMS, we also are very much involved with 21
22 other sponsors, both branded and generic companies,

1 working very hard to create a proposal for what a
2 class REMS should look like.

3 This Purdue is part of it. Of course,
4 we're not leading it, but it is a collaborative
5 effort and we're working with the agency and many
6 other stakeholders to put something together as soon
7 as we can.

8 MR. YESENKO: This might be for the FDA, a
9 high-tech question that I did not get answered from
10 the sponsor this morning regarding the ethanol
11 dissolution. Would this be an appropriate
12 time to ask that question?

13 DR. RAPPAPORT: If you're going to refer to
14 a specific methodology using the names of the
15 solution or that sort of thing, then it would not be
16 appropriate. If you have a more general question,
17 then yes.

18 MR. YESENKO: It's more general.

19 DR. RAPPAPORT: Go ahead and ask it and
20 we'll see if --

21 MR. YESENKO: Yeah. It was the question
22 that I asked this morning between the current formula

1 of OxyContin and the reformulated OxyContin in terms
2 of dissolution in ethanol.

3 I think was it Jennifer that was going to
4 provide that information? Was that information --

5 DR. LANDAU: Yes, we're happy to provide
6 it. I'm not certain we can provide it here.

7 DR. RAPPAPORT: Well, if it is confidential
8 information, that's your decision whether you want to
9 release it.

10 DR. LANDAU: Sure. Will we have an
11 opportunity to share --

12 MR. YESENKO: I didn't get the impression -
13 -

14 DR. RAPPAPORT: We could provide that
15 information to the committee members after the
16 meeting or if there's another break.

17 DR. LANDAU: Perhaps we could speak and
18 address the question without being too specific in
19 this forum. And with that, can we have slide 116,
20 please?

21 MS. GIORDANO: Thank you. If you're
22 speaking specifically about how the presence of

1 ethanol affects the rate of release of oxycodone from
2 the formulation, this is data that was in the
3 original NDA submission for intact tablets. And you
4 can see on the X axis is time in minutes, on the Y
5 axis is the amount of oxycodone released and this is
6 a dissolution profile.

7 The darkest blue is the profile in SGF,
8 light blue is 4 percent ethanol, red is 20 percent,
9 and green is 40 percent. So as you can see, as you
10 increase the amount of ethanol present, the rate of
11 release of oxycodone actually slows down.

12 I don't know if that helps clarify.

13 DR. KIRSCH: The microphone next to you is
14 working.

15 Could you use that microphone, please?

16 MR. YESENKO: Yes, that answers my
17 question. And then in terms of tamper-resistant
18 properties, you mentioned that you would not be
19 marketing that it is tamper-proof, I believe.

20 DR. LANDAU: No reference at all to in
21 vitro data tamper-resistance, abuse-resistance, or
22 abuse-deterrence. No change with respect to these

1 properties on a post-marketing clinical outcome
2 without data.

3 DR. KIRSCH: Dr. Flick.

4 DR. FLICK: This question is for the
5 sponsor. I think it's Dr. Sellers -- I apologize if
6 I get the name wrong -- but discussed some
7 information that's obtainable on websites, and I
8 think this comment is to follow up Dr. Lorenz's
9 comments about the formulation and how tamper-proof
10 or resistant this formulation is.

11 I took a moment to go out to some of those
12 websites and the quotes that I saw were somewhat
13 different than the picture that's painted on those
14 websites.

15 Within a few moments, I found out how to
16 defeat most of these products in a very clear,
17 concise way, written by a Ph.D. pharmacologist. I
18 found out how to defeat the -- to extract
19 dextromethorphan from polyethylene oxide, including
20 pictures that described it in very clear detail.

21 So I make these comments only to reinforce
22 that I don't think that any one of us expects that

1 this formulation or any formulation is going to raise
2 the bar so high that no one can defeat it, but I also
3 would emphasize, I think, that within days or weeks
4 after the release of this product, it will be
5 defeated and it will be defeated very relatively
6 simply.

7 DR. LANDAU: Okay. I'd like to address
8 that. I know it's not a question, but perhaps I can
9 respond.

10 I would agree with your assessment of the
11 information available on the Internet. It's actually
12 a very valuable resource for literally real-time
13 information on how abusers, both crude or
14 inexperienced and sophisticated, are looking to
15 deconstruct tablets.

16 We expect soon after this formulation is
17 made available that there will be information posted
18 on websites and that it will be part of what we track
19 very closely to understand what's happening as a
20 consequence.

21 We have reasonable expectations. This is
22 not, as you've mentioned, a tamper-proof formulation.

1 We don't at this moment have that technology
2 available to us. What we're looking to introduce is
3 an incremental improvement in the robustness of the
4 formulation to a variety of tablet manipulation
5 scenarios.

6 DR. KIRSCH: Did you have another question?

7 DR. FLICK: I would like to just continue
8 that question, if I could.

9 As a pediatric anesthesiologist, I think
10 one of my concerns is children. And as you may or
11 may not know, the average ingestion in children would
12 occur in a toddler. The dose of oxycodone in a
13 toddler is about one milligram. The doses that are
14 being formulated here are enormous doses. For
15 adults, they're very large doses. For children, they
16 are incredibly large. And I don't -- there was a
17 comment made that in children -- this is a safer
18 product in children because a child wouldn't bite it
19 and have immediate release.

20 It makes no sense to me that this is at all
21 safer for children. Children don't typically chew
22 these things. They would typically suck on them and

1 they would swallow them. So this product is no safer
2 for children than any previous product, and I want to
3 make sure that that's clear. And the doses here
4 would kill a child very quickly.

5 DR. LANDAU: Thank you.

6 DR. KIRSCH: Dr. Vaida.

7 DR. VAIDA: Yes, my question's for the FDA
8 and then maybe the sponsor.

9 Since this is a new drug application, that
10 would mean that if a prescription was written for
11 OxyContin substitute, you wouldn't be able to
12 substitute. Since they're not changing the name,
13 it's going to be a new formulation.

14 I mean, is that --

15 DR. HERTZ: The ability to substitute is
16 solely based on the availability of generics. So
17 that --

18 DR. VAIDA: But this would be a new drug.

19 DR. HERTZ: Right. So, for instance, a new
20 drug doesn't necessarily have exclusivity or patent
21 protection. It depends on the individuals. So there
22 are new drug products that can be approved with no

1 ability to block a generic. So if there's a
2 reasonable generic, then it could still occur.

3 DR. RAPPAPORT: There are currently no
4 generics available and that's because of the patent
5 that's outstanding.

6 DR. VAIDA: There are no generics
7 available?

8 DR. RAPPAPORT: For the current formulation
9 of OxyContin.

10 DR. VAIDA: For the current?

11 DR. RAPPAPORT: Yeah. There were for a
12 brief while, but there are no longer.

13 DR. VAIDA: Okay. And then just for the
14 sponsor, along that same line, you were saying that
15 you're not going to advertise that this is a safer
16 product or anything else. But as the patent becomes
17 due, I mean are you going to -- is it going to be
18 part of your advertisement about that other products
19 would not be able to be substituted for this?
20 Because the patent will be coming up, right?

21 DR. LANDAU: I think our expiry of patents
22 are fairly well defined and the formulations from

1 generic applicants are something we're not in a
2 position to control. So I don't know that that's a
3 question that we could answer.

4 DR. VAIDA: Okay.

5 DR. KIRSCH: Dr. Cooper.

6 DR. COOPER: This is a question for the
7 sponsor, and I certainly appreciate the expertise of
8 the consultants and their broad experience.

9 However, as one of the earlier committee
10 members noted, the wording that has been provided to
11 us throughout the morning and the day has been
12 regarding the likelihood of a reduction in abuse or
13 tampering, such as likely or directional, and the
14 data we're provided were six Internet quotations and
15 some opinions.

16 I was wondering if there's any information
17 from prior experiences, from other drugs that have
18 been reformulated that have a high likelihood of
19 abuse, that would provide some epidemiologic evidence
20 that this reformulation is likely to make a
21 difference or if there's any stronger information
22 than these Internet quotes and opinions?

1 DR. LANDAU: Thank you for your question.

2 It's a very important one.

3 Unfortunately, there's limited information
4 we can draw on to understand the influence of a
5 reformulation on patterns of abuse and shifts in
6 abuse, methods, subpopulations. We've consulted with
7 a number of highly-regarded epidemiologists to help
8 us answer this question and it's part of our
9 initiative moving forward, is to form an expert panel
10 to answer very basic questions that are very
11 difficult to answer.

12 What is the endpoint we need to be
13 measuring? What is the study design looking forward,
14 and how long will it take, and what type of change
15 given an endpoint is actually meaningful in the
16 context of a reduction in abuse?

17 Until we have that available, we'll
18 continue doing what we have been doing and monitoring
19 government source data, RADARS data and proprietary
20 surveillance system, and monitoring the very
21 informative Internet chat data for which we presented
22 representative but appropriate sampling.

1 Dr. Sellers, perhaps you can answer.

2 DR. SELLERS: There is one good example and
3 that would be Concerta. This is a controlled-release
4 dose form of methylphenidate. It's the same kind of
5 technology that was discussed yesterday. The
6 Concerta version of methylphenidate was introduced by
7 that particular company in part to address the issue
8 of the abuse of Ritalin, which is an IR dose form.
9 And it's quite clear epidemiologically that there is
10 some abuse of the IR form, but when you go to abusers
11 and you look at the epidemiology, the Concerta dose
12 form is not abused as much and it's a substantial
13 decrease. So that's one real-life kind of experience
14 we have.

15 We have a number of others. I mean, the
16 reference has been made or concern that, you know,
17 some of the things we might have presented were a
18 little selective, but, you know, when you do a search
19 of the Internet, you create these huge long threads
20 of information, and then you look at the patterns of
21 abuse of what drugs show up in treatment programs and
22 so on and so forth. And what you see is that the

1 things the abusers are saying they don't like turn
2 out to map over to what is happening in practice.
3 And Concerta is one example, but there are other
4 examples, as well.

5 I gave a reference, without mentioning the
6 drug. But there are other drugs out there that
7 contain polyethylene oxide and abusers have views on
8 what gelling is like.

9 So, you know, we don't have as much post-
10 marketing information as is needed to precisely
11 quantitate, but, I mean, that is a very important
12 step that has to be done with this product and a
13 number of others. I mean, you considered a product
14 yesterday that the same sort of issue would come up.

15 DR. KIRSCH: To be explicit about the plans
16 for this afternoon, we're running up towards the time
17 of our scheduled break, which we're not going to
18 have. There's a long list of people who want to ask
19 questions and we're not going to get to the place in
20 the agenda where we need to be by the end of the day.

21 So we're going to continue with the
22 questions and not have the break at 2:15. We will at

1 2:30 start addressing the questions of the FDA.

2 So Dr. Markman.

3 DR. MARKMAN: John Markman. I have a
4 question both for the sponsors as well as for the
5 agency.

6 Given that this is a new drug application
7 and that, if approved, this would replace the
8 existing supply of medication available. And as
9 we've heard today, there is, I think, a legacy of
10 brand identity associated with the name OxyContin as
11 a function of prior marketing practices and other
12 issues, as we heard in the open session.

13 So what I would like to understand is if
14 this new formulation is approved, would it be
15 required or would the sponsor voluntarily give it a
16 new brand identity with a new name? And the reason I
17 ask this is I think it might have a twofold purpose.

18 The first is if there is going to be new
19 messaging and new education around the properties of
20 the drug, this would be an opportunity to begin anew
21 with educating providers with the limitations
22 expressed today by the sponsor.

1 Additionally, it might facilitate the
2 epidemiologic studies, which are going to need to be
3 done in order to see whether the promise of the in
4 vitro studies is actually delivered upon when this is
5 brought to the community.

6 DR. LANDAU: Can I take it?

7 Well, thank you for your question. As I
8 understand it, the question is should we be
9 considering a new identity for the reformulated
10 product for some of the reasons you've described?

11 DR. MARKMAN: Yes, new drug, new name.

12 DR. LANDAU: Okay. Yes, so we've
13 considered this, and our position is that we're much
14 better off retaining the trade name for the following
15 reasons.

16 The name OxyContin is recognized as one
17 that requires, you know, substantial care in how it's
18 prescribed and how it's handled at the patient level.
19 We'd be afraid that changing the name of the product
20 would not only have us lose that recognition but it
21 might also create just what we're looking to avoid,
22 the fact that it's a new product perhaps that's safer

1 with less concern required over abuse liability.

2 We've discussed this with the agency and I think we
3 see things the same way.

4 DR. KIRSCH: Dr. Morrato.

5 DR. MORRATO: We're asked to comment later
6 about the overall safety profile of the drug, and in
7 my mind the overall safety is very much driven by how
8 it actually plays out and is commercialized in the
9 marketplace. So I have a series of kind of related
10 questions around that.

11 First of all, can you give us a bit more
12 clarity around part of the REMS interim requirement
13 as a communication plan, which you alluded to, which
14 includes a Dear Healthcare Professional letter as
15 well as a Dear Pharmacist letter?

16 I'm sure you've thought about the content,
17 not just that you're sending a letter. What is the
18 message you intend to deliver if it's not to talk
19 about what's different about the formulation?

20 DR. LANDAU: Yes, I understand. Perhaps,
21 can we have Dr. Haddox available? Thank you.

22 DR. HADDOX: Dave Haddox, Health Policy

1 with Purdue Pharma.

2 The message platform for both the letters
3 going to the individuals and also to the associations
4 that those individuals belong to is going to be re-
5 emphasizing -- first off informing about the
6 existence of the interim REMS, assuming that the
7 class-wide REMS is not in effect when and if this
8 drug is approved, because this drug will clearly be
9 subject to the class-wide REMS once that is approved.

10 Part of the communication plan is to let
11 people know that such a REMS exists, be it interim or
12 the class-wide. So that's going to be one issue, is
13 raising that issue.

14 I think that the message platform is
15 basically going to be calling out the importance of
16 proper patient assessment, proper management of the
17 patients, communication with the patients about
18 things, like safe storage, safe handling. Some of
19 the SAMHSA data you didn't see today talks about
20 where people who admit to non-medical use of pain
21 relievers get their medicines, and a significant
22 number of those get them from friends or family,

1 either for free, purchasing or stealing. And so the
2 supply out there in the community is very important.

3 So we want to encourage pharmacists and
4 prescribers to have those conversations with patients
5 about this is a very important medicine; you've got
6 to protect this and keep this for your use only.
7 Those sorts of messages rather than saying, gee,
8 there's something new about OxyContin. The new thing
9 will be the REMS, either the interim REMS, if this is
10 approved under an interim REMS, like Embeda was, or
11 the class-wide REMS when and if that takes effect.

12 DR. MORRATO: So essentially generic safety
13 messages?

14 DR. HADDOX: Yes, and proper assessment,
15 proper patient assessment for both pain and also for
16 substance use disorders.

17 DR. MORRATO: So if you're rolling this out
18 to pharmacies and you're going to have a huge
19 conversion within six to eight weeks, I think is what
20 you were saying, they will know it's a new product
21 number?

22 Will there be any sort of tracking or all

1 of a sudden these new tablets show up?

2 DR. HADDOX: Yes, they will have a new
3 series of NDC numbers.

4 DR. MORRATO: Right. So they will be
5 informed as pharmacy purchasers and distributors that
6 something's changed, right?

7 DR. HADDOX: Yes.

8 DR. MORRATO: Okay. So what is the message
9 then to the Dear Pharmacist? Similar?

10 DR. HADDOX: Yeah. We haven't really
11 developed our -- I'm looking to our head of Sales and
12 Marketing. We haven't really developed that. We
13 have people that go out to the trade directly, in
14 addition to the individual pharmacists, and we're
15 working on that message platform right now.

16 DR. MORRATO: Okay.

17 DR. HADDOX: Part of it will be, again, to
18 encourage and to have those conversations with
19 people. I mean, the medication guide will clearly be
20 part of the interim REMS, assuming this is approved
21 on the interim REMS. So the dispenser has the
22 obligation to hand that medication guide out.

1 Hopefully that's also the opportunity to have a
2 strategic conversation with the patient or the
3 caregiver about the content of the medication guide.

4 DR. LANDAU: Thank you, David.

5 DR. MORRATO: So I guess I would encourage
6 the FDA, as you're negotiating the actual letter -- I
7 mean this is really an opportunity to get those
8 safety messages because I would anticipate, if this
9 product is approved, it's going to come ahead of when
10 the REMS are actually in a final form.

11 The other piece I would really encourage
12 is, as I understand it at least, the FDA does not
13 have authority as to the mailing lists that companies
14 may choose to select to send to Dear Healthcare
15 Professional, and that it's up to the company to
16 provide that list. And there's variability in those
17 lists, and I just want to make sure that it's really
18 reaching everyone and not just a select high
19 prescriber list.

20 DR. LANDAU: Certainly. I can address
21 that. We have proposed how we would go about
22 selecting who we send these letters to and we're

1 reaching very deep. Of course, those that prescribe
2 drugs like OxyContin single-entity, long-acting
3 opioids are very high on the list, but we'll be
4 reaching very deep into those who prescribe short-
5 acting opioids, as well, and have prescribed drugs
6 like OxyContin. That's a good point.

7 Thank you.

8 DR. KIRSCH: Can I just answer, as well?
9 We actually do have authority under the REMS policy
10 to -- we'll work with them to make sure that it's the
11 right group of people that are getting the letter.

12 DR. MORRATO: Excellent. I didn't realize
13 that was new. Okay.

14 Then the other question is some have
15 mentioned the patent expires, as I understand it, in
16 2013. And really, the value of the reformulation is
17 the degree to which everyone is converted to the new
18 formulation and stays on it as opposed to when the
19 generic is available, they go back to it.

20 So regulatory, I don't have an answer, but
21 more to raise it as a concern is thinking ahead in
22 time in 2013, those other generics with the older

1 formulation will, when your current patent expires,
2 be on the market.

3 So what really is the risk management plan?
4 I know you can't control what generic manufacturers
5 do, but I think this needs to be thought through.

6 So do you have any comment on that?

7 DR. LANDAU: That's a very interesting
8 public health question and certainly don't have an
9 answer to it. I think what you're getting at is if
10 we're not marketing this product in 2013, which is
11 not necessarily our plan, but if this was a
12 hypothetical situation and generics were to enter the
13 market, would they be required to have some
14 equivalent physical-chemical properties that would
15 otherwise be lost if this product weren't formulated?

16 DR. MORRATO: Right, right. So this is a
17 new product with a new patent, right?

18 DR. LANDAU: Right.

19 DR. MORRATO: So the new NDA gives you a
20 new exclusivity, correct?

21 DR. LANDAU: Well, there are patents
22 associated with the new formulation, yes.

1 DR. MORRATO: Right.

2 DR. LANDAU: Yes, absolutely.

3 DR. MORRATO: Yeah. So for the FDA, when
4 the patent expires on the current formulation, those
5 generic manufacturers who submitted their ANDAs have
6 the ability to go on market with the non-modified
7 formula, correct?

8 DR. RAPPAPORT: That's correct.

9 DR. MORRATO: So we're really looking at a
10 three-year period. Unless you're successful in
11 showing that there's a benefit, in terms of this is
12 really reducing abuse and misuse, which comes to my
13 last question in terms of -- and maybe it's more of a
14 comment -- in terms of the post-marketing studies,
15 that I know that you mentioned are under development,
16 the epidemiology studies, to really see how this
17 plays out in the real world -- I'd like to see that
18 be part of a commitment perhaps as a safety follow-up
19 to see how this is happening as opposed to just a
20 marketing study that gets done on the side or some
21 transparency more as you've done with the in vitro
22 testing, really bringing in experts in critical

1 evaluation of that, because it will hinge on that in
2 the market.

3 DR. LANDAU: Certainly.

4 May I just comment on one element --

5 DR. KIRSCH: Please.

6 DR. LANDAU: -- of the previous -- one of
7 your previous statements?

8 I'm the company's chief medical officer, so
9 the patent and intellectual property considerations
10 aren't squarely in my realm of responsibility. I'll
11 have to check. I guess I affirmed that there are new
12 patents associated with the reformulation. I need to
13 check with that. That's my understanding, but I
14 could be incorrect. So my apologies if I
15 inadvertently misled you.

16 DR. KIRSCH: Ms. Solonche, you had a
17 related short question?

18 DR. SOLONCHE: Yes. Thank you. Of course,
19 we've kind of gotten off that subject now.

20 But my question is if and when the new
21 versions are available, are the old versions pulled
22 immediately or is there going to be a period of time

1 when both are available?

2 DR. LANDAU: As soon as we manufacture
3 enough supply of the reformulated product, we will
4 stop shipping the current product and will start
5 shipping the new product. Within six or eight weeks
6 or six to eight weeks roughly, 90 percent of
7 OxyContin in the supply chain down to the retail
8 pharmacy will be reformulated product.

9 DR. SOLONCHE: Thank you.

10 DR. KIRSCH: Dr. Day.

11 DR. DAY: As a member of the previous
12 advisory committee in May '08, I was one of the very
13 strong critics in terms of the methods used to assess
14 the tamper-proof abilities of the new formulation.

15 I would just like to comment first that
16 this submission has taken great strides forward and
17 is certainly much better and I was very pleased to
18 see that.

19 That being said, in looking at what data
20 are actually reported and how they're reported, I
21 sometimes have difficulty in answering some questions
22 of concern.

1 So say for example that the table on slide
2 56 has come up a few times, and it's one of those
3 tables that compares the reformulation with the
4 original. And I do understand that that's the point
5 of a lot of the studies, to see if there is
6 improvement.

7 However, giving ratios, you know, doesn't
8 let us assess what the absolute values are because
9 some of us care a lot about what would be the
10 "acceptable," if that's even a term, acceptable level
11 of tamperability. And so there are a lot of outcome
12 measures, whether it's amount of release or the speed
13 of release and many, many things. And it's good we
14 have a lot of data, but my question to the sponsor is
15 for all the data that have been presented, either in
16 the briefing materials before today, the handout for
17 today and the presentation today, does the FDA and do
18 we have all of the data both in the absolute values
19 and in the comparison between the old and the new?

20 DR. LANDAU: Yes, thank you for your
21 question. And every data point we generated through
22 this in vitro testing program has been submitted to

1 FDA in our NDA resubmission.

2 DR. DAY: And may I ask what percentage of
3 those have we had access to as members of the voting
4 committee?

5 DR. LANDAU: I understand. I'm not sure we
6 have the -- before I hand off to Jennifer, it was our
7 goal to present the information. In all of the
8 materials, the agency has asked you to consider in
9 the most transparent and easily-digestible fashion.
10 So if our approach is somewhat less than helpful,
11 we'd look to the agency to make -- or perhaps we can
12 submit additional data, raw data, if that's helpful
13 for you to consider.

14 Jennifer?

15 DR. DAY: I was going to say the
16 presentation is much better this time, too, and the
17 many displays are very helpful. However, we really
18 need an N by 2 matrix. So on the long side of the
19 matrix is every set of type of data and then across
20 the top is absolute values and then comparison
21 values, and so there's not been enough time to assess
22 what are we missing.

1 DR. LANDAU: I understand.

2 DR. KIRSCH: Dr. Deshpande.

3 DR. DESHPANDE: I've got three questions.

4 One in regard to Table 56; I mean page 56. I had the
5 same concern, that at this point where the tables are
6 showing percent compared to the current formulation,
7 I don't know whether seven percent is enough to kill
8 somebody or whether a 100 percent is not enough to
9 kill somebody. That's basically what we're asking.

10 So that even though the presentations are
11 good, the fact is when Dr. Lorenz was concerned about
12 the 100 percent, we said, oh, it's not anything to
13 worry about, but we don't really know that for a
14 fact.

15 So I think it's important to have that set of
16 information.

17 The question, I think, for the
18 FDA -- because I think you mentioned the intellectual
19 property aspect is not the sponsor's current -- the
20 medical director's purview-- is the issue of
21 extending the patent with this NDA.

22 As I understand it, the NDA corrects a

1 current problem with the product. And if this
2 correction of the issues with the product also
3 extends the patent, I think that is information that
4 would be helpful to have.

5 DR. RAPPAPORT: I think there's a little
6 confusion between patents and exclusivity perhaps.

7 The sponsor will have to speak to whether
8 they are applying for any patents, have any patents.
9 That's not within our purview, although we can't
10 approve generics if there are certain outstanding
11 patents.

12 Exclusivity is determined by the agency
13 based on a number of different factors. In this
14 case, they won't be getting any exclusivity because
15 they didn't do any clinical studies.

16 DR. DESHPANDE: Thank you. I appreciate
17 that. Not being a lawyer, it's helpful to get the
18 clarification. But it is important because this is -
19 - I see this as a correction of existing product
20 which you're trying to address in a good way.

21 I am concerned about the issue that
22 Dr. Markman brought up, and that's the name,

1 OxyContin, and that coupled with the question about
2 message to the providers with the Dear John letter
3 that Dr. Morrato brought.

4 OxyContin has a certain cache in the
5 marketplace and also on the street, and this
6 formulation is meant to address many of the issues
7 that brought it to the street in the first place.
8 However, just changing it out with a new NDC number
9 is not going to really address all of the things that
10 you wanted it to take care of coming up with a new
11 formulation.

12 So I'm a little confused about both the
13 generic message and sort of the benefit of the name.

14 DR. LANDAU: Understood. Perhaps I'd like
15 to call on a colleague of mine, Mr. Gasdia.

16 Would you mind?

17 DR. GASDIA: As was mentioned before by
18 Dr. Landau, we considered a name change, but one of
19 the things that we're also concerned with is that
20 draws new attention to a replacement of an existing
21 product that's been on the market since 1996 and has
22 been spoken about being prescribed to millions of

1 patients and by hundreds of thousands of physicians.
2 And the conversation that then starts to take place
3 in a pharmacy becomes even more about what the
4 differences are as opposed to a more transparent
5 difference.

6 There will be a different indicia. There
7 will be a different NDC. We do have to work on the
8 language because we'll definitely be asked, but we
9 want to do it in the context of what's going to be in
10 the final package insert. We don't want to draw any
11 extra attention. We certainly don't want to be
12 making false claims at this point.

13 So we have considered it. And we've come
14 down on the side that it actually may cause there to
15 be more discussion about the differences by having a
16 different brand name.

17 Thank you.

18 DR. KIRSCH: I'm going to pause for a
19 second and Dr. Margolis has been on the telephone and
20 want to make sure that we give him an opportunity to
21 ask a question, if he has any.

22 DR. MARGOLIS: I'm fine. Thank you for

1 asking, though.

2 DR. KIRSCH: Okay. Dr. Lesar.

3 DR. LESAR: Based on most of my questions
4 have been answered, so I'll pass based on time.

5 DR. KIRSCH: Thank you.

6 Dr. Lorenz.

7 DR. LORENZ: Thank you. I'd like to ask
8 the sponsor what sort of -- since this is such a
9 critical point, I'm sure there must have been some
10 thinking about it. But what epidemiologic studies
11 would be sufficient for the company to seek approval
12 to market the drug as one that is abuse-resistant?

13 Specifically, what epidemiologic designs
14 would you anticipate?

15 DR. LANDAU: That's an excellent question.
16 The simple answer is we don't know.

17 DR. LORENZ: Okay. And that's a fine
18 answer. I'd just like to make a few observations
19 then. My concern is that many of these studies
20 attributing causality are ecologic in nature, and I
21 do not think an ecologic study is adequate to
22 understand the impact of this drug for two reasons.

1 One is that -- well, first of all, it's a
2 weak causal design in the first place, and I would
3 want any design to account for trends, to account for
4 differential efforts to improve this problem in
5 general in society, the impact of the REMS, which
6 could be differential from area to area for the
7 specific drug and will be a new intervention.

8 Specifically looking at slide 84, there's a
9 potential attributability to broad classes of abuse,
10 many of which rely not only on this narrow
11 formulation, which seems to be targeted at
12 sophisticated users who are trying to manipulate the
13 tablet but also to broad issues of abuse that apply
14 to users of the entire tablet, to indeed secondary or
15 tertiary use of the drug after it's in the community.

16 So my suggestion, in the absence of any
17 others, is that causal understanding of this drug's
18 impact on abuse will require tracing the distribution
19 of the drug itself or the patients who are using it
20 to understand how those drugs are then distributed
21 and used in the community. And those are person-
22 level designs or prescription-level designs. They're

1 certainly more difficult, but that's what I would
2 think.

3 DR. LANDAU: Thank you for your input. I
4 mentioned earlier we have plans to convene an expert
5 panel of epidemiologists to have the type of
6 discussion you just started. Thank you.

7 DR. KIRSCH: Dr. Zito.

8 DR. ZITO: I'm just reiterating several
9 comments on surveillance at person level.
10 Absolutely.

11 DR. KIRSCH: Dr. Denisco.

12 DR. DENISCO: I just had a follow-up to my
13 question on new drug applications, but it was asked
14 and answered on the patents and so forth.

15 DR. KIRSCH: Okay. The last question
16 before we address the questions by the FDA will be by
17 Dr. Flick.

18 DR. FLICK: In the GAO report, they
19 outlined the sales incentives for the Purdue sales
20 force with compensation, bonus compensation up to
21 \$250,000, as I recall.

22 Do you plan to change your sales incentives

1 or do you plan to incentivize your sales force to
2 report misuse or misappropriation of this product?

3 DR. LANDAU: Yes. Thank you for your
4 question.

5 Russ, could you respond, please?

6 DR. GASDIA: Thank you. You're correct in
7 terms of what was found with the GAO, and we made
8 changes several years ago, in fact going back as far
9 as 2003, regarding the incentive plan and
10 compensation for our sales people and have addressed
11 those in a very dramatic way to prevent that from
12 occurring.

13 We certainly don't want a system in place
14 that encourages representatives to do things that are
15 counter to what's in the best interests of patients
16 and, quite frankly, in the best interests of the
17 company because it is important that we continue to
18 bring new products forward.

19 The levels of compensation are in line from
20 our expectations in the industry. We don't see
21 anything in our plan that over-incentivizes a rep to
22 have the types of behaviors that would mislead. And

1 as we've been adding new products to our promotional
2 efforts and we plan to add other new products in the
3 coming years, the OxyContin percentage of their
4 incentive plan becomes less and less.

5 DR. FLICK: So if I'm hearing you right,
6 there isn't any disincentive to misappropriate and
7 there's no incentive to report on misappropriation.

8 DR. GASDIA: I'm sorry. I forgot the
9 second question. Thanks.

10 We actually do have a policy in place.
11 It's been in place, I believe, since 2002, called the
12 Abuse and Diversion Detection Program. And it's a
13 policy that all of our representatives as well as
14 other field-level employees of the company are
15 trained on. And it provides them with a roadmap to
16 try to identify behaviors or patterns that they come
17 across during their day to day activities or they may
18 learn of during their day to day activities. And
19 there's, I believe, 13 different examples of criteria
20 that they can look to to try to identify that
21 behavior.

22 There's a roadmap to present that

1 information to our drug and pharmacovigilance group
2 as well as our general counsel. Decisions are made
3 as to whether we should continue to call on that
4 physician anymore. And if the decision is made not
5 to call on that physician or practice, the sales
6 credit for that office is no longer calculated in any
7 way, shape, or form for the rep.

8 So there actually is an incentive, and in
9 fact the program that's been in place for seven years
10 now encourages representatives to report any of that
11 kind of behavior they may see or learn about in their
12 territory.

13 Thank you.

14 DR. KIRSCH: Okay. I will end this portion
15 of the session and go on to the questions that have
16 been posed to the committee from the FDA.

17 The first is for us to discuss whether the
18 studies performed by the sponsor adequately
19 characterize the physical attributes of the
20 reformulated OxyContin product. And I guess I'll
21 start this out.

22 I'll re-emphasize or I'll agree with what

1 Dr. Day said. I was also part of the previous
2 committee meeting and I believe that they, with this
3 presentation, did a much better job of presenting
4 data that was useful, at least to me, as a member of
5 the committee.

6 I've just been told we need to take a five-
7 minute break in order so the system can be reset
8 because at the end of this, we need to have a vote
9 and the system won't vote unless they reset it.

10 So we will take five minutes. Currently,
11 it is 2:41. We'll be back here at 2:46.

12 (Whereupon, a recess is taken.)

13 DR. KIRSCH: Okay. The question that we're
14 trying to address or that we're supposed to discuss
15 is whether or not the studies performed by the
16 sponsor adequately characterize the physical
17 attributes of the reformulated OxyContin product.

18 My own opinion is that it does, they do,
19 and I'd be happy to hear -- unless there's consensus.
20 It appears that --

21 Mr. Denisco. I'm sorry. Mr. Yesenko.

22 MR. YESENKO: I'll answer for Denisco, too.

1 So this counts for two.

2 I'm just wondering why the reformulated
3 OxyContin is changing strength, unless I'm missing
4 something. You're adding a 15, 20, and 30. Is that
5 -- for the sponsor, is that --

6 DR. GASDIA: I'm sorry. Could you please
7 repeat it? I'm sorry.

8 MR. YESENKO: The question is why is the
9 reformulated OxyContin adding a 15, 20, and 30? Is
10 that -- I mean, does that have to do with the safety
11 issue? Are you looking at less liability with the
12 increments of that?

13 DR. GASDIA: No. I think there's a
14 misunderstanding with that. We have seven strengths
15 currently on the market of the current formulation.
16 They were launched over a year and a half ago and so
17 we have a 10, 15, 20, 30, 40, 60, and 80 milligram
18 currently available. So we are just making the new
19 formulation of the same strengths.

20 MR. YESENKO: Thank you.

21 DR. KIRSCH: So to summarize the opinion of
22 the committee is that the studies that were presented

1 by the sponsor do adequately characterize the
2 physical attributes of the reformulated OxyContin
3 product.

4 DR. RAPPAPORT: I actually thought I heard
5 some people in the committee who didn't fully agree
6 with that. I just want to make sure that we've
7 actually given everybody a chance to make their
8 thoughts known here.

9 DR. KIRSCH: I think Dr. Day had some
10 suggestions for how the data could be presented
11 differently, but I believe that she -- I'll let her
12 speak for herself, but didn't have recommendations
13 for new studies, just presentation of the data
14 differently.

15 DR. DAY: That is correct, but before the
16 chair characterized everyone as being in agreement
17 with the first question, do we want any straw vote or
18 we'll say that we all agree, unless someone speaks up
19 now or forever holds his or her peace?

20 DR. KIRSCH: The last time I tried to do a
21 straw vote, I got hung.

22 DR. DAY: How about the wedding question?

1 We say yes, but if anyone -- you know, speak up now
2 or forever hold your peace?

3 [Laughter.]

4 DR. KIRSCH: Dr. Lorenz.

5 DR. LORENZ: Well, my lawyerly question
6 would be whether adequately implies both the clinical
7 implications of this formulation or just simply the
8 physical attributes, and I think I would make a
9 distinction between those two.

10 DR. KIRSCH: I think the question says
11 physical attributes.

12 Dr. Zito.

13 DR. ZITO: Yes, I had reservations based on
14 the fact that the metrics that were used did not seem
15 to be adequate to adequately define the issue.

16 DR. KIRSCH: And the issue being the
17 clinical --

18 DR. ZITO: Not clinical. Based on the
19 differences, the differences, the measurement of
20 difference. And Dr. Day just raised the issue about
21 whether -- so my question becomes is the existing
22 data able to be repackaged? Is the information there

1 that would give us better understanding than the
2 ratios?

3 DR. KIRSCH: Does the sponsor want to
4 respond?

5 MS. GIORDANO: I think there's been a lot
6 of confusion about Table 56 -- excuse me -- slide 56,
7 the table there.

8 Is this what you're referring to? Could I
9 walk you through it one more time? Would that be
10 helpful?

11 I also wanted to mention that all of the
12 data points that are represented by the ratio on that
13 slide are in the briefing document. So I could give
14 you specific page numbers, if that's helpful.

15 DR. HERTZ: Not walking us through the
16 table again. This is Sharon Hertz. I was wondering,
17 do you actually have the absolute data available in a
18 slide? I think we understand that this slide doesn't
19 provide the absolute data, and I think that's what
20 people have been, you know, sort of hankering to see.

21 MS. GIORDANO: Sure. It's not put together
22 in one particular slide, but we have numbers. We can

1 give you the numbers for some of the higher numbers
2 that are represented here, if that would be helpful.
3 And as I said, the pages, I can give you also the
4 pages of the briefing document where the actual
5 numbers are presented in graphical form; whatever's
6 most helpful.

7 DR. DAY: Can I just comment? We're
8 talking and focusing on slide 56 and we have an
9 understanding of what we're looking for, but it's not
10 just this. It's through all of the outcome measures
11 for whenever we have ratios, do we have the absolute
12 values and we have absolute values, do we have the
13 ratios?

14 MS. GIORDANO: This slide and the following
15 slide are the only slides that have ratios on them.
16 I believe all the other data is expressed in either
17 percent of release or milligram amounts in the closed
18 session.

19 DR. KIRSCH: So do we have a concise way to
20 answer the question posed by Dr. Day and Dr. Zito?

21 DR. LANDAU: Is this for the sponsor? I
22 don't know that there's any concise way to provide a

1 response. We have thousands upon thousands of data
2 points.

3 Our goal was to provide it to you in as
4 digestible a fashion as possible. All of the
5 information was supplied within the submission and
6 most all of it was supplied in the briefing document.
7 Had we looked to present all of the information,
8 every data point, in the briefing document, it would
9 have been unmanageable for the committee.

10 DR. KIRSCH: Maybe I could pose a question.
11 Is there a combination of simple solvents and time
12 that creates a situation where in both the new
13 formulation as well as the old formulation there is
14 similar and near-complete availability of the drug?

15 MS. GIORDANO: Not with the simple solvent.

16 DR. KIRSCH: And how about with the
17 advanced solvents or pH-adjusted?

18 MS. GIORDANO: Your question being which
19 ones are statistically similar in release?

20 DR. KIRSCH: No. Is there a combination
21 where there is a solvent of any type that results in
22 complete release of the drug and there's a similar

1 fashion between the two formulations within 60
2 minutes?

3 MS. GIORDANO: This advanced solvent 1, the
4 non-ingestible solvent, if you can see those numbers
5 there, in 10 minutes with the smallest particles,
6 you're getting 88 percent correlation between the two
7 release rates, which is pretty similar.

8 DR. LANDAU: Again, these are non-
9 ingestible solvents.

10 DR. KIRSCH: And at that 88 percent, is
11 there near-complete release? It's not like the 17 or
12 18 percent release in both and the ratio's 88
13 percent? What you're saying, I believe, is that in
14 that one that's 88, in both formulations, there's
15 near-complete release of the drug?

16 MS. GIORDANO: That's right, and we can get
17 that number for you.

18 DR. KIRSCH: Mr. Yesenko.

19 MR. YESENKO: Hi. This is for Table 56.
20 Again, I don't think it was confusing to the panel.
21 It may have been presented in a confusing manner
22 rather than an entire panel being confused by Table

1 56.

2 I'm wondering about the briefing document
3 yesterday that I received in the mail. There's no
4 way I could have reviewed that entire document. So I
5 need to put that out on the table.

6 DR. KIRSCH: Thank you.

7 Dr. Zeltermann.

8 DR. ZELTERMAN: I think, if I can
9 paraphrase a comment made by Dr. Zito, when we asked
10 her this question, are we asking that there were an
11 adequate number of studies, should there be more
12 studies, should there be other tests of the new
13 formulation, or are we asking the sponsor to
14 summarize the data better?

15 I think the question is a little ambiguous.
16 You're asking studies performed by the sponsor
17 adequately characterized. Well, what are we talking
18 about? Is it more studies or in fact a better
19 summary of the studies already written?

20 If I can go back to 56 again, this poor
21 table, the trouble is it's very ambiguous because a
22 100 percent of a small number could be much smaller

1 than 50 percent of a much bigger number.

2 So when we talk about the actual numbers in
3 this table, it's very misleading. So the 100 was
4 said to be, well, statistically equivalent, but it's
5 equivalent of a very small number. But just below
6 that you see is a 58. Now that 58 might actually
7 represent a much larger amount of drug delivered.

8 So the numbers themselves are not quite
9 summarized correctly.

10 DR. KIRSCH: What I'd like to do is let the
11 FDA respond to the request for clarification in the
12 question and then I'll allow the sponsor to respond
13 to the question.

14 DR. RAPPAPORT: I don't think this question
15 is unclear. We're asking whether the sponsor has --
16 the studies that have been performed adequately
17 characterize the physical attributes of the
18 formulation. We're not asking whether they presented
19 it well or thoroughly, but you can certainly say they
20 haven't presented it well or thoroughly enough for us
21 to make that determination.

22 DR. KIRSCH: Okay. Sponsor, do you have a

1 response?

2 DR. LANDAU: Yes. Our response is that all
3 of the data that this slide and others are based upon
4 are included in our resubmission, and I'd like to
5 take a step back.

6 The relevant comparison -- although I
7 recognize how important understanding precisely how
8 much drug is released and under what condition, the
9 relevant comparison is over the current product. And
10 the current product, within a few seconds, is
11 rendered in an immediate release dose form. To get
12 to the numbers, however critical we are, represented
13 on this page requires time, effort, tools, and
14 determination.

15 So I just want to make that context clear.
16 We're happy to provide additional clarity or
17 transparency. It was certainly not our objective to
18 do anything short of that. We were hoping to help
19 the Advisory Committee and respect your time in
20 looking to digest so much information.

21 DR. KIRSCH: Dr. Deshpande.

22 DR. DESHPANDE: I agree with you that

1 there's a concern about the current product and
2 therefore this is an effort to improve what's on the
3 market now.

4 With that, I'll say that I am surprised
5 that current product is still on the market with the
6 difficulties that we've seen, if we're going to
7 address it. That's a different issue.

8 For me, without the data, I can't really
9 answer the question about adequate number of studies
10 because I don't know that the data really show me the
11 physical characteristics as I'd like to understand
12 them.

13 I think Dr. Lorenz had a question about
14 both water and alcohol and the duration of immersion
15 or, as Dr. Flick pointed out, of having a tablet in
16 the mouth and data from that kind of an exposure.
17 And I wasn't sure what the answer was there. So I'm
18 not comfortable answering yes on this.

19 DR. KIRSCH: Dr. Morrato.

20 DR. MORRATO: I wanted to just reflect from
21 a design of experiment standpoint in terms of the
22 scale and scope and the different solvents, the

1 different extraction, the different crushing
2 characteristics.

3 I thought it was a very comprehensive
4 program which was one of the outside experts that
5 they brought in. So from that standpoint, I think it
6 was a very adequate set of studies to look at those
7 attributes.

8 DR. KIRSCH: Dr. Lorenz.

9 DR. LORENZ: I agree as well that it was a
10 very comprehensive look at the tablet and there
11 certainly is a great deal of data available.

12 I do question whether we've seen the data
13 in ways that would help us easily comprehend its
14 clinical relevance. And I also think that it's
15 patently true that we don't really know what's
16 clinically relevant about these ratios. And so I think
17 the challenge would be what sort of a decision we
18 could make on the basis of them, but that would be my
19 concern.

20 DR. KIRSCH: Dr. Prough.

21 DR. PROUGH: It seems to me, from what
22 we've seen, it would be awfully hard to make any kind

1 of case that the available data suggest that the new
2 formulation could be more dangerous. It seems to me
3 if there were any question about that, then the
4 urgency of these questions would be very great.

5 My interpretation of the data is that the
6 only question is the extent to which the data
7 demonstrate that the product at least represents more
8 of a barrier to abuse. And I think since that seems
9 to be the fundamental question, it seems to me the
10 studies are perfectly adequate to address that
11 question, and the answer to that question is it's
12 more difficult to abuse, not impossible, just more
13 difficult.

14 DR. KIRSCH: The sponsor has repeatedly
15 indicated that in the briefing material much of the
16 information that we've been asking for is present.
17 One of the advantages that I have of having to fly
18 across country to get here, a lot of time in the
19 airplane, to read the document that was sent to us
20 the day before yesterday. And my feeling is that the
21 information that we've been provided with does
22 demonstrate that they've taken this question

1 seriously and there's always a new study that could
2 be done. There's a lot of smart people at this table
3 who can always think of something, another study that
4 could be done. And we all have different preferences
5 for how to look at data, but I think overall the
6 sponsor, in my opinion, has done a good job of
7 providing the data in a straightforward and complete
8 fashion.

9 Dr. Flick.

10 DR. FLICK: I would echo those comments. I
11 think that the data, although not well described,
12 does answer the fundamental question. Is this more
13 difficult than the previous formulation? I think
14 clearly it is. Whether that will have an impact
15 ultimately on the abuse potential and the misuse of
16 the drug I think remains to be seen. I think the
17 answer to the first question is yes.

18 DR. KIRSCH: Dr. Vaida.

19 DR. VAIDA: I was just going to echo that
20 in the sense that if the second question wasn't here,
21 I think we'd have more debate, not that I want to
22 jump ahead. And I think even just taking out that

1 with the FDA, what you're really looking for, I mean,
2 if the second question said discuss whether the
3 studies performed by the sponsor adequately
4 characterize the change in formulation, is that what
5 we really want to talk about compared to the answer
6 to the first question. But the way the first
7 question is stated, I would have to say yes.

8 DR. KIRSCH: So to summarize what I hear
9 the committee saying is that the majority, but not
10 the entirety, of the committee believe that the
11 studies that have been done by the sponsor do
12 adequately characterize the physical attributes.

13 There is some concern about how the data
14 was presented and it would be helpful for the sponsor
15 to provide a more comprehensive report of the data to
16 those who are interested. But overall the committee
17 believes that the sponsor has adequately
18 characterized the physical attributes of the new
19 formulation.

20 Are there any edits?

21 [No response.]

22 DR. KIRSCH: We will go on to the second

1 question then, which I think is a much more
2 complicated question many of the comments have
3 skirted around, and that is to discuss whether the
4 change in the formulation affects the overall safety
5 profile of OxyContin.

6 Dr. Shatin.

7 DR. SHATIN: I'd like to draw people's
8 attention to page 34. As we're talking about the
9 overall safety profile, this looks at the
10 recreational abusers of OxyContin. And the question
11 is 55 percent or the mode of abuse, was through
12 swallowing. And I think that's important to
13 recognize in terms of the "tamper-proof" aspect of
14 the new formulation and what that relationship might
15 be.

16 I had a question related whether chewing is
17 an additional set of patients or we could consider
18 that as a subset of the 55 percent. So if you added
19 those two, both would be oral and that's up to almost
20 100 percent.

21 DR. KIRSCH: Could the sponsor respond to
22 that, please? The question relates to a particular

1 graph and whether or not --

2 DR. SHATIN: Thirty-four.

3 DR. KIRSCH: -- the oral and the chewed are
4 additive or the same.

5 DR. LANDAU: Dr. Cone, maybe you could
6 respond?

7 DR. CONE: Just so I know what I'm
8 answering, this is the graph you're referring to?

9 DR. SHATIN: Yes.

10 DR. CONE: And could you repeat the
11 question. I know it's about oral, but what was the
12 specific?

13 DR. SHATIN: The question was the two
14 categories of swallowing and chew, whether they're
15 mutually exclusive or one is a subset.

16 DR. CONE: Yes, that's a point to be made.
17 These are the number of responses from the people
18 that were surveyed on the Internet. And very
19 frequently responses were -- very frequently the
20 person that was completing the response would
21 indicate two or more routes of administration. And
22 that's why the numbers don't add up to 100; they add

1 up to much more than 100.

2 So frequently they would say sometimes I
3 swallow intact, sometimes I chew it, and even
4 sometimes I snort it. That would be a typical
5 response, and that's what this data shows.

6 DR. SHATIN: Thank you.

7 DR. KIRSCH: Dr. Day.

8 DR. DAY: On that point, was this a free
9 response question where you would ask how do you do
10 it, such as, or were there blanks to fill in and
11 check or give percentage of time or say a Likert
12 scale in terms of rating most of the time, some of
13 the time, et cetera?

14 So how is the question asked, please?

15 DR. CONE: This is not a study I performed.
16 This is a study performed by Nathaniel Katz, and he
17 didn't describe to that detail. He did describe the
18 questionnaire and it was my impression that it was an
19 open response, that you could describe how you used
20 it and using various routes of administration. And
21 he did have a section on validation of his response
22 questionnaire, but that's about as far as I can go in

1 describing what he said.

2 DR. DAY: So it was open-ended, but we
3 don't know the method of scoring. And so the
4 question asked we can't answer as to whether the
5 swallowers and chewers overlap.

6 DR. CONE: No, no, no. We can answer that
7 question. Each one of those responses came from an
8 individual indicating that they used by that route.
9 The fact that some of them reported two or more
10 routes of administration was also recorded. What I
11 can't tell you is what the breakdown is between one
12 route, two routes, or three routes.

13 DR. KIRSCH: Dr. Lorenz.

14 DR. LORENZ: Yes. My comment is that I
15 think we have to ask in what population maybe the
16 change might affect the overall safety profile. And
17 I think actually I have a fair degree of suspicion
18 that it affects the safety profile in any user on the
19 basis of the fact that rather simple tools and simple
20 approaches to manipulation seem to result in the
21 release of a large proportion of the active drug
22 relative to the current oxycodone. And I'm not sure

1 that I can comment on what was illustrated in the
2 early morning session.

3 But in any case, I guess the other
4 complicating factor is whether the real issues and
5 problems we see with OxyContin are really a function
6 of the hard-core abusers and manipulation of the
7 drug, and I think to that extent, the benefits would
8 be minimal in any case. And so those are my two
9 concerns, but my answer probably then is no, if I
10 have to give a binary response.

11 DR. KIRSCH: Dr. Prough.

12 DR. PROUGH: I just had a question for
13 clarification about page 34, the swallow column. Am
14 I correct that that includes both swallowing intact
15 pills and swallowing modified pills, dissolved pills?

16 DR. KIRSCH: Can the sponsor respond to
17 that?

18 DR. LANDAU: Do I understand your question
19 to be directed at more specific information within
20 each preferred route of abuse?

21 DR. PROUGH: Just the one route, just
22 swallow. Does that include intact and modified

1 pills?

2 DR. LANDAU: Dr. Cone.

3 DR. CONE: That is only responding as I
4 swallowed the intact pill, no modification.

5 DR. KIRSCH: Dr. Crawford.

6 DR. CRAWFORD: Thank you. This is also
7 very related to some of the other comments.

8 Dr. Cone, please don't sit down yet. Would
9 you please go back up? Thank you.

10 When you were presenting, we've been
11 talking about slide 34 and from Dr. Day's question,
12 you placed what I inferred as you were discussing
13 that that was the ability for the respondents to
14 select -- in Katz's study, select more than one
15 response. However, in your study as well as the next
16 one on slide 35, because both of those do total 100,
17 do we assume that it was more forced choice
18 categories?

19 DR. CONE: The one on the left is an
20 informal survey. This is not a survey that I put on
21 the Internet and they responded to. These are the
22 experience reports from Erowid that I went through

1 individually and scored each experience report as it
2 related to OxyContin, and then I totaled up the
3 number of responses. In that case, this is percent
4 of responses. So it does add up to 100.

5 There were any number of individuals who
6 reported more than one route of administration. So
7 again, there was 51 respondents and 71 responses.

8 DR. LANDAU: Perhaps I could clarify. The
9 last few questions on preferred routes of abuse, I
10 think is great. We hold great interest in this for a
11 number of reasons. And the uncertainty and the
12 variability amongst reports are a consequence or a
13 function of the population and the methods we're
14 using to evaluate.

15 The fact is there's no national database we
16 can use to understand the baseline for preferred
17 routes of abuse. It just doesn't exist. So we rely
18 on various and sundry reports, like the ones
19 presented by Dr. Cone.

20 Dr. Sellers, would you mind --

21 DR. CRAWFORD: Actually, I don't need any
22 more elaboration. Thank you. I just wanted to make

1 one more follow-up related to what Dr. Lorenz said to
2 answer the question for the chair and the committee.

3 Discuss whether the change affects the
4 overall safety profile. My opinion of that is,
5 certainly, it is suggestive of less abuse potential,
6 but in overall clinical use, I think we have no
7 information that the reformulation would affect the
8 safety.

9 DR. KIRSCH: Dr. Cooper.

10 DR. COOPER: Clearly, I think, here, I
11 think the FDA did not present this question as a
12 binary choice for us to say yes or no. So I think I
13 would interpret that to mean that they want some
14 input from us about our opinions.

15 Guided by the fact that the current
16 formulation clearly has important safety drawbacks
17 and some important design features that create risk
18 and information about the physical properties, the
19 opinion of experts in the field, and at least some
20 evidence from other prior reformulations, that it
21 seems we don't have a burden of proof to be more
22 likely than not or beyond convincing doubt. But my

1 feeling is there would at least be some incremental
2 improvement in the safety profile.

3 DR. KIRSCH: Dr. Morrato.

4 DR. MORRATO: I thought slide 84, which was
5 presented by Dr. Sellers, was a useful framework to
6 think about it in terms of anticipated impact of
7 reformulation on different population of users,
8 experimenters, and such. And I would agree with what
9 Dr. Cooper was saying in the sense that this is
10 theoretical, right. So we're taking in vitro
11 properties, and based on what we know about behaviors
12 of abuse, we're trying to project what might happen.
13 And so from that standpoint, it theoretically might
14 shift the abusability risk curve. Probably more
15 importantly, it's going to be helping regular
16 patients who might accidentally misuse the product
17 and safety concerns.

18 But I'd like to draw back to the point
19 that, as I understand it, the current formulation, if
20 its patent expires and you have generics in line to
21 go to market with that same formulation that's
22 existing, then any benefit that we have with the

1 reformulation is going to be fleeting in the sense
2 that once the generic of the current formulation's on
3 the market, it's cheaper and market forces will drive
4 to the use of that cheaper version, which is what's
5 now, not necessarily the reformulated one, right.

6 So what we're talking about might be a
7 theoretical safety benefit and it might be short-
8 lasting, depending on market forces.

9 Do I understand the patent situation?

10 DR. JENKINS: I think you do. It's hard
11 for us to speculate what may happen four years hence.
12 The standard we generally apply is you can use a
13 withdrawn drug as the reference for approval of a
14 generic as long as FDA hasn't determined that the
15 drug was withdrawn for safety reasons.

16 So today, obviously the original
17 formulation has not been withdrawn for safety
18 reasons. It's still on the market. Whether four
19 years from now, with any new accumulating data, we
20 will consider that it was withdrawn for safety
21 reasons is hypothetical at this point. But, in
22 general, you can reference a withdrawn formulation

1 and there are many examples where the innovator has
2 withdrawn and the generics are still there.

3 DR. MORRATO: So it's not certain but
4 plausible what I'm saying could happen?

5 DR. JENKINS: Yes.

6 DR. MORRATO: Yes, thank you.

7 DR. KIRSCH: But I think you've heard from
8 the committee that there's great concern over the
9 safety of the current formulation.

10 Dr. Flick.

11 DR. FLICK: If you could put that slide
12 back up? Thank you.

13 I think we've been asked to address the
14 question does the change in formulation affect the
15 overall safety profile. And I think when we address
16 the various populations, I think some of those
17 answers are more clear.

18 Certainly in the sophisticated addict, this
19 new formulation presents, I think, probably little
20 barrier to doing what they have done in the past. I
21 think for the other populations, the formulation is
22 less important and probably matters very little.

1 I think Michael Yesenko's comment about
2 doses and the size of doses is a relevant one when we
3 look at these populations. Very few drugs on the
4 market in a single dose can cause death. The large
5 doses of this drug and other sustained-release
6 formulations of narcotics have that capacity. And
7 one wonders whether we're focused on a formulation
8 when we might do better to focus on the size of the
9 dose in any individual tablet or vehicle. And I
10 would just wonder whether the formulation is really
11 where the focus of attention should be.

12 DR. KIRSCH: Thank you.

13 Dr. Shatin.

14 DR. SHATIN: The comment I had was to link
15 pages 35 and 84. And I think, as Dr. Yesenko just
16 mentioned, that we need to look at different
17 categories of abusers of the drug.

18 As you see on page 35, there are
19 differences in the route of administration for the
20 recreational abuser versus abusers entering
21 treatment. And I would think, looking at page 84,
22 the abusers entering treatment are probably within

1 the sophisticated addict group. So I'm in agreement
2 that ways will be figured out for that category. We
3 don't know how large that group is compared to more
4 recreational users.

5 Also related to your comment about the dose
6 size, my understanding was there was a 160 that is no
7 longer available, and maybe we should consider the 80
8 milligram, as well.

9 DR. KIRSCH: Mr. Yesenko.

10 MR. YESENKO: This is addressing the second
11 question discussed, whether the change in formulation
12 affects the overall safety profile of OxyContin.
13 Well, that's why we're here.

14 It's being reformulated for safety reasons
15 because I'm assuming the first go-around, I believe
16 it was May of '08, I was in that meeting, as well,
17 didn't quite cut the cake. So that's why we're here
18 back.

19 I have a question, though, specifically
20 about the original OxyContin, and this might be for
21 Dr. Rappaport in terms of the formulation of the
22 older product and patents.

1 If that runs out, can that be used as a
2 guide for a newer reformulated OxyContin?

3 DR. JENKINS: Let me try.

4 MR. YESENKO: Dr. Jenkins.

5 DR. JENKINS: The old formulation could
6 conceivably remain as a reference-listed drug if we
7 have not determined it to be withdrawn for safety
8 reasons. That would not preclude a generic sponsor
9 from bringing forward a formulation that has some of
10 these new characteristics. They have to be
11 bioequivalent. They don't have to be exact same
12 formulation. They have to be bioequivalent, meaning
13 they have to have the same active ingredient, the
14 same route of administration, the same dose, and they
15 have to deliver the same amount to the blood, but
16 they don't necessarily have to have the same
17 controlled-release mechanism. And, in fact, they
18 often don't have the same controlled-release
19 mechanism.

20 So yes, it's possible that generic
21 manufacturers could bring forward formulations that
22 have some of these physical-chemical properties that

1 might be desirable.

2 MR. YESENKO: So would that tie in to any
3 possibility of having any further clinical hopefully
4 appropriate studies?

5 DR. JENKINS: Generic drugs are not
6 approved based on clinical studies. They're based on
7 manufacturing. As I said, they have to be the same
8 active ingredients, same route of administration, the
9 same amount of drug, and then they have to be
10 bioequivalent, meaning they deliver the same amount
11 of drug to the bloodstream as the innovator. So
12 there generally are not clinical studies conducted
13 for most generic drugs.

14 MR. YESENKO: I guess, I'm sorry, I didn't
15 say that correctly. I meant for the reformulated
16 OxyContin -- this is a question, I guess, for the
17 sponsor. Are there appropriate clinical studies that
18 have taken place? I haven't really seen a lot of --

19 DR. JENKINS: They have not conducted
20 clinical studies because they're linking the new
21 formulation to the old formulation, based on
22 bioequivalence, which is the same theory. They have

1 not been required to do new clinical trials to show
2 that the new formulation is safe and effective
3 because they've shown it's bioequivalent to the
4 existing formulation.

5 It's the same principle that's used for
6 approval of generics.

7 MR. YESENKO: But if they do, then can they
8 get exclusivity?

9 DR. JENKINS: The studies have to be
10 required for approval. So they can't just do studies
11 in hopes of gaining exclusivity. We have to
12 determine that the clinical studies were necessary
13 for approval and we have not felt that they were
14 necessary for approval. So that's why Dr. Rappaport
15 said, you know, it's not expected that they will gain
16 any exclusivity for this new formulation.

17 That's separate from patent protection,
18 which we don't regulate. We have to honor but we
19 don't regulate.

20 MR. YESENKO: Thank you.

21 DR. KIRSCH: Dr. Markman.

22 DR. MARKMAN: With respect to the intrinsic

1 properties of the drug, I do think this represents
2 the possibility of an improvement in the safety
3 profile. But I think as a field and as a society, we
4 have a history of being wrong about what we think
5 will be safer when it comes to opioids. So I say
6 that with a lot of caution.

7 I think it's going to be critical to look
8 at the extrinsic drug properties, you know, in
9 clinics and in the society as a whole, and we're
10 going to have to make a real commitment to studying
11 this at post-marketing to really answer this question
12 of the safety profile being improved, and I think
13 that approval should really be contingent on a very
14 clear plan about how we're going to demonstrate that
15 increased safety or the lack thereof because we have
16 a track record of being so wrong about it.

17 DR. KIRSCH: Dr. Deshpande.

18 DR. DESHPANDE: I'm still a little
19 confused, and so when I'm thinking about the overall
20 safety profile, particularly in comparison to the
21 current formulation, I go back to the infamous page
22 56, slide 56. And for me, when I think about safety,

1 I think about if I take this -- if a patient takes
2 this and that drug, is that enough to kill them or
3 cause them harm or do something untoward, and I don't
4 know that.

5 I know that in proportion to the current
6 formulation, we have percentages of release in vitro.
7 I don't know that a 20 kilo child or a 50 kilo adult
8 or a 70 kilo adult will get a certain amount of
9 medication that's enough to do him harm because I
10 don't have the information to do it. So I'm pretty
11 simple. I can't answer this question.

12 DR. KIRSCH: Dr. Zito.

13 DR. ZITO: I was looking at the two sheets
14 that Dr. Shatin suggested that we look at, 35 and 84,
15 and then the thought occurred to me that when I look
16 at 84, I'm not seeing therapeutic misadventures in
17 here. And then when I go back to 35, I see that
18 abusers are what Carise, et al. is listing, and I'm
19 not clear where misuse is.

20 DR. KIRSCH: Would the sponsor --

21 DR. ZITO: And should we not be thinking
22 about that in terms of this second question, you

1 know, that the overall safety profile includes a lot
2 of things, that bad things happen to good people
3 aren't intended in clinical care, either because --
4 for all the various reasons that medical uncertainty
5 brings.

6 DR. KIRSCH: Would the sponsor like to
7 respond?

8 DR. LANDAU: Can we have slide 150, please?
9 So we think this is a very important topic, patient
10 safety, the intended patient population.

11 In preparation for this meeting, and it's
12 just representative of continued pharmacovigilance,
13 we analyzed our internal safety database, August
14 database, and from the period from when the product
15 was first introduced, 12 December 1995 to, in this
16 case, 31 August, so very recent. And we queried the
17 database for any cases involving overdose,
18 intentional drug misuse, drug abuse, or
19 maladministration, medication error, all cases
20 associated with tampering, physical manipulation of
21 the tablet. And what we found were that 1,460 cases
22 existed and these were from multiple sources, all the

1 limitations of post-marketing pharmacovigilance
2 applied.

3 Eighty-five percent were related to abuse,
4 as you would expect; 15 percent were related to
5 medication errors or maladministration.

6 If we can have a subsequent slide, please?
7 Actually, go to 152.

8 You can see a breakdown of the 220 cases,
9 and I won't read through this slide. The point we're
10 trying to make here, and I think we're in agreement,
11 is that medication errors are real; they occur.
12 Fortunately, they don't occur with the frequency that
13 some of the other misadventures do, but we're hoping
14 through this slide represented, I think it was slide
15 34, that some of these misadventures would be avoided
16 with the tablet that's harder to manipulate.

17 DR. RAPPAPORT: Can I get a clarification?

18 DR. ZITO: I was just going to ask for the
19 source of the reports.

20 DR. LANDAU: There are multiple sources.
21 We maintain a post-marketing pharmacovigilance
22 database. These are reports from healthcare

1 providers, emergency rooms, literature, et cetera.
2 Most of what you see -- actually all of what you see
3 here is also included in FDA's Adverse Event
4 Reporting System, AERS.

5 DR. KIRSCH: Dr. Rappaport.

6 DR. RAPPAPORT: So can you just clarify for
7 me the company's opinion, and is that this new
8 product is going to provide increased safety compared
9 to the old product, at least for that 15 percent of
10 patients who suffer misadventures due to incorrect
11 use of the product?

12 DR. LANDAU: It's a difficult position to
13 take, but it's intuitive to me as a practitioner.
14 Any misadventure that involves chewing a tablet,
15 crushing it, administration is probably less likely
16 to occur with a tablet that's harder to crush. It's
17 only post-marketing data would support a claim that
18 the safety can be supported. So I don't know. I'm
19 reluctant to make a prediction on a clinical outcome
20 that we'd need data to support without this data.

21 DR. KIRSCH: Dr. Lorenz.

22 DR. LORENZ: I just wanted to make a

1 comment -- this is for the agency -- that these
2 debates are very nuanced. And I think, you know,
3 when something makes it out to the marketplace, it's
4 not always clear how difficult these decisions have
5 been.

6 So I just want to urge the agency to
7 maintain a public archive. And not only that, not
8 only a public archive of the entire proceedings, but
9 also a publicly-accessible transcript or, rather, a
10 summary, a publicly-accessible summary of these sorts
11 of events so that prescribers will have access to the
12 same level of ambiguity that we find ourselves in in
13 making such choices.

14 I really am saying this because, in one of
15 the recently-approved drugs by the FDA, I became
16 aware of the fact that there was no longer a public
17 record of these sorts of debates. And, in fact, it
18 was relevant to a specialty society that was putting
19 out a notice about the availability of a new drug to
20 prescribers. I feel it's very important to have this
21 sort of balanced information available.

22 DR. RAPPAPORT: I don't know. Maybe

1 Kalyani wants to speak to this. But my
2 understanding, first of all, we have our transcriber
3 here who's getting every word

4 Has there been a change in the policy?
5 We've always had complete transcripts of all of our
6 public meetings.

7 MS. BHATT: Dr. Lorenz is referring to
8 other documents. The transcripts are always
9 available.

10 DR. LORENZ: Right. I'm talking to
11 basically a web archive of the information that's
12 informed our decisions here.

13 DR. RAPPAPORT: Thank you.

14 DR. KIRSCH: Dr. Morrato.

15 DR. MORRATO: I just wanted to reiterate
16 Dr. Markman's point, maybe add a bit to it, around
17 the importance of the post-marketing study and
18 surveillance since we're making hypothetical leaps
19 between what we see in vitro and what we think might
20 happen in market.

21 I think that would justify the need for
22 post-marketing studies and perhaps as part of the

1 risk management commitment maybe a requirement, post-
2 marketing Phase IV requirement, in terms of this
3 surveillance.

4 I know the risk management plans are
5 supposed to be looking at diversion and abuse in
6 general, but maybe in the launch of this drug being
7 specific to have this drug before versus after in
8 some of those design issues could be part of the
9 requirement.

10 DR. KIRSCH: Dr. Vaida.

11 DR. VAIDA: Just a quick comment on that
12 last slide and a couple of the terms that were being
13 used.

14 When we're referring to errors and
15 misadventures, the only information I've seen is on
16 tampering of tablets. So I just want to make sure
17 everybody understands that we're not talking about a
18 lot of the other errors that happen out there with
19 opioids. This is a small fraction of errors that are
20 tampering because it was a couple other slides that
21 said patient error or that, and it was only talking
22 about patients chewing the tablet, not taking the

1 wrong strengths, not taking it in place of something
2 else.

3 So even with that last slide that was
4 shown, I just want to make sure that, from a safety
5 profile, this is a small fraction of errors.

6 DR. KIRSCH: So with that, I'll try to
7 summarize the opinion of the committee.

8 I think the committee has expressed great
9 concern over the overall safety of this class of
10 drugs, which I believe is appropriate. I think the
11 majority believe that, although for a small subset of
12 the patients taking these medications, this might be
13 a safer approach. But I think the FDA and the
14 sponsor have been loud and clear that there's enough
15 concern about this uncertainty that the committee
16 would like or recommends that there be a link to a
17 required post-marketing study that will look at the
18 clinical outcomes of this proposed new formulation.

19 Are there any edits to that comment?

20 [No response.]

21 DR. KIRSCH: Okay. With that, I will go on
22 to the third point, which is our vote. And I don't

1 know if the FDA wants to inform us as to the
2 mechanism of the vote.

3 Okay. The question is should this
4 application for a reformulated OxyContin be approved,
5 and ultimately we will vote yes or no or abstain.
6 And before we have the vote, I'd open the floor for
7 additional comments or questions.

8 Dr. Lorenz.

9 DR. LORENZ: Could you please inform us,
10 I'm asking the agency, does a yes vote imply that
11 this represents an advance in some sense or that it's
12 simply safe and effective? What should we understand
13 our vote implying?

14 DR. RAPPAPORT: We approve drugs based on
15 the fact that their benefits outweigh their risks.
16 So that would be the basis for our approval.

17 You don't have to consider this to be safer
18 than the previous formulation in order to make that
19 determination, but if that's your personal
20 inclination, we'd like to hear that, as well. Our
21 regulatory standard is that the benefits outweigh the
22 risks.

1 DR. KIRSCH: Dr. Markman.

2 DR. MARKMAN: As a practitioner of pain
3 medicine and someone who takes care of patients with
4 chronic pain virtually every day, I first want to
5 just attest I think to what was very powerful
6 testimony during the open session about the efficacy
7 of oxycodone as an analgesic or as a pain reliever.
8 It's effective for acute pain. It's effective for
9 chronic pain, cancer pain, and I do think there are
10 additional benefits with regard to having a long-
11 acting formulation of this available as a clinician.
12 Again, I just want to attest and affirm, I think what
13 we heard was very powerful during the open session.

14 I want to speak to the issue, though, of
15 brand identity or the name of the product that I
16 raised earlier, and again I would love to hear from
17 my colleagues regarding this.

18 In my mind, the widespread adoption and
19 success, if you will, of the use of this medication
20 was initially associated with an unfounded claim of
21 safety. And I think there's been a lot of unintended
22 harm but also arguably some benefit as well, on

1 measure, because patients who could obtain relief
2 from having oxycodone available have obtained it.

3 As a practitioner, one of the things I
4 struggle with commonly every day in my office is that
5 there are many patients, as a backlash to that
6 initial unfounded claim, have a profound fear of
7 opioids, and as a clinician I spend much of my time
8 trying to speak to patients and compel them to try an
9 opioid because they do have a problem from which they
10 could benefit from this class of medication, but
11 they're too afraid. And they're afraid because of
12 issues of misuse, abuse, and diversion and how that's
13 been characterized in the media, even though in their
14 particular situation, I think that there's a very
15 good possibility that it's their best option for
16 relief.

17 That is one of the challenges of being a
18 clinician, is trying to compel patients who are
19 appropriate for this type of analgesic to try it.
20 And I think that not changing the name here will
21 continue to make that part of my job harder. And
22 that's why I think it's important that if this is in

1 fact a new product and it is addressing a
2 vulnerability of the previous formulation, that we
3 consider not only a change in the name but again
4 being rigorous about the new messaging around that
5 new name and new product.

6 DR. KIRSCH: Dr. Cooper.

7 DR. COOPER: So the agency has told us that
8 sort of the standard to think about for this question
9 is deciding whether the benefits outweigh the risks
10 for this particular decision, and I think that when I
11 think about that, I'm thinking about the old
12 formulation versus the new formulation. And for me,
13 I think that, given the risks the old formulation
14 has, even recognizing the concerns that some folks
15 have addressed, the clear echo and the clear need for
16 post-marketing studies, I think that I feel
17 comfortable saying that the benefits for this new
18 formulation would outweigh the risks, if that's the
19 standard we're applying.

20 DR. KIRSCH: Dr. Denisco.

21 DR. DENISCO: Well, we've been all over the
22 map today on many different issues, but it comes down

1 to the one thing that's changed is the excipient.
2 And we're being asked to approve this reformulated
3 OxyContin, and since the only thing that's been
4 changed is the excipient, I can only say is that
5 change better?

6 The old drug will still be here, whether
7 this is changed or not. So the only thing I can do
8 is say is the new formulation better than the old?
9 We're not voting on the class of drugs or whether to
10 approve OxyContin. I do think there are some
11 implications with the name, and again that points to
12 my confusion.

13 It's a new drug application. There are
14 excipients that, according to the pharmacopeia, in
15 the previous generics that were delayed formulation
16 release excipients. So this issue gets confusing.
17 If it's a new drug, it gets a new name.

18 So this whole issue still goes around a
19 little bit. I know it's covered by laws and
20 regulations, and sometimes they'll chase their tails
21 and some of that we've done, you know, ourselves. So
22 I'm just going to make it very simple for myself and

1 base it on what has changed and is that change
2 favorable to the public health or unfavorable to the
3 public health. And I'd also like to echo that all
4 the public comments were very, very informative and
5 much appreciated.

6 DR. KIRSCH: Dr. Flick.

7 DR. FLICK: Two comments. First, I would
8 also like to acknowledge the public comments, and in
9 particular the comment of the father whose child took
10 a single dose of this medication and died.

11 I think that I've made this point before
12 and I'll try and make it again. I think one of the
13 risks that is inherent in this drug and the drug that
14 we considered yesterday is not the vehicle, it's the
15 dose. The doses that are available in a single
16 tablet here are very, very large doses, that most of
17 us around the table could not take one of these
18 upper-end doses. And it seems to me that if we're
19 interested in making this a safer product, then we
20 would consider reducing the maximum single dose. I
21 will leave that for the consideration.

22 My next comment is I'm not sure that we're

1 actually being asked to approve or disapprove of this
2 particular formulation, although in actuality I
3 suppose we are. We have an alternative. The
4 alternative is we approve this new formulation or we
5 leave the old one on the market. That's really the
6 question.

7 Clearly, this formulation is somewhat,
8 although I would say very incrementally, safer than
9 the previous formulation, it does represent a small
10 advance.

11 DR. KIRSCH: Dr. Lesar.

12 DR. LESAR: Just a couple comments. My
13 thought process is I believe this is a better dosage
14 form. If it was 1995 and this drug was just first
15 being marketed, it would clearly be a safer product.
16 However, what we've learned in the past number of
17 years in the use of this drug is that the history has
18 sort of changed the way we should think about this.
19 So I believe it's safer; it could be safer in a
20 subset of patients.

21 I believe one of the ways it could have
22 been presented clearer was what is the dose that

1 people inject, so that on that table on page 56, what
2 was the number, how much does it take for me to get
3 10 milligrams in five ccs of saline? So if I had an
4 80 milligram tablet, how easy is it to get a dose
5 that I want, either orally or by injection? So I
6 thought that could have been improved.

7 I think trying to determine what the net
8 effect on public health is very difficult to say.
9 And I think this drug is a safer dosage form.
10 However, the net effect will depend on how it's used
11 and used in people who do not disrupt the dosage
12 form, and I think that will have to do with what the
13 unintended consequences. And I just wanted to read a
14 headline about us today in what's called *MedPage*
15 *Today*. It's a news item and it says, "FDA Panel to
16 Review Tamper-Resistant Oxycodone."

17 My hope is that if we do approve this
18 product or do vote for approval, that it does not say
19 tomorrow the FDA panel votes to approve safer
20 OxyContin.

21 DR. KIRSCH: That's pretty dramatic.

22 Dr. Margolis has again been quiet. I want

1 to give him the opportunity to ask any questions or
2 make a comment, if he has one.

3 DR. MARGOLIS: Yes. Thank you. It's sort
4 of been difficult to participate in this way, but I
5 agree with the comments that are being made.

6 I mean, it does appear that this will be a
7 somewhat safer product, but it's very difficult to
8 really know how much safer it's really going to be.
9 As an epidemiologist, you know, our guesses are
10 really theoretical in terms of which groups it's
11 going to be safer in. It's certainly not going to be
12 safer in those who are taking a large dose
13 accidentally or any that are due to medication
14 errors.

15 I think post-marketing's going to be
16 incredibly important here, and just how much safer
17 it's going to be for the vast majority of the people
18 who are using it will be difficult to know.

19 DR. KIRSCH: Thank you.

20 Mr. Yesenko.

21 MR. YESENKO: I'd like to echo Dr. Flick's
22 comment about the fact that if we do vote yes on this

1 reformulated OxyContin, are we then saying or are we
2 then asking the sponsor to pull the old formula or
3 the old dosage of OxyContin?

4 DR. KIRSCH: That's what they've agreed to.

5 MR. YESENKO: Okay. And then the second
6 comment is the open session with the families and
7 friends of those who have died from OxyContin, my
8 heart goes out to you. And my fear is if we do
9 accept or do vote to approve a reformulated
10 OxyContin, my fear is that in two years, will there
11 be public comments in this open forum with some of us
12 on the panel with family members who have died from
13 taking the reformulated OxyContin.

14 Thank you.

15 DR. KIRSCH: I answered for the sponsor. I
16 hope they agree. The question was if this current
17 formulation is approved, I heard you say over and
18 over again that within six or eight weeks you would
19 have 90 percent of the pharmacies and so forth
20 retooled with this new formulation and would
21 ultimately take the old formulation off the market.

22 DR. LANDAU: That's correct.

1 DR. KIRSCH: Thank you.

2 Dr. Tortella.

3 DR. TORTELLA: Thanks. I think from the
4 industry standpoint, the data really show three
5 activities identified to abuse, and that's chew,
6 snort, and shoot. Hardening in the gel formation
7 after hydration I really think move us forward in
8 addressing those big three areas.

9 Thank you.

10 DR. KIRSCH: Thank you. Dr. Lorenz.

11 DR. LORENZ: Actually, what was I going to
12 say? I'll think about it.

13 DR. KIRSCH: Dr. Vaida.

14 DR. VAIDA: I think this product probably
15 isn't safer and I think we echoed a lot of those
16 comments in that, but we are just voting on the
17 reformulation. So I know the FDA wanted to know if
18 we thought it was a safer product. I'd have to say I
19 don't think it's a safer product, but the
20 reformulation may have less abuse potential.

21 Just to answer Dr. Markman, I appreciate
22 what you're saying about with the name changes, but I

1 think actually what you came out with is my real
2 concern with the name change, is that this is still
3 oxycodone. It's still an opioid, and even as you
4 brought it out, that you may come across the patients
5 as a safer product and as a product that maybe isn't
6 an opioid.

7 So I'd have real concerns about actually
8 even recommending a name change at this time.

9 DR. KIRSCH: Dr. Deshpande.

10 DR. DESHPANDE: I think this is a very
11 difficult vote and before we take a formal vote, I
12 appreciate the chance to comment.

13 First of all, the families that spoke, both
14 in favor of long-acting opiates and those who talked
15 about the family tragedies, are exactly the two ends
16 of my practice, the pediatric critical care and
17 pediatric anesthesia and pain management.

18 So I'm having some real conflicts here
19 because I think the drugs are important. As Dr.
20 Markman and others have pointed out, it's an
21 important part of our armamentarium. So what I've
22 not heard -- and this is where I think as an advisory

1 panel to the FDA, we need to give this advice, not
2 just to vote yes or no on this but collectively the
3 advice, as Dr. Lorenz talked about keeping a record
4 of it.

5 First of all, looking at Dr. Katz's paper
6 in *Clinical Journal of Pain*, swallowing was 55
7 percent of the abuse or the misuse. Swallowing is a
8 significant concern for both young and adolescent and
9 old patients and how that plays into the problems
10 associated with these medications is something we
11 haven't looked at.

12 The second is that we have talked about an
13 immediate REMS, but we really haven't talked about a
14 REMS for this product, and one of the things that I
15 am struggling with is that, yes, I would like to have
16 a potent opiate to use for the cancer pain patients
17 and others who have long-term chronic pain.

18 I also want to make sure that there's a
19 safety plan in place that's more than a Dear Doctor
20 letter. And we've heard that it's in the works, but
21 my advice is that we need a REMS to go along with
22 this, and I'd like that in the record as a sense of

1 the committee.

2 DR. KIRSCH: Dr. Lorenz.

3 DR. LORENZ: Just a narrow comment about the
4 issue of dose, and I just want to comment as a
5 hospice and palliative medicine physician that the
6 higher doses are extremely helpful. In fact, we use
7 extremely high doses of opioids in many patients that
8 would alarm, I'm sure, a lot of people at this table.
9 And it's just a problem, I think, to deal at such
10 dose levels sometimes with multiple tablets.

11 So I'm not saying one way or the other
12 about whether it should be done because I think this
13 is an issue of balancing public risk and benefit. I
14 don't mean to suggest that therefore enormous doses
15 should be available. It's just that it points out
16 the effect to which the eventual impact of this drug
17 on public health depends on the market that the
18 sponsor seeks. And I think one of the concerns that
19 we all have at this table is that the FDA be highly
20 vigilant about ensuring that the market is narrow and
21 appropriate and that it doesn't cause increased
22 public risk through misperception of benefit. And so

1 I think I personally have no concerns, again like Dr.
2 Prough noted before, that this is any less safe than
3 what we have to deal with and may be incrementally
4 better.

5 But if it displaces many other opioids or
6 patients with stable pain regimens, then who really
7 knows, and I think then the social consequences are
8 likely to be different.

9 DR. KIRSCH: Dr. Zito.

10 DR. ZITO: Well, I concur with many of the
11 points that have just been made, and one has to do
12 with the narrowness of the population of patients
13 that are being targeted. So I think the marketing is
14 going to be extremely critical.

15 Secondly, the point that Dr. Markman raised
16 about an opportunity could be missed here without
17 taking advantage of a change in the name, because
18 it's a busy world out there and folks are just going
19 to proceed with business as usual, I think. So while
20 we get maybe a narrow benefit here for this targeted
21 abuse population, it's everyone else that we really
22 have a chance to weigh in on now.

1 DR. KIRSCH: Dr. Crawford.

2 DR. CRAWFORD: Thank you. Just very
3 briefly, as we're looking at this question as to
4 whether we recommend approval of the reformulated
5 OxyContin, we are all keeping in mind the limited
6 scope with which this committee has been charged to
7 answer, which essentially is current formulation or
8 reformulation. And if time allows, since we might be
9 close to a vote now, perhaps the agency or the chair
10 would entertain suggestions about under which
11 conditions, because it's a yes/no vote, but perhaps
12 the members of the committee might recommend certain
13 conditions that FDA could consider if they were to
14 approve the drug.

15 DR. KIRSCH: I think that the FDA would
16 appreciate your opinion about what conditions you
17 believe are important, but I don't see that as part
18 of the vote. But if you have further comments to
19 make about what conditions you think are important,
20 I'm sure the FDA would appreciate those comments.

21 DR. CRAWFORD: Well, thank you. One has
22 been stated several times before without specificity,

1 and I won't add any more to that, except I think it's
2 extraordinarily important that a condition of
3 approval for consideration would be mandated study,
4 clinical follow-up studies on the -- it seems a clear
5 therapeutic benefit in general; we already know that,
6 but about the safety of a reformulated product.

7 DR. RAPPAPORT: Can I make a comment? It's
8 very unclear to everybody, all the stakeholders here,
9 what the right study is to do and how long you have
10 to do that study to collect the information in the
11 community, and even if it's ever going to be
12 possible.

13 So I'm not saying we don't agree with you
14 that a study should be done, but for us to mandate or
15 require a study, we have to know what that study is
16 so that we can tell the sponsor at the time of
17 approval. So if anybody here feels very strongly
18 about what that study should be, I hope you'll say
19 so.

20 There are a number of groups that are
21 looking at this right now and trying to come up with
22 at least a proposed protocol for this type of study,

1 but I think that's a ways off.

2 DR. KIRSCH: Dr. Zelterman.

3 Dr. Flick.

4 DR. FLICK: Just a response to Dr. Lorenz.

5 , I think that there's -- as a practitioner of pain,
6 as well, I recognize the need for large-dose
7 increments in a really select few patients that we
8 deal with but aren't really part of most of the
9 patients that these drugs have been used by and this
10 drug continues to be used by.

11 I think there's a psychological barrier for
12 the casual user or the occasional user, the person
13 that I have great concern about, that Dr. Deshpande
14 voiced concern about, that there's a psychological
15 barrier to taking one, two, three, four of these
16 tablets as opposed to taking a single tablet.

17 Very few of the uninitiated would believe
18 that taking a single tablet of a prescription
19 medicine is potentially a fatal dose. So that's my
20 comment about the dose size.

21 I think the problems with OxyContin have
22 come primarily less about its formulation and more

1 about its marketing and more about the way it has
2 been marketed by the company that is the sponsor. We
3 have very little reassurance and very little
4 information brought to us today that would inform the
5 committee that there is substantial change and that
6 there is an expectation that this will not happen in
7 the future.

8 I know the company has made changes, has
9 been forced to make changes, but I don't know that we
10 have a clear, as Dr. Deshpande pointed out, a clear
11 REMS that we can look at and approve and comment on.
12 So in the absence of those things, I find it
13 difficult to answer in the affirmative the question
14 whether this should be approved.

15 The conundrum once again is that we are
16 forced into a position of saying we either stick with
17 the old or go with the new. And clearly the old is
18 worse than the new, although I think the difference
19 is relatively small.

20 DR. KIRSCH: Dr. Shatin.

21 DR. SHATIN: Yes. I'd like to address a
22 benefit in patient safety that I think we should

1 explicitly recognize and that's the misuse of the
2 tablet form for both caregivers, and then thinking
3 about institutions and facilities, that if it's not
4 chewable that is a benefit.

5 DR. KIRSCH: Dr. Morrato.

6 DR. MORRATO: I had a question of
7 clarification. When we vote, is that when we're
8 supposed to provide our justification or rationale;
9 are we supposed to provide it now?

10 DR. KIRSCH: Perfect segue, I think, into
11 what will happen. For those of you who haven't voted
12 on this committee, in the very near future we'll be
13 given instructions. This thing in front of us will
14 light up and you can press yes or no or abstain, and
15 then we'll complete our voting. But before we
16 display our votes on the screen, we'll ask Dr.
17 Margolis to vote, not knowing what the rest of us
18 have voted, and then his vote will be entered into
19 the system, and then the screen will show all of our
20 votes. And then we'll go around and ask again for
21 comments as to why we voted the way that we did.

22 Did I explain that correctly?

1 [Dr. Rappaport nods yes.]

2 DR. KIRSCH: Okay. So with that, I'm going
3 to try to summarize what I believe we've said in this
4 section.

5 First and foremost, several people have
6 said, and I'll reiterate, that we all have great
7 concerns for the families who either have members who
8 suffer great pain or who have suffered great loss
9 because of inadvertent use of this drug. I think the
10 committee really feels for both sides and this is a
11 very difficult question.

12 I think the committee overall believes that
13 the new formulation is not necessarily safer but that
14 there is less chance of poor outcomes related to drug
15 manipulation or tampering with the tablet.

16 I think where there's great concern and
17 will probably shift people from saying yes to no or
18 no to yes relates to the REMS. I think there's great
19 concern expressed by many people on the committee
20 that the REMS is not well defined, and for a drug
21 with this level of danger, the REMS is very
22 important. And so I think that's a concern expressed

1 by most of the members of the committee.

2 Are there desire to edit my comments?

3 Dr. Lorenz.

4 DR. LORENZ: It's unclear to me that this
5 drug's benefits are certain or quantifiable. They
6 are hypothetical on the basis of limited physical
7 manipulations under accidental circumstances.

8 DR. KIRSCH: Thank you.

9 So with that, I'll ask that we take the
10 vote. Does someone from the FDA want to make our
11 things light up or they're lighting up? Okay.

12 So from the members of the committee, again
13 you press the yes or no or abstain button and we'll
14 be given further instructions.

15 Yes, you do it right now.

16 It will keep blinking until they finalize
17 the vote and they'll watch it on the computer to see
18 whether or not all of us have voted, and when all of
19 us have voted, they'll let us know and then we'll get
20 Dr. Margolis's vote.

21 I'll reread the question. Should this
22 application for a reformulated OxyContin be approved?

1 Yes or no or abstain. Everyone please vote again.

2 Okay. Dr. Margolis, can you tell us what
3 your vote is?

4 DR. MARGOLIS: You want just my vote or
5 vote and reason?

6 DR. KIRSCH: No, just give us your vote for
7 right now.

8 DR. MARGOLIS: My vote is yes.

9 DR. KIRSCH: Okay. So the vote was yes.
10 Now we can display the votes.

11 [Votes displayed]

12 Okay. So these are the summary votes, and
13 I assume here in a second you're going to display the
14 individual votes and what I'd like to do is read the
15 results.

16 So the voting results are yes-14, no-4, and
17 abstain-1.

18 What I'd like to do is go around the table
19 and briefly have people explain why they voted as
20 they did, and it's perfectly acceptable to say that I
21 have nothing to add for why you voted.

22 So let's start with Dr. Prough.

1 DR. PROUGH: Since it was basically a
2 question of the risk-benefit ratio of the new
3 formulation, the new formulation appeared to add no
4 risk and possibly offered some benefit.

5 DR. KIRSCH: Dr. Zito.

6 DR. ZITO: I found it difficult to vote yes
7 without conditions, namely improved oversight of
8 benefit, study of benefit, and then around the issue
9 of whether the educational program with given the
10 same name is really going to be effective.

11 DR. KIRSCH: Dr. Cooper.

12 DR. COOPER: I concur with Dr. Prough.

13 DR. KIRSCH: Dr. Crawford.

14 DR. CRAWFORD: I voted yes because
15 everything I saw, I agree with what the sponsor's
16 conclusions were, that the reformulation was "not
17 more susceptible to manipulation, not worse than."
18 And it does appear from the in vitro studies compared
19 to the existing formulation that there is lesser
20 potential, at least now, for abuse.

21 DR. KIRSCH: Dr. Deshpande.

22 DR. DESHPANDE: I voted yes with regret,

1 and it was on the narrow question of whether this was
2 not worse than the current formulation. It adds a
3 minor benefit. I would like to add strongly that the
4 FDA take into account all of the advice and the
5 concerns expressed by the committee here today.

6 DR. KIRSCH: Dr. Markman.

7 DR. MARKMAN: I voted yes for the reasons
8 stated by Dr. Cooper and Dr. Prough. I also feel
9 strongly that the risk management plan as well as the
10 post-marketing studies will be critical to really
11 understanding whether this is a safety advance.

12 DR. KIRSCH: Dr. Day.

13 DR. DAY: I abstained because I think there
14 are strong needs of patients for this drug and proper
15 use in prescribing, yet there's incredible risk in
16 other situations, and it got deadlocked for me. And
17 if it had been binary and I was forced to choose, I
18 probably could have narrowed the question more to
19 just is it no worse than the original, and I would
20 have voted yes.

21 DR. KIRSCH: Dr. Lorenz.

22 DR. LORENZ: I voted yes on the basis of

1 the fact that it appears to be no worse. My concern,
2 however, is that it could be much worse, especially
3 if marketing allows providers to drop the vigilance
4 that they typically use in prescribing opioids. And
5 so while I voted yes, it only assumes the status quo.
6 Should that change in any way, it could be a definite
7 no.

8 DR. KIRSCH: Dr. Margolis.

9 DR. MARGOLIS: I voted yes for the
10 previously-stated reasons, that it has potential to
11 be safer. However, how much safer is really unknown,
12 and it's going to be very dependent on good post-
13 marketing studies.

14 DR. KIRSCH: This is Dr. Kirsch, and I
15 voted no because I felt that, although the data was
16 much better than it was at the previous presentation,
17 I think it's unconscionable to move forward without a
18 well-defined REMS.

19 Dr. Lesar.

20 Sorry. Dr. Zeltermann.

21 DR. ZELTERMAN: I voted yes for reasons
22 already given.

1 DR. KIRSCH: Ms. Solonche.

2 DR. SOLONCHE: I voted yes for many of the
3 reasons cited and for the particular way in which
4 this question was asked.

5 DR. KIRSCH: Dr. Denisco.

6 DR. DENISCO: I voted yes for the reasons
7 given and on the principle of balance. It seemed all
8 things balance, that this was some small incremental
9 improvement. However, I must say I'm terrified over,
10 one, unintended consequences, and two, over the
11 report we heard on the Internet and how this is going
12 to be reported and publicized. And it really won't
13 matter what the REMS is if we hear tomorrow on the
14 news that all of a sudden OxyContin is safer.

15 DR. KIRSCH: Dr. Morrato.

16 DR. MORRATO: I voted yes for many of the
17 reasons already mentioned, and I just wanted to add
18 my concern, also, in terms of what gets actually
19 communicated as opposed to an implied claim versus
20 what you actually claim on a label. The message gets
21 out there nonetheless.

22 I think when given the choice between

1 leaving what's existing on the market with doing
2 nothing, at least when you have the window of launch,
3 you have a chance to have some action. And I'm
4 really concerned that the class REMS are going to
5 take far too long to really make a difference.

6 DR. KIRSCH: Dr. Lesar.

7 DR. LESAR: I voted yes for the reasons
8 already stated and have the same reservations that
9 have already been expressed.

10 DR. KIRSCH: Dr. Shatin.

11 DR. SHATIN: I voted yes for the reasons
12 already given, and I also strongly believe that the
13 post-marketing and REMS will be extremely important.

14 DR. KIRSCH: Dr. Vaida.

15 DR. VAIDA: Yes. I voted yes for the
16 reasons given and that hopefully it's not worse than
17 what's on the market.

18 DR. KIRSCH: Mr. Yesenko.

19 MR. YESENKO: I voted no because I'm
20 horrified of the fact that there is no REMS available
21 and the lack of clinical safety presented by the
22 sponsor.

1 DR. KIRSCH: Dr. Flick.

2 DR. FLICK: I voted no. I think the
3 company sponsor has done a good job of presenting
4 their product. They did good work. I think they
5 came here in good faith. And I think the new
6 formulation does, indeed, do what they set out to
7 achieve.

8 Unfortunately, by approving this drug, we
9 lose leverage. We no longer can demand -- or at
10 least our ability to demand is less than it was
11 before. We can't have them come back with a REMS or
12 ask them to reduce the dose availability.

13 So I think for that reason, I reluctantly
14 voted no, recognizing that the old formulation would
15 have remained on the market.

16 DR. KIRSCH: I'd like to thank the public
17 speakers. I'd like to thank the sponsor for their
18 excellent presentation, and I'd like to specifically
19 thank Kalyani Bhatt for pulling this all together for
20 us. I think we're done.

21 Thank you.

22 DR. RAPPAPORT: I'd like to add the FDA's

1 thanks to the committee members for helping us out.

2 This is a really difficult one, as you found out

3 yourselves today.

4 Thank you.

5 [Whereupon, the meeting was adjourned at

6 4:13 p.m.]

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